United States
Environmental Protection
Agency

Office of Pesticides
and Toxic Substances
Washington DC 20460

EPA 560/2-89-001
March 1989

EPA

Preliminary Evaluations of Initial TSCA Section 8(e) Substantial Risk Notices

January 1987 - December 1988

NOTICE TO ADMINISTRATOR OF SUBSTANTIAL RISKS. Any person who manufactures, [imports,] processes, or distributes in commerce a chemical substance or mixture and who obtains information which reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment shall immediately inform the [EPA] Administrator of such information unless such person has actual knowledge that the Administrator has been adequately informed of such information.

-- Section 8(e), Toxic Substances Control Act (1976)

EPA 560/2-89-001
MARCH 1989

PRELIMINARY EVALUATIONS OF INITIAL TSCA SECTION 8(e) SUBSTANTIAL RISK NOTICES

JANUARY 1, 1987 TO DECEMBER 31, 1988

Office of Toxic Substances
Office of Pesticides and Toxic Substances
Washington, D.C. 20460

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES AND TOXIC SUBSTANCES
WASHINGTON, D.C. 20460

Disclaimer

This volume has been reviewed by the Office of Pesticides and Toxic Substances (OPTS), U.S. Environmental Protection Agency, and approved for publication. The status reports contained in this volume present the Agency's preliminary evaluations of the submitted information and do not represent final Agency policy or intent with respect to the submissions or subject chemicals. The mention of company names, trade names, or commercial products does not constitute an Agency endorsement or recommendation for or against use.

Foreword

This volume contains, in ascending submission number order, "status reports" (i.e., preliminary evaluations) prepared by staff of the Office of Toxic Substances (OTS) in the Office of Pesticides and Toxic Substances (OPTS) for initial submissions received by the Agency from chemical manufacturers, importers, processors, distributors and others between January 1, 1987, and December 31, 1988, pursuant to Section 8(e), the "substantial risk" information reporting provision of the Toxic Substances Control Act (TSCA; 90 Stat. 2029, 15 U.S.C. 2607(e)). Status reports are prepared by OTS for all initial TSCA Section 8(e) submissions and reflect only part of the initial phase of the OTS evaluation process for such information.

This volume is being distributed through the TSCA Assistance Office (TAO) in OTS/OPTS. Persons wishing to obtain a copy of this volume of Section 8(e) status reports should write to:

TSCA Assistance Office (TS-799)
U.S. Environmental Protection Agency
401 "M" Street, S.W.
Washington, D.C. 20460

EPA plans to print a limited number of copies of this volume. Once EPA's supply is exhausted, copies can be purchased through the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, Virginia 22161. Copies of the five previously published TSCA Section 8(e) status report compendiums (PB# 80-221609, PB# 81-145732, PB# 83-187815, PB# 87-129409 and PB# 87-176004) are currently available through NTIS.

The Agency welcomes the submission of additional information for, or comments on, the evaluations presented in this volume. The submission of unpublished information relating to biological or environmental effects, production/importation volumes, use(s), and worker, consumer, and environmental exposure to the subject chemical substances and mixtures would be especially valuable. Such information will be considered at subsequent steps in the OTS chemical assessment process. The submission of additional information for, or comments on, these evaluations should be directed to:

Mr. Frank D. Kover (TS-778)
Chief, Chemical Screening Branch
Existing Chemical Assessment Division
Office of Toxic Substances/OPTS
U.S. Environmental Protection Agency
401 "M" Street, S.W.
Washington, D.C. 20460

Non-confidential versions of Section 8(e) submissions and EPA status reports can be viewed in the OPTS public files located at EPA Headquarters, Room G-004 Northeast Mall, 401 "M" Street S.W., Washington, D.C. Copies of TSCA Section 8(e) submissions and status reports can be obtained by writing to EPA's Freedom of Information Office at the following address:

Freedom of Information Office (A-101)
U.S. Environmental Protection Agency
401 "M" Street, S.W.
Washington, D.C. 20460

This and previous volumes of status reports have been published by EPA for two reasons. First, volumes of status reports will make reported information more accessible. Second, such volumes may, by providing specific examples of submitted information and EPA's evaluation of that information, help those persons subject to Section 8(e) understand better the types of information that should be submitted.

It is important to note that EPA's overall implementation of TSCA Section 8(e) has resulted in heightened chemical industry awareness of the potential risks posed by chemical substances. This heightened awareness has led in many cases to voluntary corporate actions designed to protect human health or the environment. For example, many companies have reported that in direct response to submitted Section 8(e) data, the following types of voluntary health and environmental protection measures were initiated:

- formal notification of others (e.g., workers, customers) about the reported data by way of letters and modifications to product labels and Material Safety Data Sheets;
- changes made in manufacturing, processing and handling procedures to reduce or eliminate chemical exposure;
- use or production of chemicals halted temporarily or discontinued altogether; and
- additional toxicologic and monitoring studies undertaken to improve understanding of chemical toxicity or exposure.

The chemical industry's increased awareness of potential risks is evidenced further by EPA's receipt thus far of over 670 voluntary "For Your Information" (FYI) submissions that contain valuable toxicologic, exposure and voluntary risk reduction information.

Joseph J. Merenda, Director
Existing Chemical Assessment Division/OTS

Acknowledgment

In preparing the status reports contained in this compendium, EPA's Office of Toxic Substances (OTS) has frequently found it necessary to request additional information about, or clarification of, the submitted data. OTS appreciates the efforts and cooperation of the following companies, agencies and organizations that have submitted information reflected in this volume:

3M Company
American Cyanamid Company
American Telephone and Telegraph Company
Antimony Oxide Industry Association
Amoco Chemical Company
Amoco Corporation
Amoco Oil Company
Atlantic Richfield Company
BASF Corporation
Boeing Company
Borg-Warner Chemicals, Inc.
Chemical Manufacturers Association
CIBA-GEIGY Corporation
Dow Chemical Company
Dow Corning Corporation
Eastman Kodak Company
E. I. DuPont de Nemours & Company, Inc.
Eli Lilly and Company
Gelman Sciences Inc.
General Electric Company
Henkel Corporation
Hoechst Celanese Corporation
International Isocyanate Institute, Inc.
Koppers Company, Inc.
Lever Brothers Company
Mobay Corporation
Mobil Research and Development Corporation
Monsanto Company
National Toxicology Program
Olin Corporation
Pennzoil Company
PPG Industries, Inc.
Procter & Gamble Company
Reilly Tar & Chemical Corporation
Sandoz Crop Protection Corporation
Shell Oil Company
Society of the Plastics Industry, Inc.
Stauffer Chemical Company
Texaco Inc.
Union Carbide Corporation
Valent U.S.A. Corporation
Vista Chemical Company
Wacker Chemicals (USA), Inc.
Westvaco Corporation
Xerox Corporation

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Introduction

Section 8(e) of the Toxic Substances Control Act (TSCA; the Act) states that "any person who manufactures, [imports,] processes, or distributes in commerce a chemical substance or mixture and who obtains information which reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment shall immediately inform the [EPA] Administrator of such information unless such person has actual knowledge that the Administrator has been adequately informed of such information."

In view of the fact that Section 8(e) was self-implementing (i.e., required no implementing rules), chemical manufacturers, importers, processors and distributors became subject to the Section 8(e) reporting provision as of January 1, 1977, the effective date of TSCA. In order to clarify the types of information to be submitted and the procedures for doing so, the Agency (following receipt and review of public comments) published its TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978). For easy referral when using this volume, EPA's TSCA Section 8(e) policy statement has been reproduced as Appendix A in the back of this volume.

The March 16, 1978 TSCA Section 8(e) policy statement expresses the Agency's policy that the information subject to Section 8(e) reporting is any "new" information that "reasonably supports" a conclusion that a chemical substance or mixture presents a substantial risk of injury to health or the environment but need not necessarily indicate conclusively that such a risk exists. A determination of "substantial risk" does not include an evaluation of economic or social benefits of the use of the chemical and, therefore, is not synonymous with the term "unreasonable risk" which is found in other sections of the Act. Although EPA's receipt of information under Section 8(e) of TSCA does not necessarily trigger immediate regulatory action, the information that is submitted under TSCA Section 8(e) does receive priority review and evaluation by EPA in order to determine an appropriate course of Agency action.

Thus far, EPA and the chemical industry have devoted significant efforts in fulfilling their respective responsibilities under Section 8(e) of TSCA. Since January 1, 1977, approximately 780 initial TSCA Section 8(e) submissions covering a broad range of toxicity and exposure-related information on a wide variety of chemicals have been received and given priority evaluation and follow-up attention by the Office of Toxic Substances (OTS) in EPA's Office of Pesticides and Toxic Substances (OPTS). (The OTS TSCA Section 8(e) submission review process is shown on page 4.) In general, each initial TSCA Section 8(e) submission is promptly reviewed and evaluated by OTS scientific staff to determine both

the degree of concern that should be attached to the submitted information and the initial course of any warranted OTS follow-up action(s). A "status report" is prepared which contains a brief description of the submitted information, the results of the OTS preliminary evaluation, a statement with respect to the production and use of the subject chemical(s), and the recommendations for appropriate follow-up actions. Upon approval of the status report, recommended follow-up actions are initiated. A letter containing the status report and any EPA requests for additional information is sent to the submitting company. In addition, copies of all status reports are transmitted to the OPTS public files, other designated EPA Program Offices and Federal Agencies, and to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution. Other OTS follow-up actions include consideration of further, more in-depth assessment of the reported chemical hazard or risk. It should be noted also that OTS immediately reviews, evaluates, and initiates appropriate follow-up actions or activities for all information contained in "follow-up" and "supplemental" TSCA Section 8(e) notices. By definition, follow-up notices are those that contain information submitted directly in response to an EPA request, whereas supplemental notices are those that contain information not specifically requested by EPA.

A Document Control Number is used by EPA to identify TSCA Section 8(e) submissions and takes the following form: 8EHQ-0000-0000. Starting at the left, the first four symbols identify the information as a Section 8(e) submission received by EPA Headquarters; the next four digits identify the month and year (e.g., -0588-) of the Agency's receipt of the information; the final four digits identify the submission's chronological number. In addition to the basic numerical sequence, additional characters may be added to the right end of the Document Control Number to convey other information. These additional characters and their meaning are as follows:

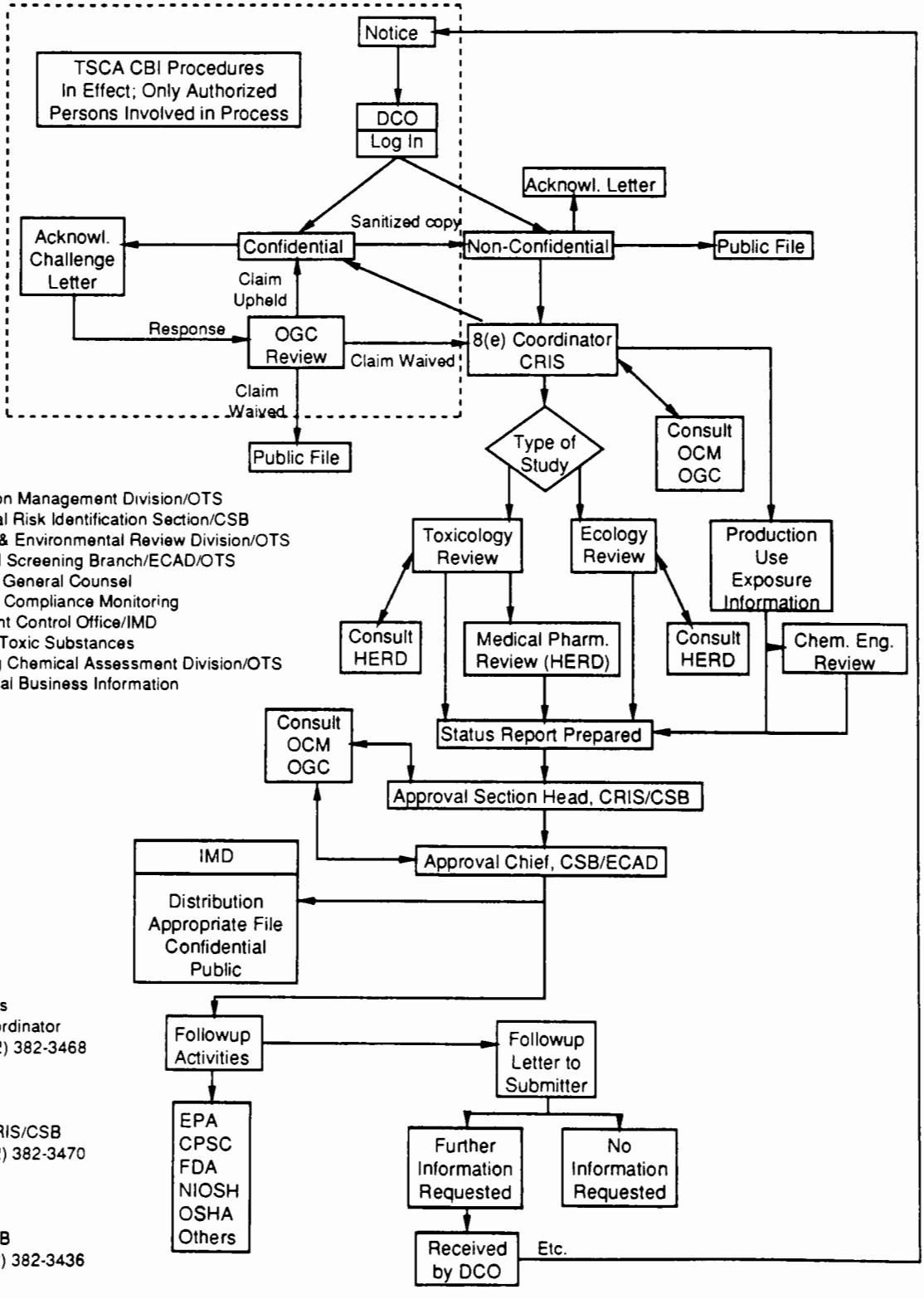
S: indicates that the TSCA Section 8(e) submission was sanitized to delete information that was claimed by the submitting company to be TSCA Confidential Business Information (TSCA CBI);

P: indicates that the TSCA Section 8(e) submission contained names or other identification (e.g., Social Security Numbers) of individuals, the release of which may violate the Privacy Act (such documents are sanitized to remove an individual's name or other identifiers); and

*: indicates that, based on a preliminary evaluation, the submission was considered by the Agency to be unwarranted for reporting pursuant to Section 8(e) of TSCA.

When reviewing the status reports contained in this volume, the reader should realize that the purpose of the OTS preliminary evaluation is to determine the significance of the submitted information in terms of a need for possible follow-up action by the Agency. This determination involves a critical analysis of the submitted data to assess the extent that the reported hazard or risk is supported by the provided information. The scope of this initial evaluation, however, is generally limited to the submitted documents and to any closely related information known by the OTS reviewer. Neither a literature search to identify other reported effects nor an in-depth analysis of possible sources of exposure to subject chemicals is part of the evaluation process. Therefore, a status report should be viewed only as a preliminary evaluation of the submitted information and not as a comprehensive assessment of the chemical substance or mixture for which a TSCA Section 8(e) notice has been filed.

Processing of 8(e) Notices of Substantial Risk



IMD: Information Management Division/OTS
CRIS: Chemical Risk Identification Section/CSB
HERD: Health & Environmental Review Division/OTS
CSB: Chemical Screening Branch/ECAD/OTS
OGC: Office of General Counsel
OCM: Office of Compliance Monitoring
DCO: Document Control Office/IMD
OTS: Office of Toxic Substances
ECAD: Existing Chemical Assessment Division/OTS
CBI: Confidential Business Information

David R. Williams
Section 8(e) Coordinator
Telephone: (202) 382-3468
FTS: 382-3468

James F. Darr
Section Head/CRIS/CSB
Telephone: (202) 382-3470
FTS. 382-3470

Frank D. Kover
Branch Chief/CSB
Telephone: (202) 382-3436
FTS: 382-3436

DATE: FEB 25 1987

SUBJECT: Status Report* 8EHQ-0187-0649 S Approved: 2/25/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

The submitting company claimed its name and the exact identity of the subject chemical to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS) will ask the submitting company to substantiate these TSCA CBI claims. In the "sanitized" version of this TSCA Section 8(e) notice, the submitter reported non-confidentially that the subject chemical was an "alkoxylated aromatic diamine" currently in research and development (R&D) and intended for commercialization.

Submission Description

The submitting company reported that a crude preparation of the subject chemical, when tested in an Ames Salmonella typhimurium (bacteria) mutagenicity assay, was found to be positive in strain TA 1538 in the presence of metabolic activation. A partially purified (i.e., semi-crude) sample tested in the Ames assay was reportedly positive in strains TA 1538, TA 100, and TA 98 in the presence of metabolic activation. According to the submitting company, this semi-crude material was non-genotoxic when tested in an in vitro Unscheduled DNA Synthesis (UDS) assay using rat hepatocytes. The submitter reported that the semi-crude material was tested also in an in vitro Chinese Hamster Ovary (CHO) cell mutagenicity assay and was non-mutagenic in the presence of metabolic activation. In the absence of activation in the CHO cell assay, the submitter reported that the semi-crude preparation was positive at certain doses but a dose-response was not observed. According to the submitter, the testing laboratory classified the positive CHO cell assay findings as being "suspect." The submitting company reported further that a "highly purified" sample of the semi-crude material was tested alone and as a "blend" in the Ames assay and was found to be negative with and without metabolic activation. In conclusion, the submitter stated that the observed mutagenic activity could be due to an impurity in the preparation.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Submission Evaluation

In order for EPA to evaluate the overall significance of the reported findings, the submitter should be asked to ensure that the Agency receives full copies of the final reports (including the actual experimental protocols, data, results of statistical analyses, etc.) from all of the studies cited in this submission.

Current Production and Use

In view of the submitter's TSCA CBI claims, no information with regard to the current TSCA Chemical Substance Inventory status of the subject material will appear in this status report.

Comments/Recommendations

The submitting company reported that its R&D personnel have been notified about the reported findings.

Although a positive in vitro genotoxicity test finding, when considered by itself, may not be sufficient to offer reasonable support for a conclusion of substantial risk (as defined in EPA's TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978)), EPA does believe that such a finding is of value in assessing the possible risk(s) posed by exposure to the tested chemical or mixture. Also, EPA believes that a positive genotoxicity test result, in combination with additional information (e.g., the knowledge of potential/actual exposure to and/or high production of the tested chemical or mixture), would suggest a need, in many cases, to conduct other studies designed to determine better the toxicity of and/or the exposure to that chemical or mixture. The results of such additional tests should be considered also for submission to EPA under Section 8(e).

a) The Chemical Screening Branch will ask the submitting company to ensure that the Agency receives full copies of the final reports (including the actual experimental protocols, data, results of any statistical analyses, etc.) from all studies that were cited in the company's Section 8(e) notice. In addition, the submitter will be asked to keep the Agency apprised about the results of further studies conducted by the company to determine the cause(s) of the observed mutagenic activity.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical(s).

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: JAN 29 1987

SUBJECT: Status Report* 8EHQ-0187-0650 Approved: 4/2/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

On behalf of the "Vinyl Acetate Task Force" (the Union Carbide Corporation, the U.S. Industrial Chemicals Company, the Celanese Corporation and E. I. DuPont de Nemours & Company, Inc.), the Society of the Plastics Industry, Inc. (SPI) provided the following information regarding the conduct and preliminary results of a two-year inhalation study of vinyl acetate (CAS No. 108-05-4) in rats:

> "In this [inhalation] study, groups of Sprague-Dawley rats were exposed to concentrations of vinyl acetate of 0, 50, 200 and 600 ppm for six hours a day, five days a week for two years. A preliminary pathology report shows 10 tumors have been observed in the nasal cavities in the 77 high dose animals examined. Two of those tumors were squamous cell carcinomas; the balance were papillomas. No tumors were observed in the other exposure concentrations or in the control animals."

It should be noted that in a previous TSCA Section 8(e) notice (8EHQ-1086-0642), SPI submitted the following information with regard to the conduct and preliminary findings from a two-year inhalation study of vinyl acetate in mice:

> "Groups of 90 CD-1 mice were exposed to concentrations of vinyl acetate of 0, 50, 200 and 600 ppm for six hours a day, five days a week, for two years. The preliminary pathology review . . . indicated that the only adverse effects observed were in the respiratory tract. Mice exposed to the 600 ppm level exhibited bronchiolar epithelial lesions in the lung which included one animal with one squamous cell nodule of a terminal bronchial

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

airway and another animal with one squamous cell carcinoma in a major airway. No such tumors were observed at the other exposure . . . [concentrations] or in the control animals. The 50 ppm concentration appeared to be a no observable effect level."

Submission Evaluation

Immediately upon receipt of these TSCA Section 8(e) submissions, the Chemical Screening Branch (CSB/ECAD/OTS) provided copies of the notices to the Risk Analysis Branch (RAB/ECAD/OTS) for inclusion in the ongoing review of available toxicologic and exposure data on vinyl acetate.

The Agency has received a number of TSCA Section 8(e) and "For Your Information" (FYI) notices on vinyl acetate. It should be noted also that the Chemical Screening Branch prepared (in 1984) a Chemical Hazard Information Profile (CHIP) on vinyl acetate. Finally, it should be noted EPA published (on December 27, 1985) a TSCA Section 8(d) information gathering rule on vinyl acetate (50 FR 52923).

Current Production and Use

A review of the production range (includes importation volumes) statistics for vinyl acetate (CAS No. 108-05-4), which is listed in the initial TSCA Chemical Substance Inventory, has shown that 521 million to 2.6 billion pounds of this chemical were reported as manufactured/imported in 1977. This production range information does not include any data claimed to be TSCA Confidential Business Information (CBI) by the person(s) reporting for the initial TSCA Inventory, nor does this production range information include any data that would compromise TSCA CBI. All of the information reported for the initial TSCA Inventory, including the production range data, is subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

According to Chemical & Engineering News (June 9, 1986 issue), 2.02 billion and 2.11 billion pounds of vinyl acetate were produced in the U.S. during 1984 and 1985, respectively. According to secondary literature sources, the major use of vinyl acetate is in the production of polymers (e.g., poly(vinyl acetate), poly(vinyl alcohol), vinyl chloride copolymer, ethylene-vinyl acetate copolymers).

Comments/Recommendations

To date, EPA has received a number of Section 8(e) submissions from trade associations on behalf of their member companies. In the Comments/Recommendations section of the status report that was prepared by EPA in response to Section 8(e) submission 8EHQ-0185-0543, the Agency reiterated its position with regard to the TSCA Section 8(e) reporting obligations of trade associations and their member companies.

In the present TSCA Section 8(e) notice, SPI stated that copies of future interim reports and the final report from the chronic vinyl acetate inhalation study in rats will be provided to EPA as soon as those reports become available.

a) The Chemical Screening Branch will ask SPI to ensure that copies of this status report are provided to the U.S. co-sponsors of the cited two-year inhalation study of vinyl acetate in rats. SPI will be asked also to ensure that EPA receives a full copy of the final report (including the actual experimental protocol, results of gross and histopathological examinations, results of any statistical analyses performed, etc.) from this two-year vinyl acetate inhalation study in rats.

b) As in the case of the initial Section 8(e) submission, the Chemical Screening Branch will immediately send all reported information to the Risk Analysis Branch for inclusion in their ongoing review of available toxicologic and exposure data on vinyl acetate.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS and RAB/ECAD/OTS. In addition, copies of this report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAR 2 1987

SUBJECT: Status Report* 8EHQ-0187-0651

Approved: 3/3/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Xerox Corporation provided preliminary findings from a study designed to assess the mortality experiences of Xerox service and manufacturing workers employed by Xerox from 1960 to 1982 with a followup performed to the end of 1984. In the cover letter to the submission, Xerox presented the following summary regarding the study findings:

> "A preliminary analysis of mortality data conducted by Xerox Corporation identified two clusters involving an increased risk of cancer of the stomach and esophagus respectively, [with] only the former being statistically significant. No correlation with any chemical or group of chemicals is known or suspected. Similarly, no correlation between job category or work location could be determined. Efforts will continue to define the causal factors, if any, in the workplace. . . . . Efforts are underway to complete the mortality study in a timely fashion."

Submission Evaluation

In order for EPA to evaluate the overall significance of the reported information, Xerox should be asked to ensure that the Agency is apprised of any significant findings obtained during the company's ongoing efforts to identify the cause(s) of the apparent increases in esophageal and stomach cancer. Also, Xerox should be asked to ensure that EPA receives a full copy of the final report from this mortality study upon completion.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Comments/Recommendations

In addition to completing the cited mortality study, Xerox stated that Xerox "employees in work groups reflected in the esophagus and stomach cancer clusters, their supervisors, and their union representatives in the appropriate work locations will be advised of the preliminary findings of the study." According to Xerox, the "discussions with these employees will focus on known risk factors with respect to cancer in general and stomach cancer specifically." In addition, Xerox reported that "an assessment of the work site and potential exposures represented by this group will be performed" and "will include a systematic review of environmental and administrative protective measures in place and the need for additional measures."

According to EPA's March 16, 1978 TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110), epidemiological findings involving increased cancer incidence, for example, would be required to be reported under Section 8(e) "if one (or a few) chemical(s) is strongly implicated." Considering that in the present Section 8(e) submission there is no correlation at this time with regard to the apparent increased incidence of stomach/esophageal cancers and job category, job location or chemical exposure(s), the Xerox Corporation's submission does not appear to have been required under Section 8(e) of TSCA. In making this statement concerning TSCA Section 8(e)-reportability, the reader should bear in mind that EPA's position is based solely on the submitted information and does not take into account any additional pertinent information that may have been considered by Xerox in deciding to submit the subject findings to EPA under Section 8(e) of TSCA.

a) The Chemical Screening Branch will ask Xerox to ensure that EPA is apprised in a timely manner about any significant findings obtained during the company's ongoing efforts to identify the cause(s) of the apparent increased incidence of esophageal/stomach cancers. Xerox will be asked also to ensure that EPA receives a full copy of the final report from this mortality study.

b) The Chemical Screening Branch will review the reported information in greater detail in order to determine the need for further OTS assessment of the information at this time.

c) The Chemical Screening Branch will send copies of this status report to NIOSH and OSHA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: FEB 13 1987

SUBJECT: Status Report* 8EHQ-0287-0652 S Approved: 2/17/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note (See NOTE on page 3 of this status report)

The Atlantic Richfield Company (ARCO) has claimed the exact identities of the constituents of the subject mixture to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS) will request ARCO to substantiate this TSCA CBI claim. In the "sanitized" version of the TSCA Section 8(e) notice, ARCO reported non-confidentially that the tested product was an amine mixture.

Submission Description

ARCO submitted the following summary information with regard to the conduct and results of primary rabbit skin and eye irritation studies of the subject amine mixture:

> "In the primary dermal irritation study, six albino rabbits (2.0 to 3.0 kg) had 0.5 ml of this product applied to their shaved backs at four sites, two intact and two abraded. The liquid was held in place by 2.5 cm square gauze patches with tape and the torso was loosely wrapped with plastic and secured with adhesive tape. After 24 hours, the patches, tape and wrapping were removed and each site was observed and scored for the appearance of irritation and/or corrosion. . . . This scoring was repeated at 48 and 72 hours and at 7 and 14 days for the surviving animals. Based on the scores obtained and the eschar noted, this product was designated as corrosive to skin.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"In addition to these findings, unexpectedly, five out of six animals died on test: one after 48 hours, two after 72 hours, one after 96 hours, and one after 10 days. The one remaining rabbit survived 14 days after treatment and demonstrated healing at the sites of application. Necropsy of the two longest surviving animals revealed substantial damage to internal organs. Since 2.0 ml of the product was applied on each rabbit back, the approximate dose of this . . . [amine mixture] was 0.7 to 1 ml/kg.

"In a second study, the primary eye irritation potential of this product was assessed using nine albino rabbits (2.0 to 3.0 kg). Six animals had 0.1 ml of the product instilled into the conjunctival sac of one eye without any subsequent washout and three were instilled with this material followed by a washout with lukewarm water 20-30 seconds later for about one minute. Rabbit eyes were [then] observed and scored by the Draize technique at 24 and 48 hours. . . . By the 48-hour observation time after instillation, the treated eyes in all of the rabbits, regardless of whether they were washed or not, exhibited pronounced corrosion of the cornea and conjunctival membranes. Due to these results, the animals were sacrificed at that time."

In submitting these findings to EPA under Section 8(e), ARCO stated that the acute toxicity studies were conducted "due to a lack of data regarding acute dermal and eye irritation potential for this product." ARCO stated further that in conducting these studies, the company "hoped to provide a scientific basis for representing the product's potential irritation hazards following acute dermal and eye exposure on its label and on the product material safety data sheet [(MSDS)]."

Submission Evaluation

In order for EPA to evaluate the overall significance of the reported acute toxicologic findings, ARCO should be asked to ensure that EPA receives complete copies of the final reports (including the actual experimental protocols, data, results of gross and histopathological examinations, etc.) from the acute primary eye and dermal irritation studies cited in the company's submission.

Current Production and Use

(See NOTE on page 3 of this status report)

In view of ARCO's TSCA CBI claims, no information regarding the use(s) or TSCA Inventory status of the tested product or its constituents will appear in this status report.

Comments/Recommendations

ARCO stated that the current product MSDS reflects the company's "earlier conservative judgement that this material is likely to be irritating to skin and eyes on contact. . . ." In addition, ARCO stated that the company believes the "protection recommended for handling this product also is effective in preventing dermal absorption which may be responsible, as well, for toxic systemic effects." ARCO stated further that the company was 1) updating the product MSDS to reflect the reported toxicologic findings, and 2) notifying ARCO workers and customers about those findings.

a) The Chemical Screening Branch will ask ARCO to ensure that EPA receives complete copies of the final reports (including the actual experimental protocols, results of gross and histopathological examinations, etc.) from the acute primary dermal and eye irritation studies cited in the company's Section 8(e) notice. In addition, ARCO will be requested to provide the CAS Registry Number for each constituent in the tested amine mixture.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure information, ARCO will be requested to describe the nature and results, if available, of all studies (other than those cited in the open scientific literature or those submitted already to the Agency) about which ARCO is aware or that ARCO has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to the subject amine mixture or its constituents.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the mixture and/or its constituents.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, NTP, FDA, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

NOTE: In a followup letter dated March 3, 1987, the Alantic Richfield Company reported non-confidentially that the tradename under which the subject amine mixture is sold is "Antistat for Arcel™ Resin."

2/1/87

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: APR 17 1987

SUBJECT: Status Report* 8EHQ-0287-0653

Approved: T. R. Torres for
APR 17 1987

FROM: Frank D. Kover, Chief
Chemical Screening Branch/ECAD

TO: Joseph J. Merenda, Director
Existing Chemical Assessment Division/OTS

Note

On a "For Your Information" (FYI) basis (FYI-OTS-0187-0527), the CIBA-GEIGY Corporation submitted the following information with regard to the conduct and preliminary results of a 28-day oral gavage study of 4-(hydroxymethyl)-4-methyl-1-phenyl-3-pyrazolidinone (Irgaform 1266; Dimezone S; CAS No. 13047-13-7) in rats:

> ". . .[The performed study] shows a dose dependent toxic anemia with the formation of inclusion bodies, as well as spermatogenesis reduction with atrophy of the testicular canals in the highest dose group (150 mg/kg bw.). The animals were treated with 10, 40 and 150 mg/kg by gavage; 10 mg/kg proved to be the no observable effect level. The demonstrated findings, especially the spermatogenesis reduction, are toxicologically significant. They show great similarity to the findings which were obtained for . . .[1-phenyl-3-pyrazolidinone (phenidone; CAS No. 92-43-3) and submitted previously to EPA by the Eastman Kodak Company under Section 8(e) of TSCA (8EHQ-0984-0529 et seq.)]."

In its FYI submission, CIBA-GEIGY 1) stated that it had received the above information in a "Flash Report" and 2) provided copies of both the original "Flash Report" (in German) and an English translation of that report. (Based on the form and substance of the reports, it appeared to EPA that the Irgaform 1266 28-day oral gavage study had been conducted by CIBA-GEIGY Ltd., Basel, Switzerland). In submitting these reports to the Agency on an FYI basis, CIBA-GEIGY stated that the company would be unable to judge the real significance or TSCA Section 8(e)-reportability of the toxicologic findings until a full copy of the final report from the 28-day study was received and evaluated by the company. The final report from the Irgaform 1266 28-day oral gavage study in rats is the subject of the present Section 8(e) submission.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Submission Description

Under Section 8(e) of TSCA, CIBA-GEIGY submitted a complete copy of the final report from the 28-day study cited in FYI-OTS-0187-0527. (As anticipated, this study was conducted by CIBA-GEIGY Ltd. in Switzerland.) In submitting this final report to EPA under Section 8(e) of TSCA, CIBA-GEIGY stated that "anemia and testicular lesions were the primary effects induced in animals which received the highest [Irgaform 1266] doses (40 and 150 mg/kg/day) by gastric intubation." CIBA-GEIGY stated also that "the NOEL [("no observed effect level")] was determined to be 10 mg/kg/day." CIBA-GEIGY stated further that the "primary effects, while significant, were produced after administration by gastric intubation and mainly had a minimal grade of severity." Finally, CIBA-GEIGY reported that the observed toxicologic effects "may be reversible."

In addition to submitting a full copy of the 28-day study final report, CIBA-GEIGY provided an updated Irgaform 1266 Material Safety Data Sheet (MSDS) and product label. According to the MSDS, Irgaform 1266 has an oral (rat) LD50 of 1000 mg/kg and a dermal (rat) LD50 of greater than 2000 mg/kg. The MSDS states further that Irgaform 1266 is minimally irritating to rabbit skin and moderately irritating to rabbit eyes. With regard to skin sensitization, the MSDS reports that Irgaform 1266 was positive when tested in a modified maximization study in guinea pigs "with 2/20 positive after [the] first challenge and 3/19 positive after [the] second challenge." The MSDS states also that Irgaform 1266 was negative in an Ames Salmonella typhimurium (bacteria) assay. In addition, the MSDS states that the results of a modified Sturm Test indicate that Irgaform 1266 is not biodegradable. Finally, the MSDS reports that Irgaform 1266 has a 96-hour LC50 of 32 ppm for rainbow trout, a 96-hour LC50 of 43 ppm for zebra fish and a 24-hour EC50 of 7.1 ppm for Daphnia magna.

Submission Evaluation

The information presented in FYI-OTS-0187-0527 (particularly the English translation of the German "Flash Report") indicates that Irgaform 1266, when administered orally by gavage to rats for 28 days, produced a toxic anemia with inclusion body formation as well as reduced spermatogenesis and testicular atrophy at the highest daily dose administered. Based solely on the information presented in FYI-OTS-0187-0527, it is quite reasonable to believe that the observed toxic effects are compound-related especially when one considers that phenidone (a close structural analog) has been reported to cause similar adverse effects when administered via the feed to rats. (The reader's attention is directed to the status report prepared by the Agency in response to the initial TSCA Section 8(e) submission (8EHQ-0984-0529) on phenidone.)

A review of the final report from the 28-day oral gavage study of Irgaform 1266 shows that although no animals died and there were no outward signs of systemic toxicity, there was a mild, slightly

macrocytic (abnormally large erythrocyte) anemia in both sexes in the high dose group. The high dose females exhibited anemia with Heinz bodies and showed decreases in blood cell count, hemoglobin concentration, and packed cell volume, and increases in mean corpuscular volume and mean corpuscular hemoglobin. The same trends were evident in the high dose male rats. The increased number of reticulocytes observed in the high dose males and females is a sign of increased hematopoiesis in order to compensate for the decline in red blood cells. Although no relevant gross changes were seen at terminal sacrifice, noteworthy microscopic changes were found in the male and female rats in the two highest dose levels. The major microscopic changes were as follows:

Spleen: congestion, hemosiderosis and extramedullary hematopoiesis in males (40 and 150 mg/kg) and females (40 and 150 mg/kg)

Liver: hepatocellular hemosiderosis in females (150 mg/kg) and Kupffer cell hemosiderosis in females (40 and 150 mg/kg)

Kidney (proximal convoluted tubule): partially PAS-positive eosinophilic bodies in males (40 and 150 mg/kg)

Epididymis: slight occurrence of cellular debris (40 and 150 mg/kg) and bilateral and unilateral spermatic granulomas (150 mg/kg)

Testis: slight atrophy of the spermatogenic epithelium, presence of a few spermatogenic giant cells, and slight hyperplasia of the Leydig cells (150 mg/kg).

Overall, the submitted final report confirms the information presented in the "Flash Report" that oral (gavage) administration of Irgaform 1266 for 28-days caused adverse hematopoietic effects in male and female rats and adverse reproductive organ effects in male rats. Based on the data contained in the final report, the no-observable-adverse-effect-level (NOAEL) for Irgaform 1266 in the 28-day study appears to be 10 mg/kg.

Current Production and Use

A review of the production range (includes importation volumes) statistics for CAS No. 13047-13-7, which is listed in the initial TSCA Chemical Substance Inventory, has shown that between 10,000 and 101,000 pounds of this chemical were reported as manufactured and/or imported in 1977. This production range information does not contain any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) who reported for the TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the information reported for the initial TSCA Inventory, including the production range information, is subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

According to the submitted MSDS, Irgaform 1266 is a water-soluble solid with a slight odor and has a melting point of approximately 120°C and a vapor pressure of less than $3X10^{-7}$ mm Hg at 20°C.

In FYI-OTS-0187-0527, the CIBA-GEIGY Corporation provided the following information regarding the current production volume and use of Irgaform 1266:

> "Irgaform 1266 is a phenidone derivative used as a photographic developing agent. . . .[CIBA-GEIGY has] imported approximately 1,200 lbs. over the past two years, 880 lbs. of which is still in inventory. Three to five major potential customers in the U.S. are already using this chemical substance commercially. Additionally, there are many smaller photographic developing companies which would purchase developer chemicals containing this substance in solution. The total U.S. market for the substance, which has been in use commercially for about 20 years, is about 110,000 lbs."

In its Section 8(e) submission, CIBA-GEIGY reported further that the "vast majority of this chemical substance used in the U.S. is produced or imported by other companies . . . [and] CIBA-GEIGY is a very minor supplier to this market." In the TSCA Section 8(e) notice, CIBA-GEIGY also provided the following information with regard to the potential for exposure to Irgaform 1266:

> "Because . . . [Irgaform 1266] is a skin sensitizer, the recommended handling precautions on . . . [the MSDS and label] would result in minimal exposure. These precautions are designed to avoid eye, skin, and inhalation exposure through engineering controls or the wearing of personal protective equipment; i.e., chemical goggles, impervious gloves, and a NIOSH approved respirator, if necessary."

Finally, CIBA-GEIGY stated in its TSCA Section 8(e) submission that the major use of Irgaform 1266 is in "professional X-ray developing . . . [and] the level of this product in commercial developer solutions is only 1 to 2 gms/Liter, i.e., 0.1 to 0.2%." According to CIBA-GEIGY, "developer personnel wear impervious gloves . . . when handling the product either neat (powder form) or in solution."

Comments/Recommendations

At the time of EPA's receipt of this TSCA Section 8(e) notice, EPA was in the process of preparing a statement outlining EPA's initial position on the Section 8(e)-applicability/reportability of the toxicologic information presented in FYI-OTS-0187-0527. It is appropriate, therefore, that this status report will serve as the forum for EPA to present its position on this matter.

Based on an EPA review of the toxicologic information contained in FYI-OTS-0187-0527 alone, EPA believes that the information (especially the adverse male rat reproductive system findings presented therein) should have been reported under Section 8(e), the substantial risk information reporting provision of TSCA. The basis for EPA's position is as follows:

> TSCA Section 8(e) states that "any person who manufactures, [imports,] processes, or distributes in commerce a chemical substance or mixture and who obtains information which reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment shall immediately inform the Administrator of such information unless such person has actual knowledge that the Administrator has been adequately informed of such information."
>
> The preface in Part V of EPA's March 16, 1978 Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110) states that "a substantial risk of injury to health . . . is a risk of considerable concern because of (a) the seriousness of the effect . . . and (b) the fact or probability of . . . [the serious effect's] occurrence." Regarding the seriousness of the effect, Part V of the TSCA Section 8(e) policy document explains that the Agency considers the types of health effects for which substantial risk information must be reported to include "any pattern of effects or evidence which reasonably supports the conclusion that the chemical substance or mixture can produce . . . toxic effects resulting in . . . serious or prolonged incapacitation." Information concerning such effects can be obtained directly or inferred from designed studies (e.g., in vivo animal studies) as described in Part VI of the Section 8(e) policy statement.
>
> With regard to the "fact or probability of . . . [the serious effect's] occurrence" criterion, Part V of the Section 8(e) policy statement explains that certain types of health effects are considered by EPA to be so serious that virtually no weight should be attached to the chemical's exposure in determining whether to report under Section 8(e) of TSCA. Further, EPA's response to Comment 31 (see Appendix B of the Section 8(e) policy document) states that the occurrence of serious toxic effects such as those described in Part V(a)(1)/(2) of the policy statement presupposes exposure to the tested chemical or mixture and must be reported to the Agency under Section 8(e) of TSCA.
>
> With regard to when to report information to EPA under Section 8(e), Part VI of the policy statement explains that a subject "person is not to delay reporting until

he obtains conclusive information that a substantial risk exists, but is to immediately report any evidence which reasonably supports that conclusion." Part VI explains also that "not only should final results from such studies be reported, but also preliminary results from incomplete studies where appropriate."

With regard to the immediate reporting requirement imposed by Section 8(e), Part IV of the policy statement explains that the EPA Administrator is considered to be informed immediately about substantial risk information "if [the] information is received by EPA [in accordance with the reporting procedures outlined in Part IX of the Section 8(e) policy statement] not later than the 15th working day after the date . . . [a subject] person obtained such information." It should be noted also that Part III of the Section 8(e) policy statement explains that EPA considers a subject company to have "obtained" substantial risk information at the time any corporate officer or employee of that company capable of appreciating the significance of the information obtains (i.e., possesses or knows of) such information.

Considering the preceding Section 8(e) policy discussion, EPA believes that the toxicologic information contained in FYI-OTS-0187-0527 (particularly the adverse male rat reproductive effects information) clearly offers reasonable support for a conclusion of substantial risk as that term is defined in the Section 8(e) policy statement and as such should have been submitted formally to the Agency under Section 8(e) of TSCA.

a) The Chemical Screening Branch (CSB/ECAD) will request CIBA-GEIGY to provide the company's rationale as to why the information presented in FYI-OTS-0187-0527 was not submitted to EPA under TSCA Section 8(e). After an EPA review of CIBA-GEIGY's response, the Chemical Screening Branch (CSB/ECAD/OTS) will, if appropriate, deliver FYI-OTS-0187-0527 to the OTS Document Control Officer for public filing under Section 8(e) of TSCA.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure information, CIBA-GEIGY will be asked also to describe the nature and results, if available, from all studies (other than those reported already to EPA via the updated Irgaform 1266 MSDS or those cited in the open scientific literature) about which CIBA-GEIGY is aware or that CIBA-GEIGY has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to the subject chemical.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of this phenidone derivative.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, NTP, FDA, OSWER/EPA, OAR/EPA, OW/EPA, ORD/EPA, and OPP/OPTS/EPA. Copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

NOTE: The reader's attention is directed to the following status report prepared by EPA in response to 8EHQ-0587-0653 Followup Response.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JAN 26 1988

SUBJECT: Status Report* 8EHQ-0587-0653 FLWP

Approved: JAN 26 1988

FROM: Frank D. Kover, Chief
Chemical Screening Branch/ECAD/OTS

TO: Joseph J. Merenda, Director
Existing Chemical Assessment Division/OTS

Note

The reader's attention is directed first to the status report that was prepared by the Agency in response to TSCA Section 8(e) submission number 8EHQ-0287-0653 Initial.

Submission Description

In response to EPA's questions with regard to the Section 8(e)-reportability of the toxicological information (especially the adverse male rat reproductive system effects information) that was presented in "For Your Information" (FYI) submission number FYI-OTS-0187-0527 Initial, the CIBA-GEIGY Corporation provided the company's rationale as to why the information was not submitted formally to EPA pursuant to Section 8(e) of TSCA. According to CIBA-GEIGY, the company's rationale was based in part on the company's opinion that the "Flash Report" on Irgaform 1266 (4-(hydroxymethyl)-4-methyl-1-phenyl-3-pyrazolidinone; CAS No. 13047-13-7) was inconclusive in that the report "did not contain pivotal information necessary to make an informed review of this chemical, which is structurally related to phenidone [(1-phenyl-3-pyrazolidinone; CAS No. 92-43-3)]." CIBA-GEIGY also provided the following information concerning the company's rationale for not reporting the findings under Section 8(e):

> "The related compound, phenidone, produced similar reproductive and blood abnormalities but also caused significant decreases in body weight and food consumption, which made it uncertain whether the effects [observed with Irgaform 1266] were truly compound related. In . . . [EPA's status report prepared in response to a previous TSCA Section 8(e) submission on phenidone (8EHQ-0984-0529 Initial)], EPA stated that

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

'the reported adverse effects are most probably real (treatment related) in that they were dose related' (emphasis added). However, the Agency also recognized the existence of a confounding factor as evidenced by the following statement: 'It is not clear that these changes [(i.e., the adverse male rat reproductive system effects)] were direct toxic effects or resulted from impaired nutrition (either general malnutrition from decreased food consumption or local impairment of nutrition of stored spermatozoa as the result of damage to the epididymides)' (emphasis added).

"The 'Flash Report' on Irgaform 1266 indicated that the male reproductive effects occurred in the high dose group only ([i.e., effects] were not dose-related) and no information was given about the general health of rats at the high dose group (body weight, food consumption, or mortality). . . . [CIBA-GEIGY] was uncertain, therefore, whether these effects were due to direct action of the test compound or were attributable to general toxicity in the high dose group resulting in malnutrition and significant weight reductions. Therefore, . . . [CIBA-GEIGY] considered it necessary to await the final report, which was targeted for completion . . . [within about a month of the company's FYI notice] in order to determine the significance of the observations. The 'Flash Report' on Irgaform 1266, which was the only information in . . . [CIBA-GEIGY's] possession at the time of . . . [the company's] initial FYI submission, was insufficient to make a judgement relative to an 8(e) reporting obligation. . . . .

"Once the final report containing the complete data was received and evaluated, it was concluded that the male reproductive effects were not related to a general systemic toxicity or malnutrition, and appeared to be a direct, specific effect. . . . ."

Comments/Recommendations

EPA maintains its position that the information presented in FYI-OTS-Ø187-Ø527 Initial (particularly the English translation of the German "Flash Report") provides reasonable support for the conclusion that Irgaform 1266, when administered via gavage to rats for 28 days, produced a dose-dependent toxic anemia with inclusion body formation as well as reduced spermatogenesis and testicular atrophy at the highest dose. Further, "Flash Reports" appear to be a mechanism by which the CIBA-GEIGY Corporation is informed by CIBA-GEIGY Ltd. (the parent company located in Basel, Switzerland) about significant results of studies conducted by or for CIBA-GEIGY Ltd; the "Flash Report" on Irgaform 1266 states that "the demonstrated findings, especially the spermatogenesis reduction, are toxicologically significant."

In addition, the "Flash Report" states that the toxicologic findings for Irgaform 1266 "show great similarity to the findings which were obtained for . . . [phenidone and reported to EPA by the Eastman Kodak Company under Section 8(e) of TSCA]." It is also important to point out that the "Flash Report" sent to the CIBA-GEIGY Corporation was based on a "Final Report for Audit" of the 28-day gavage study of Irgaform 1266 in rats and not simply on the basis of preliminary observations made during that study. Bearing this in mind, it is likely that if the serious adverse hematologic and testicular effects observed in the 28-day study of Irgaform 1266 were believed by the parent company to have resulted from malnutrition, for example, the "Flash Report" most probably would have included such a caveat.

With regard to CIBA-GEIGY's remarks about certain statements made by EPA in the Submission Evaluation section of the status report prepared by EPA in response to Eastman Kodak's TSCA Section 8(e) notice on phenidone (8EHQ-Ø984-Ø529 Initial), it must be noted that the Agency's statements were not intended to minimize the significance of the reported toxicologic findings for phenidone, nor were the statements intended to provide a basis to conclude that the submitted findings were considered by EPA not to be reportable under Section 8(e) of TSCA. In fact, the overall thrust of EPA's initial evaluation of the submitted preliminary findings on phenidone was that the observed adverse effects were most likely a direct result of treatment with the chemical.

Based on a review of CIBA-GEIGY's FYI and Section 8(e) notices on Irgaform 1266 and considering the discussion presented previously in the Comments/Recommendations section of the status report that EPA prepared for 8EHQ-Ø287-Ø653 Initial, the Agency can find no compelling reason to change its position that the toxicologic information contained in FYI-OTS-Ø187-Ø527 Initial should have been submitted formally under Section 8(e), the substantial risk information reporting provision of TSCA. Therefore, the Chemical Screening Branch will deliver FYI-OTS-Ø187-Ø527 Initial to the OTS Document Processing Center (DPC) to be logged in/processed as a supplement to 8EHQ-Ø287-Ø653.

a) The Existing Chemical Assessment Division will inform the CIBA-GEIGY Corporation about the Agency's decision with regard to the Section 8(e)-reportability of the information contained in FYI-OTS-Ø187-Ø527 Initial.

b) The Chemical Screening Branch is continuing its review of the reported information to determine the need for further OTS assessment of the subject chemical.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and OCM/OPTS/EPA; copies of this status report will be sent also to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: MAR 2 1987

SUBJECT: Status Report* 8EHQ-0287-0654 Approved: 3/3/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Union Carbide Corporation provided the following summarized information regarding the conduct and results of a number of acute in vivo and in vitro studies conducted with 3-methyl-2-benzothiazolinone hydrazone hydrochloride (MBTH):

"Acute Peroral Toxicity: The LD50 values (with 95% confidence limits) for this route of exposure were calculated to be as follows from the dose-mortality data:

Rat (male)	=	308 (182-519) mg/kg
Rat (female)	=	149 (84-264) mg/kg
Rabbit (male)	=	177 (105-298) mg/kg
Rabbit (female)	=	268 (181-396) mg/kg.

"Times to death were dose-related, and varied between 15 minutes and one day. Signs of toxicity included sluggishness, tremors, unsteady gait, excess salivation, and (in rabbits only) convulsions. The above findings indicate a moderately high acute peroral toxicity for MBTH with rapid onset of signs of toxicity and death.

"Acute Percutaneous Toxicity: Currently the mortalities are as follows by a standard 24-hour occluded cutaneous application method. None of 5 male and 5 female rats, and 5 male rabbits, died over a 14-day observation period following the application of 16.0 g/kg. Three female rabbits, of 3 dosed, died (by one day) following 16.0 g/kg, but 2 female rabbits dosed with 8.0 g/kg survived a 14 day observation period. Edema was seen at the site of application of the test material to the skin for the first post-application day. There were no signs of systemic toxicity in male or female rats, but convulsions

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

were seen in rabbits at applied doses of 4.0 g/kg and upwards . . . [and] usually occurred at 1 to 2 hours and persisted for 2 to 15 minutes. Convulsions were not seen at 2.0 g/kg. The above findings indicate a low order of acute lethal percutaneous toxicity for MBTH, but systemic toxicity was evident in one species (rabbit) in the form of convulsions.

"Acute Inhalation Toxicity: The low vapor pressure of MBTH would suggest a negligible potential for acute inhalation hazard. This was confirmed by exposing 5 male and 5 female rats for 6 hours to a statically generated substantially saturated vapor atmosphere from MBTH (24° C). There were no deaths and no symptoms of toxicity or irritancy during exposure or in a 2-week post-exposure observation period.

"Primary Skin Irritation: Using a standard 4-hour occluded application of 0.5 g of MBTH to each of 6 rabbits, no signs of local inflammation were seen on removal of the occlusive dressing, and none developed over a subsequent 14-day inspection period. These results, [when] coupled with the observation of transient local edema in the acute percutaneous toxicity study, indicate that MBTH is minimally irritant to the skin by sustained single contact.

"Primary Eye Irritation: The following inflammatory reactions were seen in the rabbit eye following the instillation of MBTH into the inferior conjunctival sac of one eye of each of six rabbits per treatment group:

80 mg: There was mild to moderate conjunctivitis (erythema and chemosis) of 48 to 72 hours duration, and minimal corneal injury which healed within 24 to about 72 hours.

10 mg: There was a just detectable conjunctivitis of less than 24 hours duration.

"The above findings indicate that MBTH is a moderate primary eye irritant without potential to cause permanent injury.

"Mutagenicity: MBTH was tested for potential mutagenic activity using a Salmonella typhimurium mutagenicity assay procedure. Based on . . . cytotoxicity studies, MBTH was tested with and without metabolic activation (rat liver S9 system) using 5 concentrations of MBTH in the range of 0.3 to 5.0 mg per plate. Dose-related mutagenic activity was seen without metabolic activation in strains TA98, TA100, TA1535 and TA1537, but not TA1538. In the presence of the metabolic activating system, mutagenic activity was present with TA1535 only."

In conclusion, Union Carbide stated that "taken overall, the results of these studies indicate that MBTH is of moderate acute peroral toxicity, has a potential to cause systemic toxicity by percutaneous absorption of high doses applied to the skin, does not present any short-term adverse health effects by vapor exposure at ambient temperature, is a minimal skin irritant, a moderate eye irritant, and is mutagenic in the standard Ames test. . . . ."

Submission Evaluation

In order for EPA to evaluate the overall significance of the reported toxicologic findings, Union Carbide should be requested to ensure that the Agency receives complete copies of the final reports (including the actual experimental protocols, results of gross and histopathological examinations, results of statistical analyses, etc.) from all studies cited in this TSCA Section 8(e) submission.

Current Production and Use

In its TSCA Section 8(e) submission, Union Carbide reported that MBTH has the following Chemical Abstract Service (CAS) Registry Number: 14448-67-0. According to published CAS Registry Number indices, CAS No. 14448-67-0 has been assigned to MBTH of variable hydrochloride composition. A review of the non-confidential computerized version of EPA's TSCA Chemical Substance Inventory has shown that CAS No. 14448-67-0 is not listed. It should be noted, however, that CAS No. 4338-98-1 has been assigned to MBTH monohydrochloride and is listed in the TSCA Inventory. A review of the production range (includes importation volumes) statistics for MBTH monohydrochloride (CAS No. 4338-98-1) shows that no 1977 manufacture or importation was reported for this chemical or that all of the manufacture/importation data reported were claimed to be TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the TSCA Inventory and cannot be disclosed (Section 14(a) of TSCA, U.S.C. 2613(a)). All of the information reported for the initial TSCA Inventory, including the production range information, is subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

According to Union Carbide, MBTH is "a widely used reagent for analysis of aldehydes." Union Carbide stated further that the company does not manufacture MBTH but rather "purchases the chemical and supplies it to customers as part of an analytical kit for. . .[Union Carbide's] glutaraldehyde products."

Comments/Recommendations

In its TSCA Section 8(e) submission, Union Carbide stated that its MBTH supplier as well as appropriate Union Carbide employees and customers were being notified about the reported toxicologic findings for MBTH.

a) The Chemical Screening Branch will request Union Carbide to ensure that the Agency receives full copies of the final reports (including actual experimental protocols, results of gross and histopathological examinations, results of any statistical analyses, etc.) from all of the studies cited in the company's Section 8(e) notice. In addition, Union Carbide will be asked to provide the exact chemical identity of the MBTH tested in the cited studies.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure information, EPA will ask Union Carbide to describe the nature and results, if available, from all studies (other than those published in the open scientific literature or those submitted already to EPA) about which Union Carbide is aware or that Union Carbide has conducted, is conducting or is planning to conduct to determine the toxicity of or the exposure to MBTH.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and the Inventory Team/IMD/OTS. In addition, copies of this report will be provided to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: MAR 11 1987

SUBJECT: Status Report* 8EHQ-0287-0655 S Approved: 3/13/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note (See NOTE on page 3 of this status report)

The submitting company claimed its name and the exact identity of the subject chemical substance to be TSCA Confidential Business Information (CBI). The Information Management Division (IMD/OTS) will request the submitter to substantiate these confidentiality claims. It should be noted that in the "sanitized" version of the Section 8(e) notice, the company stated non-confidentially that the tested chemical is a "1-phenyl substituted 2-pyrazolin-5-one" that had been the subject of the following TSCA Section 5 Pre-manufacturing Notification: PMN 86-1690.

Submission Description

The submitter provided the following summarized information with regard to the conduct and results of acute oral toxicity studies conducted with this 1-phenyl substituted 2-pyrazolin-5-one:

> "Groups of 5 male and 5 female rats were given 5000 mg/kg of the test compound in a single gavage dose as part of an acute oral LD50 study. All females and none of the males died at this dose. Additional groups of 5 females were then administered the test compound at 1250 or 2500 mg/kg; 4 of 5 animals died at the higher dose and 0 of 5 died at the lower dose. The only effects noted in the surviving animals were slight to severe weakness, prostration and brown urine. All survivors were normal by 7 days after dosing. One male at 5000 mg/kg developed an abnormal stance and lost the tip of his tail 5 days after dosing. Necropsy revealed a testicular lesion in this rat. The morphology of the testicular lesion led to the conclusion that it and the other effects were due to a pre-existing condition that

* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

only became manifested during the study. . . . . To clarify the situation, an additional 10 male rats were administered a single gavage dose of 5000 mg/kg. Five of the 10 animals died; all survivors showed clinical signs of neurological impairment. This study is still in progress."

Submission Evaluation

In order for EPA to evaluate the overall significance of the reported toxicologic findings, the submitting company should be asked to ensure that the Agency receives complete copies of the final reports (including the actual experimental protocols, results of gross and histopathological examinations, results of any statistical analyses performed, etc.) from all studies cited in the company's TSCA Section 8(e) notice.

Immediately upon receipt of the company's initial Section 8(e) notice, the Chemical Screening Branch transmitted copies of the submitted information to appropriate individuals in the Chemical Control Division (CCD/OTS) responsible for administration of the OTS "New Chemicals Program" (NCP).

Current Production and Use (See NOTE on page 3 of this status report)

According to a Material Safety Data Sheet (MSDS) provided by the company in its Section 8(e) notice, this 1-phenyl substituted 2-pyrazolin-5-one is a dark brown solid that has a melting point of 138°C (280°F) and negligible vapor pressure. In its Section 8(e) notice, the submitter stated that the chemical "is to be used as a low volume, site-limited intermediate." The submitter stated also that "potential employee exposure has been minimized during the manufacture and isolation of the damp intermediate by use of face shields, gloves, and aprons." Finally, the submitter stated that company employees "handling the dry intermediate wear air-line respirators and Tyvek® suits."

Comments/Recommendations

In its Section 8(e) notice, the submitting company stated that the MSDS for the subject chemical has been updated to include the reported neurotoxicological effects. In addition, the submitter reported that the company "is currently evaluating the need for further testing."

a) The Chemical Screening Branch will ask the submitting company to ensure that EPA receives full copies of the final reports (including the actual experimental protocols, results of gross/histopathological examinations, results of any statistical analyses, etc.) from all studies cited in the initial Section 8(e) submission.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, the Chemical Screening Branch will ask the submitting company to describe the nature and results, if available, from all studies (other than those submitted already to the Agency) about which the company is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to the subject chemical substance.

b) The Chemical Screening Branch will immediately send all reported information to the OTS New Chemicals Program for appropriate follow-up attention/action.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS, and CCD/OTS/OPTS. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

NOTE: In a followup letter dated April 13, 1987, the submitting company provided the following non-confidential and more specific generic name for the subject chemical: 1-phenyl-alkylamino-2-pyrazolin-5-one.

2/1/89

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAR 25 1987

SUBJECT: Status Report* 8EHQ-0387-0656 Approved: 3/26/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

PPG Industries, Inc. reported that 2-ethylhexanoyl chloride (CAS No. 760-67-8) was found to have an acute LC50 of 1.26 mg/l when tested via inhalation in rats. In addition, PPG stated that the study showed that 2-ethylhexanoyl chloride is very irritating to the respiratory tract and confirmed the fact that the chemical is a severe skin irritant. PPG also provided a Material Safety Data Sheet (MSDS) that had been updated by the company to reflect the reported toxicologic findings. According to the submitted MSDS, 2-ethylhexanoyl chloride has a dermal LD50 of over 2 g/kg and an oral LD50 of about 1.5 g/kg (species not specified). The MSDS also indicates that the chemical is corrosive to skin and eyes.

Submission Evaluation

It should be noted that hydrochloric acid is liberated when 2-ethylhexanoyl chloride comes in contact with moisture. It should be noted also that a chemical with an LC50 value in the range of 0.5 to 2.0 mg/l (i.e., approximately 50 to 200 ppm) is considered generally to be "highly" toxic by inhalation. In this regard, PPG stated that the observed inhalation LC50 of 1.26 mg/l in rats would result in a Department of Transportation classification of 2-ethylhexanoyl chloride as a Class B Poison.

In order for EPA to evaluate better the overall significance of the reported toxicologic information, PPG should be requested to submit complete copies of the final reports (including the actual experimental protocols, results of gross and histopathological examinations, etc.) from all toxicologic studies the results of which are cited in Section 4 (Health Hazard Data) of the provided MSDS for 2-ethylhexanoyl chloride.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Current Production and Use

A review of the production range (includes importation volumes) statistics for 2-ethylhexanoyl chloride, which is listed in the initial TSCA Chemical Substance Inventory, has shown that between 200 thousand and 2 million pounds were reported as manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the TSCA Inventory nor does it include any data that would compromise TSCA CBI. All data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

According to the secondary literature sources consulted by EPA, 2-ethylhexanoyl chloride is used primarily as an intermediate in the manufacture of peroxyesters, agricultural products and drugs.

According to the submitted MSDS, 2-ethylhexanoyl chloride is a clear, slightly colored liquid with a strong pungent odor. In addition, the MSDS states that the chemical has a boiling point of 152-154°F at 11 mmHg and a vapor pressure of 0.014 psia at 153-154°F. The MSDS states also that PPG's Internal Permissible Exposure Limit (IPEL) for 2-ethylhexanoyl chloride is 0.1 ppm (8-hour Time Weighted Average (TWA)) and PPG's Short-Term Exposure Limit (STEL) is 0.3 ppm for any 15 minute excursion.

Comments/Recommendations

In the cover letter to its Section 8(e) notice, PPG stated that in addition to updating the 2-ethylhexanoyl chloride MSDS and product label, PPG intends to inform its customers about the reported toxicologic findings.

a) The Chemical Screening Branch will request PPG to submit full copies of the final reports (including the actual experimental protocols, results of gross/histopathologic examinations, etc.) from all studies cited in Section 4 (Health Hazard Data) of the provided MSDS.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, the Chemical Screening Branch will request PPG to describe the nature and results, if available, from all studies (other than those cited in the open scientific literature or those reported already to EPA) about which PPG is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of 2-ethylhexanoyl chloride.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of 2-ethylhexanoyl chloride.

c) The Chemical Screening Branch will send copies of this status report to OSHA, NIOSH, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: MAR 18 1987

SUBJECT: Status Report* 8EHQ-0287-0657 S Approved: 3/19/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note (See NOTE on page 3 of this status report)

The submitting company has claimed its company name to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS) will request the submitting company to substantiate this confidentiality claim. It should be noted also that in the "sanitized" version of the TSCA Section 8(e) submission, the company reported that the tested chemical had been the subject of the following TSCA Section 5 Premanufacturing Notification: PMN 86-1444.

Submission Description (See NOTE on page 3 of this status report)

The submitting company provided the following summary information with regard to the conduct and results of an acute rat oral LD50 study of the methyl ester of 4-hydroxy-3-nitrobenzoic acid (CAS No. 99-42-3):

> "Groups of 5 male and 5 female rats were given 1250, 2500, or 5000 mg/kg of the test compound in a single gavage dose. . . ." All animals died at 5000 mg/kg. Abnormalities noted at necropsy included hemorrhage of the thymus and hemorrhage and edema of the glandular stomach. At 2500 mg/kg, 1 of 5 females and 0 of 5 males died. Necropsy of the dead female revealed hemorrhage of the glandular stomach. Small, soft testes were observed in 5 of 5 male rats at this dose. Microscopic examination of the testes revealed treatment-related changes consisting of seminiferous epithelium atrophy, reduction of spermatids and spermatozoa, giant cell formation, and interstitial cell hyperplasia. In the epididymides, degenerated sperm forms, hypospermia, and vacuolization of the ductal epithelium were noted in one or more animals. No treatment-related changes were noted in the testes or epididymides from the 1250 mg/kg group."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

The submitting company also provided summarized findings from several other acute toxicity studies of the subject chemical. According to the submitted information, this chemical 1) has a rat dermal LD50 of greater than 2 g/kg; 2) is slightly irritating to guinea pig skin and rabbit eyes; and 3) is not a sensitizing agent when tested in guinea pigs.

Submission Evaluation

In order for EPA to evaluate the overall significance of the reported toxicologic findings, the submitting company should be requested to provide to EPA complete copies of the final reports from all studies cited in the company's Section 8(e) submission.

Immediately upon receipt of the initial TSCA Section 8(e) notice, the Chemical Screening Branch transmitted copies of the submitted information to appropriate individuals in the Chemical Control Division (CCD/OTS) which is responsible for administering the OTS New Chemicals Program (NCP).

Current Production and Use

In its TSCA Section 8(e) notice, the submitting company provided a sanitized copy of a Material Safety Data Sheet (MSDS) for the methyl ester of 4-hydroxy-3-nitrobenzoic acid. According to the MSDS, this chemical is a yellow solid which has a melting point of 74-75°C (165-167°F) and a negligible vapor pressure. In its Section 8(e) notice, the company reported that the chemical "is to be used as a site-limited intermediate to manufacture another chemical." In addition, the submitter provided the following information regarding the potential for worker exposure to the subject chemical:

> "Potential employee exposure has been minimized during the manufacture and isolation of the water-wet intermediate by the use of coveralls (employer supplied and laundered), a hat, boots, safety glasses with side shields, neoprene rubber gloves, a vinyl smock, and a cartridge respirator with an organic vapor cartridge. The chemical is not handled as a dry material."

Comments/Recommendations

The submitting company stated that the provided MSDS for the subject chemical had been updated to reflect the reported adverse testicular effects. In addition, the submitter stated that the company is considering the need for further toxicologic testing.

a) The Chemical Screening Branch will ask the submitter to provide full copies of the final reports (including the actual experimental protocols, results of gross/histopathological examinations, results of any statistical analyses performed, etc.) from all toxicologic studies cited in the company's TSCA Section 8(e) submission.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, the Chemical Screening Branch will ask the submitting company to describe the nature and results, if available, of all studies (other than those cited in the published scientific literature or those submitted already to the Agency) about which the company is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to the methyl ester of 4-hydroxy-3-nitrobenzoic acid.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical. In addition, the Chemical Screening Branch will send copies of all reported information to appropriate individuals in the OTS New Chemicals Program.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OAR/EPA, OW/EPA, ORD/EPA, OPP/OPTS and CCD/OTS/OPTS. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

NOTE

In a letter to EPA dated April 10, 1987 (8EHQ-0487-0657 Followup Response), the Eastman Kodak Company stated that it was dropping the TSCA CBI claim involving the company's name.

Frank D. Kover 4/15/87

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: APR 21 1987

SUBJECT: Status Report* 8EHQ-0287-0658 S

Approved: 4/21/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note (See Note on Page 3 of this status report)

The submitting company has claimed its company name and the exact identity and use of the subject chemical to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division will request the submitter to substantiate these TSCA CBI claims. In the "sanitized" version of the cover letter to its Section 8(e) notice, the submitter stated non-confidentially that the subject chemical substance is a "chlorophenyl triazole" currently at the research and development (R&D) stage.

Submission Description (See Note on Page 3 of this status report)

The submitting company provided full copies of the final reports from probe (dose range-finding) teratology and full teratology studies in rats and rabbits. In addition, the submitter provided assessments of the studies by four outside consultants. In the Section 8(e) cover letter, the submitter provided the following information with regard to the conduct and results of the full teratology studies:

> "In the rat teratology study, dosages of 12 mg/kg/day and above resulted in maternal toxicity as evidenced by dosage-dependent inhibition of maternal body weight gain during the dosage period. Possible compound related developmental toxicity was demonstrated for litters of dams receiving 24 or 48 mg/kg/day of the chemical and possibly 12 mg/kg/day as well. Signs of developmental toxicity reported included resorption, decreased litter size, decreased fetal body weight and malformation. The low incidence of cleft palate (2 fetuses) occurring at 48 mg/kg/day was not significant when compared to controls. Although there is not agreement on these points between consultants, [the submitter believes that] there is biological and statistical evidence to support [the company's] view.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"In the rabbit study, a 10 mg/kg/day no-effect level was demonstrated for maternal toxicity based on both body weight loss and inhibition of food consumption at the 50 mg/kg/day level. Administration of 50 mg/kg/day of the chemical resulted in an increase in resorptions and a decrease in live litter size. A minimal decrease in fetal body weight observed for litters of this group (50 mg/kg/day) was also reported but was similar to historical controls. The incidence of hydrocephalus internus (1 from each treatment level) was relatively high for this study but was not dose related."

With regard to the assessments of the data by the four outside consultants, the submitting company reported that "significant differences of opinion exist" in that "there is no general agreement as to 1) no-effect levels for maternal and developmental toxicity, 2) whether developmental toxicity was compound-induced, and 3) adequacy of testing and reporting procedures."

With regard to its own interpretation of the results from the performed studies, however, the submitting company reported that although "no-effect levels were established for both maternal and developmental toxicity for both species", the company interprets the data to show "compound-related developmental effects in both species, but, if real, occurred only at maternally toxic doses."

Submission Evaluation

Considering the large amount of data submitted and the complexity of the issues raised by the submitting company and the outside consultants regarding interpretation of those data, full copies of provided reports and assessments were forwarded for review to the Reproductive Effects Assessment Group (REAG) in EPA's Office of Research and Development (ORD). The Chemical Screening Branch will consult with REAG/ORD in determining the needs for and scope of further OTS assessment of this chlorophenyl triazole.

It should be noted that EPA has received other TSCA Section 8(e) submissions with regard to the toxicity (including teratologic effects) of triazole derivatives (e.g., 8EHQ-0485-0548 et seq.). In 8EHQ-0485-0548 et seq., the Chevron Chemical Company reported that (E)-1-(2,4-dichlorophenyl)-4,4-dimethyl-2-(1,2,4-triazol-1-yl)-1-penten-3-ol (CAS No. 76714-88-0), when administered orally to pregnant rabbits at doses of 0, 62.5, 125, 250 or 500 mg/kg, caused dose-related malformations (including cleft palate) and developmental variations at the 2 highest doses in the presence of minimal maternal toxicity at the highest dose only.

Current Production and Use (See Note on Page 3 of this status report)

In light of the submitting company's CBI claims, no information concerning the TSCA Chemical Substance Inventory status or use of the subject chemical will appear in this status report.

Comments/Recommendations

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure information, the Chemical Screening Branch will ask the submitting company 1) to describe the actions the company has taken or plans to take to notify workers and others about the reported toxicity findings, and 2) to reduce or eliminate exposure to the subject chemical substance. In addition, the submitter will be asked to describe the nature and results, if available, from all studies (other than those submitted already to EPA) about which the company is aware or that the company has conducted, is conducting or plans to conduct to define the toxicity of or the exposure to the subject chemical.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of this chlorophenyl triazole.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

NOTE

On January 11, 1988, the Chemical Screening Branch received from the Information Management Division (IMD/OTS) the "declassified" version of this TSCA Section 8(e) submission. According to the declassified notice, the Sandoz Crop Protection Corporation is the submitting company and the exact identity of the subject chemical is "alpha-(4-chlorophenyl)-alpha-(1-cyclopropylethyl)-1H-1,2,4-triazole-1-ethanol." The declassified notice states also that this substance (also known as SAN-619F) is undergoing evaluation as a fungicide and is intended to be registered with EPA under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

James F. Darr 1/12/88

James F. Darr, Section Head
Chemical Risk Identification
Section/CSB/ECAD/OTS/OPTS

DATE: APR 6 1987

SUBJECT: Status Report* 8EHQ-0387-0659 Approved: 4/9/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The 3M Company provided a full copy of the final report from an acute inhalation study of n-butyl acetate (CAS No. 123-86-4) in rats. In its Section 8(e) notice, 3M stated that this study was "recently conducted at a European toxicology laboratory at the request of a 3M subsidiary. . . ." The Summary section of the submitted report contains the following information regarding the conduct and results of this acute inhalation study:

> "Three groups of Wistar rats, each comprising 5 males and 5 females, were exposed for 4 hours to an aerosol/vapor of. . . [n-butyl acetate] at actual concentrations in the exposure atmosphere of 0.8, 2.2, and 5.2 mg/l, respectively. The exposure was carried out in a head-only dynamic inhalation system. The values for mass median aerodynamic diameter (MMAD) and geometric standard deviation . . . for the test atmosphere at the high exposure level were 1.01 micrometers and 3.30 [micrometers], respectively. The mortality rate for the sexes combined from the low dose to high dose group was 6 out of 10, 10 out of 10, and 10 out of 10 animals, respectively. There was no evident sex related effect. All deaths occurred within 24 hours after exposure. Major signs of toxicity were lethargy, hyperpnea, tremors and ataxy. With the exception of one male, all animals that showed symptoms of systemic or local respiratory toxicity finally did not survive. Macroscopic examination at necropsy revealed bloody nose and/or mouth and hyperaemic lungs in animals among all exposure groups. Histopathology of lung tissue revealed vesicular emphysema in all animals. Based on the analytical concentration of the test substance in the animal breathing zone, the LC50 value for the sexes combined was estimated to be 0.74 mg/l or 160 ppm."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

According to 3M, "such a low LC50 was totally unexpected in light of the existing toxicity data on . . .[n-butyl acetate] and its current ACGIH [(American Conference of Governmental Industrial Hygienists)] Threshold Limit Value [(TLV)] of 150 ppm."

Submission Evaluation

According to the National Institute for Occupational Safety and Health (NIOSH) "Registry of Toxic Effects of Chemical Substances" (RTECS), the 4-hour inhalation LC50 for n-butyl acetate in rats is 2000 ppm. Under general inhalation toxicity classification systems, a chemical with a 4-hour LC50 value of 2000 ppm is considered to be only "slightly" to "moderately" hazardous while a chemical with a 4-hour LC50 value of 160 ppm is considered to be "highly" hazardous.

Considering the discrepancy between the 4-hour rat inhalation LC50 value of record and the 4-hour rat inhalation value reported by 3M under Section 8(e) for n-butyl acetate, a prudent action to take at this time would be to verify the purity of the n-butyl acetate tested in the European study performed for the 3M subsidiary. This action is recommended despite the fact that page 4 of the final report provided by 3M states that the tested n-butyl acetate was "pure." If the tested sample is determined to be pure, the European study should be repeated in order to determine the validity of the findings presented in the final report submitted by 3M. (It should be noted at this point that the 4-hour n-butyl acetate inhalation toxicity study in rats that is cited in RTECS was not reviewed by EPA as to the adequacy of design or purity of the test material.) Finally, if the 160 ppm 4-hour rat inhalation LC50 value for n-butyl acetate is indeed correct, a change should be considered immediately for the current 150 ppm TLV for this chemical substance.

Current Production and Use

A review of the production range (includes importation volumes) statistics for n-butyl acetate (CAS No. 123-86-4), which is listed in the initial TSCA Chemical Substance Inventory, shows that between 21 million and 111 million pounds of this chemical substance were reported as manufactured/imported in 1977. This production range information does not contain any data that were claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

According to secondary literature sources, n-butyl acetate is a fruity smelling colorless liquid used primarily as a solvent and a gasoline additive.

Comments/Recommendations

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure information, the Chemical Screening Branch will ask 3M to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported toxicologic findings, and 2) to reduce or eliminate exposure to n-butyl acetate. In addition, 3M will be asked to describe the nature and results of all studies (other than those submitted already to EPA or those published in the open scientific literature) about which the company is aware or that the company has conducted, is conducting, or is planning to conduct to determine the toxicity of or the exposure to n-butyl acetate. Finally, 3M will be informed that EPA is interested especially in results of studies designed to determine 1) the purity of the n-butyl acetate tested in the European inhalation study, and 2) the validity of the results of that inhalation study.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of n-butyl acetate.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, ACGIH, OSWER/EPA, OW/EPA, ORD/EPA, OAR/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: APR 22 1987

SUBJECT: Status Report* 8EHQ-0387-0660

Approved: 4/22/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

Wacker Chemicals (USA), Inc. submitted full copies of the final reports from 1-hour inhalation LC50 studies of chloracetone (CAS No. 78-95-5) and chloracetaldehyde (CAS No. 107-20-0) in rats. The following information regarding the conduct and results of these studies was presented in the "SUMMARY" sections of the submitted reports:

Chloracetaldehyde

"The acute inhalation toxicity of chloracetaldehyde was studied by exposing different groups of 5 male and 5 female rats one single time for a period of 1 hour to test atmospheres containing chloracetaldehyde at a concentration between 0.14 and 8.47 g/m^3 in air. From the results of the present study, it appeared that the 1-hour LC50 of chloracetaldehyde for the combined male and female responses was between 0.65 and 0.78 g/m^3, the most near to the former value. As a result of the narrow range between these values, it was not possible to give a better estimate of the 1-hour LC50 value with 95% confidence limits. Animals which died shortly after exposure showed signs of edema and atelectasis in the lungs after autopsy, in most cases accompanied by a hydro-thorax which could be explained by an induced hypertension. These findings together with the edema and atelectasis [observed] in [the] lungs were signs of an impairment of lung functioning. Air in the stomach as well as in [the] intestine was due to mouth breathing."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Chloracetone

"The acute inhalation toxicity of chloracetone was studied by exposing different groups of 5 male and 5 female rats one single time for a period of 1 hour to test atmospheres containing chloracetone at a concentration between 0.5 and 7.9 g/m^3 in air. From the results of the present study, it appeared that the 1-hour LC50 of chloracetone for the combined male and female responses was 1.9 g/m^3 with 95% confidence limits of 1.6 g/m^3 and 2.2 g/m^3. Adding sex as an extra independent variable in the original data base allowed calculation of the LC50 values for males and females. For the females, the 1-hour LC50 was 2.7 g/m^3 with the 95% confidence limits of 2.5 g/m^3 and 2.9 g/m^3. For the males, the 1-hour LC50 was 1.2 g/m^3 with the 95% confidence limits of 1.1 g/m^3 and 1.3 g/m^3. Animals which died shortly after exposure showed signs of edema in the lungs after autopsy, in most cases accompanied by a hydro-thorax. Both the hydro-thorax and the observed red coloring of the skin of the extremities could be explained by an induced hypertension. These findings together with the edema in [the] lungs were signs of an impairment of lung functioning. Mouth breathing caused [the] stomach, caecum as well as [the] intestine to be filled with air."

In providing this acute toxicity information to the Agency under Section 8(e), Wacker stated that the data show "a significant risk of injury by inhalation, despite the fact [that] the extent of toxicity of these chemicals is already recorded by oral and dermal toxicity studies."

Submission Evaluation

Seven groups of rats (each consisting of 5 animals per sex) were exposed (whole body) to chloracetaldehyde concentrations that ranged from .14 mg/l to 8.47 mg/l. The relative humidity range of 51-91% was high compared to the ideal humidity range of 30-60%) for such studies. The high relative humidity was reportedly due to the high amount of water in the test material. Following the 1-hour inhalation exposure period, the animals were to be observed for two weeks. Signs of discomfort included closed eyes, salivation, wet nares and nasal discharge (in the animals in the higher dose groups), along with wet and soiled heads and breasts. Labored respiration accompanied by dyspnea and mouth breathing was detected in the highest dose group animals. The animals exposed to .78, .99, 1.91 and 8.47 mg/l all died, whereas the mortalities for animals exposed to .65, .51 and .14 mg/l were 40%, 30% and 0%, respectively. The deaths were observed during and shortly after the exposure period as well as within 1 to 2 days following exposure. Many of the rats that died had blood stains around the nose and mouth; rats exposed to the highest

chloracetaldehyde concentrations that did not die immediately were reported to have breathed "wheezingly." In addition, it should be noted that 2 rats exposed to 1.91 mg/l became blind. The animals that died during exposure or within the first 2 days of observation showed edema of the lungs which was accompanied in some cases by atelectasis (i.e., collapsed lung) and in most cases by hydrothorax (i.e., watery fluid in the pleural cavity). In many cases, the stomachs were found to be filled with air (due to mouth breathing) and in some cases the intestines were also found to contain air. Also, an occasional thrombus was detected in the heart area. In addition, lung edema was observed in those low dose animals that survived to terminal sacrifice.

Based on dose level conversions and considering the fact that the recommended threshold limit value (TLV) for chloracetaldehyde is 1 ppm, the doses used in this 1-hour study were extremely high (43 to 2643 ppm). According to Patty's Industrial Hygiene and Toxicology (3rd Edition), inhalation of chloracetaldehyde by mice "is acutely toxic, demonstrating a lethal time of 2.57 minutes under conditions in which the chamber concentrations reached 45% equilibrium with an incoming mixture of air bubbled through a 30% solution of chloracetaldehyde."

In the chloracetone study, the same basic experimental protocol was used with exposure levels ranging from 0.5 mg/l to 7.9 mg/l. As was the case in the chloracetaldehdye study, the humidity in the chloracetone study was elevated - approximately 83% in the highest dose group and from 30% to 70% in the other dose groups. Overall, the results obtained for chloracetone were similar to those found for chloracetaldehyde, except that no blindness was observed. The animals exposed to 4.2 and 7.9 mg/l all died and animals exposed to 3.1, 2.1, 1.0 and 0.5 mg/l experienced 80%, 60%, 10% and 0% mortality, respectively. Although no TLV for chloracetone was located, the doses used in this 1-hour study also appear to be quite high (132 to 2091 ppm).

In conclusion, it should be noted that the Merck Index (9th Edition) states that chloracetone and chloracetaldehyde are "intensely irritating to the skin, eyes, and mucous membranes."

Current Production and Use

A review of the production range (includes importation volumes) statistics for the subject chemicals, which are listed in the initial TSCA Chemical Substance Inventory, has shown that the following amounts were reported as manufactured and/or imported in 1977:

CHEMICAL NAME	CAS NUMBER	PRODUCTION RANGE
Chloracetaldehyde	107-20-0	1 million to 10 million pounds
Chloracetone	78-95-5	100 thousand to 1 million pounds

It is important to note that this production range information does not include any data claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Chemical Substance Inventory nor does it include any information that would compromise TSCA CBI. All of the information reported for the initial TSCA Inventory, including the production range information, is subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

According to secondary literature sources consulted by EPA, both cloracetone and chloracetaldehyde are used primarily as chemical intermediates.

Comments/Recommendations

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, the Chemical Screening Branch will ask Wacker Chemicals (USA), Inc. to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported toxicologic findings, and 2) to reduce or eliminate exposure to the subject chemicals. In addition, Wacker will be asked to describe the nature and results, if available, of all studies (other than those cited in the open scientific literature or those reported already to EPA) about which the company is aware or that the company has conducted, is conducting or plans to conduct to define the toxicity of or the exposure to chloracetaldehyde or chloracetone.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of chloracetone or chloracetaldehyde.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and ACGIH. In addition, copies of this report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAY 20 1987

SUBJECT: Status Report* 8EHQ-0487-0661 S Approved: 5/22/87

FROM: James F. Darr, Section Head James F. Darr
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note (See NOTE on page 4 of this status report)

The CIBA-GEIGY Corporation has claimed the exact identity of the subject chemical as TSCA Confidential Business Information (TSCA CBI); the Information Management Division (IMD/OTS) will request CIBA-GEIGY to substantiate this CBI claim. In the "sanitized" version of the TSCA Section 8(e) submission, CIBA-GEIGY reported that the tested product (D17-1242) "is a 20% aqueous solution of a high molecular weight polyquaternary compound" with a molecular weight of 5000 ± 2000.

Submission Description (See NOTE on page 4 of this status report)

It should be noted first that D17-1242 was the subject of a recent "For Your Information" (FYI) notice (FYI-OTS-0187-0530 S) in which CIBA-GEIGY provided summarized results from an attempted dermal senzitization study of D17-1242 in guinea pigs. According to this FYI notice, all animals in the test group died following intradermal injection of 3-4 mg/kg D17-1242 (i.e., 0.6-0.8 mg/kg polyquaternary compound). In addition, CIBA-GEIGY reported that guinea pigs injected intradermally with lower doses of D17-1242 died also. In submitting these findings to the Agency on an FYI basis, CIBA-GEIGY reported that the D17-1242 results conflicted significantly with the results of a guinea pig dermal sensitization study conducted by CIBA-GEIGY in 1978 with FAT 60134/A, a 30% solution of a "presumably identical" polyquaternary compound. CIBA-GEIGY reported that intradermal injection of FAT 60134/A did not cause death or sensitization in this 1978 study. CIBA-GEIGY stated also in its FYI notice that FAT 60134/A had an oral LD50 of >2000 mg/kg (species not specified) and was non-mutagenic in an Ames Salmonella typhimurium (bacteria) test.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

In light of the vast discrepancy in the results obtained from the guinea pig sensitization studies conducted with D17-1242 and FAT 60134/A, CIBA-GEIGY stated that although the severe toxic effects observed in the D17-1242 study were viewed as serious enough to merit consideration for reporting to EPA under TSCA Section 8(e), the company could not reliably ascribe the observed toxicity to any chemical(s) until the company received analytical data on the composition of D17-1242. CIBA-GEIGY reported also that oral rat LD50 and intraperitoneal mouse and rat LD50 studies were planned for D17-1242.

In its Section 8(e) submission, CIBA-GEIGY reported that based on recently received analytical data showing D17-1242 to be pure (except for water), CIBA-GEIGY concluded that the highly toxic effects observed after intradermal injection of D17-1242 in the attempted sensitization study were attributable to D17-1242 per se and that FYI-OTS-0187-0530 S should be treated now as a TSCA Section 8(e) submission.

In its Section 8(e) notice, CIBA-GEIGY also provided information concerning the results of acute oral rat LD50 and intraperitoneal mouse and rat LD50 studies of D17-1242. According to the submitted information, no male or female rats died following oral administration of D17-1242 at a dose of 2 g/kg; the animals were reported to have exhibited dyspnea, exophthalmos, ruffled fur, and curved body position but did recover within 11 days. CIBA-GEIGY also submitted the following information regarding the results of the study in which D17-1242 was injected intraperitoneally at a single dose of 2, 10 or 50 mg/kg body weight (bw) to 1 male and 1 female mouse at each dose level:

> "No symptoms were observed in the animals of the 2 mg/kg bw dose group. The animals in the 10 mg/kg bw dose group died within 17 minutes after injection [and] the animals in the 50 mg/kg bw dose group [died] within 6 minutes. In both [the 10 and 50 mg/kg bw] dose groups, dyspnea, cyanosis, ataxia, clonicotonic convulsions, exophthalmos and abnormal body positions were observed. At autopsy, no deviations from normal morphology were found in the animals of the 2 mg/kg bw dose group. Narrow heart ventricles were found in the animals of the 10 and the 50 mg/kg bw dose groups. Additionally, the animals of the 50 mg/kg bw dose group showed stasis of the veins (v.v. cavae portaid)."

With regard to a study in which 2 rats (1 male and 1 female) were injected intraperitoneally with D17-1242 at a single dose of 50 mg/kg bw, CIBA-GEIGY stated that the rats "showed similar symptoms as the mice and died within 15 minutes after injection."

It should be noted that CIBA-GEIGY also submitted a supplemental FYI notice (FYI-OTS-0387-0530 S SUPP) reporting that D17-1242 had a 48 hour EC50 of 0.038 mg/liter for Daphnia magna and a 96 hour LC50 of 0.25 mg/liter for rainbow trout.

Submission Evaluation

The submitted data give rise to a concern for human skin exposure (especially abraded skin exposure) to even small amounts of the subject polyquaternary compound (D17-1242). In addition, the submitted data from the 1978 study with FAT 60134/A indicate that although intradermal challenge with this material did not cause sensitization, the epidermal challenge did evoke a sensitization response; this particular observation indicates that FAT 60134/A is a sensitizing agent. Further, it is important to note that in 1986, EPA received a TSCA Section 8(e) submission (8EHQ-0386-0591 et seq.) in which cardiotoxicity was reportedly observed as the result of repeated dermal application of dioctyldimethylammonium chloride (DODMAC) to rabbits; the reader's attention is directed to the status report prepared by EPA in response to this earlier TSCA Section 8(e) notice. Finally, it should be noted that the submitted aquatic LC50 and EC50 values for D17-1242 are of concern to EPA should there be significant environmental exposure to this polyquaternary compound.

Current Production and Use

According to CIBA-GEIGY's TSCA Section 8(e) submission, D17-1242 is an imported research and development (R&D) material. In the initial FYI notice, CIBA-GEIGY stated that "the only [D17-1242] distribution in the U.S. was an 8 oz. sample to one potential customer for evaluation" and this "customer used up some of the sample in testing and has decided not to pursue development any further." CIBA-GEIGY stated also in the initial FYI notice that this customer had been informed by CIBA-GEIGY both by phone and in writing about the results of the attempted guinea pig dermal sensitization study of D17-1242 and that the customer returned the unused portion of the sample to CIBA-GEIGY for disposal.

Comments/Recommendations

The Chemical Screening Branch (CSB/ECAD/OTS) will request the OTS Document Control Office (DCO) to process both FYI-OTS-0187-0530 S and FYI-OTS-0387-0530 S SUPP as supplemental submissions to TSCA Section 8(e) submission number 8EHQ-0487-0661 S.

a) In light of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, the Chemical Screening Branch will ask CIBA-GEIGY to describe the actions the company has taken or plans to take 1) to notify its own workers about the reported toxicological findings for D17-1242, and 2) to reduce or eliminate exposure to the subject polyquaternary compound. CIBA-GEIGY will be asked also to describe the nature and results, if available, from all studies (other than those reported already to EPA) about which CIBA-GEIGY is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of this polyquaternary compound.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject polyquaternary compound.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, ORD/EPA, OAR/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

NOTE:

In a letter dated June 24, 1987 (8EHQ-0787-0661 FLWP), CIBA-GEIGY withdrew its TSCA CBI claim covering the chemical identity of the tested polyquaternary compound. According to the "declassified" version of CIBA-GEIGY's initial Section 8(e) notice, the subject chemical is a "poly addition product of bischloromethyldiphenyl and N,N,N',N'-tetramethylhexanediamine" (CAS No. 63943-38-4).

7/13/87

DATE: APR 6 1987

SUBJECT: Status Report* 8EHQ-0487-0662 Approved: 4/8/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Vista Chemical Company reported that ethylene dichloride (EDC; 1,2-dichloroethane; CAS No. 107-06-2) was detected recently in the soil and groundwater at the company's vinyl chloride manufacturing facility located in Westlake, Louisiana. According to Vista, "soil samples taken from a boring hole located on the western fence line of the plant property indicated levels of ethylene dichloride in the 0.3 - 1.0 ppm range." In addition, Vista reported that "subsequent water samples taken from that boring have indicated EDC levels of 0.3 - 2.5 ppm." Vista stated that the reported analytical results "indicate previously unknown lateral migration of the contamination at the site." Finally, Vista reported that 1) the company's investigation was conducted in response to a Louisiana Department of Environmental Quality (LDEQ) compliance order, and 2) the company "is continuing to investigate potential off-site migration and potential for human exposure from the groundwater in this aquifer."

Comments/Recommendations

Immediately upon receipt of the Vista Chemical Company's TSCA Section 8(e) notice, the Chemical Screening Branch transmitted copies of the notice to the Office of Groundwater/EPA Region 6 (Dallas, Texas), the Office of Water (OW/EPA), the Office of Groundwater Protection (OGWP/OW/EPA), the Office of Solid Waste and Emergency Response (OSWER/EPA) and the Office of Air and Radiation (OAR/EPA) for any warranted followup attention by EPA.

The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, OW/EPA, OSWER/EPA, OAR/EPA, OGWP/OW/EPA, and OGW/EPA Region 6. Copies of this status report will be sent also to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

DATE: APR 13 1987

SUBJECT: Status Report* 8EHQ-0487-0663

Approved: 4/13/87

FROM: David R. Williams for
James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

In submitting this notice under Section 8(e) of TSCA, the Eastman Kodak Company stated non-confidentially that the tested chemical had been the subject of a "Premanufacture Notification" (PMN No. 86-1259) filed previously with EPA under Section 5 of TSCA.

Submission Description

Eastman Kodak provided the following information with regard to the conduct and results of an acute oral toxicity study of (1-ethoxyethylidene)propanedinitrile (CAS No. 5417-82-3) in rats:

> "Groups of 5 male and 5 female rats were given 156, 312 or 625 mg/kg of the test compound in a single gavage dose as part of an acute oral LD50 study. All animals died at 625 mg/kg. Abnormalities noted at necropsy included hemorrhage of the thymus, edema, necrosis and hemorrhage of the glandular stomach, and necrosis of the non-glandular stomach. At 312 mg/kg, 4 of 5 males and 1 of 5 females died. Treatment-related abnormalities included edema, necrosis and hemorrhage of the glandular stomach, enlarged pale livers, and fibrous adhesions between lobes of the liver. Additional abnormalities noted in one or more animals included yellow discoloration of the liver, rough appearance of the liver capsule, and enlarged or darkened spleens. Kidney lesions involving the cortical tubular epithelium were seen in one female rat. At 156 mg/kg, all animals survived. Abnormalities included enlarged pale livers, fibrous adhesions between lobes of the liver and darkened spleens. At the lowest dose, liver lesions noted through histopathology examination of the tissues included diffuse and focal necrosis, mineralization, hemorrhage, inflammation, diffuse fibrosis, the presence of pigmented macrophages,

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> and bile duct proliferation. Cellular changes in hepatocytes included hydropic degeneration, cytoplasmic lipid vacuolation, cytoplasmic basophilia, hypertrophy, increased mitosis, and hyalin degeneration. . . . ."

In its Section 8(e) notice, Eastman Kodak also submitted summary results from an acute dermal LD50 study in rats and an acute dermal irritation study in guinea pigs. According to the provided information, the subject chemical has an acute dermal LD50 of greater than 2 g/kg and is slightly irritating to guinea pig skin. Finally, Eastman Kodak submitted a Material Safety Data Sheet (MSDS) that had been updated to reflect the toxicologic findings reported to EPA under Section 8(e).

Submission Evaluation

In order for the Agency to evaluate the overall significance of the reported findings, Eastman Kodak should be asked to provide full copies of the final reports (including the actual experimental protocols, results of gross/histopathologic examinations, etc.) from all studies cited in the Section 8(e) notice.

Immediately upon receipt of this Section 8(e) submission, the Chemical Screening Branch (CSB/ECAD/OTS) transmitted copies of the notice to appropriate individuals in the Chemical Control Division (CCD/OTS) responsible for administering the OTS "New Chemicals Program" (NCP).

Current Production and Use

According to the submitted MSDS, the subject chemical substance is a water insoluble white solid with a melting point of 91-92°C (196-198°F). In its Section 8(e) notice, Eastman Kodak reported that the subject chemical "is used as a low volume site-limited intermediate." With regard to the potential for worker exposure, Eastman Kodak provided the following information:

> "Potential employee exposure has been minimized during the manufacture and isolation of the damp intermediate by the use of company supplied/laundered work clothes, boots, gloves, and a face shield. Employees handling the dry intermediate wear fresh-air supplied respirators, company laundered work clothes, boots and gloves."

Finally, Eastman Kodak reported that the company "is not aware of any adverse health problems associated with [manufacture of the subject chemical] or its use to make the final product."

Comments/Recommendations

In addition to modifying the MSDS, Eastman Kodak stated that the company is "currently evaluating the need for further testing" of (1-ethoxyethylidene)propanedinitrile.

a) The Chemical Screening Branch will request Eastman Kodak to submit full copies of the final reports (including the actual experimental protocols, results of gross and histopathological examinations, etc.) from all studies cited in the company's TSCA Section 8(e) notice.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, the Chemical Screening Branch will request Eastman Kodak to describe the nature and results, if available, from all studies (other than those submitted already to EPA or those cited in the open scientific literature) about which Eastman Kodak is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to (1-ethoxyethylidene)propanedinitrile.

b) The Chemical Screening Branch will send all reported information to the OTS New Chemicals Program for any appropriate followup attention/actions.

c) The Chemical Screening Branch will send copies of this status report to OSHA, NIOSH, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS and CCD/OTS/OPTS. In addition, copies of this status report will be provided to the TSCA Assistance Office (TAO/OTS/OTPS) for further distribution.

DATE: APR 21 1987

SUBJECT: Status Report* 8EHQ-0487-0664 S

Approved: 4/21/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

E. I. du Pont de Nemours & Company, Inc. has claimed the exact identity of the subject chemical to be TSCA Confidential Business Information (TSCA CBI); the Information Management Division/OTS will request Du Pont to substantiate this confidentiality claim. In the sanitized version of its TSCA Section 8(e) notice, Du Pont stated non-confidentially that 1) the tested chemical is a haloalkyl substituted cyclic ether, and 2) the chemical had been the subject of a "Premanufacture Notification" (PMN 85-368) submitted to EPA under Section 5 of TSCA. According to EPA's public file for PMN 85-368, EPA issued a TSCA Section 5(e) "Consent Order" for the haloalkyl substituted cyclic ethers that were cited in PMN 85-367, PMN 85-368 and PMN 85-369. It should be noted also that a TSCA Section 8(e) submission (8EHQ-0986-0633 S) was submitted previously by Du Pont on the haloalkyl substituted cyclic ether that was the subject of PMN 85-367. The reader's attention is directed to the status report prepared by EPA in response to 8EHQ-0986-0633 S.

Submission Description

In its Section 8(e) submission, Du Pont provided the following summary information regarding the conduct and results of a two-week inhalation study of the subject haloalkyl substituted alkyl ether in rats:

> "Groups of ten male and ten female rats were exposed by inhalation to concentrations of haloalkyl substituted cyclic ether of 0, 5, 50 or 500 ppm for six hours a day, five days a week for two weeks. Male rats exposed to 500 ppm had significantly depressed body weights during the exposure period, and depressed testes weights immediately following the last exposure and at the end of the [14-day] recovery period. Microscopic examination revealed degeneration of the seminiferous epithelium in

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

the testes of male rats from all exposure groups. The lesion was discovered in two rats each from the 5 and 50 ppm exposure groups and in all rats from the 500 ppm exposure group. The severity of the lesion was generally dose-dependent, and no evidence of regeneration was observed after 14 days of recovery. In addition, male and female rats exposed to 500 ppm had hepatocellular hypertrophy in the liver with accompanying liver weight elevation, and clinical chemical changes indicative of altered hepatic metabolism. No changes were seen in female rats exposed to either 5 ppm or 50 ppm."

In its Section 8(e) notice, Du Pont reported that another study (using haloalkyl substituted cyclic ether concentrations that will overlap the 5 ppm dose level in the present study) would be conducted "to better define the toxic effects on the reproductive system."

Submission Evaluation

In view of the fact that the Agency issued a TSCA Section 5(e) Consent Order covering PMN 85-368, copies of this Section 8(e) submission were sent immediately by the Chemical Screening Branch (CSB/ECAD/OTS) for review and appropriate followup attention by the Chemical Control Division (CCD/OTS) which is responsible for administering the OTS "New Chemicals Program" (NCP).

Current Production and Use

According to the public file copy of PMN 85-368, this haloalkyl substituted cyclic ether is used as an intermediate and solvent. In its Section 8(e) submission, Du Pont stated that this chemical substance "is currently considered [by Du Pont to be] a research and development material and is being evaluated captively within Du Pont." In addition, Du Pont reported that an interim workplace exposure limit of 0.1 ppm has been established for this haloalkyl substituted cyclic ether.

Comments/Recommendations

In its Section 8(e) notice, Du Pont stated that the company plans to notify all Du Pont workers potentially exposed to the subject chemical about the toxicologic findings reported to the Agency under Section 8(e) of TSCA.

a) The Chemical Screening Branch will ask Du Pont to ensure that EPA receives complete copies of the final reports (including the actual experimental protocols, results of gross and histopathological examinations, etc.) from the two-week study and the planned followup study cited in the company's TSCA Section 8(e) submission.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, the Chemical Screening Branch will ask Du Pont to describe the nature and results, if available, from all studies (other than those reported already to EPA) about which Du Pont is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of or exposure to this haloalkyl substituted cyclic ether.

b) As in the case of the initial Section 8(e) notice, the Chemical Screening Branch will transmit immediately all reported information to the Chemical Control Division for review and appropriate followup attention.

c) The Chemical Screening Branch will send copies of this status report to OSHA, NIOSH, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS and CCD/OTS/OPTS. In addition, copies of this status report will be provided to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

DATE: MAY 14 1987

SUBJECT: Status Report* 8EHQ-0487-0665 S

Approved: 5/14/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

The submitting company has claimed its company name and the exact identity of the subject chemical to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will request the submitting company to substantiate these CBI claims. In the "sanitized" version of the company's Section 8(e) notice, the subject chemical was identified non-confidentially as BSC-125, a research and development (R&D) surfactant. In addition, the submitter reported by phone to the OTS Document Control Office (DCO) that the subject chemical substance could be identified non-confidentially as an "ethylene oxide/propylene oxide blocked polymer."

Submission Description

The submitting company provided a copy of the final report from an acute rabbit eye irritation study of BSC-125. The "ABSTRACT" section of the submitted report presents the following information regarding the conduct and results of this study:

> "BSC-125 was evaluated for potential eye irritation using nine New Zealand White rabbits. Each rabbit was administered 0.1 ml of the test article to the conjunctival sac of one eye. The untreated contralateral eye of each rabbit served as a control. The treated eye of three rabbits was irrigated with lukewarm water thirty seconds after test article administration. Treated and untreated eyes were examined at 1, 24, 48 and 72 hours

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

> as well as 4 days post-administration and ocular irritation scored according to the Draize method. Irritated eyes were further examined at 7, 10, 13, 16, 19 and 21 days post-administration. Under the conditions of this study, BSC-125 produced corneal opacity and conjunctival irritation to rabbits' eyes without irrigation. These effects persisted to day 21 in all animals. Conjunctival irritation was produced by BSC-125 in three rabbits' eyes irrigated thirty seconds after administration. Corneal opacity and conjunctival irritation were [found to be] reversible by days 7 and 19, respectively."

According to the "Test Article Preparation Data" section of the submitted final report, BCS-125 was received and tested "as is" (undiluted liquid) by the performing laboratory. It should be noted also that the performing laboratory determined that a 10% weight/volume aqueous mixture of the test material had a pH of 6.

Submission Evaluation

According to the submitted information, eye exposure to BSC-125 may result in corneal opacity and eye irritation if BSC-125 is not washed away immediately following contact with the eyes; these effects appear to be reversible following irrigation of the eyes immediately after eye contact with BSC-125. The submitting company should be requested to provide the exact identity of the subject chemical substance.

Current Production and Use

In view of the submitter's TSCA CBI claims, no information with regard to the current TSCA Chemical Substance Inventory status of this ethylene oxide/propylene oxide blocked polymer will appear in this status report. As stated previously, the subject chemical was reported to be an R&D material being considered by the company for potential use as a surfactant. The submitter also provided the following information regarding the potential for exposure to this R&D surfactant:

> "The extent of the risk was and is currently limited by the fact that only a small amount of this compound has been made under the direction of technically qualified staff. The evaluation of the [R&D] material has been conducted by a limited number of the submitter's personnel and qualified [outside] toxicologists . . . who are normally involved in evaluating toxic effects of chemicals. Personnel with potential for exposure are protected by use of protective facilities, equipment and clothing, i.e., laboratory hoods, impervious gloves, lab coats and eye protective equipment."

Comments/Recommendations

In its Section 8(e) submission, the company reported that 1) "all personnel with potential exposure to . . . [BSC-125 surfactant] will be informed of the [reported toxicological] findings and quidelines for handling," and 2) "the Experimental Product Data Sheet will include a statement concerning the severe eye irritant finding as will the experimental sample label."

It should be noted that although EPA is concerned in general about the acute toxicity of chemicals, the acute toxicologic information as presented in this Section 8(e) submission does not appear to be of the type required for submission to EPA pursuant to Section 8(e), the "substantial risk" information reporting provision of TSCA. In making this statement with regard to TSCA Section 8(e)-reportability, however, it must be noted also that EPA is not aware of any additional information that may have been considered by the company in making its decision to submit the subject findings to the Agency under Section 8(e) of TSCA.

a) The Chemical Screening Branch (CSB/ECAD) will request the submitter to provide the exact identity (including CAS Registry Number, if known) for the subject chemical substance. In addition, the submitter will be asked to provide further information with regard to the company's rationale for submitting the subject findings to EPA under Section 8(e) of TSCA.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, the Chemical Screening Branch will ask the submitting company to describe the nature and results, if available, from all studies (other than those cited in the open scientific literature or those submitted already to EPA) about which the company is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of this R&D surfactant.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of this ethylene oxide/propylene oxide blocked polymer.

c) The Chemical Screening Branch will send copies of this status report to OSHA, NIOSH, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAY 21 1987

SUBJECT: Status Report* 8EHQ-0487-0666 S Approved: 5/21/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

The submitting company has claimed its company name to be TSCA Confidential Business Information (TSCA CBI); the Information Management Division (IMD/OTS) will request the submitter to substantiate this TSCA CBI claim.

Submission Description

The submitting company reported that it had recently received from PPG Industries, Inc. a diallyl diglycol carbonate (CR-39® Monomer; CAS No. 142-22-3) Material Safety Data Sheet (MSDS) which provided the following summarized information with regard to the results of a dermal teratology study in rabbits:

> "A [CR®-39 Monomer] teratology study using skin exposure of pregnant rabbits produced significant toxicities in the unborn (increased rate of abortion and eye anomalies) at dose levels which also caused significant maternal toxicities (mortalities, body weight suppression and liver effects). However, there was no evidence that CR®-39 Monomer exposure to the skin caused effects on the unborn in the absence of significant harmful effects to the mother. Skin irritation was present in all monomer-treated groups. . . . ."

In reporting this information to EPA under Section 8(e) of TSCA, the submitting company stated that it was informed by PPG that "the fetal effects were caused by maternal toxicity and were not compound related." The submitting company reported also that it was unable to obtain a copy of the final report from this study from PPG.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Shortly after EPA's receipt of this TSCA Section 8(e) submission, PPG Industries, Inc. provided to EPA on a "For Your Information" (FYI) basis (FYI-OTS-0487-0538) a copy of the CR®-39 Monomer MSDS as well as the following summarized information concerning the conduct and results of the subject teratology study:

> "The CR®-39 teratology study was conducted as part of a series of studies investigating [the] potential toxic endpoints of this commercial product. Because the most probable route of exposure to CR®-39 in the workplace is through skin contact, the teratology study was conducted . . .[by CR®-39 monomer application] to the shaved backs of female rabbits on days 6-18 of pregnancy at doses of 0, 0.1, 0.5 or 1.0 ml monomer/kg body weight/day. The test site remained uncovered. Exposures were terminated 6 hours after test material application by swabbing clean the skin test sites. Salient findings of the bio-assay were the following:
>
> 1. Significant toxicities in the maternal animals were caused by both 0.5 and 1.0 ml monomer/kg dose levels. An increased number of mortalities were seen at the high dose. Depressions in body weight gain and liver changes were seen in both dose groups. Skin lesions were present in all monomer-treated groups.
>
> 2. Other findings in the two highest dose groups were increased rates of abortion as well as lens opacities and small lenses in the eyes of fetuses. Minor skeletal findings were also seen in the 0.5 ml/kg group. These fetal anomalies are considered minor in nature, and all of the effects occurred only at dose levels causing harm to the maternal animals.
>
> 3. At a dose level of 0.1 ml/kg, there were (a) no maternal toxicities except for the skin lesions which are not a significant indicator of maternal toxicity for teratology studies, and (b) no developmental toxic effects as evidenced by no increase in fetal anomalies with dose. Therefore, 0.1 ml/kg can be considered a no-observed-effect-level (NOEL).
>
> The finding of small lenses, lens opacities and associated anomalies in the eyes of fetuses from some high and mid-dose litters was discussed with the Study Director at [the private contract laboratory that performed the teratologic study]. These findings are indicative of developmental toxic effects during the later stages of ocular development and occurred only at doses where there was significant maternal toxicity. Similarly, the minor skeletal findings, which occurred only when there was an accompanying adverse effect upon maternal weight gain, were not considered to be of teratological significance.

> The conclusions drawn from the [performed] study were: no teratologic findings were demonstrated at any dose levels; the developmental toxic effects occurred at dose levels where there was accompanying maternal toxicity; [and] a no-observed-effect-level (NOEL) of 0.1 ml/kg was established for both maternal and corresponding developmental toxic effects."

In submitting the preceding information to EPA on an FYI basis, PPG stated its belief that the performed teratology study is a well-conducted "negative" study that "provides practical information in the assessment of potential human effects because the primary occupational exposure is dermal and the worker population is predominantly female (ophthalmic lens production industry)."

According to the submitted MSDS, CR®-39 Monomer can be moderately to severely irritating to human eyes and severely irritating to human skin; accidental swallowing (by humans) of CR®-39 Monomer can cause burns to the mouth and gastrointestinal tract, illness and possibly death. With regard to skin absorption, the MSDS states that studies conducted with rhesus monkeys show that the CR®-39 Monomer "penetrates the skin and . . . 90% of the amount absorbed is eliminated from the body within 4 days." The submitted MSDS also provides the following information with regard to the conduct, results and interpretation of an acute inhalation toxicity study of CR®-39 Monomer in rats:

> "One-hour exposures at a concentration of 0.73 mg/liter (maximum attainable concentration at 25°C) caused no deaths in test animals. Due to its low vapor pressure [(2 mm Hg at 166°C)], CR®-39 Monomer is not considered to be a hazard by inhalation of vapors; however, if conditions exist which generate substantial vapors or mists, inhalation would be expected to result in severe irritation of the eyes, mucous membranes and respiratory tract."

The submitted MSDS also contains the following information with regard to the toxicity of CR®-39 Monomer to aquatic species:

96-hr LC50 (Bluegill)	0.57 mg/l	(highly toxic)
48-hr LC50 (Water Flea)	18 mg/l	(moderately toxic)
96-hr LC50 (Sheepshead Minnows)	0.7 ppm	(highly toxic)
96-hr LC50 (Mysid Shrimp)	70.7 mg/l	(slightly toxic)
96-hr EC50 (Marine Alga)	>10.0 ul/l	(moderately toxic)

Finally, PPG provided in its FYI submission a copy of a technical bulletin detailing the conduct and results of a CR®-39 Monomer permeation study using nine (9) different types of commercially available protective gloves. According to the provided technical bulletin, permeation of CR®-39 Monomer varies depending on the type of material from which the glove is made and the duration of exposure; the bulletin recommends that all CR®-39 Monomer users evaluate their own glove program to minimize exposure.

Submission Evaluation

In order for the Agency to evaluate properly the results of the diallyl diglycol carbonate dermal teratology study in rabbits, PPG should be requested to submit a complete copy of the final report from that study. It should be noted at the present time, however, that there have been a number of developmental toxicity studies conducted in which the tested chemicals caused maternal toxicity (in some cases, severe maternal toxicity, e.g., lethality) but did not cause adverse developmental effects. In other words, the mere fact that maternal toxicity occurs does not preclude the possibility that the tested chemical can cause developmental toxicity independent of that maternal toxicity. Further, EPA's published developmental toxicity risk assessment quidelines (51 FR 34028-34040; September 14, 1986) state that developmental effects that occur at maternally toxic levels should not be discounted. In addition, these EPA guidelines were supported at an Agency-sponsored public workshop on maternal and developmental toxicity held in Rockville, Maryland in May of 1986 (proceedings from this workshop will be published in an upcoming issue of Teratogenesis, Carcinogenesis and Mutagenesis). Finally, it is important to note that maternal effects may be reversible while the effects on the offspring may be permanent.

Current Production and Use

A review of the production range (includes importation volumes) statistics for diallyl diglycol carbonate (CAS No. 142-22-3), which is listed in the initial TSCA Chemical Substance Inventory, shows that approximately 1 million to 10 million pounds of this chemical substance were reported as manufactured and/or imported in 1977. This production range information does not include 1) any information claimed as TSCA Confidential Business Information (CBI) by the person(s) reporting for the initial TSCA Inventory, or 2) any data that would compromise TSCA CBI; all of the data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

According to information obtained by the Agency via a search of publicly available computerized data bases, diallyl diglycol carbonate monomer is used in the manufacture of optical quality transparent plastic materials (e.g., aircraft windows, lenses).

Comments/Recommendations

It should be noted that in a 1979 TSCA Section 8(e) notice (8EHQ-0979-0311), PPG submitted final results from an acute rabbit eye irritation study of a mixture containing diallyl diglycol carbonate (75%), maleic anhydride (20%), tungsten hexacarbonyl (5%)

and hydroquinone monomethyl ether (100 ppm). In this earlier Section 8(e) notice, PPG stated that the mixture produced corneal clouding within 20 seconds after instillation to rabbits' eyes. PPG stated also that a subsequent water wash of the affected eyes for 1 minute did not alleviate the condition (corneal cloudiness and ulcers were still evident 14 days post-instillation).

a) The Chemical Screening Branch will request PPG to submit a full copy of the final report (including the actual experimental protocols, results of gross/histopathologic examinations, results of statistical analyses, etc.) from the teratology study cited in the submitted MSDS.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, both PPG and the submitter of the present TSCA Section 8(e) submission will be asked to describe the nature and results, if available, of all studies (other than those cited in either the published scientific literature or the CR®-39 MSDS or those submitted already to the Agency) about which the companies are aware or that the companies have conducted, are conducting, or plan to conduct to determine the toxicity of or the exposure to diallyl diglycol carbonate.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of diallyl diglycol carbonate.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

NOTE: The reader's attention is directed to the following status report that was prepared by EPA in response to 8EHQ-0787-0666 FLWP.

DATE: AUG 31 1988

SUBJECT: Status Report* 8EHQ-0787-0666 FLWP Approved: JDK for 8/31/88

FROM: James F. Darr, Section Head James F. Darr
Chemical Risk Identification Section/CSB/ECAD

TO: Joseph J. Merenda, Director
Existing Chemical Assessment Division/OTS/OPTS

Note

The reader's attention is directed first to the "Status Report" prepared by EPA in response to initial TSCA Section 8(e) notice number 8EHQ-0487-0666 S.

Submission Description

In response to a written request (EPA letter dated May 26, 1987), PPG Industries, Inc. submitted complete copies of final reports from range-finding dermal teratology and full dermal teratology studies of CR-39 Monomer (diallyl diglycol carbonate; CAS No. 142-22-3) in rabbits. In addition, PPG submitted summarized results of a number of acute/sub-acute animal toxicity studies, absorption/metabolism studies in Rhesus monkeys and guinea pigs, in vitro genotoxicity studies, a skin irritation study in humans, and aquatic toxicity studies of CR-39 Monomer. (The results of most of the reported studies are presented in the CR-39 Monomer Material Safety Data Sheet (MSDS) and described in the "Status Report" prepared for 8EHQ-0487-0666 S Initial.)

In the full dermal teratology study, groups of 18 inseminated New Zealand white rabbits were exposed to the CR-39 Monomer at levels of 0.1, 0.5 or 1.0 ml/kg/day applied to the skin on days 6-18 of gestation; control animals were exposed to a sterile isotonic saline solution at the same dosage volume as treated animals in the high dose group. (The CR-39 Monomer dose levels were selected on the basis of the results from the dermal range-finding study in which levels of 0.1, 0.5, 1.0 and 3.0 ml/kg/day were applied.) A 4 x 9 inch section on the back of each animal was shaved free of hair. The test liquid or control solution was spread on the shaved area and remained unoccluded during the exposure period.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Restraint collars were fitted on each animal immediately prior to dosage. Residual CR-39 Monomer or control solution was removed after 6 hours by blotting the treated area with nonabsorbent cotton. The collars were removed following this procedure.

Pregnant animals were killed by intravenous (iv) injection of a euthanasia solution followed by exsanguination by incision of the axillary arteries on day 29 of gestation. The ovaries were then dissected out and the number of corpora lutea recorded. The uterus was then removed and the following information recorded: number and position of live fetuses, dead fetuses, empty implantation sites, and early, middle and late resorptions. Next, the fetuses were removed from the uterus, weighed, and killed by a subcutaneous injection of the euthanasia solution. All fetuses were examined for external malformations and were sexed/examined internally for malformations. The heads of about one-third of the fetuses in each litter were removed and fixed for subsequent examination. The bodies of these and the remaining fetuses were cleared, stained and subjected to a skeletal analysis.

With regard to maternal effects, 6 animals in the 1.Ø ml/kg/day group died (3 after one or two days of treatment and 3 on days 2Ø-22 of gestation) and 1 was killed (on day 22 of gestation) in a moribund state. Gross pathologic findings common to the 3 rabbits that died early in the study included effects on the stomach, vagina and bladder. One rabbit also exhibited effects on the endocardium and kidneys. Gross pathologic findings among the 4 rabbits that died later in the study included effects on the liver, kidneys and stomach. Dark red/black discrete or diffuse areas were reported to be commonly seen at the dosage sites in animals among all treatment groups. Some animals among all treatment groups exhibited red secretions from the black thickened areas. These lesions often developed yellow coloration at their periphery and underwent scab formation. According to the submitted report, the incidence of the lesions increased in a dose-related manner. In the 1.Ø ml/kg/day group, there was a significant decrease in body weight on days 12, 15, 18 and 24 of gestation. In addition, animals in this group had a significant decrease in body weight gain during the periods of days 6-9, 9-12, 12-15, 15-18, 18-24 and 6-18. In the Ø.5 ml/kg/day group, there was a significant decrease in maternal body weight gain during the periods of days 9-12, 15-18 and 6-18 while the body weights and body weight gains among those animals in the Ø.1 ml/kg/day group were comparable to those of control animals.

The findings at necropsy revealed adverse effects on the heart, kidney, liver, stomach, vagina, mesentery and bladder of animals in the 1.Ø ml/kg/day dose group. Rabbits in the Ø.5 ml/kg/day group exhibited adverse effects on the mesentery and bladder. Adverse effects were observed in the stomachs of animals in the Ø.1 ml/kg/day group. The incidence of abortion among all groups was 1, Ø, 3 and 6 for does in the control, Ø.1, Ø.5 and 1.Ø ml/kg/day group, respectively. Furthermore, one control and two 1.Ø ml/kg/day rabbits littered early. The number of pregnant.

animals at the start of the study was 16, 18, 16 and 18 for the control, Ø.1, Ø.5 and 1.Ø ml/kg/day groups, respectively. At the time of scheduled sacrifice on day 29 of gestation there were 14, 18, 13 and 3 rabbits with live fetuses for the control, Ø.1, Ø.5 and 1.Ø groups, respectively.

With regard to developmental effects, there were no significant differences among the control, Ø.1 and Ø.5 ml/kg/day groups for rabbits that survived to day 29 of gestation for the following parameters evaluated: number of corpora lutea, implantation sites, live fetuses, dead fetuses, resorptions, individual fetal weights, litter weights, gravid uterine weights and preimplantation and postimplantation losses. However, 2 of the 3 does in the Ø.5 ml/kg/day group that aborted had an increased incidence of resorptions. Furthermore, in the 1.Ø ml/kg/day group, among the rabbits that either aborted, littered early, died or were sacrificed preterm, there was a marked increase in the incidence of resorptions.

There was a significant increase in the incidence of ocular opacities and small lenses among fetuses (5 out of 12 fetuses examined in 1 of the 3 litters) in the 1.Ø ml/kg/day group. Three of these fetuses also had lenses formed in two-layers. In addition, some of the fetuses that were prematurely delivered also had abnormalities of the lens. There was a significant increase in the number of fetuses (6 out of 34 examined in 3 of 12 litters) in the Ø.5 ml/kg/day group that had small lenses. Three of these fetuses in 2 litters had opacity of the lenses as well. In addition among these three, in one fetus, one lens was adhered to the cornea, in a second fetus, one lens was encapsulated by retinal/choroid tissue, and in the third fetus, retinal tissue covered the front of one lens and the other lens was formed in two layers and connected to retinal/choroid tissue.

The overall incidence of what was defined in the submitted report as minor skeletal anomalies did not differ among the treated and control groups; however, the report indicated that fetuses with major malformations were excluded from the total minor skeletal anomalies. There was a significant increase in the number of fetuses with absent pubic bones and reduced number of phalanges and metatarsals among those fetuses in the Ø.1 ml/kg/day group. According to the report, because these findings occurred among fetuses from a single litter, the findings were dismissed as not being treatment related.

There were no significant differences reported in the incidence of sternebral variations in fetuses from the treated or control animals. In fetuses from the Ø.5 ml/kg/day exposure group, there was a significant decrease in the occurrence of single 13th rib and a concomitant increase in the incidence of paired 13th ribs and a significant elevation in the incidence of 27 presacral vertebrae. The following findings were reported among fetuses in the 1.Ø ml/kg/day group that were aborted on days 19-22: open eyes, domed skull and eventration of the intestines and liver at

the umbilicus. Two fetuses in one litter reportedly had clefts in the vertebral column. According to the report, open eyes and domed skull may be indicative of the early stage of development. The other findings were regarded in the report as perhaps being attributed to trauma during abortion.

In the June 26, 1987 cover letter to 8EHQ-0787-0666 Followup Response, PPG stated the company "is not currently conducting any toxicology studies on diallyl diglycol carbonate nor are any studies planned for the near future." PPG also stated, however, that a recently conducted study indicated that North Silver Shield gloves "did not degrade after extended exposure and the volatile components of CR-39 Monomer did not permeate through the glove material."

In answer to the Agency's questions concerning worker exposure to CR-39 Monomer, PPG reported that "no exposure measurements have been made for diallyl diglycol carbonate." PPG noted, however, that "industrial hygiene reviews" of PPG manufacturing plants and "walk-thru surveys" of certain customers' facilities have been conducted by PPG in order to "offer advice on limiting the degree of skin and eye contact with this chemical."

Submission Evaluation

The provided toxicologic information has numerous inconsistencies and is incomplete with regard to data reporting. Some examples of these problems are as follows:

o In the range-finding teratology study, the applied doses of CR-39 Monomer are reported to be 0.1, 0.5, 1.0 and 3.0 ml/kg/day. The equivalent CR-39 Monomer doses in terms of mg/kg/day are given as 0.11, 0.57, 1.14 and 3.43 mg/kg/day, respectively. In the full teratology study, CR-39 Monomer dose levels of 0.1, 0.5 and 1.0 ml/kg/day are expressed as 114, 572 and 1143 mg/kg/day, respectively. Because the specific gravity of CR-39 is given as 1.143, EPA assumes that the latter figures are the accurate ones.

o In the cover letter to 8EHQ-0787-0666 Followup Response, PPG cites a number of toxicologic studies conducted on CR-39 Monomer. The results of the acute eye irritation study in New Zealand white rabbits were summarized as follows: "All studies reveal that the chemical only produces slight, reversible [eye] irritation . . ." The results of PPG's CR-39 Monomer teratology study suggest that the chemical caused severe skin irritation. It is difficult to understand how a chemical that produced such serious skin irritation would produce only "slight, reversible irritation" of the eyes.

o The same cover letter indicates that the acute dermal LD50 of CR-39 Monomer was in excess of 10 ml/kg/day when tested in New Zealand white rabbits. No mention of skin irritation is made;

nor is there any such discussion under the provided descriptions of percutaneous absorption studies conducted in the monkey and guinea pig. The cover letter and the MSDS, however, indicate that in humans, repeated skin contact with even small amounts of CR-39 Monomer can cause severe irritation, possibly leading to blistering and secondary infection while some individuals may experience urticaria. The degree of reaction was reported to differ significantly among individuals.

o There appear to be inconsistencies in what is presented in the full teratology final report text under "Results" and the results presented in Table 6 ("Incidence of Gross Pathological Findings"). From the written description, one is led to believe that many of the exposed rabbits were adversely affected by the dermal and systemic effects of CR-39 Monomer. However, according to Table 6, the incidences of these effects are clearly not as great as one was led to believe. For example, the description of the skin effects suggests that many animals from all groups were adversely affected, while according to Table 6, only 1-2 animals, with one exception, exhibited each effect noted. Furthermore, the severity of the effects described in Table 6 are nowhere near as grotesque as those described in the text. Interpretation of the dermal findings are further complicated by failure of the report to include the results of daily clinical observations. Had this information been included in the report, it would be easier to determine whether the findings described in the text relate to what was observed during the course of treatment. It is possible that once treatment stopped, the skin lesions began to heal to the point that what was observed at necropsy and reported in Table 6 are the results of reversible lesions.

o The text of the full teratology study final report stated: "Qualitative assessment of food consumption and fecal volume indicated dose-related increased incidences in the Ø.5 and 1.Ø ml/kg/day groups . . ." Unfortunately, it is not known to what incidences this statement refers. At first glance, it appears that food consumption was increased at these particular doses. However, further in the report (in discussing the stomach lesions found in the 1.Ø ml/kg/day group), it is reported that these lesions may be correlated with the greater occurrence of rabbits not eating in this group. Quantitative data on food consumption would be needed in order to attempt to interpret the significance of the stomach lesions. At this point, however, it is impossible to determine whether the stomach lesions were due to 1) decreased food consumption (because it is not known for sure that this was actually a finding) or 2) the direct result of dermal exposure to CR-39 Monomer.

Despite the above-described inconsistencies and incomplete data, it is clear that dermal application of CR-39 Monomer to pregnant rabbits during the major period of organogenesis resulted in systemic toxicity in the mothers and developmental toxicity in their offspring.

Regarding maternal toxicity, dermal exposure to CR-39 Monomer at the 1.Ø ml/kg/day dose level caused adverse effects on the skin, heart, kidney, liver, stomach, vagina, mesentery and urinary bladder of the dams. This dose level also produced maternal mortality, abortion and early littering as well as decreased maternal body weight and body weight gain. Exposure to CR-39 Monomer at Ø.5 ml/kg/day resulted in adverse effects on the skin, mesentery and urinary bladder in the dams. In addition, this level also resulted in decreased maternal body weight and body weight gain. Further, dose levels of Ø.1 ml/kg/day caused adverse effects on the skin and stomachs of the exposed dams. It should be noted that there was no no-observed-effect-level (NOEL) for maternal effects.

With regard to developmental toxicity, dermal application of CR-39 Monomer to pregnant rabbits at doses of 1.Ø ml/kg/day produced an increased incidence of resorptions among animals that died, aborted, littered early or were sacrificed preterminally. Values for the 3 litters of the does that remained alive on day 29 were similar to those of the control animals. This dose level also produced a significant increase in the number of fetuses with ocular anomalies. EPA cannot agree with PPG's statement that the observed ocular anomalies were caused by the maternal toxicity. There are insufficient data available to reach this conclusion. Further, there were several cases of aborted fetuses with eventration of the liver and intestines; according to the submitted report, the eventration may have been the result of trauma during abortion. Again, EPA cannot agree with this interpretation without supporting documentation. The Agency has reviewed many other teratologic studies in which fetuses were aborted and such observations were not made. Prenatal exposure to Ø.5 ml/kg/day resulted in an increased incidence of ocular anomalies and a significant decrease in the incidence of single 13th rib and an accompanying increase in the incidence of paired 13th ribs and 27 presacral vertebrae. Finally, there were no statistically significant developmental effects found following exposure to Ø.1 ml/kg/day. Therefore, Ø.1 ml/kg/day is the NOEL for developmental toxicity.

In conclusion, the performed teratologic study shows that dermal application of CR-39 Monomer to pregnant rabbits resulted in both maternal and developmental toxicities. It is difficult to understand, therefore, why PPG stated in the April 14, 1987 cover letter to FYI-OTS-Ø487-Ø538 Initial that "negative teratology study results were reported on the [CR-39 Monomer] MSDS . . ." Perhaps PPG's labeling the dermal teratology study as being "negative" arises from a major misconception with regard to the utility of the adult to developmental (A/D) toxicity ratio. In the April 14, 1987 cover letter, PPG stated that "compounds with A/D ratios near unity represent less potential risk to the unborn than do materials with high A/D ratios." EPA disagrees with this statement. Overall risk depends upon the hazard and the exposure levels. If humans are exposed to levels that are hazardous then the risk is great. This is independent of the A/D ratio value.

An excellent example in this case is alcohol. Although alcohol probably has an A/D ratio close to unity, humans can be exposed to hazardous levels and the potential of fetal alcohol syndrome is very real. Alcohol also provides a good example regarding the fact that the mother may very well recover from the toxic effects of the agent (e.g., headache, nausea, vomiting) but her offspring may be adversely affected (e.g., learning disabilities, mental retardation, facial anomalies).

Comments/Recommendations

After reviewing the information presented in 8EHQ-0787-0666 Followup Response and FYI-OTS-0487-0538 Initial, EPA believes that the findings from PPG's rabbit dermal teratology study of CR-39 Monomer should have been reported earlier to EPA under Section 8(e), the "substantial risk" information reporting provision of the Toxic Substances Control Act (TSCA). The following discussion provides the basis for EPA's position on this matter:

> Section 8(e) states that "any person who manufactures, [imports,] processes or distributes in commerce a chemical substance or mixture and who obtains information which reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment shall immediately inform the [EPA] Administrator of such information unless such person has actual knowledge that the Administrator has been adequately informed of such information."
>
> The preface to Part V of EPA's TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978) explains that a "substantial risk of injury to health . . . is a risk of considerable concern because of (a) the seriousness of the effect . . . and (b) the fact or probability of its occurrence." With regard to the seriousness of the effect, Part V explains that EPA considers the types of health effects for which substantial risk information must be reported to include "any pattern of effects or evidence that the subject chemical or mixture can produce . . . birth defects . . . or serious or prolonged incapacitation." Information concerning such serious toxic effects can be obtained directly or inferred from designed studies (e.g., studies conducted in animals) as described in Part VI of the Section 8(e) policy statement. Part VI explains also that a subject "person is not to delay reporting until he obtains conclusive evidence that a substantial risk exists, but is to immediately report any evidence that reasonably supports that conclusion."

With regard to "the fact or probability of its [(i.e., the serious effect's)] occurrence" criterion, Part V of the Section 8(e) policy statement explains that certain types of adverse health effects (e.g., birth defects) are considered by EPA to be "so serious that relatively little or no weight is given to exposure [in terms of determining whether risk is substantial]; the mere fact that the implicated chemical is in commerce constitutes sufficient evidence of exposure." Also, EPA's response to Comment 31 in Appendix B of the TSCA Section 8(e) policy statement explains that the mere occurrence of serious effects such as those described in Part V(a) of the policy statement (e.g., birth defects) presuppose exposure to the subject chemical substance or mixture and must be submitted to the Agency immediately under Section 8(e) of TSCA.

Considering the preceding discussion and EPA's evaluation of the information presented in FYI-OTS-0487-0538 Initial and 8EHQ-0787-0666 Followup Response, it is EPA's initial position that the results of PPG's rabbit dermal teratology study of CR-39 Monomer should have been submitted earlier to EPA under Section 8(e) of TSCA. In formulating this initial position on TSCA Section 8(e)-applicability/reportability, EPA has considered also the fact that numerous developmental toxicity studies have been conducted in which the tested chemicals caused maternal toxicity (in some cases, severe maternal toxicity (e.g., death)) but did not cause adverse developmental effects. In other words, the mere fact that maternal toxicity occurs does not preclude the possibility that the tested chemical substance or mixture can cause adverse developmental effects. Finally, it is important to note that EPA's developmental toxicity risk assessment guidelines (51 FR 34028-34040; September 14, 1986) reaffirm the Agency's position that developmental effects that occur at maternally toxic dose levels should not be discounted.

a) PPG will be requested to provide its rationale as to why the findings from the company's dermal teratology study of CR-39 Monomer in rabbits were not submitted to EPA earlier under Section 8(e) of TSCA. Following a review of PPG's response, the Chemical Screening Branch will, if appropriate, deliver FYI-OTS-0487-0538 Initial to the OTS Document Control Office (DCO) for handling and filing under Section 8(e) of TSCA.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of diallyl diglycol carbonate.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OW/EPA, OSWER/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: APR 27 1987

SUBJECT: Status Report* 8EHQ-0487-0667 S Approved: 4/27/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

The submitting company has claimed its company name and the exact identity of the subject chemical to be TSCA Confidential Business (TSCA CBI); the Information Management Division (IMD/OTS) will request the submitter to substantiate these TSCA CBI claims. In the sanitized version of the TSCA Section 8(e) submission (dated April 15, 1987) the company reported non-confidentially that 1) the tested chemical is an aryl ester of carbonochloridothioic acid, and 2) the chemical is the subject of a "Premanufacture Notice" (PMN) submitted to EPA on March 31, 1987 under Section 5 of TSCA. A search of the OTS public PMN files for a recent PMN concerning an aryl ester of carbonochloridothioic acid showed that this chemical was the subject of PMN 87-915 (received by EPA on April 1, 1987). This status report is based on information obtained from the non-confidential versions of PMN 87-915 and 8EHQ-0487-0667 S.

Submission Description

In the TSCA Section 8(e) submission, the company stated that a copy of the final report from an acute (1 and 4 hour) whole body inhalation study of this aryl ester of carbonochloridothioic acid in rats had been submitted to EPA in the company's March 31, 1987 PMN. According to the submitting company, "the 4-hour exposure resulted in death to all ten rats during exposure to an atmosphere containing an actual mean concentration of 2.10 mg/l" and "the 1-hour exposure produced 80% mortality within nine days after exposure to an atmosphere containing an actual mean concentration of 1.99 mg/l." In addition, the submitter reported that "labored breathing evident in all rats prior to death suggested pulmonary insufficiency as the probable cause of death."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

In its TSCA Section 8(e) submission, the company stated further that "it is important to note that the vapor pressure of the substance required that an aerosol be artificially generated in order to conduct the inhalation toxicity test, i.e., a worst case situation." The submitting company reported also that "during manufacture, aerosol formation is unlikely and, in addition, exposure to the substance is prevented by the protective means. . . [described in the Current Production and Use section of this status report]." Finally, the submitting company reported that based on the results of the acute inhalation study, the chemical would be labelled as a Class B Poison under U.S. Department of Transportation regulations.

Submission Evaluation

The acute inhalation toxicity study cited in this Section 8(e) submission is being evaluated by EPA at this time in conjunction with the Agency's review of PMN 87-915. Immediately upon receipt of this Section 8(e) submission, the Chemical Screening Branch sent copies of the submission to the Chemical Control Division (CCD/OTS) which is responsible for administering the OTS "New Chemicals Program" (NCP).

It should be noted that the final report of the acute inhalation study that was attached to PMN 87-915 states that "post exposure body weighings and necropsies were not obtained because of the unpleasant odor of this material and its ability to penetrate protective clothing." In addition, PMN 87-915 states that the subject chemical substance was found to have an oral (rat) LD50 of approximately 3 g/kg and a dermal (rabbit) LD50 of in excess of 2 g/kg. The chemical was reported also to be a moderate skin irritant and a moderate/severe eye irritant (test species not specified).

Current Production and Use

According to PMN 87-915, this aryl ester of carbonochloridothioic acid is an "extremely odoriferous" colorless to yellow to black liquid with a molecular weight of 186.5, a boiling point of 80°C at 0.13 mm Hg, and a specific gravity of 1.269; a vapor pressure study is reported to be currently underway. In addition, this chemical reportedly reacts with water and is soluble in organic solvents (e.g., acetone and toluene).

According to the Section 8(e) submission, the chemical "is a site-limited, destructive use intermediate which is completely destroyed in the manufacture of another product." In addition, the Section 8(e) submission presented the following information with regard to the potential for exposure to this aryl ester of carbonochloridothioic acid:

"During the manufacturing process, engineering, work practice, and protective equipment controls prevent operator exposure. During sampling and sample analysis, the operator and technician are equipped with a NIOSH-approved respirator, rainsuit, rubber gloves, rubber boots, and chemical safety goggles. During the manufacture of the final product and [the] cleaning of the storage tanks, there is no potential for operator exposure. During removal of the filter, which contains the residual new substance, the operator is equipped with the above-mentioned safety equipment. The process is designed to prevent any atmospheric release of the new substance. Any other releases to the environment will be controlled by the use of RCRA-approved waste handling sites and commercial solvent recovery. . . . ."

Comments/Recommendations

It should be noted that Part VII of the Agency's March 26, 1978 TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110) explains that information need not be submitted separately under Section 8(e) if that information has been submitted already to the Agency under another mandatory TSCA reporting provision. In general, the Agency's TSCA Section 5 "Premanufacture Notice" rule (40 CFR Part 720) requires a company that submits a PMN to also submit studies/data (that are in the company's possession or control or that are reasonably ascertainable by the company) that address the subject chemical's toxicity or lack thereof. In the case of the present TSCA Section 8(e) submission, therefore, once the acute inhalation toxicity data were submitted to the Agency as required under Section 5 of TSCA, submission of the results of that same study under Section 8(e) of TSCA became unnecessary.

a) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS, and CCD/OTS/OPTS. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

DATE: MAY 27 1987

SUBJECT: Status Report* 8EHQ-0487-0668 Approved: 6/3/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

For background information on xerographic toners, the reader's attention is directed first to the "status report" prepared by EPA in response to data submitted by the Xerox Corporation on a "For Your Information" (FYI) basis (FYI-OTS-0480-0070 et seq.). In addition, it should be noted that EPA has received a number of Section 8(e) and FYI notices regarding photocopying toners and/or processes (8EHQ-0480-0339 et seq., 8EHQ-0880-0351 et seq., FYI-OTS-0680-0099 et seq., FYI-OTS-1181-0145 et seq.) The reader's attention is directed also to a draft production/exposure profile (PEP) on chemical substances used in plain paper copying (EPA Contract No. 68-01-6239; October 8, 1983; Dynamac Corporation, Rockville, MD). Finally, it should be noted that the Agency has prepared "Chemical Hazard Information Profiles" (CHIPs) on a number of chemicals associated with photocopying processes.

Submission Description

In its TSCA Section 8(e) notice, the Xerox Corporation submitted the protocol and interim findings from an ongoing chronic study of a Xerox 9000-type photocopying toner administered at doses of 1.0, 4.0 and 16.0 mg/m^3 by inhalation to Fischer 344 rats. (The composition of the tested material can be found in the Current Production and Use section of this status report.) According to the submitted information, the doses used in this chronic inhalation study correspond to American Conference of Governmental Industrial Hygienists (ACGIH) respirable concentrations of 0.35, 1.4 and 5.6 mg/m^3, respectively. In its submission, Xerox stated that in addition to air-only controls, silicon dioxide (SiO_2, a known fibrogenic agent) and titanium dioxide (TiO_2, a "nuisance dust") were evaluated in this chronic inhalation study. The following summarized information concerning the 15-month sacrifice was presented by Xerox in its Section 8(e) submission cover letter:

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"A preliminary evaluation of the chronic rat study data indicates no unusual histopathological findings . . . The low (1 mg/m^3) and middle (4 mg/m^3) exposure groups are similar to the negative control (TiO_2) at 5 mg/m^3. The high toner exposure group (16 mg/m^3) is essentially similar except for minimal increase in collagen possibly the result of [an] artifact associated with thickly cut histologic sections. Animals in the toner-exposed groups are essentially healthy at this time and without evidence of decrease in body weight. At the high toner exposure level, however, there is evidence of increased lung weight, increased retention of the test material as a function of exposure concentration over time, and retardation of alveolar macrophage mediated clearance. It should be noted that the toner material used in this study has been enriched ten-fold in respirable size particles with respect to the commercially available toner material. With respect to the [ongoing] study, the high toner exposure level (16 mg/m^3 total or 5.6 mg/m^3 respirable) should be compared with the present [Occupational Safety and Health Administration (OSHA)] nuisance dust limit of 5 mg/m^3. Measurements of respirable dust in [Xerox manufacturing, service and customer environments] are far below the respirable level referred to above. All of the validated health and safety information in Xerox's data base are consistent with the categorization of Xerox toners as "Nuisance Dusts" and of low inherent toxicity."

In addition to submitting the above described interim findings from the chronic inhalation study, Xerox provided a complete copy of the final report from a subchronic inhalation study of the subject toner in Fischer 344 rats. The Abstract section of the submitted report presented the following information with regard to the purposes, conduct and results of the 90-day study:

"The primary purposes of this [subchronic inhalation] study were to ensure the suitability of the inhalation facilities, dedicated instrumental designs and the experimental layout of the study for long-term exposures as well as to find an appropriate range of dose levels of the test material for a lifespan study. Particular attention was focussed upon lung dynamics influenced by the deposition and retention of the test material and upon the occurrence of a Maximum Functionally Tolerated Dose (MFTD).

"The test material used was a specially prepared and characterized powder sample identical to 9000-type xerographic test material, except that its ACGIH respirable fraction was enriched about 10-fold to 35%. The [toner] exposure concentrations used were 0, 1.0, 4.0, 16.0 and 64.0 mg/m^3 of total mass concentration corresponding to 0, 0.35, 1.2, 5.6 and 22.4 mg/m^3 of respirable material.

"The MFTD of a test material is defined as the maximum lung burden for which macrophage mediated lung clearance is not significantly impaired. In order to establish MFTD value and suitable lifespan exposure concentrations for the test material, a 90-day subchronic inhalation study of a test material fraction was conducted by exposure of groups of [Fischer 344] rats for 6 hours/day, 5 days /week for 13 weeks. . . . .

"No unscheduled death occurred during the study. A Sendai virus infection was detected about half-way through the study . . ., but its source could not be identified. Body weights, organ weights and food consumption were normal in groups exposed to [the] 1 and 4 mg/m^3 exposure concentration levels. An increase in lung weight was observed at the 16 and 64 mg/m^3 dose levels. At the highest [toner] exposure level of 64 mg/m^3, food consumption in both male and female rats was slightly decreased, but body weight was not affected.

"Alveolar lung clearance results of the toner test material and an iron oxide tracer were essentially unchanged at exposure concentrations of 0, 1 and 4 mg/m^3. At 16 mg/m^3, some indications of slightly retarded iron oxide tracer clearance were noted after 90 days of exposure. At the 64 mg/m^3 level of the test material, no appreciable toner material clearance was observed after 60 and 90 days of exposure, and clearance of the iron oxide tracer material was significantly retarded after 30, 60 and 90 days. Histopathological examination of the lungs indicated a dose-related increase in particle-laden alveolar macrophages. A slight thickening of alveolar walls was observed in the high exposure groups.

"Based upon the above observations, the . . . [MFTD] in this subchronic study of the toner test material was exceeded at the 64 mg/m^3 exposure level. For a chronic inhalation test using the same material over 2 years, the MFTD would probably be exceeded at the 16 mg/m^3 level."

In its Section 8(e) notice, Xerox also provided several papers and poster presentations that address the conduct and results of the 90-day enriched toner inhalation study as well as inhalation studies in general.

Submission Evaluation

EPA's review of the results from Xerox's ongoing chronic toner inhalation study in rats will be conducted in context with other available data on photocopying toners received to date by EPA (see Note at the top of the first page of this status report). Xerox should be asked to ensure that EPA receives a full copy of the final report (including any protocol amendments, results of

gross/histopathological examinations, results of any statistical analyses, etc.) from the chronic toner inhalation study cited in the company's TSCA Section 8(e) notice.

Current Production and Use

According to the submitted information, the tested toner is a 90%/10% mixture of the following constituents, respectively:

1-butylmethacrylate/styrene random copolymer (ratio 42:58; CAS No. 25213-39-2); and

high purity medium color furnace carbon black (CAS No. 7440-44-0).

Further, the tested toner (which had been enriched 10-fold to increase the amount of respirable particles) was reported to be a combustible, pigmented plastic powder with a solid density of about 1.1-1.2 g/cm^3, a softening range of approximately 80-100°C, a mass median aerodynamic diameter of almost 4.0 um (geometric standard deviation of about 1.3 um) and a molecular weight of approximately 70,000 Daltons. According to the submission, the respirable fraction of the tested toner is about 35% (determined by using ACGIH criteria) while the respirable fraction of the commercially available Xerox 9000 toners ranges from 2-5%.

Finally, Xerox provided the following information with regard to toner exposure in Xerox toner manufacturing plants and customer facilities:

> "Currently available industrial hygiene information from . . . [Xerox Corporation] toner manufacturing plants, where presumably the highest airborne toner dust levels may be found, appears to be quite satisfactory. Limited respirable sampling data indicate that more than 95% of the airborne respirable dust levels are below 0.25 mg/m^3 and corresponding respirable toner levels are less than 0.15 mg/m^3. [Note: The OSHA limit for "nuisance dusts" in occupational settings is 15 mg/m^3 total or 5.0 mg/m^3 for respirable particles.] Based on other available data, the respirable dust levels with respect to both [the Xerox machine service] population and the customer environment are far below the levels mentioned above."

Comments/Recommendations

In the cover letter to its Section 8(e) submission, Xerox stated that in accordance with standard company practices, Xerox toner manufacturing employees will continue to be apprised about toner exposure levels as well as further results of the ongoing chronic toner inhalation study in rats. In addition, Xerox stated that the company is continuing "to evaluate respirable dust levels in all appropriate operations." Finally, Xerox stated that the company's "Exposure Limit Committee is in the process of reviewing

all health and safety data with respect to toner, as well as other materials, and will determine whether . . . [the company's] internal [exposure] limit for toner (5 mg/m^3 total dust) should be modified."

It should be noted that the Agency has received TSCA Section 8(e) and FYI notices on titanium dioxide (8EHQ-1083-0497 et seq. and FYI-OTS-0880-0125) and silicon dioxide (8EHQ-0780-0354 et seq. and FYI-OTS-0880-0125).

a) The Chemical Screening Branch will ask Xerox to ensure that EPA receives a complete copy of the final report (including any protocol amendments, results of all gross and histopathologic examinations, results of statistical analyses, etc.) from the company's ongoing chronic toner inhalation study in rats.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the tested toner or its constituents.

c) The Chemical Screening Branch will send copies of this status report to OSHA, NIOSH, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, ORD/EPA and OAR/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

DATE: MAY 7 1987

SUBJECT: Status Report* 8EHQ-0487-0669 Approved: 5/8/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description (See NOTE on page 3 of this status report)

PPG Industries, Inc. provided the following information regarding the conduct and results of acute rabbit eye irritation studies of two halogenated imidazolidinones ($C_7N_2Cl_2H_{12}O$ and $C_7N_2Br_2H_{12}O$):

> "[Two] eye irritation studies in rabbits were conducted with these materials in their pure form (100% active ingredient). Results for both materials indicate that they caused severe irritation to the eye that resulted in irreversible destruction."

It should be noted that PPG did not provide any additional information concerning the identities of the tested materials or the acute eye irritation studies conducted with those materials.

Submission Evaluation (See Note on page 3 of this status report)

In order for EPA to evaluate the overall significance of the reported data, PPG should be asked to submit 1) full copies of the final reports from the cited acute rabbit eye irritation studies, and 2) exact identities of the tested chemicals.

Current Production and Use

In its Section 8(e) submission, PPG stated that these halogenated imidazolidinones are research and development (R&D) chemicals "being evaluated for use as biocides and possible other uses." PPG stated also that because the chemicals are at an R&D stage, "only a limited number of technically qualified personnel are potentially exposed to these chemicals." In addition, PPG stated

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

that "PPG personnel with potential exposure are protected by the use of protective facilities, equipment, and clothing, e.g., laboratory hoods, protective gloves and eye protection." PPG stated further that samples of these halogenated imidazolidinones "sent outside the company for evaluation are always accompanied by an Experimental Product Data Sheet that indicates these materials cause eye irritation and prescribe the appropriate protective measures."

Comments/Recommendations

In its Section 8(e) submission, PPG stated that 1) "all personnel with potential exposure to these materials will be informed of these [toxicologic] findings and guidelines for handling," and 2) "the Experimental Product Data Sheet will be modified to include a statement about the severity of the eye irritation associated with exposure to these materials."

Based on an initial review of the information presented in this TSCA Section 8(e) submission, it is not entirely clear that the provided information warranted reporting under Section 8(e), the "substantial risk" information reporting provision of TSCA. The submitter's rationale for reporting the subject findings to EPA pursuant to TSCA Section 8(e) may become more apparent upon EPA's receipt of further information concerning the performed studies and the identities of the tested chemical substances.

a) The Chemical Screening Branch will ask PPG to submit complete copies of the final reports (including the actual experimental protocols, results of gross and histopathologic examinations, etc.) from the acute rabbit eye irritation studies cited in the company's Section 8(e) notice. In addition, PPG will be asked to report 1) the exact identities (including CAS Registry Numbers, if known), and 2) additional information with regard to actual/planned use(s) of the tested chemicals.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, the Chemical Screening Branch will request PPG to describe the nature and results, if available, from all studies (other than those submitted already to the Agency or those cited in the published scientific literature) about which PPG is aware or that PPG has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to these halogenated imidazolidinones.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substances.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, ORD/EPA, OAR/EPA, OW/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

NOTE:

In a letter dated June 4, 1987 (8EHQ-0687-0669 FLWP), PPG reported non-confidentially that the subject chemicals were 1,3-dichloro-4,4,5,5-tetramethyl-2-imidazolidinone and 1,3-dibromo-4,4,5,5-tetramethyl-2-imidazolidinone.

7/13/87

DATE: MAY 7 1987

SUBJECT: Status Report* 8EHQ-0487-0670 S Approved: 5/11/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

The submitting company claimed its identity and the identity of the subject chemical substance to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will request the submitter to substantiate these TSCA CBI claims. In the "sanitized" version of this TSCA Section 8(e) notice, the submitter reported non-confidentially that the tested chemical is a "substituted nitrobenzene" currently in research and development (R&D).

Submission Description

The submitting company reported that a significant increase in corneal opacity was found at all substituted nitrobenzene dose levels in a feeding study conducted using Sprague Dawley rats. In submitting these preliminary findings under Section 8(e), the submitter stated that "while corneal opacity is unusual, it is not unique to this [substituted nitrobenzene] substance, but has been reported to occur from the administration of several drugs, including indomethacin, chloroquine, amiodarone and others."

Submission Evaluation

In order for the Agency to evaluate the overall significance of the submitted toxicologic findings, the company should be asked to submit a full copy of the final report (including the actual experimental protocol, results of gross and histopathological examinations, results of statistical analyses, etc.) from the performed dietary feeding study of this substituted nitrobenzene in rats.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

It should be noted that in 1986, EPA received two other TSCA Section 8(e) notices (8EHQ-0986-0624 S and 8EHQ-0986-0625 S) in which corneal opacity was reportedly observed in dietary feeding studies conducted with rats. The reader's attention is directed to the single status report prepared by EPA in response to these particular Section 8(e) notices.

Current Production and Use

According to the submitting company, the subject R&D chemical is being evaluated as an "experimental pesticide candidate." In addition, the submitter provided the following information concerning the potential for exposure to the subject chemical:

> "Since the [tested] material is an R&D chemical, it has only been manufactured in small quantities with limited, controlled distribution. The material is handled only by technically qualified persons including consulting scientists and company scientific personnel using prudent laboratory practices."

Comments/Recommendations

In its TSCA Section 8(e) submission, the submitter stated that in accordance with standard policy, the company has notified all persons evaluating this particular class of chemicals about the reported toxicological findings. In addition, the company stated that "personnel protection and work practices will be evaluated and modified if necessary."

a) The Chemical Screening Branch will request the company to submit a complete copy of the final report (including the actual experimental protocol, results of gross and histopathological examinations, results of statistical analyses, etc.) from the dietary feeding study cited in the submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, the Chemical Screening Branch will ask the submitting company to describe the nature and results, if available, from all studies (other than those submitted already to the Agency) about which the company is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of this substituted nitrobenzene.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of this substituted nitrobenzene.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: MAY 7 1987

SUBJECT: Status Report* 8EHQ-0487-0671 Approved: 5/11/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Koppers Company, Inc. provided the following information with regard to a recent incident at a Koppers Company facility located in Oroville, California:

> "On April 6, 1987, an accident occurred at the mixing unit for the Cellon process of wood preservation treatment at the Koppers Company, Inc. plant in Oroville, California. The accident resulted in a fire which burned for approximately nine hours. The Cellon process is a proprietary process which employs pressure treatment of wood with pentachlorophenol (CAS No. 87-86-5) in a mixture of butane, isopropyl ether and diesel oil. As a result of the fire and fire-fighting procedures, an undetermined amount of pentachlorophenol was released onto the immediate site around the Cellon mixing unit or burned. It is possible that some pentachlorophenol was dispersed into the air. The maximum amount of pentachlorophenol potentially involved in the fire was 9000 lbs., but subsequent visual inspection of pentachlorophenol levels remaining in the equipment indicates that perhaps the pentachlorophenol loss was limited to 3000 lbs. The combustion of pentachlorophenol may have led to the formation of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans. Pentachlorodi-benzo-p-dioxins as well as hexachloro-, heptachloro-, and octachloro-isomers were present in the soil at the site prior to the accident on April 6, and [the Koppers Company is] now aware of one measurement of 2.4 ppb 2,3,7,8-tetrachlorodibenzo-p-dioxin in ashed material on the ground at the fire site. Soil and wipe samples have been collected by Koppers as well as State and Federal agencies for additional chemical analyses. The fire site and surrounding areas are now secure and stabilized according to California OSHA and U.S. EPA specifications.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"Because of the possibility of pentachlorophenol becoming airborne during the fire and because of concerns that hazardous levels of pentachlorophenol may settle in some off-site areas, warnings were given to local residents and a health clinic was established to evaluate residents who believe they may have been overexposed to chemicals as the result of the fire. The clinic was staffed by California Department of Health Service physicians. On Monday, April 13, 1987, Koppers learned that a physician at the clinic [who] examined a number of citizens . . . felt that she had seen symptoms that could be attributable to acute exposure to pentachlorophenol. [Koppers understands] that the symptoms reported to the clinic physician included mucous membrane irritation and skin irritation. [Koppers does] not have further information about these individuals or their complaints. . . . [Koppers reported also] that there are no reports of adverse health affects related to chemical exposure among the Koppers employees on-site during and after the fire. . . . In addition, the . . . [California State Health Director] reports that after analyzing more that 62 samples of soil, vegetation and surface wipes from the facility and the community, pentachlorophenol has not been found in significant levels in samples taken from the community."

Comments/Recommendations

Immediately upon receipt of this TSCA Section 8(e) notification, the Chemical Screening Branch transmitted copies of the notice to OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and to the EPA Region IX Office in San Francisco, California. In addition, a copy of the submission was provided immediately to the Chemical Regulation Branch/EED/OTS/OPTS/EPA which is in the process of finalizing a TSCA Section 4 testing/Section 8 data gathering rule on polyhalogenated dibenzo-p-dioxins/dibenzofurans

The Chemical Screening Branch will transmit copies of this status report to NIOSH and OSHA as well as to all EPA Offices mentioned in the preceding paragraph.

DATE: JUN 9 1987

SUBJECT: Status Report* 8EHQ-0587-0672 S Approved: JMc 6/9/87

FROM: James F. Darr, Section Head James F. Darr
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Shell Oil Company submitted a paper entitled "Teratogenicity of Di(2-ethylhexyl) Phthalate, 2-Ethylhexanol, 2-Ethylhexanoic Acid, and Valproic Acid, and Potentiation by Caffeine" published recently in Teratology (1987; Vol. 35; pg. 41-46). The ABSTRACT section of the provided paper presents the following information regarding the conduct and results of the performed study:

> "It is hypothesized that the teratogen di(2-ethylhexyl) phthalate (DEHP) acts by in vivo hydrolysis to 2-ethylhexanol (2-EHXO), which in turn is metabolized to 2-ethylhexanoic acid (2-EHXA), the proximate teratogen. Teratological studies were conducted with Wistar rats, with [a single oral] administration of [equimolar doses] of these agents on day 12 of gestation. [According to text of the paper, "a dose of 12.5 mmol/kg of DEHP is equivalent to 5.0 ml/kg; doses of 2-EHXO and 2-EHXA of 12.5 mmol/kg are equivalent to 2.0 ml/kg."] On an equimolar basis, DEHP was [the] least potent, 2-EHXO was intermediate, and 2-EHXA was the most potent of the three agents, which is consistent with the hypothesis. Similarity in the types of defects [("hydronephrosis, levocardia, iv septal defect, and other heart malformations, short and kinky tail, ectrodactyly, misplaced digits and bowed radius")] found with these agents also suggests a common mechanism with 2-EHXA as the proximate teratogen. All three [test] agents were potentiated by caffeine. Valproic acid, which is an isomer of 2-EHXA, also produced similar defects, and was approximately twice as potent as 2-EHXA."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

In the cover letter to its Section 8(e) notice, Shell stated that although the cited study was not well designed to demonstrate teratogenic effects (because of deviations from "conventional" teratologic study protocols), "these deviations do not negate the basic finding that [2-ethylhexanol] at a one-time dose of 2 ml/kg resulted in malformations in the offspring." In its submission, Shell stated also that the data from the study are "not adequate for risk assessment [in that] the effect level (2 ml/kg by the oral route) translates to 120 ml for a 60 kg person." Shell did state, however, that "without knowledge of the degree of skin absorption or animal-to-man translation factor, nothing definitive can be determined as to risk." Shell stated further that the "application of the usual discount factors and moderate degrees of skin penetration, results in projected dermal levels of concern."

In its TSCA Section 8(e) notice, Shell also provided monitoring data from Shell's 2-ethylhexanol manufacturing facility. With regard to the submitted exposure data, Shell stated that because all workplace "inhalation results were less than the detectable limits of the methods used (1 ppm for all but one measurement which was carried out using a method with a limit of 10 ppm)," Shell concluded that while the inhalation risk is small, dermal contact with 2-ethylhexanol remains the company's major concern.

Submission Evaluation

In view of the fact that di(2-ethylhexyl) phthalate, 2-ethylhexanol and 2-ethylhexanoic acid are being assessed by the Test Rules Development Branch (TRDB/ECAD/OTS) and di(2-ethylhexyl) phthalate is being assessed by the Risk Analysis Branch (RAB/ECAD/OTS), full copies of this Section 8(e) submission were sent immediately by the Chemical Screening Branch (CSB/ECAD/OTS) to TRDB and RAB for inclusion in their ongoing assessments.

Comments/Recommendations

In its Section 8(e) submission, Shell stated that the company is 1) revising its 2-ethylhexanol Material Safety Data Sheet, and 2) informing Shell workers about the reported teratologic findings.

In submitting this particular article to EPA under Section 8(e) of TSCA, Shell stated that although the study findings had been published already in Teratology in 1985 and 1986 as abstracts of oral presentations and abstracted by Biological Abstracts in 1986, all of these abstracts require actual reading in order to learn about the teratogenic effects of 2-ethylhexanol because the abstract titles do not indicate that 2-ethylhexanol was tested and "scanning of the abstracts alone is not sufficient to obtain this information."

Further, Shell noted that Part VII of EPA's Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978) explains that information need not be reported if, for example, the information "has been published in the scientific literature and referenced by . . . Biological Abstracts . . . ." In formally submitting this article to EPA under Section 8(e) of TSCA, however, it appears that Shell has relied quite heavily on the statutory language of TSCA Section 8(e) (i.e., substantial risk information must be submitted immediately to EPA under Section 8(e) of TSCA unless the person who obtains the information has "actual knowledge" that the EPA Administrator has been already "adequately informed" about that information). Rather than address at this point whether the subject teratological findings for 2-ethylhexanol have or have not been titled or referenced in a such manner as to make the findings easily recognizable to or readily retrievable by EPA or others, EPA believes that in this case it is more appropriate to express the Agency's appreciation to Shell for the company's apparent consideration of both the "spirit" and statutory language of Section 8(e) in deciding to submit the teratologic findings formally under Section 8(e); other companies that are subject to Section 8(e) are encouraged to incorporate such prudent considerations in their own Section 8(e) reporting deliberations.

a) The Chemical Screening Branch will send copies of this status report to OSHA, NIOSH, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA, and to TRDB and RAB/ECAD/OTS/OPTS/EPA; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

DATE: JUN 22 1987

SUBJECT: Status Report* 8EHQ-0587-0673

Approved: 6/22/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Stauffer Chemical Company (a subsidiary of Chesebrough-Ponds Inc.) provided a complete copy of a final report from an acute (1-hour) inhalation study of N-1386 HAN, a mixture of bis(trichloromethyl)sulfone (CAS No. 3064-70-8) and petroleum naphtha solvent (CAS No. 64742-95-6) in rats. The SUMMARY section of the provided report presents the following information regarding the conduct and results of the study:

> "The purpose of this study was to determine the acute inhalation toxicity of N-1386 HAN . . . according to the requirements set by the Department of Transportation . . . ." N-1386 HAN, a yellow colored liquid at standard temperature and pressure, was generated [by] using a Solosphere® nebulizer. The chamber atmosphere consisted of a mixture of aerosol and vapor (approximately 50% each) for both exposures conducted.
>
> "Two groups of 5 male and 5 female Sprague-Dawley rats received a whole-body exposure for 1 hour to an atmosphere containing mean concentrations of either of 6.96 mg/l or 1.91 mg/l of N-1386 HAN. Particle size analysis indicated the mass mean aerodynamic diameter ($MMAD_{ar}$) of the aerosol to be 2.60 um. Two control groups, consisting of 5 male and 5 female rats for each group, were sham exposed using the same experimental conditions but without generation of the test material.
>
> "Exposure of rats to N-1386 HAN resulted in death to all 10 rats for both the 6.96 mg/l and 1.91 mg/l exposures. Most of the rats died during or immediately after the exposure so that in-life clinical observations could not be obtained. At necropsy, pulmonary congestion was evident in all of the treated rats. The lungs were reddened

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

and failed to collapse in all exposed animals. Measurement of pulmonary edema was performed for rats exposed to 6.96 mg/l using wet/dry lung weight ratios and significant increases in the weight ratios were evident in both male and female rats when compared to controls.

"In conclusion, N-1386 HAN produced significant pulmonary effects leading to the deaths of all exposed rats after one-hour inhalation exposures at 6.96 mg/l or 1.91 mg/l. Therefore, the one-hour LC50 for N-1386 HAN is less than 1.91 mg/l."

In its Section 8(e) submission, Stauffer stated that in 1986, the company reviewed N-1386 HAN in order to determine if this product was subject to a U.S. Department of Transportation final rule on "Liquids Toxic by Inhalation" (HM-196). According to Stauffer, "based on preliminary inhalation data (LC50 <1,000 ppm) and a calculated saturated vapor concentration (27,895 ppm), it was determined that N-1386 HAN was an inhalation hazard" and "the product was reclassified and labeled accordingly.

Submission Evaluation

The administered dose levels of 1.91 and 6.96 mg/l correspond approximately to 38.6 and 138.2 mg/kg/day, respectively. Six of 10 rats at the low concentration and 9/10 rats at the high concentration died on the day of exposure; the remaining rats were found dead on the following day. Clinical observations were obtained only for those rats surviving past the day of exposure. Due to the high mortality, no body weight comparisons were made. In all animals at both dose levels, the lungs were reddened and failed to collapse. Clear fluid was found in the chest cavity in 4/5 males and 5/5 females at the 6.96 mg/l dose level. Also at this high level, the trachea was froth-filled in 3/5 males and 4/5 females, 5/5 males and 4/5 females had gas-distended stomachs and either one or both eyes were cloudy white in all 5 males and 3/5 females. When compared to controls, significant pulmonary edema was observed in both sexes at both dose levels. Labored breathing and salivation were included among the toxic symptoms observed in this study.

According to information obtained from other available sources, bis(trichloromethyl)sulfone has some degree of antiseptic/antimicrobial capacity, has an oral (rat) LD50 of 651 mg/kg and an intravenous (mouse) LD50 of 18 mg/kg.

Current Production and Use

A review of the production range (includes importation volumes) statistics for bis(trichloromethyl)sulfone, which is listed in the initial TSCA Chemical Substance Inventory, has shown that no 1977 manufacture/importation was reported or that all of the

manufacture and/or importation information reported was claimed to be TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory and cannot be disclosed (Section 14(a) of TSCA, U.S.C. 2613(a)).

A review of the production range (includes importation volumes) statistics for petroleum naphtha solvent (CAS No. 64742-95-6), which is listed also in the initial TSCA Inventory, has shown that over 1 billion pounds were reported as manufactured and/or imported in 1977. This production range information does not contain any data claimed as TSCA CBI by the person(s) reporting for the initial TSCA Iventory nor does it include any information that would compromise TSCA CBI.

It should be noted that all data provided for the initial TSCA Inventory, including the production range data, are subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

According to the submitted information, N-1386 HAN is a light yellow liquid with a vapor pressure of 25.8 mm Hg at 25°C. In the cover letter to its Section 8(e) submission, Stauffer stated that although bis(trichloromethyl)sulfone is an active ingredient registered with EPA under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), N-1386 HAN is not a registered pesticide but is sold (primarily to one customer at the present time) as an intermediate in formulating a FIFRA-registered pesticide.

Comments/Recommendations

According to Stauffer, N-1386 HAN customers are being informed in writing about the reported toxicologic findings, and the product has been relabeled to reflect the inhalation toxicity findings.

It should be noted that bis(trichloromethyl)sulfone was the subject of a FIFRA "Data-Call-In" issued by EPA in March 1987. In addition, it should be noted that EPA has received many TSCA Section 8(e) and "For Your Information" (FYI) submissions on petroleum distillates, including the petroleum naphtha solvent cited in this Section 8(e) submission. It should be noted also that the Chemical Screening Branch (CSB/ECAD/OTS) prepared (in 1984) a Chemical Hazard Information Profile (CHIP) covering a number of petroleum naphtha solvents and the Risk Analysis Branch (RAB/ECAD/OTS) is currently evaluating toxicity and exposure data on petroleum naphtha solvents.

a) The Chemical Screening Branch will request the Stauffer Chemical Company to report the exact amount of each component in N-1386 HAN.

In view of EPA's general interest in corporate actions that are taken on a voluntary basis in response to chemical toxicity or exposure data, Stauffer will be asked to describe the nature and results, if available, of all studies (other than those submitted already to EPA or those cited in the open scientific literature) about which Stauffer is aware or that Stauffer has conducted, is conducting, or plans to conduct to determine the toxicity of or the exposure to N-1386 HAN or its constituents.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of N-1386 HAN or its constituents.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, NTP, FDA, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and RAB/ECAD/OTS; copies of this status report will be transmitted also to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

DATE: JUL 7 1987

SUBJECT: Status Report* 8EHQ-0587-0674 S
8EHQ-0687-0674 S SUPP

Approved: 7/7/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

The submitting company has claimed its company name and the exact identity of the subject chemicals as TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will request the submitter to substantiate these CBI claims. In the non-confidential versions of the initial and/or supplemental TSCA Section 8(e) notices, the submitter stated that the tested product ("an experimental metalworking lubricant additive formulation") is a chemical mixture containing a major (97%) component identified generically as a "sulfurized olefin" and a minor (3%) component identified generically as a "substituted ammonium carboxylate." In the non-confidential version of the supplemental Section 8(e) notice, the company stated that the minor component of the product is the subject of a TSCA Section 5 "Premanufacture Notification" (PMN No. 86-476) currently under review by the OTS New Chemicals Program (NCP).

Submission Description

In its initial Section 8(e) notice, the submitter provided the following information concerning the results of acute oral, dermal and inhalation studies and a 28-day inhalation study of the subject mixture and/or its component(s):

> "The most profound effect observed in the 28-day inhalation study is the death of 4 of 10 female rats during the course of the exposure phase at a dose of 170 mg/M^3 which is the highest of three doses used in the study. No mortality was observed in male rats at any dose level. This observation reasonably supports the conclusion that substantial risk may exist, especially because of the existence of supporting evidence that suggests the agent toxic to females is the minor constituent of the mixture and not the major constituent (the sulfurized olefin).

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"This sex-specific effect is also noted on acute inhalation exposure on the same mixture. In a previously conducted acute inhalation study, no deaths were observed in male rats after a four hour exposure to 5,000 mg/M^3. Mortality was observed in female rats at this dose. The four hour LC-50 was determined to be 2,170 mg/M^3 for female rats. No other data are available on the mixture.

"The sulfurized olefin did not cause mortality in either sex of rats and rabbits, respectively, in acute oral and dermal exposures. In an oral toxicity range finding study on the minor component, a dose of 5 g/kg killed all five female rats treated in the study, while no deaths were observed in males at this dose. At a dose of 2 g/kg of the minor component, no rats of either sex died. This observation raises the suspicion that the selective mortality to females in the 28-day study is due to the minor component.

"Other effects noted in the 28-day study include:

"1. Urinary casts were observed at all doses (40, 80 and 170 mg/M^3) in male rats. An increased accumulation of hyaline droplets of the kidneys in males was found at the two highest doses. The significance of these findings is unknown. Hyaline droplet formation is an effect unique to the kidneys of male rats and is increased by many chemicals, most notably by low to medium molecular weight hydrocarbons. Possible indication of kidney pathology was observed in only 3 of 10 male rats at the high dose.

"2. A slight decrease in hematocrit and blood glucose was observed in high dose male rats. No associated pathology was observed which was related to these observations.

"3. A slight, but statistically significant, increase in testicular weight to body weight ratio was observed at all doses in male rats. The effect was not graded with dose.

"4. Irritation of the nasal turbinates was found in both sexes at the highest dose level.

"The only other effect unique to female rats in the 28-day study was the observation of sporadic and transient ataxia, usually immediately after exposure to the test material. Ataxia is commonly observed in inhalation studies. It is believed to be related to anoxia resulting from [a] reduced respiratory rate as a voluntary defensive response to toxic materials. Therefore, it is not apparent whether the ataxia is due to a specific

toxic effect of the test material. No other information is available which sheds light on this increased toxicity in female rats exposed by inhalation."

In its supplemental TSCA Section 8(e) submission, the company provided a complete copy of the final report from the 28-day inhalation study.

Submission Evaluation

Immediately upon receipt of these TSCA Section 8(e) submissions, the Chemical Screening Branch transmitted copies to the Chemical Control Division (CCD) which is responsible for administering the NCP under Section 5 of TSCA.

Current Production Use

In view of the submitter's TSCA CBI claims no information with regard to the current TSCA Chemical Substance Inventory status of the components of the tested product will appear in this report. In its initial Section 8(e) submission, the company provided the following information concerning the use of and the potential for exposure to the tested product/constituents:

"Various sulfurized olefins are supplied by many additive manufacturers as extreme pressure antiwear additives for industrial lubricants. They are supplied to lubricant blenders and typically used at a concentration of 10% or less in the final lubricants. No untoward effects have been reported in any workers handling the substance in over 10 years experience with this and competitive products of similar chemical structure.

"For the intended use, a typical metalworking fluid would be 5% of this mixture in mineral oil. A maximum concentration of the additive package would be 10%. Users observing the TLV for oil mist would be exposed to no more than 0.5 mg/M^3 of the mixture or 1/80 of the lowest dose tested."

Comments/Recommendations

In its initial Section 8(e) notice, the submitter stated that although there is or will be low exposure to the constituents of the addititive package during use of typical metalworking fluid formulations, the following actions were being taken:

"1. [R]equest OTS to extend the review period of the premanufacture notification . . . until further inhalation data is obtained on the PMN substance. If [the submitter] determines that the product can be used safely, the information will be added to the PMN file with a request that the notice review be completed. Otherwise, the PMN will be withdrawn.

"2. Acute oral and acute dermal [toxicity] studies will be conducted on the experimental lubricant additive formulation to determine if the acute toxicity is unique to inhalation exposure.

"3. Additional histopathology will be conducted on other organs from the 28-day study not examined in the original protocol to attempt to determine the etiology of the mortality in female rats.

"4. The hyaline droplet formation data will be reviewed with experts at the Chemical Industry Institute of Toxicology to help determine the significance of this effect."

It should be noted that the Agency has received a number of TSCA Section 8(e) and "For Your Information" (FYI) notices on metal-working fluids and/or components of such products.

It should be noted also that Part VII of EPA's March 16, 1978 TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110) explains that information need not be reported to EPA under Section 8(e) if, for example, the information has been submitted already to EPA under some other mandatory reporting provision of TSCA (e.g., Section 5) or other authority that is administered by EPA (e.g., CERCLA, RCRA, CAA, CWA, etc.).

a) The Chemical Screening Branch will ask the submitting company to ensure that EPA receives full copies of the final reports (including the actual experimental protocols, results of gross/histopathological examinations, results of statistical analyses, etc.) from all studies cited in the company's TSCA Section 8(e) submissions.

   In view of EPA's general interest in corporate actions that are taken on a voluntary basis in response to chemical toxicity or exposure data, the submitter will be asked also to describe the actions the company has taken or plans to take to notify its workers about the reported toxicologic findings.

b) As was the case for the initial and supplemental TSCA Section 8(e) submissions, the Chemical Screening Branch will immediately transmit all reported information to the Chemical Control Division for review and appropriate followup attention.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and CCD/OTS/OPTS. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OPTS) for further distribution.

DATE: JUN 12 1987

SUBJECT: Status Report* 8EHQ-0587-0675 Approved: 6/15/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Chemical Manufacturers Association (CMA) submitted a complete copy of the final report from a chronic mouse skin-painting study of a mixture containing calcium naphthenate (CAS No. 61789-36-4) and a mineral oil. In the Section 8(e) notice cover letter, CMA provided the following information with regard to the conduct and results of this chronic mouse skin-application study which had been conducted by Shell Research Limited, London, United Kingdom:

> ". . . [Groups] of 50 female STCF mice were treated twice weekly for up to two years with epidermal applications of 0.05 ml of the mixture of oil and calcium naphthenate, undiluted oil, [or] a 37.5 ug/ml solution of benzo(a)pyrene. The animals were observed daily and subjected to necropsy and histological examination at the end of the two-year period of application.
>
> "Forty-two mice (84%) in the benzo(a)pyrene positive control group developed a total of 104 cutaneous tumors of the treated site, demonstrating the susceptibility of the STCF mouse to a known skin carcinogen and the validity of the animal model. No epidermal or dermal tumors of the shorn site were seen in the untreated negative control mice. Eight mice (16%) developed a total of 13 tumors (12 epidermal and one dermal) of the treated site when the mixture of mineral oil and calcium naphthenate was applied. The tumors were two squamous-cell carcinomata, one basal-cell carcinoma, one dermal fibrosarcoma, seven squamous-cell papillomata and two regressed/sloughed papillomata, with latencies of 392 to 736 days. Application of the carrier oil alone did not give rise to any cutaneous tumors of the treated site.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

> "On the basis of the historical control data, the testing laboratory concluded that the incidence of eight tumor bearing mice in a group of 50 should be considered biologically significant. As a result, the laboratory [has] determined that the mixture of calcium naphthenate and mineral oil is a cutaneous carcinogen in mice."

In providing this report to EPA under Section 8(e) of TSCA, CMA stated that the information was being submitted on behalf of the members of the CMA Naphthenates Program Panel (Nuodex, Inc.; Mooney Chemicals, Inc.; the Troy Chemical Corporation; Interstab Chemicals, Inc.; and the Shepherd Chemical Company). In addition, CMA stated that because calcium naphthenate is the subject of a TSCA Section 8(d) "health and safety study" reporting rule (in support of "Test Rule Development" under Section 4 of TSCA), the the Shell Oil Company (which is not a member of the Naphthenates Program Panel) had already submitted full copies of the interim and final reports of this chronic mouse skin-application study to EPA's Test Rules Development Branch (TRDB/ECAD/OTS) and, as required, to the TSCA Section 8(d) reporting docket.

Submission Evaluation

Immediately upon receipt of this TSCA Section 8(e) submission, a copy of the notice was sent to the calcium naphthenate project manager in EPA's Test Rules Development Branch (TRDB/ECAD/OTS).

Current Production and Use

According to CMA, the members of the CMA Naphthenates Program Panel that manufacture calcium naphthenate are: Mooney Chemicals, Inc.; the Troy Chemical Corporation; Interstab Chemicals, Inc.; and Nuodex, Inc.; the other panel member (the Shepherd Chemical Company) only distributes this chemical. According to CMA, the Shell Oil Company (which is not member of the CMA Naphthenates Program Panel) "discontinued [in late 1983] the importation of oils containing calcium naphthenate and no longer processes nor distributes this material."

For information on the uses and additional information regarding the manufacture/importation of calcium naphthenate, the reader's attention is directed to 49 FEDERAL REGISTER (FR) 21411 (Monday, May 21, 1984).

Comments/Recommendations

Part VII of EPA's March 16, 1978 Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110) explains that information need not be reported to EPA under Section 8(e) if, for example, the information has been submitted already to EPA pursuant to a

mandatory reporting provision of TSCA. Considering the fact that the Shell Oil Company had already submitted the interim and final reports of the chronic calcium naphthenate mouse skin-painting study to EPA as required under TSCA Section 8(d), submission of the final report from the study on behalf of the CMA Naphthenates Program Panel members was not then required under Section 8(e) of TSCA.

It should be noted also that EPA has received a number of TSCA Section 8(e) notices that were submitted formally by chemical industry trade associations on behalf of their member companies; EPA has addressed this aspect of Section 8(e) reporting in the status reports prepared in response to several such submissions (e.g., 8EHQ-0285-0546).

a) The Chemical Screening Branch will ask CMA to transmit copies of this status report to the CMA Naphthenates Program Panel members.

b) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OAR/EPA, OW/EPA, ORD/EPA, OPP/OPTS and TRDB/OTS/OPTS. In addition, copies of this report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUN 9 1987

SUBJECT: Status Report* 8EHQ-0587-0676

Approved: 6/9/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

E. I. Du Pont de Nemours & Company, Inc. provided the following information regarding the conduct and interim results of an on-going 90-day inhalation study of 1,2-dichloro-1,1-difluoroethane (HCFC-132b; CAS No. 1649-08-7) in rats:

> "In this study, groups of 20 rats of each sex are being exposed by inhalation to HCFC-132b at exposure concentrations of either 0, 500, 2000 or 5000 ppm (v/v) for 6 hours/day, 5 days/week for approximately 14 weeks. During the first ten weeks of the study, exposed rats of both sexes gained less weight than the controls in a dose-dependent fashion. At about the midpoint in the exposure regimen, half of the rats were sacrificed for gross and microscopic pathological examinations. In [the HCFC-132b-treated] male rats, the testes showed microscopic, bilateral aspermatogenesis and germ cell degeneration. These lesions were mainly minimal to mild in severity and seen in 10 of 10 rats at both the 5000 and 2000 ppm exposure levels, but only in 2 of 10 rats in the 500 ppm group. No significant histopathological effects attributable to HCFC-132b were seen in female rats at the midpoint of the experiment."

Submission Evaluation

The reported interim findings indicate that inhalation exposure to this chlorofluorocarbon can adversely affect the reproductive organs/function in male rats; further evaluation of the findings should be possible upon EPA's receipt of a full copy of the final report of the ongoing 90-day inhalation study.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Immediately upon receipt of DuPont's initial Section 8(e) notice, the Chemical Screening Branch sent a copy of the submission to EPA's Stratospheric Ozone Protection Program/Office of Air and Radiation (OAR).

Current Production and Use

According to Du Pont, although HCFC-132b "is produced in only research quantities and is not used or sold commercially by Du Pont," this "chemical has been the subject of [research and development (R&D)] work by Du Pont and others." Du Pont stated also that "no samples of this compound have been distributed outside of Du Pont or its affiliates for evaluation by customers." Further, Du Pont stated that "a provisional workplace exposure limit of 5 ppm (8-hour Time Weighted Average) has also been established" for this substance.

A review of the production range (includes importation volumes) statistics for 1,2-dichloro-1,1-difluoroethane (CAS No. 1649-08-7), which is listed in the initial TSCA Chemical Substance Inventory, has shown that no 1977 manufacture or importation was reported or that all of the manufacture and/or importation data reported were claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the TSCA Inventory and cannot be disclosed (Section 14(a) of TSCA; U.S.C. 2613(a)). All of the information submitted for the initial TSCA Inventory, including the production range information, is subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

Comments/Recommendations

In its Section 8(e) submission, Du Pont reported that the company has advised its researchers as well as other chlorofluorocarbon producers about the submitted interim findings. Du Pont reported also that during "recent Congressional testimony dealing with substitutes for commercial chlorofluorocarbons, [Du Pont] advised members of the Senate Environment and Public Works Committee of these preliminary findings." Finally, Du Pont stated that the company has "suspended further R&D work until after the [90-day] test is completed and its results evaluated."

EPA's Office of Toxic Substances has received several TSCA Section 8(e) and "For Your Information" (FYI) submissions on a number of chlorofluorocarbons (CFCs).

a) The Chemical Screening Branch will request Du Pont to ensure that 1) EPA is informed in a timely manner about any further significant toxicologic findings from the ongoing 90-day HCFC-132b inhalation study in rats, and 2) EPA receives a complete copy of the final report

(including the actual experimental protocol, results of gross and histopathological examinations, results of statistical analyses, etc.) from that 90-day inhalation study.

In view of EPA's general interest in corporate actions that are taken on a voluntary basis in response to chemical toxicity or exposure data, Du Pont will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those published in the scientific literature) about which Du Pont is aware or that Du Pont has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to 1,2-dichloro-1,1-difluoroethane.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of 1,2-dichloro-1,1-difluoroethane.

c) The Chemical Screening Branch will send copies of this status report to OSHA, NIOSH, CPSC, FDA, NTP. OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: JUN 23 1987

SUBJECT: Status Report* 8EHQ-0687-0677 Approved: James F. Darr for Frank V. Kover 6/23/87

FROM: James F. Darr, Section Head James F. Darr
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Lever Brothers Company reported that it was recently informed (by phone) by its contract testing laboratory that Pyrazol Yellow BG 250% (C.I. Direct Yellow 28 (CAS No. 8005-72-9) as supplied by the Sandoz Chemicals Corporation) was found to be a weak mutagen in a "modified" Ames Salmonella typhimurium (bacteria) assay. According to Lever Brothers, Pyrazol Yellow BG 250% was positive both with and without exogenous metabolic activation in bacteria strains TA98, TA1537 and TA1538; strains TA100 and TA 1535 were reported to be negative.

Submission Evaluation

In order for EPA to evaluate the overall significance of the reported genotoxicologic findings, Lever Brothers should be asked to ensure that the Agency receives a complete copy of the final report (including the actual experimental protocol, data, results of any statistical analyses, etc.) from the modified Ames test cited in the company's Section 8(e) submission.

It should be noted that in an earlier TSCA Section 8(e) notice (8EHQ-01286-0645), Lever Brothers stated that Yellow Shade 18569 (C.I. Direct Yellow 28 as supplied by Tricon Colors Corporation) was found to be mutagenic in strains TA98 and TA1538 in an Ames assay. The reader's attention is directed to the status report prepared by EPA in response to this earlier TSCA Section 8(e) submission.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Current Production and Use

A review of the production range (includes importation volumes) statistics for CAS No. 8005-72-9, which is listed in the initial TSCA Chemical Substance Inventory, has shown that between 12,000 and 120,000 pounds of this chemical were reported as manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

According to secondary literature sources, C.I. Direct Yellow 28 is a thiazole derivative [*] that is used to dye/stain a variety of natural and synthetic materials. In its TSCA Section 8(e) submission, Lever Brothers stated that "Pyrazol Yellow BG 250% is not currently used in any of Lever Brothers' products."

[*] According to a C.I. Direct Yellow 28 structure obtained from the secondary literature, the chemical identity of this dye is: 6-methyl-2-(4-(4-(6-methyl-7-sulfobenzothiazol-2-yl)phenylazo)-phenyl)-7-benzothiazolesulfonic acid.

Comments/Recommendations

In its Section 8(e) submission, Lever Brothers reported that its "decision to further investigate . . .[Pyrazol Yellow BG 250%] or to conduct additional safety testing will be made after further discussion with the . . . [Sandoz Chemicals Corporation] and after assessment of [Lever Brothers'] continued interest in the material." In addition, Lever Brothers stated that its workers and the Sandoz Chemicals Corporation were being notified about the reported genotoxicologic findings. Lever Brothers stated further that the company will affix additional precautionary labels on the research quantity size containers of Pyrazol Yellow BG 250% received from Sandoz Chemicals.

It should be noted that although a positive *in vitro* genotoxicity finding, when considered alone, may not be sufficient to offer reasonable support for a conclusion of substantial risk (as that term is defined in EPA's March 16, 1978 TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110)), EPA does believe that a single positive genotoxicologic finding is of value in assessing the possible risk(s) posed by exposure to the tested chemical substance or mixture. In addition, the Agency believes that a positive genotoxicologic finding, in combination with other information (e.g., knowledge of real or potential exposure to and/or high production of the subject chemical or mixture)

would suggest the need, in many cases, to conduct further studies designed to better determine the toxicity of or the exposure to that chemical substance or mixture. The results of such further testing should be considered also for submission to EPA under Section 8(e) of TSCA.

a) The Chemical Screening Branch will ask Lever Brothers to ensure that the Agency receives a complete copy of the final report (including the actual experimental protocol, data, results of any statistical analyses, etc.) from the modified Ames test cited in the company's TSCA Section 8(e) submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, the Chemical Screening Branch will ask the Sandoz Chemicals Corporation to describe the actions the company has taken or plans to take 1) to notify its workers and others about the reported genotoxicologic findings for C.I. Direct Yellow 28, and 2) to reduce or eliminate exposure to this material. In addition, Sandoz Chemicals will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to C.I. Direct Yellow 28. It should be noted that similar questions were asked of the Lever Brothers Company and the Tricon Colors Corporation in response to Lever Brothers' earlier TSCA Section 8(e) submission on Yellow Shade 18569 (8EHQ-1286-0645).

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of C.I. Direct Yellow 28.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: JUN 12 1987

SUBJECT: Status Report* 8EHQ-0587-0678 Approved: 6/12/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

In this TSCA Section 8(e) submission, the Eastman Kodak Company reported that the tested chemical (pentachlorocyclopropane) had been the subject of a "Low Volume Exemption" (LVE 86-218) under Section 5, the "Premanufacture Notification" (PMN) provision of TSCA. Immediately upon receipt of this Section 8(e) submission, the Chemical Screening Branch transmitted copies of that notice to the Chemical Control Division (CCD) which is responsible for administering the Office of Toxic Substances (OTS) "New Chemicals Program" (NCP) under Section 5 of TSCA.

Submission Description

The Eastman Kodak Company provided the following information with regard to the conduct and preliminary results of acute oral and dermal toxicity studies of pentachlorocyclopropane (CAS No. 6262-51-7) in rats:

> "Groups of 5 male and 5 female rats were given 39, 78 or 156 mg/kg body weight of the test compound in a single gavage dose as part of an acute oral LD50 study. All animals died at 156 mg/kg. At 78 mg/kg, six of ten animals died within five days of dosing. All animals at this dose showed significant functional abnormalities on Day 1. These abnormalities included depression, spontaneous convulsions characterized by slight to severe clonic tremors of the entire body, tail dragging, and walking with significant hypotonic gait of the fore- and hind-limbs. Impairment of visual orientation and of visual placing was noted in all animals. Abnormalities noted in animals surviving to study termination included tremor, casual to vigorous scratching movements, varied

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

response to tail pinch, depressed reflexes, and poor muscle tone. Treatment-related pathological abnormalities in [the] animals dying prior to study termination included hemorrhage, necrosis, and congestion of the glandular stomach, and thymic hemorrhage. [The] seminal vesicles in all 4 males dying on Day 2 were moderately reduced in size. No treatment-related gross pathology abnormalities were noted in animals surviving the 14 day observation period. At 39 mg/kg, all animals survived. No abnormal clinical signs were observed at this dose level.

"An acute dermal toxicity study was conducted on groups of male and female rats exposed at doses of 0.5, 2 or 20 mL/kg. At 20 mL/kg, all animals died. Abnormalities noted at necropsy included thymic hemorrhage, and significant congestion and necrosis of the glandular stomach. At 2 mL/kg, significant clinical signs were observed. Four of five females died within 2 days or were euthanized. Functional abnormalities noted on Day 1 included abnormal home cage activity, piloerection, flushed mucous membranes, spontaneous clonic convulsions, moderately severe tremors at rest, hypotonic gait of fore- and hind-limbs, absence of extensor postural thrust reflex, and tense or flaccid muscle tone. By Day 14, significant abnormalities noted in survivors included abnormal or hypotonic gait, sluggish righting reflex, aggressive behavior, and absence of the extensor postural thrust reflex. Abnormalities noted at necropsy included thymic hemorrhage, and congestion and hemorrhage of the glandular stomach. At 0.5 mL/kg, all animals survived. Abnormalities were restricted to edema, necrosis and eschar formation at the site of [the test material] application. Other than dermal irritation, no abnormal clinical signs were noted. Abnormalities at necropsy were restricted to eschars. [Note: The Section 8(e) submission did not indicate how many animals were tested in this study.]"

Eastman Kodak's TSCA Section 8(e) submission also presented the following information with regard to the conduct and preliminary results of a skin irritation study of pentachlorocyclopropane in guinea pigs:

"In the dermal irritation study, [which was] conducted on depilated skin of guinea pig abdomens, the test material was rated a strong irritant. It caused edema, erythema, necrosis, and eschar formation. Two of five animals died prior to scheduled study termination. The three surviving animals developed eschars at the application site. Two of the animals which survived lost weight during the first week of the study, and one did not regain its initial weight over the 14-day course of the study. The weight loss may have been due to [the]

irritant properties of the material, or to systemic effects subsequent to absorption of the test material through the skin. No necropsies were conducted on the animals used in the dermal irritation study. [Note: The Section 8(e) submission did not present any information regarding the number of animals tested, the amount of test material applied or the duration of exposure.]"

Submission Evaluation

In order for EPA to evaluate the overall significance of the reported neurotoxicologic findings, Eastman Kodak should be asked to submit to EPA full copies of the final reports from the acute oral (rat) and dermal (rat and guinea pig) toxicity studies of pentachlorocyclopropane cited in the company's TSCA Section 8(e) submission.

Current Production and Use

According to a submitted pentachlorocyclopropane Material Safety Data Sheet (MSDS), this chemical is a non-combustible, colorless liquid having a vapor pressure of 9 mmHg at 54°C (129°F) and a boiling point of 54°C (129°F) at 9 mmHg. In the Section 8(e) notice, Eastman Kodak stated that the subject chemical "is used as a low volume (less than 250 kg/yr) intermediate." Eastman Kodak also provided the following information with regard to the potential for worker exposure to pentachlorocyclopropane:

"Potential employee exposure is being minimized during manufacture and use of the intermediate by the use of gloves, safety glasses, full face protection, safety shoes, rubber aprons, general and local exhaust, and [National Institute for Occupational Safety and Health (NIOSH)] approved organic vapor respirators."

Comments/Recommendations

In its Section 8(e) submission, Eastman Kodak stated that the pentachlorocyclopropane MSDS (which already carried a warning about the strong irritating properties of the chemical) had been updated to reflect the reported neurotoxicologic effects information. Eastman Kodak stated also that the company is evaluating the need for further testing of pentachlorocyclopropane.

a) The Chemical Screening Branch will request Eastman Kodak to submit full copies of the final reports (including the actual experimental protocols, results of gross and histopathologic examinations, results of any statistical analyses performed, etc.) from the acute oral (rat) and acute dermal (rat and guinea pig) toxicity studies cited in the company's TSCA Section 8(e) submission.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, Eastman Kodak will be asked to describe the nature and results, if available, of all studies (other than those submitted already to EPA or those published in the open scientific literature) about which Eastman Kodak is aware or that Eastman Kodak has conducted, is conducting or plans to conduct to determine the toxicologic properties of or the exposure to pentachlorocyclopropane.

b) The Chemical Screening Branch will immediately transmit full copies of all reported information to the Chemical Control Division (CCD/OTS) for review and appropriate followup attention.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS, and CCD/OTS; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUL 13 1987

SUBJECT: Status Report* 8EHQ-0687-0679

Approved: 7/13/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The CIBA-GEIGY Corporation provided full copies of final reports from six (6) in vitro genotoxicologic studies of the reaction product of D-glucitol and epichlorohydrin (CAS No. 68412-01-1). According to CIBA-GEIGY, the studies that gave positive results were an Ames Salmonella typhimurium (bacteria) assay, a point mutation assay in cultured V79 Chinese hamster cells and a chromosomal aberration assay in cultured human lymphocytes; studies reportedly showing negative results were a DNA repair assay in cultured human fibroblasts, a DNA repair assay in cultured rat hepatocytes and a cell transformation assay in cultured BALB/3T3 mouse cells. In its Section 8(e) submission, CIBA-GEIGY stated that the provided studies were conducted by CIBA-GEIGY's parent company (CIBA-GEIGY Limited) in Basel, Switzerland.

Submission Evaluation

In the Ames assay, the subject chemical was tested (up to 5000 ug/plate) in Salmonella typhimurium strains TA98, TA100, TA102, TA1535 and TA1537 in the presence and absence of exogenous metabolic activation. Positive results were obtained in the base substitution strains, TA100 and TA1535, both with and without activation. The magnitude of the observed responses were up to 3X and 13X background for TA100 and TA1535, respectively, without activation, and up to 5X and 37X background for TA100 and TA1535, respectively, with activation.

The cultured V79 Chinese hamster cell mutation test was performed with two selection agents, 6-thioguanine (6-TG) and 8-azaguanine (8-AG). Without exogenous metabolic activation, an increase in mutant frequency, up to 10X background (6-TG) and 30X background (8-AG), was induced over the concentration range of 16-32 ug/ml. With activation, an increase in mutant frequency, up to 3X background (6-TG and 8-AG), was induced up to concentrations of 108 and 180 ug/ml, respectively.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

The tested material induced significant increases in aberration frequency in cultured human lymphocytes. Over 50% of scored metaphases were found to have specific aberrations under non-activation conditions (test article concentrations of up to 54 nl/ml). Similar results were found in the presence of activation (over 40% of scored metaphases had aberrations at test article concentrations of up to 185 nl/ml).

No evidence of genotoxicity was found in the two Unscheduled DNA Synthesis (UDS) assays conducted at test article concentrations up to toxicity limits. No increases in nuclear grain counts over cytoplasmic background were observed.

No apparent increases were seen in the cell transformation assay using cultured BALB/3T3 fibroblasts. The assay without metabolic activation appears to be negative at test article concentrations of up to 20 ug/ml. In the presence of metabolic activation, however, the test cultures had the same relative viability as that in the solvent control cultures indicating no apparent induced toxicity by the test article. Therefore, the metabolic activation portion of this assay is considered to be inadequate to allow a conclusion to be drawn as to the transforming capability of the tested material in the presence of exogenous metabolic activation.

Overall, the test article is capable of inducing gene mutations most probably via a direct-acting mechanism. In addition, the test article is clastogenic as evidenced by the observed increase in aberrations in cultured human lymphocytes.

Current Production and Use

A review of the production range (includes importation volumes) statistics for CAS No. 68412-01-1, which is listed in the initial TSCA Chemical Substance Inventory, shows that no 1977 manufacture or importation of the subject chemical was reported or that all of the manufacture and/or importation data reported were claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory and cannot be disclosed (Section 14(a) of TSCA; U.S.C. 2613(a)). All of the data submitted for the initial TSCA Inventory (including the production range data) are subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

According to CIBA-GEIGY, the tested chemical substance, which is toll manufactured for CIBA-GEIGY at a purity of approximately 99%, "is a developmental resin intended primarily for use in automotive coatings." In addition, CIBA-GEIGY reported that although the material has not as yet been sold commercially by CIBA-GEIGY, "samples have been distributed to several potential customers in quantities of one to five gallons for technical performance evaluations." CIBA-GEIGY stated also that the current Material Safety Data Sheet (MSDS) carries the following warning:

Warning!
May cause irritation, dermatitis and sensitization.
Avoid contact with eyes, skin or clothing.
Avoid breathing vapor, mist or spray.

CIBA-GEIGY reported that "when used by customers in accordance with the recommended handling precautions in the MSDS, exposure should be minimal or nil." CIBA-GEIGY stated further that "once the product is used in its intended application, it becomes a highly crosslinked, high molecular weight, insoluble and inert material." Finally, CIBA-GEIGY stated that "there is no consumer exposure to the product."

Commments/Recommendations

In its TSCA Section 8(e) submission, CIBA-GEIGY stated that the company is 1) revising the Material Safety Data Sheet (MSDS) to reflect both the negative and positive genotoxicologic results, and 2) informing by letter all customers who had received samples of the subject product about the reported negative and positive genotoxicologic findings.

Although a positive *in vitro* genotoxicity test finding, when considered alone, may not be sufficient to offer reasonable support for a conclusion of substantial risk (as that term is defined in the Agency's March 16, 1978 TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110), EPA does believe that such a finding is of value in assessing the possible risk(s) posed by exposure to the tested chemical(s). Also, EPA believes that a positive genotoxicity finding, in combination with other information (e.g., the knowledge of actual/potential exposure to and/or high production of the subject chemical(s)), would suggest the need, in many cases, to conduct other studies designed to determine better the toxicity of or the exposure to the subject chemical(s). The results of such additional testing should be considered also for possible submission to the Agency pursuant to Section 8(e) of TSCA.

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure information, the Chemical Screening Branch will ask CIBA-GEIGY to describe the nature and results of all studies (other than those submitted already to EPA or those cited in the published scientific literature) about which CIBA-GEIGY is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to the subject chemical substance.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, ORD/EPA, OW/EPA, OAR/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: JUL 14 1987

SUBJECT: Status Report* 8EHQ-0687-0680 Approved: 7/14/87

FROM: David R. Williams for
James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Eastman Kodak Company submitted a copy of the final report from a repeated oral gavage study of a mixture of di-, tri- and tetraiodonaphthalenes in male and female rats. In the cover letter to its Section 8(e) submission, Eastman Kodak provided the following information with regard to the background, conduct, results and interpretation of the performed study:

> "Groups of 5 male and 5 female rats were given 200, 100, or 20 mg/kg of the test material in corn oil for 9 doses over 11 days or 10, 2 or 0.2 mg/kg of the test material in corn oil for 22 doses over 30 days. Repeated doses of the test material were lethal at doses of 10-200 mg/kg/day and resulted in [a] dose-dependent hepatotoxicity. Hepatic effects included elevation of serum enzymes and total bilirubin levels, increased liver weights, discoloration of the liver, and degenerative and regenerative changes in the hepatocytes. Circulating white blood cells and those in the spleen, thymus, and bone marrow were also affected. The stomach mucosa may have been damaged by direct contact with the test material. Toxicity to other organ systems, including red blood cells, adrenal glands, kidneys, and male reproductive organs, appeared to be secondary to [the] hepatotoxicity. The no-observed-effect-level (NOEL) for both male and female rats was 0.2 mg/kg. . . . .
>
> "In a similar four-week oral toxicity study [conducted with] a sample of 2,6-diiodonaphthalene that contained approximately 1% triiodonaphthalenes and no detectable tetraiodonaphthalenes, hepatic toxicity was found at dietary levels of 0.3% and 1.0% (equivalent to daily

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

doses of 209 and 636 mg/kg/day for males and 213 and 630 mg/kg/day for females); however, toxic effects on the liver at dietary levels of 0.1% (equivalent to daily doses of 73 mg/kg/day for both sexes) were so slight that this concentration appears to be close to a NOEL. Thus the sample of mixed di-, tri-, and tetraiodonaphthalenes [tested in the previously described oral gavage study] was approximately 365 times more toxic than the sample of 2,6-diiodonaphthalene. From these findings, [the Eastman Kodak Company believes] that the components of the mixed iodonaphthalenes that are producing the severe degree of hepatic toxicity are the tri- and tetraiodonaphthalenes. This conclusion is consistent with data in the scientific literature for chlorinated naphthalenes that their toxicity increases with increasing halogenation."

According to a submitted Material Safety Data Sheet (MSDS), the mixed iodonaphthalenes have an average oral (male and female rat) LD50 of approximately 1650 mg/kg and a dermal (guinea pig) LD50 of greater than 2000 mg/kg. In addition, the MSDS reports that the mixture is slightly irritating to guinea pig skin and rabbit eyes, but is not a sensitizing agent in guinea pigs. The MSDS reports also that evidence of hepatotoxicity had been observed at 156 mg/kg, the lowest dose tested in the oral (rat) LD50 study.

Submission Evaluation

An initial review of the provided study shows that repeated oral doses of the test material at levels of 10-200 mg/kg/day for up to 30 days were lethal to male and female rats. The NOEL for the study was 0.2 mg/kg/day. Adverse liver effects such as increased liver weight, liver discoloration, degenerative and regenerative changes in hepatocytes, elevated serum enzymes and elevated total bilirubin levels were evident in the exposed animals. (It should be noted that naphthalenes are known to cause liver injury (e.g., necrosis and poisoning) following ingestion, inhalation or dermal absorption.) In addition to the observed adverse liver effects, circulating white blood cells and those in the spleen, thymus, and bone marrow were affected. As stated by Eastman Kodak, the observed hemorrhage of the stomach was most likely due to direct contact with the test material.

In view of the fact that iodine is of great importance to the proper functioning of the thyroid gland and even though no adverse thyroid effects were found grossly or histologically in the exposed animals, the same finding may not be evident following chronic exposure to the test material. In occupational settings, intermittent monitoring for thyroid function/dysfunction could prove to be very beneficial in answering any questions regarding the possible adverse effects of iodonaphthalenes on the thyroid gland.

Current Production and Use

According to the submitted MSDS, the iodonaphthalenes mixture is a virtually odorless and water-insoluble tan solid that has a negligible vapor pressure, a specific gravity of 2.5 (water = 1), a melting point of 78°C (172°F), and a boiling point of 452°C (846°F). In its Section 8(e) submission, Eastman Kodak provided the following information regarding 1) the company's activities involving iodonaphthalenes, and 2) the potential for exposure to these chemicals:

> "[The] Eastman Kodak Company is conducting research involving iodonaphthalenes as site-limited chemical intermediates. While the process under investigation involves synthesis of 2,6-diiodonaphthalene, there was a concern for the toxicity of other iodonaphthalenes since small quantities might exist in process streams in a commercial plant. Therefore, a sample was prepared of iodonaphthalenes having the highest iodine content possible under the preparation conditions for use in the [repeated oral gavage study in rats]. There has been no industrial exposure to the material that is the subject of . . . [Eastman Kodak's TSCA Section 8(e)] letter.
>
> "The analytical methods used to characterize the test sample reported the results by area percent. This method may underestimate the actual amount of the more highly iodinated components. Therefore, additional analytical characterization of this sample will be conducted. The results will be incorporated into the final report as an addendum that will be sent to the Agency.
>
> "Approximately 50 employees work in research and development involving potential exposure to process streams containing low concentrations of tri- and tetra-iodonaphthalenes. Such potential exposure is intermittent and transient and averages $\leq$ 2 hours/day for the total employee group ($\leq$ 2.5 minutes/person/day). When working in these operations, employees wear company laundered coveralls, impermeable suits, gloves, boots, and a hooded, air-supplied respirator."

Comments/Recommendations

It should be noted that Eastman Kodak had updated the provided iodonaphthalenes MSDS to reflect the observed hepatotoxicity.

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure information, the Chemical Screening Branch will request Eastman Kodak to describe the nature and results of all studies (other than those reported already to EPA or those cited in the open scientific

literature) about which Eastman Kodak is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to iodonaphthalenes.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of iodonaphthalenes.

c) The Chemical Screening Branch will send copies of this status report to OSHA, NIOSH, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: JUN 23 1987

SUBJECT: Status Report* 8EHQ-0786-0681 and 8EHQ-0187-0681 FLWP

Approved: JUN 23 1987

FROM: Frank D. Kover, Chief
Chemical Screening Branch/ECAD/OTS

TO: Joseph J. Merenda, Director
Existing Chemical Assessment Division/OTS

Submission Description

On a "For Your Information" (FYI) basis (FYI-OTS-0786-0500), the Monsanto Company submitted a copy of the ABSTRACT section and several tables from the final report of a two-year oncogenicity/chronic toxicity study of Santogard® PVI in rats. (The company reported by phone on July 15, 1986 that the tested product is N-(cyclohexylthio)phthalimide; Chemical Abstract Service (CAS) Registry Number: 17796-82-6.) The following information with regard to the conduct and results of the performed study was presented in the submitted ABSTRACT:

> "A two-year chronic toxicity and carcinogenicity study in the rat was conducted to determine potential adverse toxicologic effects of . . .Santogard® PVI when added to the diet of rats at dietary levels [in parts per million (ppm)] to provide daily intakes of 0, 50, 150, or 500 mg/kg bd.wt./day. [Monsanto reported by phone that this study involved Sprague-Dawley rats.] Each experimental group consisted of 75 males and 75 females. Body weight was determined on each animal prior to initiation of the study at Day "0", weekly during the first 14 weeks, bi-weekly from weeks 16 to 30, and every four weeks thereafter. Feed consumption was measured on 15 animals per sex per group prior to initiation of the study during weekly intervals when body weights were determined. Animals were observed daily for clinical signs of toxicity and appearance of tumors. Blood biochemical and hematological parameters and urinalyses were conducted on animals sacrificed at 6, 12 and 18 months and at the termination of the study. All animals were necropsied and examined for gross pathological lesions; organs/tissues were preserved in 10% neutral buffered formalin for microscopic examination. [The] organs from animals at scheduled sacrifices were weighed after fixation for

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

calculation of [the] mean organ weight and organ-to-body weight ratios.

"The test chemical (Santogard® PVI) at levels used in this study did not produce adverse effects on endpoints including clinical signs, survival, feed consumption, blood biochemistry or urinalysis. However, body weights and weight gains were significantly reduced in males and females at the high-dose level, 500 mg/kg/day, and thus were considered to be compound-related; decreased body weights of the mid-dose (150 mg/kg/day) males probably reflected an effect of the chemical. Feed consumption was similar in all groups. Non-tumor clinical signs observed in all dose groups consisted primarily of alopecia and skin lesions which were incidental to chemical treatment. Most [of the] tumors observed in animals in the various test groups were considered to be of mammary gland origin.

"Decreased erythrocyte indices in high-dose males and females represented an apparent borderline response to the chemical. Mean absolute and relative organ weights, primarily of the liver, were significantly increased in the high-dose males; in females, the relative hepatic weight was also increased at the high-dose level. Histological lesions attributed to the chemical consisted of benign hepatic adenomas in high-dose females (the response was considered borderline in mid-dose females), hepatic fatty infiltration and bile duct hyperplasia in mid- and high-dose females and hepatic fatty infiltration in high-dose males.

"Responses obtained in this study indicate that the mid- and high-dose levels (150 and 500 mg/kg of body weight/day, respectively) represent apparent adverse effect levels whereas the low-dose level (50 mg/kg of body weight/day) represents an apparent no effect level."

According to a submitted table that summarized several types of observed benign/malignant tumors, there were 0, 0, 4, and 11 hepatocellular adenomas found in the control, low-, mid- and high-dose female rats, respectively; 1 hepatocellular carcinoma and 1 histiocytic lymphoma were found in mid-dose females but not in females in any other dose group or in the concurrent control group. In the male rats, there were 2 hepatocellular adenomas observed (1 each at the low- and mid-dose levels); no hepatocellular adenomas were found in the high-dose males or in males in the concurrent control group. Further, no hepatocellular carcinomas or histiocytic lymphomas were found in male rats in any group in the study.

In its initial FYI notice, Monsanto also provided the following background information with regard to the company's conclusions on the significance of the findings:

> "It was concluded at the time of receipt of the final report [(March 6, 1984)] that the finding of benign liver tumors in one sex [(females)] at dose levels that were associated with liver toxicity and body weight depression did not represent a significant health risk. This conclusion was supported by the negative genotoxic activity of the compound based on four in vitro and one in vivo mutagenicity assays and the low levels of exposure monitored in the workplace." [Note: In the initial FYI notice, Monsanto did not identify the mutagenicity assays that the company had conducted.]
>
> "During a recent[ly conducted] review of proposed experimental approaches to evaluate these liver effects, a pathology consultant noted that a trend in scientific thought with regard to rodent tumors was that many benign tumor diagnoses represent a stage of progression to malignancy. As a result, the test results have been reviewed in light of a trend in scientific thinking."

Monsanto noted that during this review, the company considered 1) the January 17, 1986 National Toxicology Program (NTP) proposal "to continue using benign neoplasia as a useful biologic indication for selecting levels of evidence" (51 FR 2579-2582); and 2) the April 7, 1986 NTP statement that when "selecting a conclusion for a particular experiment, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence" (51 FR 11843-11844).

Monsanto reported in its initial FYI notice that the following key factors were among those that had been considered by the company in evaluating the results of the company's chronic feeding study of Santogard® PVI in male and female rats:

> "A lack of progression from benign to malignant lesions. Since the one exception [(i.e., hepatocellular carcinoma observed in one female rat)] occurred at the mid-dose level, there is an increased likelihood that this was a chance event unrelated to dosing."
>
> "[A] lack of supporting information, such as proliferative lesions from the same site in [the] other sex or proliferative effects in other organs or tissues of either sex."
>
> "Negative genetic toxicology findings."

In conclusion, Monsanto stated that in the company's "judgement, the findings in this [dietary] study do not indicate a significant health risk." In addition, Monsanto stated also that the "Proceedings of the International Symposium of the Society of Toxicologic Pathologists entitled Rodent Liver Nodules: Significance to Human Cancer Risk (Toxicologic Pathology; Vol.10, 1982), reflects the scientific debate about the significance of benign

tumors in rodent models." Finally, Monsanto stated that "the debate continues to the present time as noted by NTP (51 FR 1579-2582, January 17 1986) . . . [that] the issue of benign neoplasia in relation to the carcinogenic potential of a compound remains an area of active discussion among scientists."

In its initial review of the provided information, EPA noted that the submitted information from Monsanto's 24-month feeding study showed that 1) Santogard® PVI caused a dose-related incidence of hepatocellular adenomas in female rats, and 2) the incidence was statistically significant at the highest dose. In addition, EPA noted that the observed liver toxicity, body weight depression, lack of progression of the liver tumors from a benign to malignant state, and the reportedly negative genotoxicity results did not negate the observed oncogenic activity of Santogard® PVI. EPA noted also that the concurrent controls were found not to have any liver tumors. Finally, EPA noted that the historical control incidence of liver tumors in female Sprague-Dawley rats is considered generally to be less than 1%.

Based on EPA's review of the information contained in the initial FYI notice, EPA informed Monsanto by letter on December 10, 1986, that the Agency believed that the oncogenicity findings from the company's chronic dietary feeding study of Santogard® PVI in rats provided reasonable support for a conclusion that this chemical substance can cause cancer and should have been reported formally under Section 8(e), the "substantial risk" information reporting provision of the Toxic Substances Control Act (TSCA).

In its December 10, 1986 letter, EPA requested Monsanto to submit a full copy of the final report from the company's 2-year feeding study of Santogard® PVI as well as descriptions of the results of any other studies (especially teratologic studies that Monsanto had conducted to determine the toxicity of this chemical). In addition, Monsanto was requested to provide further information regarding Monsanto's decision not to submit the chronic feeding study findings to the Agency under Section 8(e) of TSCA.

In response to EPA's letter, Monsanto provided (FYI-OTS-0187-0500 Followup Response) all of the information requested by EPA. In addition to a full copy of the final report from the Santogard® PVI chronic feeding study, Monsanto provided full copies of the final reports from in vitro bacteria, yeast, mouse and hamster cell mutagenicity assays; in vitro/in vivo Unscheduled DNA Synthesis (UDS) and DNA Replication assays using rat hepatocytes; and an in vivo rat bone marrow clastogenicity study. According to Monsanto, Santogard® PVI did not show "any evidence of mutagenic or DNA interactive effects [in these particular tests]."

In its followup response, Monsanto also provided full copies of the final reports from two teratology studies of Santogard® PVI in rabbits. The following excerpts are from the Conclusions sections of Monsanto documents that accompanied these reports:

> "[In a pilot teratology study of Santogard® PVI at oral gavage doses of 3, 10, 30, 100 or 300 mg/kg/day on days 7 through 19 of gestation,] significant maternal toxicity occurred following administration of. . .[300 mg/kg/day]. . . . Slight decreases in maternal body weight were reported during treatment for animals dosed at . . . [100 mg/kg/day]. No significant adverse maternal or fetal effects were observed at the other doses used in this pilot study. On the basis of the results of this pilot study, dose levels of . . . [10, 30 and 100 mg/kg/day] were selected for the teratogenicity study in rabbits. . . ."
>
> "[In the full teratogenicity study,] Santogard® PVI, administered [orally by gavage at doses of 10, 30 or 100 mg/kg/day] to pregnant rabbits on days 7 through 19 of gestational development, did not produce a teratogenic response. No difference in the number of resorptions, live or dead fetuses, or fetal weights were present at 10 or 30 mg/kg, and these doses did not produce an increase in either soft tissue or skeletal malformations in offspring from treated animals. Slight decreases in fetal body weight and slight increases in skeletal ossification variations, accompanied by decreases in [the] maternal body weight gain during the treatment period, were present at [the] 100 mg/kg dose level and demonstrated a marginally toxic response at this dosage. Thus, the no-effect level in this study was considered to be the mid-dose level of 30 mg/kg/day."

Further with regard to the potential for reproductive system toxicity, Monsanto submitted the following summarized information concerning a two-generation reproduction study of Santogard® PVI in rats:

> ". . .[Santogard® PVI] was evaluated in a two-generation reproduction study with rats given 0, 50, 150 or 500 ppm of the test material in the diet from gestation onward of the first generation and through the entire duration of the second generation. No treatment-related effects were observed in the F_0 generation. Mean body weights were lower in the first generation (F_1) high-dose animals. High-dose females also exhibited a lower body weight gain during gestation. A lower mean number of live pups and an increase in the mean number of dead pups at birth were observed for the F_{2a} litters at the high dose. Pup body weights, sex ratio, and necropsy findings were not different between the control and treated groups. No consistent reproductive effects were noted in this study."

In addition to providing the previously described information, Monsanto also reported that Santogard® PVI has been shown to be 1) slightly toxic when administered orally to rats (LD50 of 2.6

g/kg), 2) practically non-toxic when applied dermally to rabbits (LD50 of >5 g/kg), and 3) slightly irritating to eyes and non-irritating to skin (species tested were not specified). Monsanto stated further that "no adverse effects were observed in a four-week . . . inhalation study with rats exposed to Santogard® PVI [dust] at 52, 157, or 536 mg/m^3 for 6 hours per day, 5 days per week." Monsanto also provided the following summary information regarding the results of a subchronic study in which male/female rats were exposed via inhalation to Santogard® PVI dust at dose levels of 15, 50 or 150 mg/m^3 for 6 hours per day for 90 days:

> "High-dose animals and mid-dose females had decreased body weights. Elevations in kidney weight were found in the high-dose males. Male rats showed dose-related increases in [the] incidence of kidney lesions which were characterized by eosinophilic droplets in the proximal tubule, degeneration and regeneration of [the] tubular epithelium, and granular casts occluding and causing dilation of [the] renal tubules. Scattered granulomas of the lung were noted in the controls and treated animals; these were more frequent in high-dose males. No no-effect level was established for male rats in this study. The no-effect level for females was considered to be 15 mg/m^3."

With regard to sub-acute oral toxicity, Monsanto reported that no treatment related adverse effects had been observed (except for reduced body weights at the two highest dose levels) in a study in which Santogard® PVI was administered in the diet (species not specified) at doses of 0, 50, 150, 300, 600 or 1500 ppm for four weeks.

Monsanto also submitted summarized information concerning the findings of human skin patch tests conducted with Santogard® PVI alone and compounded with rubber stock. According to Monsanto, a repeated insult human patch test involving 55 volunteers showed that Santogard® PVI alone is "a primary and cumulative irritant and a sensitizing agent." Monsanto stated also that rubber stock compounded with up to 2 pounds Santogard® PVI per 100 pounds of rubber "produced only mild cumulative irritation in a repeated insult human patch test using 53 volunteers."

With regard to the toxicity of Santogard® PVI to aquatic species, the following information was contained in a Material Safety Data Sheet (MSDS) submitted by Monsanto in its followup response:

"96-hr LC50 Bluegill:	1.2 mg/l,	Moderately Toxic
96-hr LC50 Trout:	0.4 mg/l,	Highly Toxic
96-hr LC50 Fathead Minnow:	.42 mg/l,	Highly Toxic
96-hr EC50 Algae, . . .:	22 mg/l,	Slightly Toxic
48-hr LC50 Daphnia:	32 mg/l,	Slightly Toxic"

In addition to restating most of its previous arguments as to why the Santogard® PVI cancer study findings were not considered by

the company to be reportable to EPA under Section 8(e) of TSCA, Monsanto pointed to the following documents as providing further strength to Monsanto's position: 1) a 1986 EPA Risk Assessment Forum publication ("Proliferative Hepatocellular Lesions of the Rat; Review and Future Use in Risk Assessment" EPA/625/3-86/011; February 1986), 2) a September 1986 proposed revision to the preamble to International Agency for Research on Cancer (IARC) Monographs and 3) a 1985 Office of Science and Technology Policy (OSTP) report ("Chemical Carcinogens; A Review of the Science and its Associated Principles" 50 FR 10372-10442; March 14, 1985).

Submission Evaluation

Based on a review of the full final report of Monsanto's 2-year feeding study of Santogard® PVI in rats, EPA believes that 1) the study was adequately designed and conducted, and 2) the doses used were based appropriately on an accurate maximum tolerated dose (MTD). Although body weights were significantly reduced in the high dose male and female groups, no significant weight loss was found in the mid or low dose groups of either sex. The dose levels used in this chronic study did not produce adverse effects on survival, clinical signs, feed consumption, blood chemistry or urinalysis in any test group. Histologically, hepatic fatty infiltration and bile duct hyperplasia were observed in the mid and high dose females while high dose males showed only hepatic fatty infiltration.

Hepatocellular adenomas were found to occur in a dose-related increased manner in the mid and high dose female rats with the incidence showing statistical significance at the high dose ($P<.001$). It should be noted that a combination of the adenomas and the single hepatocellular carcinoma found among the mid dose females also resulted in statistical significance ($P=.029$). No hepatocellular adenomas were observed in female rats in either the low dose or control groups. In male rats, one hepatocellular adenoma was found in both the low and mid dose groups; no liver tumors were found in males in either the high dose or concurrent control groups. Historically, the incidence of spontaneously occurring primary liver tumors in Sprague-Dawley male and female rats is quite low (i.e., typically less than 1%). It is also important to note that serial sacrifices at predetermined intervals in Monsanto's chronic Santogard® PVI feeding study showed that the "time to tumor" was shorter for the high dose female rats than for the mid dose female rats. Hepatocellular adenomas were induced as early as day 338 in the high dose females, while the first tumor noted in the mid dose females occurred at day 526 of the study. This reduced "time to tumor" observation supports the significance of the hepatocellular adenomas as being treatment-related.

Based on a statistically significant incidence of hepatocellular adenomas induced in the high dose females and an overall positive trend of induced tumors among the dosed female groups (Cochran-Armitage Trend Test; $P<.001$), the oncogenic response observed in

female rats exposed chronically to Santogard® PVI via the feed in this adequately designed study is considered by the Agency to be a direct response to exposure to this chemical substance.

With regard to the submitted genotoxicity studies, the results of the Ames (bacteria) and yeast assays demonstrate clearly that Santogard® PVI was not mutagenic under the conditions of these tests. In addition, the in vitro rat primary hepatocyte assay findings demonstrate that Santogard® PVI did not induce unscheduled DNA synthesis. Further, the results of the in vivo rat bone marrow study demonstrated that Santogard® PVI did not induce chromosomal aberrations, either structural or numerical, in rats exposed via gavage. In the in vitro mouse lymphoma (L5178Y) cell mutagenicity assay, the results were clearly negative in the absence of exogenous metabolic activation; however, the doses used in the exogenous metabolic activation portion of the assay may have been insufficiently high rendering this component of the assay inconclusive. With regard to the results of the in vivo/in vitro rat hepatocyte DNA repair and replication assay, there is no indication that Santogard® PVI induced unscheduled DNA synthesis or S-phase replication; it must be pointed out, however, that this particular study may not have been conducted at a dose level high enough to detect activity therefore rendering the interpretation of the data to be inconclusively negative. Finally, and contrary to the submitter's statements that Santogard® PVI was not found to be mutagenic in cultured Chinese Hamster Ovary (CHO) cells, the provided data do suggest that Santogard® PVI is a mutagen in CHO cells when tested with or without exogenous metabolic activation (a doubling to quadrupling of mutation frequencies observed as compared to controls); insufficiently high dose levels cause the data from this assay to be inconclusive.

In summary, the submitted genotoxicity data demonstrate that Santogard® PVI did not cause chromosomal aberrations in rat bone marrow in vivo; did not induce gene mutations in prokaryotes, lower eukaryotes or in cultured mouse cells (without metabolic exogenous activation); and did not induce DNA effects in cultured rat primary liver cells. Due to a possible failure to test a sufficiently high dose, however, the evidence is inconclusive that Santogard® PVI is not mutagenic in cultured mammalian cells in the presence of exogenous metabolic activation or that the chemical does not induce unscheduled DNA synthesis or S-phase replication in vivo. Further, there is some suggestion that Santogard® PVI can induce gene mutations in cultured CHO cells; this particular study would need to be conducted at higher dose levels to verify or refute the suggestive mutagenic activity. In conclusion, the Agency believes that the weight-of-the-evidence that Santogard® PVI is not genotoxic is not as strong as that claimed by Monsanto.

With regard to the provided pilot teratology study report, 80% maternal death occurred at 300 mg/kg/day. Although a maternal weight loss was observed at 100 mg/kg/day, it should be noted that maternal weight loss should not be considered as a reliable

indicator of toxicity in the rabbit. In addition, a 30% decrease in fetal weight was observed at the 100 mg/kg/day dose level. In view of the fact that the study authors concluded that maternal and fetal effects occurred at 100 mg/kg/day and above (making 30 mg/kg/day the lowest-observed-effect-level (LOEL)), 100 mg/kg/day was chosen as the highest dose level for the full teratology study. In view of the fact that EPA considers the maternal toxicity observed at 100 mg/kg/day to be minimal, EPA believes that a dose somewhere between 150 and 225 mg/kg/day would have been more appropriate as the highest dose for the full teratology study.

In the full rabbit teratology study, no statistically significant effects were reportedly observed at any dose level tested. The observed slight decrease in fetal body weight at 100 mg/kg/day, when coupled with delayed ossification, suggests a dose-related effect and indicates that the threshold dose level may be in that vicinity. Also at the 100 mg/kg/day dose level, a very specific endpoint (enlarged fontanel) showed a 19-fold increase (17.5% as compared to 0.9% in controls). Further, there was an increased incidence of incompletely ossified frontal bones found in fetuses at the high dose. Therefore, 100 mg/kg/day appears to be a LOEL for developmental effects in the absence of maternal toxicity and the no-observed-effect-level (NOEL) appears to be 30 mg/kg/day.

Current Production and Use

A review of the production range (includes importation volumes) statistics for N-(cyclohexylthio)phthalimide (CAS No. 17796-82-6) which is listed in the initial TSCA Chemical Substance Inventory, has shown that no 1977 manufacture/importation was reported or that all of the production range information that was reported was claimed to be TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the TSCA Inventory and cannot be disclosed (Section 14(a) of TSCA, U.S.C. 2613(a)). All of the information reported for the TSCA Chemical Substance Inventory, including the production range information, is subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

Monsanto reported by phone on July 15, 1986, that Santogard® PVI is a pre-vulcanization inhibitor used in the production of both natural and synthetic rubber products.

According to the MSDS contained in Monsanto's followup response, Santogard® PVI is a water-insoluble solid (light tan to white crystals/pellets) with a slight mercaptan odor and a melting point of approximately 90-95°C.

In its followup response, Monsanto stated that employees working with Santogard® PVI "have reported a strong mercaptan-like odor on the skin which appears to be released by perspiration, washing or showering." In order to reduce this body odor as well as skin and eye irritation, Monsanto stated that the following workplace modifications and exposure controls were instituted:

"In 1981, a new drier and a new exit screw conveyor from the drier were installed. This reduced employee exposure by improving containment and limiting equipment clean-outs. These measures, along with the use of personal protective equipment, such as dust respirators for short periods, reduced the potential for irritation and odor. To further reduce exposure potential, a new local exhaust ventilation system was installed in 1982 at the [Santogard® PVI] bagging station. In 1985, the screw conveyor was replaced and the practice of adding oil to the product as a dust suppressant was begun. Housekeeping in the PVI Department has always been especially emphasized. The PVI production building at [Monsanto's] U.S. site is washed down approximately six times per year during routine shut-downs and maintenance overhauls. In 1982, Monsanto adopted an internal exposure guideline of 1 mg/m^3 or 0.09 ppm (8-hour time-weighted average [(TWA)]) with a skin contact precaution to minimize potential irritation and odor. During the period from 1982 to 1986, [the Santogard® PVI] dust exposure values were below the 1 mg/m^3 [internal guideline] as averaged over an 8-hour day; however, body odor and infrequent eye irritation continued to be reported. To minimize these effects even further, Monsanto installed a sauna for [the company's] PVI workers and lowered the internal exposure guideline to 0.5 mg/m^3 or 0.05 ppm (8-hour TWA) with a skin contact restriction. [Monsanto believes] that maintaining [Santogard® PVI] airborne exposures below 0.5 mg/m^3 (8-hour TWA), avoiding skin contact, using personal protective equipment when exposure potential exists and encouraging the use of the sauna will eliminate irritation and body odor."

Comments/Recommendations

In its followup submission, Monsanto reported that in addition to the previously described workplace modifications, the company had 1) updated the Santogard® PVI MSDS to reflect the findings from the 2-year feeding study, and 2) notified Monsanto workers and customers formally about the findings from that chronic study. Monsanto stated also that in an "effort to determine the biological significance of the [rat] liver lesions, . . . [Monsanto has] begun studies to evaluate initiation-promotion and peroxisome proliferation effects in rat liver models."

Although Monsanto's FYI notices give the reader the impression that there is a new trend of thought regarding the biological significance of benign tumors, it should be noted that it has been EPA's longstanding and highly publicized position that a treatment-related increase (especially a significant increase) in the incidence of benign tumors, even in one sex of one species, should be viewed as evidence that the tested chemical(s) can

cause cancer. In a May 19, 1976 press release announcing the adoption of EPA's interim cancer assessment guidelines, then EPA Administrator Russell Train stated that "in very few cases is it possible to prove that a [chemical] substance will cause cancer in man, because in most instances the evidence is limited to animal studies." Administrator Train stated further that "in this regard, a substance will be considered [by the Agency to be] a presumptive cancer risk when it causes a statistically significant excess incidence of benign or malignant tumors in humans or animals." According to the adopted interim cancer assessment guidelines document, "substantial evidence [of cancer] is provided by animal tests that demonstrate the induction of malignant tumors in one or more species including benign tumors that are recognized as early stages of malignancies" and "suggestive evidence [of cancer] includes the induction of only those nonlife shortening benign tumors which are generally accepted as not progressing to malignancy. . . ."

It should be noted that EPA's policy concerning the biological significance of benign tumors observed in animals has not changed to any great degree since 1976. For example, EPA's 1984 proposed (49 FR 46294) and 1986 final (51 FR 33992) cancer assessment guidelines both reflect EPA's historical position concerning the biologic significance of benign tumors. According to EPA's 1984 proposed cancer assessment guidelines, "limited evidence of carcinogenicity, . . . means that the data suggest a carcinogenic effect but are limited because: (a) the studies involve a single species, strain, or experiment; or (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) an increase in the incidence of benign tumors only." The term "limited evidence" is defined in essentially the same manner in the Agency's 1986 final cancer assessment guidelines.

It should be noted further that EPA's 1986 Risk Assessment Forum publication ("Proliferative Hepatocellular Lesions of the Rat; Review and Future Use in Risk Assessment" EPA/625/3-86/011) states that "a determination of carcinogenic hazard will be based upon consideration of the incidence of hepatocellular carcinoma alone, neoplastic nodule alone and a combination of carcinoma and nodule." This 1986 EPA document states also that in cases "where increases in lesions and statistical significance are restricted to neoplastic nodules alone, such data will be interpreted [by EPA] as only limited evidence of animal carcinogenicity."

It is clear that EPA's position with regard to benign tumors is not new and is one that has been made public. Further, EPA's position is consistent with that of other scientific/regulatory bodies. For example, the National Toxicology Program (NTP) announced on January 17, 1986 (51 FR 2579) that NTP would continue to hold its position that "some" evidence of carcinogenicity "is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign

or combined) . . . ." In addition, the September 1986 proposed revision to the IARC Monograph preamble states that limited evidence of carcinogenicity of a chemical in animal studies will be defined by IARC as "one or more studies that show an increased incidence of neoplasms in animals exposed to the agent in comparison with animals not exposed but . . . only benign neoplasms have been observed to be increased in incidence." Further, the existing preamble to the IARC Monographs published since 1978 states:

> "Many chemicals induce both benign and malignant tumors. Among chemicals that have been studied extensively, there are few instances in which the only neoplasms induced are benign. Benign tumors may represent a stage in the evolution of a malignant neoplasm or they may be end-points that do not readily undergo transition to malignancy. If a [chemical] substance is found to induce only benign tumors in experimental animals, it should nevertheless be suspected of being a carcinogen, and it requires further investigation."

Further to the above point, a 1981 review article by Chu et al. which appeared in the Journal of Toxicology and Environmental Health (Vol. 8: 250-280), reported that a previous (1975) review of the morphology/histogenesis of rat liver tumors showed that in general this type of tumor begins with hyperplasia which then progresses to a neoplastic nodule and on to hepatocellular carcinoma which eventually becomes a metastatic carcinoma.

Finally, it is important to note that "suggestive", "limited" or "some" evidence of carcinogenicity (as those terms are used by EPA or others) should not be interpreted to mean that such evidence can be dismissed or that the evidence is not reasonable in terms of its ability to support a conclusion that a chemical can cause cancer. Furthermore, EPA's March 16, 1978 Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110) as it relates to cancer has been and continues to be consistent with EPA's cancer assessment guidelines as well as those of other regulatory agencies and scientific organizations.

Following a review of FYI-OTS-0786-0500 and FYI-OTS-0187-0500 Followup Response, EPA has determined that the oncogenicity findings from Monsanto's 2-year feeding study of Santogard® PVI in rats should have been submitted to EPA under Section 8(e) of TSCA. The basis for EPA's determination is as follows:

> Section 8(e) states that "any person who manufactures, [imports,] processes, or distributes in commerce a chemical substance or mixture and who obtains information which reasonably supports the conclusion that such substance or mixture presents a substantial risk of

injury to health or the environment shall immediately inform the Administrator of such information unless such person has actual knowledge that the Administrator has been adequately informed of such information."

The preface in Part V of EPA's March 16, 1978 Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110) states that "a substantial risk of injury to health . . . is a risk of considerable concern because of (a) the seriousness of the effect . . . and (b) the fact or probability of its occurrence." With regard to the seriousness of the effect, Part V explains that EPA considers the types of health effects for which substantial risk information must be reported to include "any pattern of effects or evidence which reasonably supports the conclusion that the chemical substance or mixture can produce cancer, mutation, birth defects . . . ." The information concerning these effects can be obtained directly or inferred from designed studies (e.g., in vivo animal studies) as described in Part VI. Part VI explains also that a subject "person is not to delay reporting until he obtains conclusive information that a substantial risk exists, but is to immediately report any evidence which reasonably supports that conclusion." Part V explains further that "such evidence will generally not be conclusive as to the substantiality of the risk; it should, however, reliably ascribe the effect to the chemical." In addition, Part VI states that "not only should final results from such studies be reported, but also preliminary results from incomplete studies. . . ."

With regard to the "fact or probability of its [i.e., the serious effect's] occurrence" criterion, Part V of the Section 8(e) policy document states that certain types of health effects (e.g., cancer) are considered to be so serious that relatively little weight should be attached to chemical exposure in determining whether a risk is substantial. Part V explains further that "the mere fact that the implicated chemical is in commerce constitutes sufficient evidence of exposure." In addition, EPA's response to Comment 31 (see Appendix B of the Section 8(e) policy statement) explains that the occurrence of serious effects such as those alluded to in Part V(a) of the TSCA Section 8(e) policy statement (e.g., cancer, reproductive toxicity) presupposes exposure to the subject chemical or mixture and must be reported immediately to EPA under Section 8(e) of TSCA.

It is important to note that previously unknown evidence (preliminary or otherwise) of chemical-induced oncogenic activity observed in an animal study, regardless of how such evidence would be classified ultimately under the

various cancer risk assessment systems/guidelines cannot be dismissed and must be considered for immediate submission to EPA under Section 8(e) of TSCA. The Agency views the overall assessment of the ultimate risk of cancer in humans as requiring a broad analysis that extends well beyond the scope of assessing the significance of either the preliminary or final results of an animal study. Therefore, a company's decision to submit information to EPA under Section 8(e) of TSCA should not involve an exhaustive human risk assessment of an implicated chemical substance or mixture.

In light of the preceding discussion, EPA has determined that the findings from the Monsanto Company's 2-year dietary feeding study of Santogard® PVI in rats reasonably support the conclusion that this chemical substance can cause cancer and as such should have been submitted in a timely manner to EPA pursuant to Section 8(e) of TSCA.

a) The Existing Chemical Assessment Division (ECAD/OTS) will inform Monsanto about EPA's determination with regard to the TSCA Section 8(e)-reportability of the company's cancer findings for Santogard® PVI. Monsanto will be informed also that the Chemical Screening Branch has forwarded both Monsanto's initial and followup FYI submissions to the OTS Document Control Office for processing/public filing under Section 8(e) of TSCA.

   The Existing Chemical Assessment Division will request Monsanto to submit a full copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, results of any statistical analyses, etc.) from the two-generation rat reproduction study that was cited in Monsanto's followup response. In addition, Monsanto will be requested to submit a full copy of Volume I of the October 15, 1981 draft final report from the company's 2-year dietary feeding study of Santogard® PVI in rats.

b) The Chemical Screening Branch will review the reported findings in greater detail to determine the need for further OTS assessment of N-(cyclohexylthio)phthalimide.

c) The Chemical Screening Branch will send copies of this status report to OSHA, NIOSH, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and OCM/OPTS/EPA. In addition, copies of this status report will be transmitted to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUL 6 1987

SUBJECT: Status Report* 8EHQ-0687-0682 Approved: 7/6/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Monsanto Company reported that "maternal toxicity, embryotoxicity, fetotoxicity and skeletal abnormalities" were observed at the highest dose (300 mg/kg/day) of dodecylphenol (CAS No. 27193-86-8) administered via gavage to pregnant rats. According to Monsanto, "no maternal or developmental toxicity was observed at the lower doses (100 mg/kg/day and 20 mg/kg/day) tested."

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon the Agency's receipt of a complete copy of the final report (including the actual experimental protocol, results of gross and histopathological examinations, results of statistical analyses, etc.) from the oral teratology study cited in Monsanto's Section 8(e) submission.

Current Production and Use

A review of the production range (includes importation volumes) statistics for dodecylphenol (CAS No. 27193-86-8), which is listed in the initial TSCA Chemical Substance Inventory, shows that 10 million to 50 million pounds of this chemical substance were reported as manufactured and/or imported in 1977. This production range information does not include any data claimed to be TSCA Confidential Business Information (TSCA CBI) by the person(s) who reported for the initial TSCA Inventory, nor does it include any data that would compromise TSCA CBI. All of the data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

According to Monsanto, the company manufactures dodecylphenol and uses the chemical "in the production of non-ionic detergents." In addition, Monsanto reported that the company markets dodecylphenol "on a limited basis as an intermediate chemical." Also, Monsanto provided the following information with regard to the potential for exposure and possible risks posed by exposure to dodecylphenol in the workplace:

> "[The Monsanto Company does not beleve that] exposure to the chemical is significant. First, exposure levels in [Monsanto's] facilities are well below 0.1 mg/m^3 of air. In calculating [the] exposure at a level of 0.1 mg/m^3, assuming absorption and retention of all inhaled material over an eight-hour workday, there would be a safety factor of over 5,000 with respect to the no-effect dose of 100 mg/kg/day. Second, [Monsanto believes that] exposure to customers is self-limiting because the material is non-volatile. Further, its irritant effects would be evident before dosages equal to the no-effect levels in the rats were attained."

Comments/Recommendations

In its TSCA Section 8(e) submission, Monsanto reported that the company's dodecylphenol Material Safety Data Sheet (MSDS) would be updated to reflect the submitted toxicologic findings.

a) The Chemical Screening Branch will request Monsanto to ensure that EPA receives a full copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, results of any statistical analyses, etc.) from the teratologic study cited in the company's TSCA Section 8(e) notice.

   In view of EPA's general interest in corporate actions that are taken on a voluntary basis in response to chemical toxicity or exposure information, Monsanto will be asked to describe the nature and results, if available, of all studies (other than those cited in the published scientific literature or those submitted already to EPA) about which Monsanto is aware or that Monsanto has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to dodecylphenol.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of dodecylphenol.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUL 7 1987

SUBJECT: Status Report* 8EHQ-0687-0683

Approved: 7/7/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Union Carbide Corporation provided the following information regarding the conduct and preliminary findings of a short-term repeated inhalation study of NIAX® Catalyst A-99 (i.e., bis(2-dimethylaminoethyl)ether or DMAEE; CAS No.3033-62-3) in rats:

> "The purpose of the study was to determine the potential for adverse effects by short-term repeated exposure (9 days) of rats to vapor generated from DMAEE at ambient temperature. The protocol design allowed for male and female Sprague-Dawley rats to be exposed for 6 hours a day for 9 days (over an 11-day period) to target DMAEE vapor concentrations of 20, 40 and 80 ppm. An additional air-alone exposure group served as a control. There were 10 male and 10 female rats per exposure group, with an additional 15 male rats in the highest concentration group [(80 ppm DMAEE)] for post-exposure recovery and ultrastructural studies. Monitors for toxicity included daily observations, body weight, food and water consumption, peripheral blood hematology, serum chemistry, urinalysis, necropsy, organ weight and light microscopic examination of tissues and organs removed at necropsy.
>
> "The results of the study to date are as follows:
>
> "[1] The mean analytically measured concentrations of DMAEE [vapor] were 0, 22, 47 and 90 ppm over the exposure periods.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"[2] Mortalities:

0 ppm - none

22 ppm - none

47 ppm - all 10 males and 10 females died between the sixth and eleventh days from the start of exposures.

90 ppm - all 25 males and 10 females died on the third or fourth exposure days.

"[3] Food and water consumption were significantly reduced at 47 ppm.

"[4] Body weight loss occurred in a concentration-related fashion.

"[5] Histological examination of lungs from males (the only tissues examined at the time of . . .[the company's TSCA Section 8(e) notice], showed cytoplasmic vacuolation of bronchial epithelial cells at all DMAEE [vapor] concentrations and a mild pneumonitis at 47 and 90 ppm."

Submission Evaluation

An EPA evaluation of the overall significance of the reported toxicologic findings should be possible upon EPA's receipt of a complete copy of the final report of Union Carbide's short-term repeated DMAEE vapor inhalation study in rats.

Current Production and Use

A review of the production range (includes importation volumes) statistics for CAS No. 3033-62-3, which is listed in the initial TSCA Chemical Substance Inventory, shows that no 1977 manufacture or importation was reported or that all manufacture/importation information reported was claimed to be TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory and cannot be disclosed (Section 14(a) of TSCA; U.S.C. 2613(a)). All of the information reported for the initial TSCA Inventory, including the production range information, is subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

In its TSCA Section 8(e) submission, Union Carbide provided the following information regarding the use of NIAX® Catalyst A-99:

"NIAX® Catalyst A-99 is used as a catalyst in the manufacture of urethane foam. The product is not used in its pure form, but is diluted with other ingredients. Typical use levels of A-99 in a urethane formulation range from 0.02 to 0.15 parts per 100 parts of toluene diisocyanate (TDI)."

Union Carbide stated further in its TSCA Section 8(e) submission that "when viewed against current work practices, recommended protective and precautionary measures, and industrial hygiene monitoring, . . . [Union Carbide does] not believe that the . . . [reported] preliminary findings represent an unreasonable risk."

Comments/Recommendations

a) The Chemical Screening Branch will ask Union Carbide to ensure that EPA receives a full copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, results of any statistical analyses, etc.) from the short-term repeated DMAEE inhalation study cited in the Section 8(e) notice.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity and/or exposure data, Union Carbide will be asked to describe the actions that Union Carbide has taken or is planning to take to notify workers and others about the reported preliminary toxicologic findings for DMAEE. Union Carbide will be asked also to describe the nature and results, if available, of all studies (other than those cited in the open scientific literature or those submitted already to EPA) about which Union Carbide is aware or that Union Carbide has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to DMAEE during manufacture or use.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of DMAEE.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: AUG 31 1987

SUBJECT: Status Report* 8EHQ-0787-0684 S Approved: 8/31/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

Under Section 8(e) of TSCA, the Dow Corning Corporation provided the following information:

> "Dow Corning Corporation received verbal information from a customer that squamous cell carcinomas were found in rats that were surgically implanted in the uterus with a [U.S. Food and Drug Administration (FDA)] regulated device. The specific composition of the material used in the [implanted] device is unknown to Dow Corning Corporation. However, based upon the information provided [by the customer, Dow Corning] believes that the material implanted is similar in composition to Dow Corning® S-5370 RTV. . ., [a mixture of siloxane polymers and organic substances and a metal salt].
>
> [Note: Dow Corning has claimed the exact composition of Dow Corning® S-5370 RTV to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will be requesting Dow Corning to substantiate this TSCA CBI claim.]
>
> "The customer has informed Dow Corning that although the data are preliminary, they have been reported to . . . [FDA under an approved Investigational Device Exemption (IDE)].
>
> "Based on the very preliminary nature of the information available, it is not possible to assess the significance or reliably establish a cause and effect relationship.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"Published information from the supplier of the metal salt identifies 2-ethylhexanoic acid as a reaction by-product. Published literature has identified this substance to be teratogenic in rats.

"Other published literature reports 2-ethylhexanoic acid as an in vivo conversion by-product of di(2-ethylhexyl)-phthalate (DEHP). DEHP is [listed as a carcinogen by the National Toxicology Program (NTP)]. It has been suggested in the literature that 2-ethylhexanoic acid may be associated with the cancer found in bioassays with DEHP, although there is no published data which substantiate this inference. [2-Ethylhexanoic acid] is presently subject to a TSCA Section 4 Test Rule, which includes a two-year bioassay in mice and rats.

"Studies previously conducted on the cured Dow Corning device material used as the basis for the implant bio-assay . . . [that provided the impetus for Dow Corning's TSCA Section 8(e) notice], detected an acid in extract solution. These data are suggestive of the presence of 2-ethylhexanoic acid."

Submission Evaluation

Immediately upon receipt of this TSCA Section 8(e) submission, the Chemical Screening Branch sent a copy of the submission to the Test Rules Development Branch (TRDB/ECAD/OTS) for inclusion in the ongoing review of 2-ethylhexanoic acid under Section 4 of TSCA.

Current Production and Use

In the Section 8(e) notice, Dow Corning® S-5370 RTV was reported to be "an industrial product used almost exclusively in defense/aerospace as a foam for potting [(encapsulation)] applications.

Comments/Recommendations

Dow Corning stated that the company is investigating the reported matter and would keep the Agency apprised of any new relevant information.

a) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical(s).

b) The Chemical Screening Branch will send copies of this status report to OSHA, NIOSH, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS and TRDB/ECAD/OTS; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: AUG 28 1987

SUBJECT: Status Report* 8EHQ-0787-0685 Approved: 8/31/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The CIBA-GEIGY Corporation provided full copies of final reports from five genotoxicity studies of pentaerythritol, tetraglycidyl ether (CAS No. 3126-63-4). According to CIBA-GEIGY, the chemical was positive in an Ames Salmonella typhimurium (bacteria) mutagenicity assay, a point mutation test in cultured V79 Chinese hamster cells and a test for chromosomal aberrations in cultured human lymphocytes; the studies reported by CIBA-GEIGY to be negative were Unscheduled DNA Synthesis (UDS) assays using cultured rat hepatocytes and cultured human fibroblasts.

Submission Evaluation

In the Ames assay, the subject compound induced concentration-dependent increases in bacterial strains TA100 and TA1535 to approximately 3X and 8X over background mutation frequencies, respectively, in the absence of exogenous metabolic activation. Greater increases were seen in the presence of activation (i.e., up to 6.5X and 40X over background in strains TA100 and TA1535, respectively). Again, the responses were concentration-dependent. Therefore, the compound appears to induce base-substitution mutations (based on strain specificity) and is more active in the presence of exogenous metabolic activation. Strains TA98 and TA1537 were also examined in the Ames assay both with and without activation but no mutagenic activity was seen up to test chemical concentrations of 5000 ug/plate.

The in vitro V79 Chinese hamster cell mutation test was performed under two separate selection conditions. One set of exposed cell cultures was selected with 6-thioguanine (6-TG) and the other set was selected with 8-azaguanine (8-AG). The selected cultures were exposed to up to 6.0 ug/ml of the test compound for 21 hours without exogenous metabolic activation and up to 23.0 ug/ml for 5

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

hours (with wash and incubation for the remaining culture time) with activation. All of the experiments conducted with 8-AG were negative. The selection studies with 6-TG, however, revealed an increased mutation frequency with the test compound of greater than 8X over solvent controls in the absence of activation; a slight increase in mutation frequency was found in the presence of activation but this was not duplicated in a replicate assay. Based on the test findings, the subject chemical is active in cultured V79 Chinese hamster cells by inducing point mutations at a specific gene locus (HPRT) under non-activation conditions.

Lymphocytes from healthy human donors were used to assay for the induction of chromosomal aberrations. Lymphocytes were pre-incubated for 46 hours, exposed to the test compound for 3 hours and then washed and incubated for approximately 43.5 hours until harvesting. Cultures were exposed to up to 7.0 nl/ml of the test substance without exogenous metabolic activation and up to 100.0 nl/ml with activation. At the high test compound concentration (7.0 nl/ml) without activation, 10 out of 100 metaphases had specific aberrations (e.g., chromatid breaks and exchanges as well as minutes). At the next two lower concentrations, fewer cells with aberrations were seen but were still significantly elevated over the negative control. In the presence of metabolic activation, the highest test material concentration (i.e., 100.0 nl/ml) induced the same types of aberrations noted above in 37 out of 100 metaphases. The next lower concentration had smaller aberration numbers but these were still significantly elevated over the negative control group. These test results indicate that the subject chemical can induce chromosomal aberrations in cultured human lymphocytes and the chemical appears to be more active in the presence of metabolic activation.

Two in vitro UDS assays were performed with the subject chemical substance. One assay was conducted in cultured rat hepatocytes that maintain continuous metabolic activation; the second assay was conducted in cultured human fibroblasts and measured direct action of the compound. The top concentrations used (based on cell viability) were 31.25 ug/ml in the rat cell assay and 50 ug/ml in the human cell assay. The cultures were exposed to the test compound and tritiated (^{3}H)-thymidine for 5 hours and then fixed for autoradiography. Usually, cell cultures are exposed for 18 hours and then fixed, or exposed for 4 to 5 hours, then incubated overnight in test article-free/^{3}H-thymidine-free medium ("chase") before fixation; these longer exposure and incubation times are presumed to allow greater time for DNA repair to occur. Although current EPA guidelines do not give specific exposure and incubation times, the protocols used in the case of CIBA-GEIGY's UDS assays are adequate. The chemical did not increase the mean number of grains/nucleus over negative controls or in relation to the number of grains/cytoplasm test area. Further, the cultures produced very few nuclei with more than 5 grains/nucleus. Under the conditions used for these assays, the subject chemical did not induce UDS in cultured rat hepatocytes or in cultured human fibroblasts.

Current Production and Use

The subject chemical is not listed in the non-confidential computerized version of the TSCA Chemical Substance Inventory. In its Section 8(e) notice, CIBA-GEIGY stated that the chemical is "an imported research and development resin intended primarily for use in automotive coatings." CIBA-GEIGY stated further that "only 25 kg (approximately 5½ gallons) have been imported to date" and that "samples have been distributed to two potential customers for technical performance evaluations." No additional information concerning use(s) of the subject chemical substance was located in the secondary literature sources consulted by EPA.

With regard to the potential exposure to the subject chemical, CIBA-GEIGY reported that the Material Safety Data Sheet (MSDS) carries numerous warnings for workers to avoid breathing vapor, mist or spray and recommends that workers wear impervious gloves, splash-proof chemical goggles and protective clothing in order to avoid personal contact with the chemical. CIBA-GEIGY stated also that "once the product is used in its intended application, it becomes a highly crosslinked, high molecular weight, insoluble and inert material." Finally, CIBA-GEIGY reported that there is no consumer exposure to the subject chemical substance.

Comments/Recommendations

In its Section 8(e) notice, CIBA-GEIGY stated that the company is revising the product MSDS to reflect the reported positive and negative genotoxicity findings and is notifying (in writing) all customers who have received samples of the subject chemical about the reported findings.

Although a positive *in vitro* genotoxicity test finding, when considered by itself, may not be sufficient to offer reasonable support for a conclusion of substantial risk (as defined in EPA's TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978)), EPA does believe that such a finding is of value in assessing the possible risks posed by exposure to the tested chemical or mixture. Also, EPA believes that a positive genotoxicity test result in combination with additional relevant information (e.g., knowledge of potential exposure to and/or high production of the subject chemical or mixture) would suggest, in many cases, the need to conduct other studies designed to better define the toxicity of or exposure to that chemical or mixture. The results of such additional studies should be considered also for submission to EPA pursuant to Section 8(e) of TSCA.

a) Considering EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure information, the Chemical Screening Branch will ask CIBA-GEIGY to describe the nature and results, if available, of all studies (other than those reported already to EPA or those published in the open

scientific literature) about which CIBA-GEIGY is aware or that CIBA-GEIGY has conducted, is conducting or plans to conduct to determine the toxicity of or exposure to the subject chemical substance.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical.

c) The Chemical Screening Branch will send copies of this status report to OSHA, NIOSH, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Asssistance Office (TAO/OTS) for further distribution.

DATE: SEP 8 1987

SUBJECT: Status Report* 8EHQ-0787-0686 S Approved: 9/10/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

The submitting company has claimed its identity and the identity of the subject chemical as TSCA Confidential Business Information (TSCA CBI); the Information Management Division (IMD/OTS) will request the submitter to substantiate these TSCA CBI claims. In the "sanitized" version of the Section 8(e) notice, the submitter stated non-confidentially that the tested chemical substance was a "modified alkyl phenol."

Submission Description

The submitting company provided a full copy of the final report from a 28-day oral study of the subject chemical in rats. In the cover letter to its Section 8(e) submission, the company provided the following information with regard to the conduct and results of this 28-day study:

> "Doses of 30, 100 and 300 mg/kg [of the subject chemical substance] in corn oil were administered daily [via gavage to male and female Sprague-Dawley rats] for 28 days. The study was started with a dose of 1,000 mg/kg; however, virtually all animals at 1,000 mg/kg died within 5 days. The acute oral LD50 was known to be between 500 and 2,000 mg/kg based on previous studies. Antemortem abnormalities seen in some animals in the 1,000 mg/kg group included hypoactivity, tremors, hypothermia, irregular respiration, moist rales, brown stains on the snout and fecal and urinary staining in the anogenital area. All animals in the other dose groups survived the treatment period.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"A variety of effects were observed at the 300 mg/kg dose. Upon gross necropsy, discolored kidneys were observed in three of five male rats and three of five female rats. Mean organ weights and mean organ to body weight ratio were generally found to be elevated for the kidney, liver and adrenal gland. Affected animals were also found to have elevated blood urea nitrogen and gamma glutamyl transpeptidase levels. Slight increases in blood total protein and globulin levels were observed in females. Histopathological examination revealed [an] increased severity of acute/subacute inflammation of the kidney and a significant incidence of dilated convoluted tubules in the kidney.

"No definite treatment related effects were seen at 30 or 100 mg/kg. A slight increase in liver to body weight ratio was seen in males at 100 mg/kg. A slight increase in kidney to body weight ratio was observed in females at 30 mg/kg, but not at 100 mg/kg."

[Note: The submitting company stated also that EPA would be apprised of the results of additional histopathologic examinations of kidney tissue from the animals in the 30 mg/kg and 100 mg/kg dose groups from the 28-day study in order to determine a no-observed-effect level (NOEL) for the chemical.]

In addition to the final report from the 28-day gavage study, the company provided final reports of an Ames Salmonella typhimurium (bacteria) mutagenicity assay and a chromosomal aberration assay in cultured Chinese hamster ovary (CHO) cells. According to the submitter, the Ames assay was negative and an apparent positive result obtained in the CHO chromosomal aberration assay was not reproducible.

The submitting company also provided final reports from a number of acute in vivo toxicity studies of the modified alkyl phenol. According to the submitted reports, the chemical 1) has an oral (rat) LD50 of greater than .5 g/kg but less than 2 g/kg, 2) has a dermal (rabbit) LD50 of greater than 2 g/kg, 3) produces moderate conjunctival irritation in rabbit eyes, 4) is corrosive to rabbit skin, and 4) is not a primary skin irritant, fatiguing agent or skin sensitizer when tested in guinea pigs.

Submission Evaluation

Based on a review of the final reports from the acute animal toxicity studies, this modified alkyl phenol is moderately toxic via the oral route and slightly toxic (at a maximum) via the dermal route. These acute studies also show that this chemical is a strong eye irritant and severe skin irritant. However, the chemical does not induce dermal sensitization nor does it act as a fatiguing agent.

Although other target organs may exist among those not studied histologically, the results of the 28-day study show that the kidney is clearly a target organ for the tested chemical substance. Nephrotoxicity was induced at the 300 mg/kg/day dose level as indicated by the discoloration of the kidneys, increased incidence and severity of dilated convoluted tubules, increased severity of kidney inflammation, increased absolute and relative kidney weights, and increases in serum components indicative of renal insufficiency (blood urea nitrogen, gamma glutamyl transpeptidase, and creatinine). The determination of a NOEL and/or lowest-observed-effect level (LOEL) for nephrotoxicity should be possible upon the Agency's receipt of the pathologic examination reported to be currently underway for animals exposed to the test substance at 30 and 100 mg/kg/day.

In the Ames assay, the subject chemical substance was tested with and without exogenous metabolic activation in bacterial strains TA98, TA100, TA1535, TA1537 and TA1538. A preliminary toxicity study indicated use of 250 and 33 ug/plate as top concentrations for activated and non-activated conditions, respectively. The assay was performed in two separate experiments. No evidence of an increase in mutant frequency was found in any strain at any test chemical concentration either with or without activation.

In the cultured CHO cell assay, the subject chemical was tested (in two separate experiments) with and without activation. A preliminary toxicity study based on cell proliferation kinetics indicated the use of 8 ug/plate and 5 ug/plate for activated and non-activated conditions, respectively. Cultures were treated for 12 hours without activation and 5 hours with activation. Cells were then washed to remove the test chemical and harvested 2 hours later (for non-activated) or 4 and 11 hours later (for activated). There were no significant increases in aberration frequency under any condition in one of the separate experiments. In the second experiment, slight (but significant) increases were observed at the top test substance concentrations for the non-activated portion and for the longer (11-hour) incubation period in the presence of activation; the activated 4-hour incubation was negative. These slight statistically significant increases may be indicative of borderline positive responses. However, the concurrent solvent controls appear much lower than the performing laboratory's historical control average and lower than that seen in the replicate experiment. Therefore, the test compound is probably not active in this assay.

Current Production and Use

In view of the submitter's TSCA CBI claims involving chemical identity, no information concerning the TSCA Chemical Substance Inventory status of this modified alkyl phenol will appear in this report.

According to the submitter, the subject chemical "is used as a component of a stabilizer for polymers." In addition, the company provided the following information regarding the potential for exposure to the chemical:

> "The health risks associated with this chemical in the workplace and in end use application are believed to be low. Based on an acute dermal study in rats, it appears the chemical substance is not absorbed through skin. The propensity for inhalation exposure in the workplace appears low. The chemical substance is non-volatile. The estimated vapor pressure contribution of this chemical in [the company's] product is 0.3 torr. The chemical substance is manufactured in and supplied to customers in a liquid stabilizer formulation containing mineral oil. Compliance with the [U.S. Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL)] for mineral oil in the workplace provides a large margin of safety. Little potential is thought to exist for aerosol formation under [the] conditions of use in the workplace. Moreover, the chemical substance is not approved for food use applications."

Comments/Recommendations

In its Section 8(e) submission, the company reported that the product Material Safety Data Sheet (MSDS), modified to reflect the reported toxicologic findings, is being provided to customers and company employees working with the subject chemical.

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, the submitting company will be asked to describe the nature and results, if available, of all studies (other than those submitted already to EPA or those published in the open scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to this modified alkyl phenol.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, ORD/EPA, OAR/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: SEP 1 1987

SUBJECT: Status Report* 8EHQ-0887-0687 Approved: 9/1/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

Texaco Inc. provided summarized preliminary findings from a chronic mouse skin-painting study of hydrodesulfurized heavy vacuum gas oil (Cas No. 64742-86-5). According to the submitter, this chemical "causes skin cancer on laboratory mice when [50 ul was] applied undiluted two times per week for six months with no attempt to remove the material from the [shaved] backs of mice at any time during the study." The reported findings are summarized in the following table:

Group	No. of Animals	Papillomas	Advanced Tumors
A	48	0	0
B	47	0	0
C	47	13	4
D	48	15	2

A: Negative Control (no treatment)

B: Negative Control (USP Mineral Oil)

C: Positive Control (Benzo(a)pyrene 0.05% in acetone)

D: Hydrodesulfurized heavy vacuum gas oil (undiluted)

With regard to the above findings, Texaco stated that "there is a significant increase in the incidence of papillomas and advanced tumors" in the benzo(a)pyrene and hydrodesulfurized heavy vacuum gas oil groups when compared to the negative control groups. In

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

addition, Texaco stated that the potency of the petroleum process stream is equivalent to that of the benzo(a)pyrene "applied at 0.05% [in acetone], the standard positive control concentration." Texaco stated also that the latency of onset of the observed oncogenic response for this petroleum process stream was short (i.e., approximately 6 months). Finally, Texaco stated that the performing laboratory reported that "ulcerative dermatitis is present to a clinically significant degree in a number of . . . [hydrodesulfurized heavy vacuum gas oil-]treated mice."

Submission Evaluation

The submitted information indicates that the subject petroleum process stream possesses oncogenic activity towards the skin of mice. An evaluation of the overall significance of the reported findings should be possible upon EPA's receipt of a copy of the final report from the performed chronic skin-painting study.

Current Production and Use

A review of the production range (includes importation volumes) statistics for hydrodesulfurized heavy vacuum gas oil (CAS No. 64742-86-5), which is listed in the initial TSCA Chemical Substance Inventory, has shown that over 9 billion pounds were reported as manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

Appendix A of the printed TSCA Chemical Substance Inventory (1985 Edition) gives the following definition for CAS No. 64742-86-5:

> "A complex combination of hydrocarbons obtained from a catalytic hydrodesulfurization process. It consists of hydrocarbons having carbon numbers predominantly in the range of C20 through C50 and boiling in the range of approximately 350°C to 600°C (662°F to 1112°F). This stream is likely to contain 5 wt. % or more of 4- to 6-membered condensed ring aromatic hydrocarbons."

In its Section 8(e) submission, Texaco reported that the subject chemical "is a non-isolated, site limited refinery process stream which is used as a feed to the catalytic cracking unit or is recycled in the H-Oil process." In addition, Texaco stated that "twelve shift personnel operate the unit; however, exposure is limited since the unit is a closed system and closed sampling procedures are used."

Comments/Recommendations

Texaco stated in its Section 8(e) notice that the reported toxicologic findings will be included in the company's "hazard communication program and workers will be warned again of the potential for adverse health effects from skin contact from certain oils and refinery streams." In addition, Texaco stated that the company will 1) keep EPA apprised as further results from the mouse skin painting study are received, and 2) provide a copy of the final report from the study to EPA when that report is completed.

a) The Chemical Screening Branch will request Texaco to ensure that EPA receives a full copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, results of any statistical analyses, etc.) from the mouse skin-painting study cited in the company's TSCA Section 8(e) notice.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure information, Texaco will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the published scientific literature) about which Texaco is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of the subject petroleum process stream.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of this petroleum process stream.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: SEP 28 1987

SUBJECT: Status Report* 8EHQ-0887-0688 Approved: 9/29/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The American Cyanamid Company reported that in conducting an epidemiologic study, the company "detected a statistically significant excess of respiratory cancer among former employees who worked in muriatic acid [(hydrochloric acid)] production and packaging facilities which were operated between 1928 and 1956 at [American Cyanamid's] Linden, New Jersey plant." In addition, American Cyanamid reported that its "investigation revealed a Standard Mortality Ratio (SMR) of 1.31 for respiratory cancer (observed: 182; expected: 138.8) among males hired between 1925 and 1973 (7153 [men at the Linden plant site])." The company reported also that "no statistically significant excesses were detected for 26 other cancer types." American Cyanamid stated further that the "results of linear logistic regression analysis indicates that this respiratory cancer excess occurred in two groups of males, muriatic acid facility workers and short-term workers." The following additional information with regard to the observed excess of respiratory cancer was contained in the company's TSCA Section 8(e) notice:

> "Eleven (11) cases occurred in males working in the muriatic acid facility between 1928 and 1956. This excess may be due to work factors, though this is unconfirmed, or may be due to chance. Muriatic acid production was the only process in this facility from 1928 to the late 1930's. The acid was produced by reacting 60° Baume sulfuric acid with sodium chloride. A by-product, sodium sulfate, was collected and bagged. Production ceased in the late 1930's and muriatic acid was purchased and repackaged for sale. No excess was observed in the analysis of 26 other facilities within the plant.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"Fifty-two (52) cases occurred in males hired between 1940 and 1949 who worked at [the Linden] plant for less than one year in a variety of facilities. These cases are not, in [American Cyanamid's] opinion, related to occupational factors at Linden because of their short work duration and varied work histories.

"Of further interest is the fact that, where smoking history records were available, all [of the] cases of respiratory cancer were observed in documented smokers.

"The muriatic acid facility was shut down in 1956 and none of the current employees ever worked there."

Submission Evaluation

Although American Cyanamid's Section 8(e) submission reports an excess in respiratory cancer among all males hired at the Linden, New Jersey plant between 1925 and 1973 (SMR = 131; $p < 0.05$) as well as among males working in the muriatic acid facility between 1928 and 1956 (11 observed deaths; the SMR, expected number of deaths, and p-value were not given in the notice), the company's submission lacks information on a number of important aspects of the study. American Cyanamid should be requested to ensure that the final report (or the company's cover letter transmitting that report to the Agency) addresses the following questions:

1) What chemical processes were ongoing in the muriatic acid facility after muriatic acid production ceased and during what years were those processes ongoing? What was the exact year in which muriatic acid production ceased at the Linden plant?

2) What industrial hygiene monitoring data exist for the entire Linden plant and for the muriatic acid facility? What were the historic exposure levels for muriatic acid, sulfuric acid, and other chemical substances? Was an exposure matrix for specific jobs at the Linden plant constructed before the mortality analyses were performed?

3) What other facilities were in operation at the Linden plant during the time period covered by the mortality study?

4) Against what population were the rates standardized (e.g., County, State, or U.S.)? What is the racial mix of the study population, and were rates that were age-race specific used as standards?

5) What are the observed and expected numbers of deaths for a) males working in the muriatic acid facility between 1928 and 1956, and b) males hired between 1940 and 1949 who had worked less than 1 year at the Linden plant site?

6) For what percent of the total study population were smoking histories available? For those workers with known histories, what percent were smokers? For both questions, answers are needed for the entire Linden plant and for each facility (e.g., the muriatic acid facility). What data exist with regard to exposure to alcohol? This question should be answered in the same way as that for smoking.

7) How many observed and expected deaths occurred among study subjects in the muriatic acid facility for cancer of the larynx and for other specific sites in the upper respiratory tract? What are the results of analyses using company mortality rates as the standard? What are the results of analyses that deal with relative risks as opposed to SMR's?

8) What are the results of analyses that incorporate both latency and length of exposure for examining total respiratory cancer mortality and site-specific upper respiratory cancer mortality?

Comments/Recommendations

In its Section 8(e) submission, American Cyanamid reported that all workers at the company's Linden, New Jersey facility are being notified about the results of the epidemiologic study. In addition, American Cyanamid stated that the company will be 1) communicating the results of the study to former employees of the muriatic acid facility, and 2) encouraging those former workers to participate in American Cyanamid's annual physical program and to stop smoking. It should be noted also that American Cyanamid sent copies of the company's TSCA Section 8(e) submission to the Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH). Finally, American Cyanamid stated the company expects to complete the final report of the epidemiologic study by late 1987 and will provide a copy of that report to EPA at that time.

a) The Chemical Screening Branch will request the American Cyanamid Company to ensure that the Agency receives a full copy of the final report (including the actual experimental protocol, results of statistical analyses, etc.) from the cited epidemiologic study. In addition,

American Cyanamid will be asked to ensure that answers are provided for each question found in the Submission Evaluation section of this status report.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the reported epidemiologic findings.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: SEP 28 1987

SUBJECT: Status Report* 8EHQ-0887-0689 Approved: 9/28/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The National Institute of Environmental Health Sciences (NIEHS) provided a copy of a manuscript detailing the final results of a National Toxicology Program (NTP)-sponsored cytogenetic study of isoprene (CAS No. 78-79-5) and chloroprene (CAS No. 126-99-8) in mice. The ABSTRACT section of the provided manuscript contains the following information with regard to the conduct and results of the performed study:

> "Groups of male B6C3F1 mice (N = 15) were exposed for 6 hours per day to ambient air, to isoprene (438, 1750, and 7000 ppm) or to chloroprene (12, 32, 80, and 200 ppm) for 12 exposure days. These compounds are the 2-methyl and the 2-chloro analogues, respectively, of 1,3-butadiene, a genotoxic and carcinogenic chemical in B6C3F1 mice. Exposure to isoprene induced significant increases at all [of the] exposure concentrations in the frequency of sister chromatid exchanges (SCE) in bone marrow cells and in the level of micronucleated polychromatic erythrocytes (PCE) and of micronucleated normochromatic erythrocytes in peripheral blood. In addition, a significant lengthening of the bone marrow average generation time and a significant decrease in the percentage of circulating PCE was detected. Under these exposure conditions, isoprene did not induce in bone marrow a significant increase in the frequency of chromosomal aberrations (CA) nor did the exposure significantly alter the mitotic index. The dose response curves for SCE and micronuclei induction were non-linear, appearing to saturate at 438 and 1750 ppm, respectively. Under similar exposure conditions, exposure to chloroprene resulted in complete mortality among the mice exposed to 200 ppm. At exposure concentrations of 80 ppm and below, chloroprene did not induce a significant increase in CA, SCE, or micro-

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nucleated erythrocytes, nor did the exposure significantly alter the rate of erythropoiesis or of bone marrow cellular proliferation kinetics. Exposure to chloroprene did result in a significantly increased bone marrow MI."

Submission Evaluation

For positive responses such as those obtained for isoprene in micronucleated polychromatic erythrocytes (PCEs), micronucleated normochromatic erythrocytes (NCEs), and sister chromatid exchanges (SCEs), one sex is sufficient to provide an unequivocal positive. On the other hand, for negative responses, such as those obtained for chromosome aberrations (CAs), percent micronucleated PCEs (%PCEs), mitotic index (MI), and average cell generation time (AGT), with isoprene and 6 of the 7 measured endpoints for chloroprene (all but MI), data from only one sex can only yield an equivocal result. Therefore, all of the negative responses are considered equivocal on this basis alone.

It should be noted also that because toxicity could not be used in selecting the high dose in the isoprene studies, the high dose selected was "several orders of magnitude below [the] explosive concentration." This safety factor seems overly cautious, and may have resulted in a high dose that was significantly lower than necessary. On this basis, the negative responses are viewed as inconclusive, while the positives are acceptable even at such low doses.

It is also important to point out that slightly different dosing regimens were used for the chemicals. Isoprene was administered for 6 hours/day for 3 days, followed by 2 days of non-exposure, 5 days of exposure, 2 days of non-exposure and finally 4 days of exposure. Chloroprene was administered for 6 hours/day but for 4 days, followed by 2 days of non-exposure, 5 days of exposure, 2 days of non-exposure, and finally 3 days of exposure. While the differences seem trivial, they could be important especially considering that the report ultimately compares the two chemicals with each other and then with 1,3-butadiene.

In summary, the reported information shows that isoprene induces significant increases in micronucleated PCEs, micronucleated NCEs, SCEs, and AGT, while chloroprene induces a significant increase in the MI of erythropoietic cells. Considering the protocol deficiencies noted above, none of the negative results obtained for either chemical are considered conclusive.

Current Production and Use

A review of the production range (includes importation volumes) statistics for isoprene (CAS No. 78-79-5), which is listed in the initial TSCA Chemical Substance Inventory, shows that 191 million to 510 million pounds of this chemical substance were reported as manufactured and/or imported in 1977.

A review of the production range (includes importation volumes) statistics for chloroprene (CAS No. 126-99-8), which is listed in the initial TSCA Inventory, shows that 61 million to 160 million pounds of this chemical substance were reported as manufactured and/or imported in 1977.

The preceding production range information does not include any information claimed to be TSCA Confidential Business Information (CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

According to the submitted manuscript, chloroprene and isoprene are used primarily in the production of synthetic elastomers. Chloroprene is used primarily in the manufacture of neoprene (polychloroprene) elastomer while isoprene is used primarily to produce cis-1,4-polyisoprene.

Comments/Recommendations

Although anyone may submit information to EPA under Section 8(e), the "substantial risk" information reporting provision of TSCA, only certain persons are required to do so. According to TSCA Section 8(e), "any person who manufactures, [imports,] processes, or distributes in commerce a chemical substance or mixture and who obtains information which reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment shall immediately inform the [EPA] Administrator of such information unless such person has actual knowledge that the Administrator has been adequately informed of such information." The Agency's TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" March 16, 1978; 43 FR 11110) defines the term "person" to include "any natural person, corporation, firm, company, joint-venture, sole proprietorship, association, or any other business entity, any State or political subdivision thereof, any municipality, any interstate body, and any department, agency or instrumentality of the Federal Government." [emphasis added] While it is clear that NIEHS is a "person" within EPA's Section 8(e) policy statement definition, the mandatory obligation to report substantial risk information to EPA under Section 8(e) would not be incurred by NIEHS unless it is engaged commercially in the manufacture, import, processing or distribution of the chemical substance or mixture about which substantial risk information is obtained.

Further, it should be noted that Part VII of EPA's Section 8(e) policy statement provides a number of examples of the kinds of information that need not be reported to EPA under Section 8(e) (i.e., information about which subject persons can automatically assume the Agency to be "adequately informed"). In addition to

the examples cited in Part VII, subject persons can automatically assume, for the purposes of Section 8(e) reporting, that EPA has been adequately informed about substantial risk information that is contained in a formal publication or a report made available to the general public by an agency of the U.S. Government (including EPA). It cannot be automatically assumed, however, that EPA has been adequately informed about information contained in a report not formally published or otherwise made available to the general public by an agency of the U.S. Government (other than EPA). Therefore, if a subject person obtains (i.e., knows of or possesses), for example, unpublished findings (including preliminary findings) of a toxicologic study conducted by or for an agency of the U.S. Government (other than EPA), that person should consider the need to report such information immediately (i.e., within 15 workings days) to EPA pursuant to Section 8(e) of TSCA. Since 1977, EPA has received a number of Section 8(e) notices filed by companies that obtained unpublished results of toxicologic studies conducted by or for other Federal agencies. In each of those instances, EPA immediately established direct contact with those other agencies in order to obtain the needed followup information.

a) The Chemical Screening Branch will review the reported information in greater detail in order to determine the need for further OTS assessment of the subject chemical substances.

b) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: SEP 10 1987

SUBJECT: Status Report* 8EHQ-0887-0690 Approved: 9/10/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Atlantic Richfield Company provided the following information with regard to the conduct and preliminary results of a Guinea Pig Maximization Test (GPMT) with N-phenyl maleimide (NPMI; CAS No. 941-69-5):

> "The test group consisted of 20 animals. In addition, each of the following groups had 10 animals per group: the naive controls, vehicle controls, positive controls and naive positive controls. The test substance was dissolved in acetone for use in the intradermal and topical induction phases. Formalin was employed as the positive control substance for the induction and challenge phases of this study. Following the topical challenge, readings of the resulting dermal reaction were recorded at approximately 24 and 48 hours thereafter.
>
> "The results of the primary challenge indicated that NPMI is a strong skin sensitizer: 19/20 NPMI test animals gave a positive reaction to a 0.0625% solution in acetone. In the positive control group, 8/9 formalin treated animals reacted positively to a 5% formalin solution. The NPMI treated animals exhibited a significantly greater dermal response than did those in the formalin control group. By contrast, none of the animals in the remaining control groups exhibited a positive reaction when challenged with their respective test solution."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

In its Section 8(e) notice, Atlantic Richfield stated that its decision to conduct the GPMT was based in part on "reports from employees of skin problems which were alleged to have resulted from exposure to NPMI." The submitter added that the GPMT "was chosen because it is regarded as the best predictor for skin sensitization in man." In addition, the company reported that previously conducted animal studies showed that NPMI was severely irritating to the skin.

Submission Evaluation

An evaluation of the overall significance of the reported findings should be possible upon EPA's receipt of a complete copy of the final report of the NPMI sensitization study as well as full copies of the previously conducted animal studies showing NPMI to be a severe skin irritant. Further, Atlantic Richfield should be asked to describe in more detail the "skin problems" alleged by employees to have resulted from exposure to NPMI.

Current Production and Use

A review of the production range (includes importation volumes) statistics for N-phenyl maleimide (CAS No. 941-69-5), which is listed in the initial TSCA Chemical Substance Inventory, has shown that no 1977 manufacture/importation of the chemical was reported or that all of the manufacturing and/or importation data reported were claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial Inventory and cannot be disclosed (Section 14(a) of TSCA; U.S.C. 2613(a)). All of the information submitted for the initial TSCA Inventory, including the production range information, is subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

In its Section 8(e) submission, Atlantic Richfield reported that NPMI "is imported and manufactured under pilot plant conditions for research [and development (R&D)] purposes by ARCO Chemical Company . . . a subsidiary of [the] Atlantic Richfield Company." Atlantic Richfield did not provide any information regarding the company's use(s) of NPMI nor was such information located in the secondary literature sources consulted by EPA.

Comments/Recommendations

Atlantic Richfield reported that based on the submitted data, "special handling procedures for NPMI are being recommended." In addition, the company reported that "the Material Safety Data Sheet [(MSDS)] developed for worker use with this R&D product will be revised to reflect the [GPMT] study results." Finally, the company stated that copies of the revised MSDS and final report of the skin sensitization study would be sent to EPA.

a) The Chemical Screening Branch will request Atlantic Richfield to ensure that EPA receives a full copy of the final report (including the actual experimental protocol, results of any gross or histopathological examinations, results of any statistical analyses, etc.) from the GPMT cited in the company's submission. In addition, Atlantic Richfield will be asked to submit full copies of the final reports from the company's "previous animal studies" showing NPMI to be a severe skin irritant. Finally, Atlantic Richfield will be asked to describe in greater detail the "skin problems" alleged by employees to be due to exposure to NPMI.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Atlantic Richfield will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Atlantic Richfield is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to NPMI.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: SEP 11 1987

SUBJECT: Status Report* 8EHQ-0887-0691 S

Approved: 9/11/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The submitting company (company identity claimed to be TSCA Confidential Business Information (TSCA CBI)) reported that "in January 1986, due to a lack of published data regarding the relationship between the severity of hydrotreatment and dermal carcinogenicity of hydrotreated naphthenic oils, . . . [the company] initiated a [2-year] dermal carcinogenicity study in mice." The submitter stated that the data from this study are expected "to provide the scientific basis for assessing the dermal carcinogenic potential of hydrotreated naphthenic oils for preparing precautionary labels and material safety data sheets." The submitter provided the following information regarding the conduct and preliminary results of the ongoing study:

> "In the [2-year] carcinogenicity study, fifty (50) male C3H/HEJ mice, 6-8 weeks of age when received, had 50 ul of the test material applied topically three days per week to the clipped interscapular region of the back. This study was initiated in two phases; Phase I started in January, 1986, and Phase II started December, 1986. The . . .[following] table summarizes the data obtained to date. The tested materials, designated L1 to L5 and L12 to L19 can be generically described as Hydrotreated Light or Heavy Naphthenic Distillates (Petroleum). The tested materials designated L6 to L8 and L20 to L21 can be generically described as Light or Heavy Naphthenic Distillates (Petroleum). The tested materials designated L9 to L10 can be generically described as Severely Solvent-refined and Solvent-dewaxed Heavy Paraffinic Distillates (Petroleum). These materials are defined by the CAS Registry Numbers shown in the table. The SUS viscosity at 100°F, a DMSO extractable (IP 346) and an aromatic carbon content (ASTM D 2140) level shown in the table further defines each of the tested materials. . . . ."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"TWO-YEAR DERMAL CARCINOGENICITY TESTING - NAPHTHENIC OIL STUDY[a]

L-No.	C.A.S. No.	Viscosity SUS at 100°F	DMSO	CA	START	Number of Mice with Tumors Phase I WK 80	Phase II WK 36
12-01	64742-53-6*	55	1.5	7	12/86	-	0
13-01	64742-52-5*	100	1.5	7	12/86	-	0
17-01	64742-52-5*	100	2.0	8	12/86	-	0
15-01	64742-52-5*	300	2.0	8	12/86	-	0
14-01	64742-52-5*	100	2.5	9	12/86	-	0
16-01	64742-52-5*	300	3.0	11	12/86	-	0
18-01	64742-52-5*	100	3.0	10	12/86	-	0
1-01	64742-53-6*	55	3.3	11	1/86	37	-
3-01	64742-52-5*	300	3.7	13	1/86	30	-
2-01	64742-52-5*	100	3.9	13	1/86	40	-
19-01	64742-52-5*	225	4.0	14	12/86	-	6
6-01	64741-52-2*	55	5.0	14	1/86	25[d]	-
20-01	64741-53-3*	100	6.0	17	12/86	-	0
7-01	64741-53-3*	300	6.2	17	1/86	48[d]	-
21-01	64741-53-3*	300	7.0	21	12/86	-	31[d]
4-01	64742-52-5*	1200	2.2	12	1/86	0	-
5-01	64742-52-5*	3000	2.0	12	1/86	1	-
8-01	64741-53-3*	5000	8.0	18	1/86	8[d]	-
9-01	b	100	0	2	1/86	0	-
10-01	b	600	0	2	1/86	0	-
B(a)P (0.01%)		-	-	-	1&12/86	29[e]	3[e]
B(a)P (0.05%)		-	-	-	1&12/86	47[e]	44[e]
Toluene Only[c]		-	-	-	1&12/86	1	0
Shaved only		-	-	-	1&12/86	0	0

a Testing status as of August 6, 1987

b C.A.S. Numbers 64741-88-4* and 64742-65-0*

c Carrier Solvent for B(a)P

d Previously reported as carcinogenic (IARC Monograph No. 33, 1984)

e Previously reported as carcinogenic (IARC Monograph No. 32, 1983)

DMSO = DMSO Extractables (IP 346)

CA = Aromatic Carbon Content (ASTM D 2140)"

In submitting these preliminary findings to EPA for processing "in accordance with EPA's 'substantial risk' procedures," the company reported that it "intends to pursue these preliminary findings with quality assurance and a scientific assessment of these specific findings." In addition, the company stated that "when the studies end, and final evaluation of the study data has been performed, such evaluation in addition to the final report, will be made available to the Agency." The submitter noted that the submission of this information should occur in about 2 years.

Submission Evaluation

As shown in the submitted table, several of the tested materials have exhibited tumorigenic activity thus far in this ongoing chronic mouse skin-painting study. The submitter should be asked to ensure that EPA is apprised about any further significant findings (e.g., from interim sacrifices) from this study. In addition, the submitter should be requested to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, results of gross/histopathologic examinations, results of statistical analyses, etc.) from the ongoing study.

Current Production and Use

A review of the production range (includes importation volumes) statistics for the tested petroleum process streams, which are all listed in the initial TSCA Chemical Substance Inventory, has shown that over 1 billion pounds of each of these materials were reported as manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

Appendix A ("Chemical Substance Definitions") of Volume I of the printed TSCA Chemical Substance Inventory (1985 Edition) gives the following definitions for the CAS Registry Numbers cited in this submission:

- **Light Naphthenic Distillates (Petroleum)**
  CAS No. 64741-52-2

  "A complex combination of hydrocarbons produced by vacuum distillation of the residuum from atmospheric distillation of crude oil. It consists of hydrocarbons having carbon numbers predominantly in the range of C15 through C30 and produces a finished oil with a viscosity of less than 100 SUS at 100°F (19cST at 40°C). It contains relatively few normal paraffins."

- Heavy Naphthenic Distillates (Petroleum)
  CAS No. 64741-53-3

  "A complex combination of hydrocarbons produced by vacuum distillation of the residuum from atmospheric distillation of crude oil. It consists of hydrocarbons having carbon numbers predominantly in the range of C20 through C50 and produces a finished oil with a viscosity of at least 100 SUS at 100°F (19cST at 40°C). It contains relatively few normal paraffins."

- Solvent-Refined Heavy Paraffinic Distillates (Petroleum)
  CAS No. 64741-88-4

  "A complex combination of hydrocarbons obtained as the raffinate from a solvent extraction process. It consists predominantly of saturated hydrocarbons having carbon numbers predominantly in the range of C20 through C50 and produces a finished oil with a viscosity of at least 100 SUS at 100°F (19cSt at 40°C)."

- Hydrotreated Heavy Naphthenic Distillates (Petroleum)
  CAS No. 64742-52-5

  "A complex combination of hydrocarbons obtained by treating a petroleum fraction with hydrogen in the presence of a catalyst. It consists of hydrocarbons having carbon numbers predominantly in the range of C20 through C50 and produces a finished oil [with a viscosity] of at least 100 SUS at 100°F (19cSt at 40°C). It contains relatively few normal paraffins."

- Hydrotreated Light Naphthenic Distillates (Petroleum)
  CAS No. 64742-53-6

  "A complex combination of hydrocarbons obtained by treating a petroleum fraction with hydrogen in the presence of a catalyst. It consists of hydrocarbons having carbon numbers predominantly in the range of C15 through C30 and produces a finished oil with a viscosity of less than 100 SUS at 100°F (19cSt at 40°C). It contains relatively few normal paraffins."

- Solvent-Dewaxed Heavy Paraffinic Distillates (Petroleum)
  CAS No. 64742-65-0

  "A complex combination of hydrocarbons obtained by removal of normal paraffins from a petroleum fraction by solvent crystallization. It consists predominantly of hydrocarbons having carbon numbers predominantly in the range of C20 through C50 and produces a finished oil with a viscosity of not less than 100 SUS at 100°F (19cSt at 40°C)."

In its submission, the company stated that it "does not currently market a product with the same description as those showing positive tumorigenicity [in the ongoing 2-year skin-painting study in mice]."

Comments/Recommendations

The Agency has received numerous TSCA Section 8(e) and "For Your Information" (FYI) submissions containing new toxicologic and exposure data on a wide variety of petroleum process streams.

a) The Chemical Screening Branch will ask the submitter to ensure that the Agency is apprised about any further significant findings from the company's ongoing 2-year skin-painting study in mice. In addition, the company will be asked to ensure that EPA receives a full copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, results of any statistical analyses, etc.) from this ongoing chronic study.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, the submitter will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to the tested materials.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the tested materials.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: SEP 28 1987

SUBJECT: Status Report* 8EHQ-0987-0692 Approved: 9/29/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

In its Section 8(e) submission, the Monsanto Company reported that the subject chemical ("acetic acid, oxo-, methyl ester or ethyl ester, homopolymer, reaction products with ethoxyethene and reaction products with methoxyethene, sodium salts") was the subject of a "Premanufacture Notice " (PMN No. 84-535) submitted previously to EPA under Section 5 of TSCA. According to the non-confidential version of PMN No. 84-535, which was obtained from the OTS Public Files, the name of the submitting company and the exact identity of the subject chemical were claimed to be TSCA Confidential Business Information (TSCA CBI); the chemical was identified generically, however, as an "Alkali Metal Carboxylate" in the non-confidential version of the PMN.

Submission Description

In its Section 8(e) submission, Monsanto provided the following information regarding the conduct and results of chronic studies of the PMN chemical in mice and rats:

> "PMN substance No. 84-535 was administered to groups of 60 male and 60 female Sprague Dawley rats at target levels of 0, 400, 2,000 or 10,000 ppm for approximately two years. Because of excessive mortality, the high dose concentration was reduced to 5,000 ppm after 84 weeks into the study. Groups of 60 male and 60 female mice were given 0, 600, 3,000 or 15,000 ppm PMN substance No. 84-535 in their drinking water for a period of 18 months. Since the test material is the sodium salt of a polycarboxylic acid, this would result in a

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

high sodium load (approximately 2,000 ppm) to the test animals. Therefore, sodium control groups consisting of 60 animals/sex were administered sodium hippurate at levels such that the sodium load in each group was equivalent to the sodium load in the high concentration group for each species.

"The incidence of neoplasms was comparable among all groups in mice of both sexes and male rats. In [the] female rats, the incidence of neoplastic nodules in the liver was 1 of 60, 5 of 60, 3 of 60, 8 of 58 and 6 of 59 in the drinking water control group (DWC), sodium control (SC), low-, mid- and high-concentration groups, respectively. The incidence of neoplastic nodules in the mid-dose group was statistically significant (less than or equal to .05) when compared to [the] DWC group but not when compared to the SC group using the Fisher Exact Test."

In submitting the preceding information to EPA, Monsanto stated that "the toxicological significance of the slight increase in neoplastic nodules in female rats is considered to be limited because:

"The [observed] incidence of neoplastic nodules is not significantly different from the sodium control group, which was run concurrently and is the most appropriate for comparison.

"The historical control incidence of neoplastic nodules in female Sprague Dawley rats for 3 previous chronic studies of equivalent length at the testing laboratory where the study was conducted is 2 of 70, 14 of 60 and 4 of 70. Thus the highest incidence in this study is within historical limits.

"With known hepatocarcinogens, neoplastic nodules are generally thought to progress to hepatocellular carcinomas. In the present study, the incidence of hepatocellular carcinoma was 0, 1, 1, 0 and 0 for the DWC, SC, low-, mid- and high-dose group, respectively. Thus, there was no progression to a malignant lesion.

"No sex-related differences in toxicity have been observed with this compound previously. In the present study, the incidence of neoplastic nodules among male rats in treated groups was actually lower than in the drinking water control group (neoplastic nodules - DWC 8 of 59, SC 3 of 60, low 7 of 60, mid 6 of 58, high 3 of 59).

"PMN substance No. 84-535 produced no increase in the incidence of liver adenomas or carcinomas in mice, a species which has been shown to be extremely responsive

to other known hepato-oncogens even though the dosage level of the test material in mice was 4-5 times that in the rats. The dosage of the test material in the low-, mid- and high-group on a mg/kg/day basis for female rats was 54, 253 and 951, respectively, and for female mice was 183, 923 and 4670, respectively.

"PMN substance No. 84-535 was not found to be mutagenic in the Ames/Salmonella assay, CHO/HGPRT assay, in vivo cytogenetics assay in rats, in vitro rat hepatocyte DNA repair assay and [an] in vivo - in vitro rat liver DNA repair assay."

Submission Evaluation

In order for EPA to evaluate the overall significance of the reported findings, Monsanto should be asked to submit complete copies of the final reports (including the actual experimental protocols, results of gross and histopathologic examinations, results of statistical analyses, etc.) from the chronic studies of PMN substance No. 84-535 in mice and rats. In addition, the company should be asked to submit complete copies of the final reports from any of the cited genotoxicity studies not submitted already to EPA.

Immediately upon receipt of this TSCA Section 8(e) submission, the Chemical Screening Branch transmitted copies of the notice to the Chemical Control Division (CCD/OTS) which is responsible for administering the OTS "New Chemicals Program" (NCP).

Current Production and Use

In its Section 8(e) submission, Monsanto reported that although PMN No. 84-535 was commercialized initially, commercial activity with the chemical has ceased. Monsanto also reported, however, that "stores of this substance have been used in research and development quantities and continue to be used for test panel evaluation." According to the sanitized version of the PMN, the subject chemical was intended for use as "component of industrial and consumer products."

Comments/Recommendations

a) The Chemical Screening Branch will request Monsanto to submit complete copies of the final reports (including the actual experimental protocols, data, results of any statistical analyses, etc.) from all studies (including the genotoxicity tests) cited in the TSCA Section 8(e) notice that have not been submitted already to EPA.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Monsanto will be asked to describe the nature and results, if available,

of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Monsanto is aware or that Monsanto has conducted, is conducting or plans to conduct to determine the toxicity of or exposure to the subject chemical.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and CCD/OTS/OPTS/EPA. In addition, copies of this status report will be provided to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: SEP 23 1987

SUBJECT: Status Report* 8EHQ-0987-0693

Approved: 9/24/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Union Carbide Corporation provided the following information with regard to the conduct and results of a number of in vitro and in vivo genotoxicity studies of tetraethylene glycol (CAS No. 112-60-7):

> "There were no dose-related or statistically significant increases in gene mutations in a Salmonella typhimurium assay using 5 strains of bacteria both in the presence and absence of a metabolic activating system.
>
> "In a forward gene mutation test in Chinese Hamster Ovary cells (HGPRT-locus), there were no dose-related or statistically significant increases in gene mutation activity, either in the presence or absence of a metabolic activating system.
>
> "A sister chromatid exchange test, conducted using Chinese Hamster Ovary cells, showed statistically significant increases in the numbers of exchanges compared with the controls, both in the presence and absence of metabolic activation. The increases, however, were not dose-related. In view of the weak nature of the response, and because of no clear dose-response relationship, a repeat test was conducted using a second sample of tetraethylene glycol. This repeat test produced essentially a similar weak increase in sister chromatid exchanges but, again, was not dose-related.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"An in vitro evaluation of the potential to produce clastogenic effects was undertaken using Chinese Hamster Ovary cells. Overall, there was an increase in the incidence of chromosome aberrations (most notably simple breaks), but the biological significance of the finding was uncertain because of the absence of any clear dose-response relationship and inconsistencies between duplicate cultures.

"Because of the increase, in vitro, of sister chromatid exchanges and chromosome aberrations, but in an inconsistent manner, it was considered appropriate to conduct a study to determine the in vivo clastogenic potential of tetraethylene glycol. The mouse micronucleus test was chosen, using groups of 5 male and 5 female mice for each dose. The intraperitoneal doses used were 2500, 4000 and 5000 mg/kg, and blood samples were taken for counting of micronucleated polychromatophilic erythrocytes (MN-PCE) at 30, 48 and 72 hours postdosing. Based on a reading of 1000 PCE per animal, there were increases in the incidence of MN-PCE for males at the 30 hour sampling time only, as follows:

Dose	Sex	MN-PCE/1000 PCE (Mean ± SD)
2500 mg/kg	M	4.8 ± 3.42
	F	2.4 ± 1.67
4000 mg/kg	M	3.8 ± 1.30
	F	2.2 ± 2.28
5000 mg/kg	M	5.6 ± 2.61[a]
	F	3.7 ± 1.92
Water Control	M	2.8 ± 2.59
(10 ml/kg)	F	1.8 ± 0.84
TEM[b]	M	36.6 ± 11.95
(0.3 mg/kg)	F	34.0 ± 12.88

[a] $p<0.01$

[b] TEM = Triethylenemelamine (positive control)

"As with the in vitro studies, there was no clear dose-response relationship. In view of this, and because of variability between animals, the number of PCEs counted for male animals was increased to 2000. Using this larger sample, there was reasonably good agreement with the first count. The incidence of MN-PCEs was increased at all doses for the 2000 cell count, being statistically significant at 2500 and 5000 mg/kg, as follows:

Dose	Count	MN-PCE/1000 PCE (Mean ± SD)	p*
2500 mg/kg	1st 1000	4.8 ± 3.42	<0.05
	2nd 1000	4.4 ± 2.97	
4000 mg/kg	1st 1000	3.8 ± 1.30	
	2nd 1000	4.0 ± 0.71	
5000 mg/kg	1st 1000	5.6 ± 2.61	<0.001
	2nd 1000	5.8 ± 2.59	
Water Control (10 ml/kg)	1st 1000	2.8 ± 2.59	
	2nd 1000	2.4 ± 2.07	

*Relative to water control

"These results confirm the clastogenic potential of tetraethylene glycol, as exhibited by the micronucleus test, with statistically significant increases for the low and high, but not intermediate, dose. The absence of a dose-response relationship is still evident.

"These findings indicate a clastogenic potential for tetraethylene glycol by in vitro tests and confirmed by a single in vivo method. However, the absence of clear dose-response relationships, and inconsistency between test data, do not allow a definition of the possible biological significance of the findings with respect to any adverse health effects."

In its Section 8(e) submission, Union Carbide provided complete copies of the final reports from the cited in vitro studies and stated that the final reports for the cited in vivo studies are being completed and would be sent to EPA as soon as those reports are issued.

Submission Evaluation

The Agency's review of the reported genotoxicologic findings for tetraethylene glycol will take place upon receipt of complete copies of the final reports from the cited in vivo studies.

Current Production and Use

A review of the production range (includes importation volumes) statistics for tetraethylene glycol (CAS No. 112-60-7), which is listed in the initial TSCA Chemical Substance Inventory, shows that approximately 103 million to 535 million pounds of this chemical substance were reported as manufactured and/or imported in 1977. This production range information does not include any data claimed as TSCA Confidential Business Information (TSCA CBI)

by the person(s) reporting for the initial TSCA Inventory, nor does it include any data that would compromise TSCA CBI. All of the data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

According to the Condensed Chemical Dictionary (10th Edition), tetraethylene glycol uses include: "Solvent for nitrocellulose; plasticizer; lacquers; coating compositions."

Comments/Recommendations

In its Section 8(e) submission, Union Carbide stated that the company is advising its customers and other U.S. manufacturers of tetraethylene glycol about the reported genotoxicologic findings.

Although a positive in vitro genotoxicologic assay result, when considered alone, may not be sufficient to reasonably support a conclusion of substantial risk (as that term is defined in EPA's TSCA Section 8(e) policy document ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978)), EPA believes that such results are of value in assessing possible risks posed by exposure to chemical substances or mixtures. The Agency also believes that positive genotoxicity findings, when considered in combination with other pertinent information (e.g., knowledge of potential exposure to and/or high production of the subject chemical or mixture), would suggest the need, in many cases, to conduct further studies that are designed to better define the toxicologic properties of or exposure to the subject chemical(s). The results of such further testing should be considered also for submission to EPA pursuant to Section 8(e) of TSCA.

a) The Chemical Screening Branch will ask Union Carbide to ensure that EPA receives complete copies of the final reports (including the actual experimental protocols, results of statistical analyses, etc.) from the in vivo studies cited in the company's Section 8(e) submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Union Carbide will be asked to describe the actions the company has taken or plans to take to notify its workers about the reported information. In addition, Union Carbide will be asked to describe the nature and results, if available, of all studies (other than those reported already to the Agency or those published in the scientific literature) about which Union Carbide is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of or exposure to tetraethylene glycol.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of tetraethylene glycol.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: OCT 26 1987

SUBJECT: Status Report* 8EHQ-0987-0694

Approved: 10/27/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Westvaco Corporation reported that the company had recently received a letter from a physician indicating that "exposure to sodium lauryl sulfate (SLS) residues from a carpet shampoo caused chronic respiratory effects in patients treated by her." In its submission, Westvaco stated its belief that the physician had sent the letter to Westvaco because it "formerly manufactured an aqueous solution of SLS." Westvaco stated further that although it does not currently produce SLS, the company purchases SLS for use "as a raw material in two products which are manufactured by Westvaco." Westvaco noted, however, that neither of these two products are used in carpet shampoo applications. In its TSCA Section 8(e) submission, Westvaco stated that 1) the company considers the physician's statements to be allegations, and 2) the company has placed the physician's letter in the company's TSCA Section 8(c) files.

Comments/Recommendations

Although the information provided by Westvaco does not appear to be of the type required for submission under Section 8(e), the "substantial risk" information reporting provision of TSCA, the subject information does appear to be of the type required to be recorded/maintained by Westvaco under Section 8(c), a mandatory recordkeeping provision of TSCA. On August 22, 1983, the Agency published (48 FR 38178) a final rule that requires chemical manufacturers and certain chemical processors to maintain records of significant adverse reactions alleged to have been caused by a TSCA-covered chemical substance or mixture. This TSCA Section 8(c) rule also requires that allegations that involve significant adverse reactions in workers be maintained for 30 years and that other recordable allegations be kept for 5 years. It should be noted also that the Agency is empowered to inspect and/or require submission of corporate TSCA Section 8(c) records and has done so on a number of occasions to date.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

a) The Chemical Screening Branch will review the reported information in more detail to determine the need for and scope of further OTS assessment.

b) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: NOV 4 1987

SUBJECT: Status Report* 8EHQ-1087-0695

Approved: 11/04/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The CIBA-GEIGY Corporation provided final reports from mouse and rat teratology studies of 1-methyl-2-pyrrolidinone (N-methyl-pyrrolidone; CAS No. 872-50-4) conducted in 1970-1971 by BASF Aktiengesellschaft in West Germany. The mouse study, which was conducted in 1970, involved administration of the test material intraperitoneally to pregnant NMRI mice at doses of 610 and 1525 mm^3/kg or orally at doses of 1026 and 2565 mm^3/kg on the 11th through the 15th day of gestation. (The provided report states that previous studies in mice had shown the intraperitoneal and oral LD50's for N-methylpyrrolidone to be 3050 and 5130 mm^3/kg, respectively.) According to the mouse study report, the higher oral and intraperitoneal doses (which were in total 2 1/2 times the respective LD50's) were tolerated well by the dams but not by the developing offspring. The submitted study report states that there was an "increased resorption rate as well as the increased appearance of runts and reductions in the weight and lengths of the fetuses." The study report also states that there was an increase in the rate of birth defects with cleft palate being the primary teratogenic effect observed. In the lower dose groups, no embryotoxic effects were reportedly observed (i.e., "the resorption rate, number of runts, average weight and length of fetuses were identical to normal values") nor was there any increased incidence in birth defects found.

According to an English Summary of the rat study (the rat study report itself is in German; the study was conducted in 1971), N-methylpyrrolidone was administered orally at doses of 323 or 970 $mm^3/kg/day$ to pregnant Sprague-Dawley rats on days 6 through 15 of gestation. These daily doses were reported to correspond, respectively, to 1/15 and 1/5 of the oral LD50 in rats. The submitted Summary states that the dams tolerated well the 10 low and high oral doses of N-methylpyrrolidone (i.e., the mothers did not show any "visible toxic symptoms or macroscopically recognizable

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

pathological changes"). In the developing offspring, however, administration of the high dose reportedly produced 95% embryolethality and caused deformities in 8/15 surviving fetuses. In the lower dose group, administration of N-methylpyrrolidone was reported not to have resulted in any embryotoxic or teratogenic effects (i.e., "the observed deformities or anomalies in the fetuses of this test group corresponded in type and number to spontaneously occurring changes in Sprague-Dawley rats").

It should be noted that the submitted mouse study report contains the following information with regard to BASF's rationale for conducting its teratologic studies of N-methylpyrrolidone:

> "[The] testing of N-methylpyrrolidone for a possible teratogenic action proved to be necessary after an analgesic [(not identified in the report)] containing a component with a pyrrolidone ring as [a] substituent had proved to have a teratogenic action in rats which was absent in the comparison product containing the component without the pyrrolidone ring."

Finally, it should be noted that the submitted mouse study report states that a teratology study (route and species not specified) of pyrrolidone itself had been conducted and a report (dated May 29, 1970) prepared; no further information on this pyrrolidone study was found in the mouse study report on N-methylpyrrolidone.

Submission Evaluation

The submitted information indicates that N-methylpyrrolidone caused embryotoxic and teratogenic effects in rats and mice following oral (mice and rats) or intraperitoneal administration (mice). Upon obtaining an English translation of the rat study report, a more detailed review of the reported findings will be undertaken. It should be noted in the interim, however, that EPA has located a published article by Becci et al. (Fundamental and Applied Toxicology; 2:73-76; 1982) concerning a study of the teratogenic potential of N-methylpyrrolidone applied dermally to pregnant Sprague-Dawley rats. The ABSTRACT section of this paper contains the following information with regard to the conduct and results of the study:

> "Doses of 75, 237 and 750 mg of N-methylpyrrolidone/kg body weight/day were administered dermally to groups of 25 pregnant Sprague-Dawley rats on days 6 through 15 of gestation. Additionally, the study used a positive dermal control. Hexafluoroacetone was chosen based on its dermal teratogenic activity. An oral positive control, aspirin, was included in order to add significance to the data generated in the experimental positive dermal control group. All animals were killed and subjected to uterine examination on day 20 of gestation. Maternal toxicity was indicated at 750 mg of N-methylpyrrolidone /kg by reduced body weight gain during gestation. [The]

> treatment with N-methylpyrrolidone resulted in a dose-dependent brightly colored yellow urine and dry skin. Treatment at the high dosage level resulted in fewer live fetuses per dam, an increase in the percentage of resorption sites and skeletal abnormalities. These effects could be the result of maternal toxicity. There was no evidence of teratogenic effects nor effects on the dams at 75 and 237 mg/kg of body weight."

The INTRODUCTION section of the Becci et al. paper presents the following information with regard to the conduct and results of an earlier study performed by Schmitt (Biol. Rundsch.; 14:38-41; 1976) in which N-methylpyrrolidone was administered intraperitoneally (i.p.) to pregnant mice:

> "Schmitt (1976) found that N-methylpyrrolidone caused dose-dependent embryotoxic and teratogenic effects in AJ JENA and C57BL mice when given in single or repeated i.p. doses on various days of gestation. The most pronounced embryotoxic effect of N-methylpyrrolidone was noted after a single i.p. administration of 166 mg/kg was given on the 7th day post-conception. Twenty-three percent of all implanted fetuses died. The same dose level of N-methylpyrrolidone given [i.p.] on the 9th day [post-conception] caused the highest rate of fetal malformations, (18.6%)."

The INTRODUCTION section of the Becci et al. paper states that the dermal teratology study of N-methylpyrrolidone in rats was conducted because of "the absence of teratogenicity information [on the chemical] by a practical route of exposure for industrial uses . . . [(i.e., 'as a solvent used extensively in chemical processing')]." Becci et al. stated further that the dermal route of exposure for the study in rats was judged to be more significant than the inhalation route because N-methylpyrrolidone (which has a boiling point of 202°C) "is of limited volatility." Becci et al. noted also that N-methylpyrrolidone is known to be "capable of dermal penetration."

Current Production and Use

A review of the production range (includes importation volumes) statistics for N-methylpyrrolidone (CAS No. 872-50-4), which is listed in the initial TSCA Chemical Substance Inventory, has shown that over 1 billion pounds of this chemical were reported as manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the information reported for the initial TSCA Inventory, including the production range information, is subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

According to secondary literature sources, N-methylpyrrolidone is used mainly as a solvent (e.g., for resins), as a chemical intermediate, as a "spinning agent" for polyvinyl chloride (PVC), and as a dispersant for pigments.

In its TSCA Section 8(e) submission, CIBA-GEIGY reported that the company "processes N-methylpyrrolidone at one U.S. facility and imports minor quantities in two of its products, both of which are mixtures." (CIBA-GEIGY did not disclose the names of either of the two imported products.) According to information contained in the provided mouse teratology study report, BASF Aktiengesellschaft was manufacturing N-methylpyrrolidone for sale as a solvent.

Comments/Recommendations

In its TSCA Section 8(e) submission, CIBA-GEIGY stated that the company plans to revise its Material Safety Data Sheets (MSDSs) and product labels to reflect the reported toxicologic findings.

It should be noted that the Agency has received TSCA Section 8(e) submissions containing toxicologic and/or exposure information on other pyrrolidone derivatives (N-vinylpyrrolidone, 8EHQ-Ø785-Ø561 S et seq. and N-(2-hydroxyethyl)pyrrolidone, 8EHQ-Ø682-Ø448 S et seq.).

a) The Chemical Screening Branch will review the reported/published information on N-methylpyrrolidone in order to determine the need for further OTS assessment of this chemical. In addition, the Chemical Screening Branch will contact BASF Aktiengesellschaft in an attempt to obtain a full copy of the company's 197Ø teratology study of pyrrolidone. Also, the Chemical Screening Branch will ask the OTS Library to obtain a copy of the 1976 paper by Schmitt.

b) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OW/EPA, OSWER/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: OCT 30 1987

SUBJECT: Status Report* 8EHQ-1087-0696

Approved: 11/02/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Union Carbide Corporation provided the following information with regard to the preliminary results of acute toxicity studies conducted by Union Carbide over the last year-and-a-half on a series of 18 different alkoxylate nonionic surfactants:

> "The acute lethal toxicity of these materials, as expressed by peroral or 24-hour percutaneous LD50, varied between moderate to very low (i.e., LD50 values ranged between 0.4 to >16 ml/kg by peroral administration and between 0.8 to >16 ml/kg by percutaneous application). An unusual pattern of toxicity, however, was observed in the 24-hour occluded cutaneous application in the rabbit portion of these studies. The pattern was characterized by delayed deaths and macroscopic evidence of lung injury. Microscopic examination of lung tissue was recently conducted on animals treated with the last 7 of the 18 of these materials, these tissues being saved only after recognizing that this pattern of toxicity had emerged. Microscopic findings included bronchopneumonia, pneumonitis, alveolar histiocytosis, edema, congestion and necrosis. In almost all cases, the injury was associated with the presence of foreign vegetable matter in the lower respiratory tract and lung. The foreign vegetable matter was presumably feed particles which had been aspirated.

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> "No one of these studies by itself would trigger a concern regarding substantial risk of adverse health effects. However, when these results are considered together, and taken across the entire family of these surfactants, there appears to be a consistent pattern of toxicity. A review of acute toxicity studies conducted over the past 40 years on various alkoxylated nonionic surfactants further substantiates a pattern of delayed deaths and visual evidence of lung injury. Based upon this review and the recent studies, . . . [Union Carbide believes] that not only do long chain alcohol ethoxylates and ethoxy/propoxy copolymer surfactants produce this pattern of toxicity, but that nonylphenol ethoxylates may also exhibit a similar pattern of toxicity. However, the relevance of these studies to human health is unknown."

In submitting this information to EPA under Section 8(e) of TSCA, Union Carbide stated that copies of the final reports from the recently conducted studies will be provided to EPA as soon as those reports are issued. According to Union Carbide, these final reports will "describe in detail the toxic response (days to death), macroscopic and microscopic observations on the recent surfactant acute toxicity and primary irritancy studies."

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon the Agency's receipt of complete copies of the final reports of the performed studies.

Comments/Recommendations

In its Section 8(e) notice, Union Carbide stated that the company is "advising employees and customers who handle, use or otherwise may be potentially exposed to these types of surfactants" about the results of these studies and the fact that the study findings had been reported to EPA. In addition, Union Carbide stated that "studies are currently being conducted and further information is being sought to clarify this toxic response and better place it in perspective to potential human health risks."

a) The Chemical Screening Branch will ask Union Carbide to ensure that EPA receives complete copies of the final reports (including the actual experimental protocols, the exact identity, including CAS Registry Number (if known), of each of the test materials, etc.) from the series of acute toxicity studies cited in the company's TSCA Section 8(e) submission.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Union Carbide will be asked to describe the nature and results, if available, of the company's ongoing studies designed to clarify the reported toxicologic findings.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: NOV 25 1987

SUBJECT: Status Report* 8EHQ-1187-0697 Approved: 11/25/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Amoco Corporation submitted the following information with regard to the conduct and preliminary results of a chronic dermal application study of "furnace oil and several fractions thereof" in mice:

> "The purpose of the [performed] study was to define the component(s) of furnace oil which may have been responsible for the reported tumorigenic and tumor promoting properties. In a [previously conducted] lifetime skin painting study, furnace oil produced tumors in 10 of 50 mice with a mean latency period of 90 weeks. This furnace oil has been tested and found not to be an initiator in a mouse skin tumor initiation bioassay.
>
> "In the current study, furnace oil was separated into [the following] four fractions:
>
> 1. low-boiling fraction;
> 2. aromatic fraction;
> 3. iso- and cyclo-paraffin fraction; [and]
> 4. n-paraffin fraction.
>
> "Male mice were initiated with dimethylbenzanthracene (DMBA) or acetone (control), rested for two weeks and then exposed dermally to furnace oil or one of the furnace oil fractions. One DMBA-initiated group received no promoting treatment and served as sham control. The following table enumerates skin masses observed grossly (no histology results are available at [the time of Amoco's submission]:

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"INITIATOR	PROMOTER	SKIN MASSES
DMBA	Furnace Oil	14
DMBA	Low Boiling Fraction	19
DMBA	Aromatic Fraction	22
DMBA	Iso/Cyclo-paraffin	3
DMBA	n-Paraffin	2
DMBA	None (sham)	Ø
Acetone	Furnace Oil	Ø
Acetone	Low Boiling Fraction	Ø
Acetone	Aromatic Fraction	Ø
Acetone	Iso/Cyclo-paraffin	Ø
Acetone	n-Paraffin	Ø

"Numbers of masses in the furnace oil, low boiling, and aromatic groups were significantly increased above control group numbers. No masses were present in the acetone-initiated or sham control groups."

According to Amoco, the results obtained from this study 1) "can be interpreted as supporting previous knowledge concerning the tumorigenic and promoting potential of furnace oil" and 2) "indicate that the [observed] promoting effects of furnace oil are associated with two specific fractions of furnace oil."

Submission Evaluation

In order for EPA to evaluate the overall significance of the reported findings, Amoco should be asked to ensure that EPA receives full copies of the final reports from mouse bioassays cited in the company's TSCA Section 8(e) submission.

Current Production and Use

Amoco Corporation reported non-confidentially (by phone on November 23, 1987) that the tested furnace oil has the following CAS Registry Number: 68476-3Ø-2. According to Appendix A of the 1985 Edition of the printed version of the initial TSCA Chemical Substance Inventory, CAS No. 68476-3Ø-2 refers to Number 2 fuel oil, a petroleum distillate oil "having a minimum viscosity of 32.6 SUS at 1ØØ°F to a maximum [viscosity] of 37.9 SUS at 1ØØ°F."

A review of the production range (includes importation volumes) statistics for CAS No. 68476-30-2, which is listed in the initial TSCA Chemical Substance Inventory, has shown that over 1 billion pounds of this chemical substance were reported as manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

Comments/Recommendations

It should be noted that EPA's Office of Toxic Substances has received a number of TSCA Section 8(e) and "For Your Information" (FYI) submissions containing toxicologic and/or exposure data on a wide variety of petroleum and synfuel process streams.

a) The Chemical Screening Branch will request Amoco to ensure that EPA receives full copies of the final reports (including the actual experimental protocols, the results of gross/histopathologic examinations, the results of statistical analyses, etc.) from the mouse bioassays cited in the company's Section 8(e) notice.

   In view of EPA's general interest in corporate actions that are taken on a voluntary basis in response to chemical toxicity or exposure information, Amoco will be asked to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported information, and 2) to reduce or eliminate exposure to the tested material(s).

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the tested material(s).

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: NOV 30 1987

SUBJECT: Status Report* 8EHQ-1187-0698 Approved: 11/30/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Union Carbide Corporation provided the following information with regard to the conduct and preliminary findings of an ongoing epidemiologic study:

> "In 1979, epidemiologists from the Union Carbide Corporation (Union Carbide) and the National Institute for Occupational Safety and Health (NIOSH) began a joint epidemiology study of Union Carbide's employees at three facilities in the Kanawha Valley of West Virginia. As part of this study, Union Carbide examined the mortality experience of a cohort of 2,174 men who were employed between 1940 and 1979 and were assigned, for one day or more before December 31, 1978, to a chemical production department that used or produced ethylene oxide (EO). Compared with the general population, the standardized mortality ratio (SMR) for all causes was 79 (95% Confidence Interval (CI) = 70, 89) and for all malignant neoplasms was 81 (95% CI = 61, 104). There were no statistically significant excesses of deaths due to any cause.
>
> "Analyses by duration of exposure in EO departments revealed positive trends in pancreatic cancer and leukemia mortality, which were not present when analyzed by estimated cumulative EO dose. Further analyses by general work area indicated that the excesses were largely confined to employees who had been first assigned before 1947 to the ethylene chlorohydrin [(CAS No. 107-07-3)] production department where potential for EO exposure is thought to have been low.

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"Analysis by duration of assignment to that department demonstrated noteworthy trends for both causes with increasing duration. Observed and expected deaths in the 0, less than 1 year, 1 - 9 years, and 10 + years duration categories are 53 observed (obs.)/63 expected (exp.), 0 obs./0.22 exp., 2 obs./0.49, and 4 obs./0.28 exp., respectively, for pancreatic cancer. Analogous statistics for leukemia are 50 obs./48 exp., 1 obs./ 0.16 exp., 1 obs./0.35 exp., and 2 obs./0.19 exp., respectively. Although the number of observed deaths is small, the relative difference between the observed and expected deaths clearly increases with duration for both causes.

"Since any chemical production in the department before 1947, other than ethylene chlorohydrin, is thought to have been minor, these [epidemiological] findings currently appear to be associated with the production of ethylene chlorohydrin. To [the best of the Union Carbide Corporation's] knowledge, the association of the production of ethylene chlorohydrin with increased risk of pancreatic cancer or leukemia represents new information."

Submission Evaluation

In its submission, Union Carbide reported that the company has more detailed analyses underway and that the results of these analyses will be provided to EPA as part of the final report of the epidemiologic study. In order for EPA to evaluate the overall significance of the obtained results, Union Carbide should be asked to ensure that EPA receives a full copy of the final report (including the protocols, data, results of all statistical analyses, etc.) from the company's epidemiologic study as soon as that report becomes available. In addition, Union Carbide should be requested to keep the Agency apprised of any further significant findings from the company's ongoing study/analyses.

Current Production and Use

A review of the production range (includes importation volumes) statistics for ethylene chlorohydrin (CAS No. 107-07-3), which is listed in the initial TSCA Chemical Substance Inventory, has shown that approximately 10.3 million to 53 million pounds of this chemical substance were reported as manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the information reported for the initial TSCA Inventory, including the production range information, is subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (see 40 CFR 710).

According to the Condensed Chemical Dictionary (10th Edition), the uses of ethylene chlorohydrin include: "solvent for cellulose acetate, ethylcellulose; introduction of hydroxyethyl group in organic synthesis; to activate sprouting of dormant potatoes; mfg. of ethylene oxide and ethylene glycol; insecticides." It is not known at the present time, which (if any) of the cited uses are current uses of ethylene chlorohydrin. It should be noted, however, that the Union Carbide Corporation reported by phone on November 24, 1987, that the company 1) stopped manufacturing ethylene oxide via a process using ethylene chlorohydrin in 1957, and 2) has not, to the best of the company's knowledge, engaged in manufacture/processing of ethylene chlorohydrin since 1957.

Comments/Recommendations

The discussion pertains to the TSCA Section 8(e)** reporting obligation of a company that obtains "new" information that reasonably supports a conclusion that a chemical substance or mixture that the subject company did, but does not any longer, manufacture, import, process or distribute presents a substantial risk of injury to health or the environment. A company that finds itself in this particular situation should be aware that although it may not be required technically to submit such information to EPA under Section 8(e) of TSCA, EPA believes that a timely formal submission of such information would fall clearly within the "spirit" of the Section 8(e) reporting provision. EPA believes also that, in many cases, such a report would be of great benefit to others who currently handle the subject chemical(s) and who can then initiate any warranted actions to reduce or eliminate health or environmental risks. Finally, the Agency believes that the timely formal submission of such risk-related information would be a demonstration of the reporting company's chemical stewardship practices.

It should be noted that EPA's Office of Toxic Substances has received both TSCA Section 8(e) and "For Your Information" (FYI) submissions on ethylene chlorohydrin.

a) The Chemical Screening Branch will ask Union Carbide to ensure that EPA receives a complete copy of the final report (including all protocols, data, results of any statistical analyses, etc.) from the company's ongoing epidemiologic study. In addition, Union Carbide will be asked to keep EPA apprised of any further significant findings from the ongoing study/analyses.

** Section 8(e) of TSCA states that "any person who manufactures, [imports], processes, or distributes in commerce a chemical substance or mixture and who obtains information which reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment shall immediately inform the [EPA] Administrator of such information unless such person has actual knowledge that the Administrator has been adequately informed of such information."

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity/exposure information, Union Carbide will be asked to describe the actions the company has taken or plans to take to notify workers and others about the reported epidemiologic findings.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance(s).

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JAN - 5 1988

SUBJECT: Status Report* 8EHQ-1287-0699 Approved: James F. Darr 1/6/88

FROM: David R. Williams, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The E. I. DuPont de Nemours & Company, Inc. provided the results of a recently completed lung cancer case control mortality study of workers at a DuPont plant in Belle, West Virginia. According to DuPont, this epidemiologic study was started in 1984 when excesses of lung cancer deaths among wage and salary roll workers were found during the company's conduct of routine cancer surveillance activities. The following information regarding the results and conduct of the epidemiologic study is presented in the "ABSTRACT" section of the submitted report:

> "Routine cancer surveillance reports have identified excesses of lung cancer deaths among wage and salary roll Belle Plant employees. The present study was begun in 1984 to determine whether the Belle employee's risk of dying from lung cancer was associated with any particular work area or job. Special attention was to be given to employment in work areas and jobs with potential exposure to two known carcinogens: coke oven emissions and asbestos.
>
> "This was a case-control study of 107 male lung cancer deaths that occurred among [the] Belle Plant's active and pensioned employees during the period 1957 through 1979. Work histories were developed by [Belle] plant personnel. Smoking histories of cases and controls were completed by proxies. For all work area and job title categories, odds ratios were computed to measure the lung cancer risk of having worked in a particular area or job relative to not having worked there. Job titles of mechanics and craftsmen other than machinists and metal workers were grouped because of their generally higher potential exposure to asbestos prior to the 1950s.

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"In summary, the study found elevated lung cancer risks for Mycoban[**]-catalyst area (odds ratio = 6.7) and for craftsmen (odds ratio = 2.5) other than machinists and metal workers. These elevations were statistically significant after adjusting for birth date, pay class, cigarette smoking, and employment in other areas and jobs. Employment in the coke oven area showed little association with lung cancer risk. Lung cancer risks among operators, laborers, and helpers were lower than among other occupations. Lung cancer risk in smokers was higher than in never smokers and increased with amount smoked (heavy smokers showed risks 9 times higher than never smokers).

"Although the numbers in any given craft group were small, the jobs of pipefitter, pipecoverer, millwright, painter, rigger, carpenter, auto mechanic, welder, and instrument mechanic had elevated odds ratios. Possible explanations for these elevations included prior asbestos exposure (either during or prior to DuPont employment), greater potential for high-level acute exposures to other materials, inadequate measurement and control of lifestyle factors such as cigarette smoking, and chance. . . . .

"During the course of this study, it became apparent that Belle Plant employees had also experienced excesses of non-neoplastic, non-infectious respiratory disease (e.g., chronic obstructive pulmonary disease) as measured by Accident and Health (A&H) insurance claims over the period 1956-1984. . . . ."

The "ABSTRACT" section also presents the following information on the need and recommendations for further studies:

"The elevated odds ratios [that were] found for the Mycoban-catalyst area and for craftsmen warrant a more in-depth epidemiologic investigation into lung cancer risks at [the] Belle Plant. The present study should be updated to include deaths that occurred from 1980 through 1986. The update will provide about 60 more lung cancer cases for analysis. For the more recent cases, it should be possible to obtain more accurate employment and smoking histories. The 1980-1986 group will be analyzed separately and in combination with the 1957-1979 group [in order] to confirm or modify the present findings. . . . . Although [the excesses of non-neoplastic, non-infectious respiratory disease] may simply reflect geographic or lifestyle differences, it is recommended that a case-control study of these excesses also be initiated."

[**] According to the Condensed Chemical Dictionary (10th Ed.), Mycoban is a trademark for sodium and calcium propionates.

The submitted epidemiologic study report presents a list of the chemical substances/materials used in the Mycoban-catalyst area. The reader's attention is directed to the 2-page attachment (Appendix A) to this status report.

Submission Evaluation

Dupont's routine occupational health surveillance of Belle plant employees identified statistically significant elevations in lung cancer mortality among male wage roll and salary roll workers employed at the Belle plant during the period of 1957 to 1979. One hundred fifty one (151) lung cancer deaths were observed among the Belle employees whereas 102.6 deaths would have been expected (SMR = 147, $p<0.001$). The text of the report does not state, however, on what population the expected number of deaths is based. A similar trend was observed for nonneoplastic, non-infectious respiratory disease claims (274 observed, 217.7 expected, $p<0.001$). Further, Table 2 of the submitted report provides an SMR; however, the report does not state whether this represents the standardized morbidity ratio. For both endpoints, the trend began in the 1960's and continued through the 1970's.

Based on these observations, Dupont employed a case-control study design in order to investigate potential agents associated with the apparent increased lung cancer risk. Of primary concern to Dupont epidemiologists was exposure to asbestos and to coke oven emissions (the Belle facility contains a coke plant). Each lung cancer case was matched to a control individual by age (within 5 years), adjusted service date, and termination date. Dupont obtained smoking histories for each case and its control by a questionnaire completed some years earlier by proxies, i.e., former supervisor, family member and coworkers. DuPont's study report does not give the frequency distribution of respondents. Preliminary analyses were adjusted for age (birthdate), pay class, and smoking habits using Mantel-Haenszel stratified methods. These analyses examined how lung cancer risk, as defined by the odds ratio, varied with exposure, assessed by process area, job title and craft. Exposures in which the stratified analyses showed an elevated odds were evaluated further using logistic regression methods. The Dupont epidemiologists accounted for work in other areas with these later analyses.

Exposure classification was based on a job and area coding scheme used in a previous study (Fayerweather et al. 1982) that examined lung cancer and potential formaldehyde exposure at certain Dupont facilities. The Belle plant provided work histories for each case and control and these histories were coded by Dupont using the 1982 coding scheme. The present study report does not identify the source for the job histories, whether they were based on personnel records, job rosters, or supervisor interviews nor whether they were old interviews coded again or new interviews

coded by an earlier scheme. In contrast to the 1982 study, the present study is unable to identify potential exposure to specific chemicals for each job, and this inability limits the interpretation of the results.

The results from DuPont's many data analyses are summarized in Appendix B of this status report. Logistic regression analyses showed that smoking, as would be expected, and salary pay class are major risk factors for lung cancer. These data analyses also show that work in the Mycoban process and in job titles such as craftsmen are associated with increases in lung cancer that cannot be attributed to smoking. (It should be noted that nickel and chromate compounds are listed in Appendix A of this status report and these agents have been shown in other studies to be human lung carcinogens.)

According to the submitted information, Dupont is continuing to investigate exposures in these categories. Contrary to previous studies, work in the coke oven area was not related to increased lung cancer risk. However, this study might have had sufficient power to detect only a high level of risk. Likewise, the increased lung cancer risk associated with pipefitting/pipecovering job titles may in fact be due to asbestos, an "a priori" hypothesis.

Several inconsistencies appear in this study that are cause for concern. First, the text is confusing regarding the total number of lung cancer cases on which the data analyses are based. For example, the report text cites a number of cases and controls with exposures in a particular area; however, the total number of lung cancer cases is difficult to determine. The cohort analyses identified 151 lung cancer deaths. Tables III through VI of the submitted report identify descriptive characteristics such as smoking, pay class, and year of birth for only 94 cases. In addition, DuPont's cover letter states that these analyses are based on 107 lung cancer cases. It is very important to know the reason for excluding 44 (151-107) cases or 57 (151-94) cases. The excluded cases represent approximately one-third of the total number of identified lung cancer deaths and their exclusion from the analyses could seriously bias the results.

Second, a previous study of lung cancer mortality among Dupont employees (Fayerweather et al. 1982) identified 17 lung cancer cases at the Belle plant with potential formaldehyde exposure. In the current analyses, however, no cases were identified as having been exposed in the Belle plant's hexamine/formaldehyde/thylox work areas. Therefore, the present findings appear to be in conflict with the 1982 findings. It is very important to know whether any of the 17 cases with formaldehyde exposure in the 1982 study were included in the present study. In addition, it is important to know the number of cases and controls that are common to the 1982 study and the current study.

In conclusion, although the present submission states that exposures in the Mycoban catalyst process and to craftsmen may be associated with increased lung cancer risk, the submission suffers from potentially biased case identification, recall bias from the proxy smoking histories and lack of exposure specificity (the inability to pinpoint specific exposures). At this time, EPA is not able to support Dupont's statement that asbestos may be the primary etiologic agent responsible for the increased lung cancer mortality among Belle workers. In addition, this study cannot exonerate any specific exposure encountered in the Belle plant. DuPont should be asked to ensure that future analyses define the inclusion criteria for the cases and controls, and also, identify exclusion rules. The future analyses also need to carefully evaluate job histories and relevant exposures in order to draw more firm conclusions with regard to the increased lung cancer mortality among the Belle plant employees.

Comments/Recommendations

In its Section 8(e) notice, DuPont stated that the company has informed its workers about the reported findings and is currently "evaluating what additional studies, if any, should be undertaken at the Belle plant." In addition, DuPont stated that the company plans to "update the study to include deaths that occurred from 1980 to confirm or modify the present findings." Finally, DuPont stated that the results of any further studies would be submitted to EPA as soon as those results are available.

a) The Chemical Screening Branch will request DuPont to address the questions/concerns found in the Submission Evaluation section of this status report. In addition, Dupont will be asked to ensure that 1) EPA is apprised of any significant findings from the planned update of the company's epidemiologic study, and 2) EPA receives a complete copy of the updated study report.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the findings.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

Reference

Fayerweather, W. E. et al. (unpublished 1982 study entitled "Case-Control Study of Cancer Deaths in DuPont Workers with Potential Exposure to Formaldehyde" OPTS Docket No. 62033)

Attachments: Appendix A (2 pages) and Appendix B (1 page)

"APPENDIX A:
CHEMICALS AND MATERIALS IN THE MYCOBAN-CATALYST AREA

1946-1948 - Operator - Catalyst Plant

copper chromite	
zinc chromite	
copper sulfate	
zinc sulfate	
chromic acid	
ammonia	
ammonium bicarbonate	
soda ash	
sulfuric acid	
graphite	
nickel chromite	
nickel pellets	
nitric acid	
copper nitrate	
copper oxide (mill scale)	
barium nitrate	
magnesium oxide	
manganese sulfate	
manganese chromite	
barium chromite	(stopped 1950)
filter aid	
copper metal	
barium carbonate	
iron molybdate	
ferric chloride	
hydrochloric acid	
cobalt carbonate	
cobalt metal	
cobalt nitrate	
ammonium carbonate	
cobalt oxide	
sterotex	
powdered cobalt	(stopped 1948)
sodium metasilicate	(stopped 1948)
hydrogen	(stopped 1953)
nickel carbonate	(stopped 1953)
powdered nickel	(stopped 1953)
boric acid	(stopped 1958)
phosphoric acid	(stopped 1958)
ammonium molybdate	

"APPENDIX A (CONTINUED):
CHEMICALS AND MATERIALS IN THE MYCOBAN-CATALYST AREA

Mycoban Plant

calcium propionate
sodium propionate
propionic acid
soda ash
lime
filter aid

Carbonate Plant

ammonium carbonate
ammonium bicarbonate
ammonia carbon dioxide

Catalyst Plant

iron bars
iron oxide
oxygen
alundum
magnesium oxide
potassium bichromate
potassium carbonate
silica
raney alloy (aluminum-nickel)
nitric
hydrogen
soda ash
boric acid
phosphoric acid
copper chromite
copper ammonia
chromic acid
graphite
nickel carbonate
powdered nickel
nickel pellets
filter aid
zinc sulfate
copper nitrate
copper oxide (mill scale)
barium nitrate
nickel chromite
ammonium bicarbonate
sulfuric acid
soda ash
cobalt carbonate
cobalt metal
cobalt nitrate
ammonium carbonate
cobalt oxide
sterotex
manganese chromite
zinc chromite
copper sulfate
manganese sulfate
iron molybdate
ferric chloride
ammonium molybdate
hydrochloric acid"

APPENDIX B

Odds Ratios from Stratified Mantel-Haenszel and Logistic Regression Analyses for Individual Exposure Areas.

Stratified Analyses:	No. of Cases	Odds Ratio	95% Conf. Int. LOW	HIGH
Work Area-				
Mycoban-catalyst	9	4.7	Ø.9	25.3
Hexamine/formaldehyde/ thylox	Ø	-	-	-
Job Title-				
Mechanical trades	57	2.Ø	1.1	3.7
Crafts-				
All craftsmen and mechanics	57	2.Ø	1.1	3.7
All craftsmen except metal workers and mechanics	52	2.7	1.4	4.3
Auto mechanic	3	*	-	-
Carpenter	2	*	-	-
Cement finisher/brick mason	2	*	-	-
Logistic Regression Analyses:**				
Crafts-				
Craftsmen other than metal workers and machinists	?	2.5	1.3	4.7
Pipecoverer/pipefitter	?	3.8	1.1	2.3
Process Area-				
Mycoban-catalyst	?	6.7	1.2	36.3

* Odds Ratio = Infinity

** Referent group is Belle plant male wage roll employees born prior to 1905 who never smoked, never worked as craftsman/ mechanic, and never worked in Mycoban-catalyst, coke oven, or gas house areas.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: DEC 30 1987

SUBJECT: Status Report* 8EHQ-1287-0700 Approved: 12/30/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Shell Oil Company provided the following information with regard to the conduct and results of a 14-day dermal study of 9,9-bis(4-hydroxyphenyl) fluorene (BPFL; CAS No. 3236-71-3) in rabbits:

> "Groups of ten rabbits, five males and five females, were treated topically with 0.25, 1.0 or 2.0 g/kg body weight of BPFL (moistened with saline) or saline (control) for 14 consecutive days. Two male rabbits in the high dose group died during the study. Both male and female rabbits in the 1.0 and 2.0 g/kg dosage groups had decreased body weights relative to controls and some animals showed clinical signs of toxicity (hunched posture). Clinical pathology findings and relative organ weights suggested renal effects in the 1.0 and 2.0 g/kg dosage group rabbits. Pathologist's report indicated that bile duct hyperplasia and nephropathy were observed in the 1.0 and 2.0 g/kg dose groups but not in the 0.25 g/kg dose group or in the controls. The no-effect level for the test article was 0.25 g/kg for both males and females."

In its submission, Shell stated that, when completed, the final report of the 14-day dermal study in rabbits would be provided to EPA along with final reports of other studies (i.e., "negative" acute and primary dermal irritation studies in rabbits and a "negative" skin sensitization study in guinea pigs). Shell also stated that "despite the lack of irritation effects in the test animals, there have been occurrences of human skin irritation associated with BPFL." Shell provided the following information related to the observed human skin irritation:

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"This irritation is believed to be caused by direct skin contact [with BPFL], often when protective clothing is improperly removed following completion of the operations. Irritation typically occurs on the hands, arms or elbows of exposed persons as well as the around the eyes and nose. This irritation is readily reversible and has been treated by the application of steroid cream. The current [BPFL] safety data sheet describes the irritation effects." [Note: A copy of the current BPFL safety data sheet was included in Shell's TSCA Section 8(e) submission.]

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon EPA's receipt of full copies of the final reports (including the actual experimental protocols, results of gross and histopathologic examinations, etc.) from all BPFL studies cited in Shell's submission. In the interim, it should be noted that the "HEALTH INFORMATION" section of the provided BPFL safety data sheet states that 1) "based on human experience, . . . [BPFL] is moderately to severely irritating to the eyes . . . [and] the skin . . . [and] may cause skin sensitization." and 2) "based on similar product testing, [BPFL] dust is presumed to be irritating to the nose, throat and respiratory tract . . . [and] moderately toxic and may be harmful if swallowed." In order to facilitate EPA's evaluation of the reported toxicity of BPFL, Shell should be requested also to provide 1) the exact identity of the "similar product" tested (including the CAS Registry Number, if known), and 2) the final reports of the studies of this similar product that formed the basis for the ingestion and inhalation toxicity statements presented in the BPFL safety data sheet.

Current Production and Use

In its Section 8(e) submission, Shell stated that BPFL is a research and development (R&D) chemical not listed on the TSCA Chemical Substance Inventory. Shell also stated that a TSCA Section 5 Premanufacture Notification (PMN) has not been filed for BPFL. Shell stated further that 1) the intended use of BPFL "is strictly as a site-limited intermediate and feedstock for other products" and 2) "BPFL would be consumed in downstream reactions and would not be a component of final products." Finally, Shell reported that the company "plans to continue development of BPFL as an R&D substance."

Comments/Recommendations

In its Section 8(e) submission, Shell stated that the company is updating the BPFL safety data sheet in order to 1) reflect the reported toxicologic findings, and 2) provide revised worker protection recommendations. In addition, Shell reported that the company intends "to notify all persons who have come in contact with this substance during research and development activities by means of a letter and the revised safety data sheet." Shell noted that this notification "included about 15 Shell employees and four companies outside Shell." Finally, Shell reported that a copy of the updated BPFL safety data sheet would be transmitted to EPA.

a) The Chemical Screening Branch will request Shell to ensure that EPA receives full copies of the final reports (including the actual experimental protocols, results of gross and histopathologic examination, etc.) from all animal studies cited in the cover letter to the company's Section 8(e) submission. In addition, Shell will be requested to provide the exact chemical identity (including CAS Registry Number, if known) of the "similar product" the studies of which provided the basis for the information presented in the "INHALATION" and "INGESTION" subsections of the "HEALTH INFORMATION" portion of the submitted BPFL safety data sheet. Shell will be asked also to provide complete copies of the final reports of the cited toxicologic studies of this "similar" chemical substance.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Shell will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA) about which Shell is aware or that Shell has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to BPFL.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of BPFL.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and CCD/OTS/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: DEC 30 1987

SUBJECT: Status Report* 8EHQ-1287-0701

Approved: 12/30/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

As background information for this TSCA Section 8(e) submission, the Union Carbide Corporation (UCC) reported that, in 1986, epidemiologists from UCC and the National Institute for Occupational Safety and Health (NIOSH) "completed an overall cohort mortality epidemiology study of UCC employees at three facilities in the Kanawha Valley (KV) of West Virginia.[1]" Union Carbide provided the following information regarding the completed study as well as other ongoing studies:

> "The findings of this [1986] study included an excess number of deaths due to four types of lymphatic and hematopoietic tissue cancers. There were 120 deaths due to non-Hodgkin's lymphoma, multiple myeloma, non-lymphocytic leukemia and lymphocytic leukemia and 99 deaths expected, based on comparisons to the U.S. population. The observation period for this study was 1940 to 1978. In order to investigate whether the occurrence of these excesses was work-related, nested case/control studies were simultaneously undertaken for each of these four causes of death. Exposure odds ratios were examined in relation to 6 major work activity groups, 111 work areas, 21 specific chemicals and 52 chemical groups representing over 1000 distinct chemical substances present in these manufacturing facilities."

In its letter to EPA, Union Carbide stated that the following information concerning the preliminary findings of these ongoing studies is believed by the company to be reportable to the Agency under Section 8(e) of TSCA:

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

> "An association was observed between non-Hodgkin's lymphoma and assignment to the South Charleston [West Virginia] plant's ethanol and isopropanol production units, which used the strong acid process (odds ratio = 8.3; 95% Confidence Interval: 2.3; 30.7). Six of 52 cases of this disease (12%) vs. 4 of 260 controls (2%) held assignments in these work areas. The cases were first assigned to these units in the following years: 1930, 1931, 1934, 1942, 1952, and 1960. These findings were not supported by duration response trends. Three of the six cases worked less than two months in these units.
>
> "At the South Charleston plant, the ethanol strong acid process operated from 1930 to 1960, and isopropanol strong acid process operated from 1928 to 1949. Strong acid processes have been reported in the literature to be associated with cancer of the upper respiratory tract.[2,3] . . . [To the best of Union Carbide's] knowledge, an association of increased risk of non-Hodgkin's lymphoma with assignment to the ethanol and isopropanol strong acid process units represents new information."

In addition, Union Carbide pointed out that the company recently notified EPA under Section 8(e) of TSCA (see 8EHQ-1187-0698 et seq.) that "the non-lymphocytic leukemia case/control comparisons revealed an association of this cause of death with assignment to the chlorohydrin unit." The reader's attention is directed also to the status report that was prepared by the Agency in response to 8EHQ-1187-0698.

Submission Evaluation

In the present Section 8(e) submission, Union Carbide stated that the case/control studies have not been completed and that further details regarding the reported findings will appear in the final report which will be submitted to EPA as soon as the report is available. In order for EPA to evaluate the overall significance of the reported findings, Union Carbide should be asked to ensure that EPA receives a complete copy of the final report (including the actual protocols, data, results of statistical analyses, etc.) from the company's epidemiologic studies. In addition, Union Carbide should be asked to ensure that EPA is kept apprised of any further significant findings from the company's ongoing studies.

Comments/Recommendations

The discussion pertains to the TSCA Section 8(e) reporting obligation of a company that obtains "new" information that reasonably supports a conclusion that a chemical substance or mixture that the subject company did, but does not any longer, manufacture, import, process or distribute presents a substantial

risk of injury to health or the environment. A company that finds itself in this particular situation should be aware that although it may not be required technically to submit such information to EPA under Section 8(e) of TSCA, EPA believes that a timely formal submission of such information would fall clearly within the "spirit" of the Section 8(e) reporting provision. EPA believes also that, in many cases, such a report would be of great benefit to others who currently handle the subject chemical(s) and who can then initiate any warranted actions to reduce or eliminate health or environmental risks. Finally, the Agency believes that the timely formal submission of such risk-related information would be a demonstration of the reporting company's chemical stewardship practices.

a) The Chemical Screening Branch will ask Union Carbide to ensure that EPA receives a full copy of the final report (including the actual protocols, data, results of statistical analyses, etc.) from the epidemiologic studies/analyses cited in the company's Section 8(e) submission. In addition, Union Carbide will be asked to keep EPA apprised about any further significant findings from the ongoing epidemiologic studies.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Union Carbide will be asked to describe the actions the company has taken or plans to take to notify affected workers and others about the reported epidemiologic findings.

b) The Chemical Screening Branch will review the reported information to determine the need for further OTS assessment of the submitted epidemiologic findings.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

References

1 Rinsky, R.A. et al. "Study of Mortality Among Chemical Workers in the Kanawha Valley of West Virginia" Am J Ind Med (in press)

2 Weil, C.S. et al. "Quest for a Suspected Industrial Carcinogen" Arch Ind Hyg and Occ Med 1952; 5:533-547

3 Lynch, J. et al. "An Association of Upper Respiratory Cancer with Exposure to Diethyl Sulfate" J Occup Med 1979; 21:333-341

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: DEC 31 1987

SUBJECT: Status Report* 8EHQ-1287-0702
8EHQ-1287-0703

Approved: 12/31/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

This status report covers two separate Section 8(e) submissions regarding the same chemical substance (N-isopropylaniline; N-IPA; CAS No. 768-52-5). In Section 8(e) submission 8EHQ-1287-0702, the Monsanto Company provided preliminary findings from a 3-month inhalation study of N-IPA in rats and in Section 8(e) submission 8EHQ-1287-0703, Monsanto provided the final report of a 1-month dermal study of N-IPA in rats.

Submission Description

In the cover letter to Section 8(e) submission 8EHQ-1287-0703, Monsanto presented the following summary information concerning the conduct and results of a 1-month dermal application study of N-IPA in rats:

> "In this study . . . N-isopropylaniline (N-IPA) was applied to and left unoccluded on the shaved skin (approximately 25 square centimeters; approximately 10% of the total body surface area) of groups of 10 male and 10 female Sprague-Dawley rats at targeted doses of 0, 25, 100 or 400 milligrams/kilogram (mg/kg) per day, five days per week, for 4 weeks. Plastic collars were used to prevent ingestion of the test material. Negative controls were handled identically to [the] treated animals, except [that] nothing was applied to the skin. Analyses were conducted to determine stability under simulated in-use conditions. Over a 6-hour period under simulated conditions, approximately one-third of the test material apparently volatilized.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"Cumulative body weight gains were statistically significantly reduced from that of controls for males at the 400 mg/kg/day level. Food consumption was also reduced for males at this exposure level [for] the first week of testing. Clinical signs of redness, dryness, abrasions and/or scabs were primarily seen in females at the highest two levels.

"Anemia and methemoglobinemia, with associated splenic changes of increased weight and hemosiderin deposition and hemosiderosis were present at the middle and/or high [N-IPA] exposure levels in both sexes. Epidermal thickening (acanthosis) was seen at all test levels in males and at the two highest levels in females.

"Based on the above results, N-isopropylaniline appeared to be absorbed through intact skin of rats and produced a mild skin irritation and thickening as well as anemia, methemoglobinemia, and associated splenic changes. A no observed effect level (NOEL) was not established in this study, although effects seen at the 25 mg/kg/day dosage level were minor in severity."

In the cover letter to Section 8(e) submission 8EHQ-1287-0702, Monsanto presented the following summary information concerning the conduct and preliminary results of a 3-month inhalation study of N-IPA in rats:

"Four groups of 15 male and 15 female Sprague-Dawley rats per group were exposed to mean analytical concentrations of 0, 5.3, 20 or 100 mg N-isopropylaniline per cubic meter of air in 10 m^3 inhalation chambers. A minimum of sixty-four 6-hour exposures were conducted over an approximate 14-week period. All animals survived the scheduled exposures except for one non-study related death of a high exposure level male. Notable after-exposure observations included red/brown perinasal encrustation (three occurrences) and focal loss of hair (control animals only). Observations noted on weekly weigh days were considered non-study related and were focal loss of hair, malocclusion and piloerection. A slight increase in body weight did occur in the high exposure level animals from Week 2 to study's end. Ophthalmic examination of the control and high level animals showed no ocular changes that could be attributed to test material exposure. Methemoglobinemia, occurring in all exposure groups, was considered a direct effect of N-isopropylaniline exposure and displayed a definite dose response. Decreased hemoglobin levels in the high exposure males and increased MCV [(Mean Corpuscular Volume)] values in high exposure males and females appeared to be related to [the] test material exposure. However, the [obtained] values were either within the historical control range (hemoglobin

and MCV - males) or very slightly above this range (MCV - females) and therefore, these changes are of questionable biological significance. The deviations in clinical chemistry values observed in treated animals were randomly distributed among the various exposure groups and therefore not interpreted as effects of test material exposure. The increase in both relative and absolute kidney weights in the high level animals and the dark discoloration of the high level male kidneys could be associated to test material exposure. These changes were not accompanied by any obvious microscopic abnormalities and therefore their biological significance is unknown. Microscopically, [the] increased hemosiderin in the spleens of all the high level animals was considered [to be] a direct effect of N-isopropylaniline exposure and may have contributed to the slight increase in splenic weight for this group. The increase in hemosiderin pigment in concert with the aforementioned changes in hematology suggest that there may be some alteration in red blood cells kinetics leading to accelerated red blood cell destruction. The mild increase in absolute spleen weight for mid exposure females was not accompanied by any obvious microscopic abnormality and therefore was probably of no biological or toxicological significance. All other microscopic changes were considered non-exposure related. In conclusion, the occurrence of elevated methemoglobin concentrations in all exposure groups precludes the identification of a 'no-effect' level for the inhalation of N-isopropylaniline aerosol, as [the chemical was] administered in this study."

According to Monsanto's TSCA Section 8(e) submissions, "dermal contact and inhalation are expected to be the primary routes of occupational exposure to N-isopropylaniline." In addition, Monsanto reported that "man is known to be much more sensitive to methemoglobinemia following exposure to aromatic nitro (and amino) compounds than the rat or rabbit."

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible once the Agency receives a complete copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, etc.) from Monsanto's 3-month inhalation study of N-IPA in rats.

Current Production and Use

A review of the production range (includes importation volumes) statistics for N-isopropylaniline (CAS No. 768-52-5), which is listed in the initial TSCA Chemical Substance Inventory, has shown that approximately 1 million to 10.1 million pounds of this chemical substance were reported as manufactured and/or imported

in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

In its TSCA Section 8(e) submissions, Monsanto provided the following information with regard to the potential for exposure to N-IPA:

> "Appropriate personal protective measures and effective engineering controls are utilized in order to control workplace exposure to N-IPA at or below acceptable levels (ACGIH TLV/TWA: 2 ppm, 10 mg/m^3). The hazards of N-isopropylaniline exposure and the protective measures necessary to minimize exposure are detailed in the Material Safety Data Sheet (MSDS) for N-IPA."

According to the Condensed Chemical Dictionary (10th Edition), N-isopropylaniline is a yellow liquid (boiling point 206°C) used as a chemical intermediate and in the dyeing of acrylic fibers.

Comments/Recommendations

a) The Chemical Screening Branch will request Monsanto to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, etc.) from the 3-month N-isopropylaniline inhalation study that was the subject of 8EHQ-1287-0702.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Monsanto will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Monsanto is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of N-isopropylaniline.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of N-isopropylaniline.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: DEC 31 1987

SUBJECT: Status Report* 8EHQ-1287-0704 Approved: 12/31/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

Texaco Inc. reported that the company recently learned that a National Toxicology Program (NTP) bioassay of naphthalene (CAS No. 91-20-3) in male and female B6C3F1 mice had been completed. According to Texaco, the final report of the study is awaiting quality assurance review and is not ready for distribution by NTP. Texaco reported also that it was the impression of the NTP investigator in charge of the study that "naphthalene caused lung tumors in male mice." Texaco stated further that during recent phone conversations with NTP, the company obtained the following information with regard to the conduct and results of the study:

"Respiratory Response - Naphthalene

ppm	Adenomas* Males	Adenomas* Females	Carcinomas Males	Carcinomas Females
0	7/70	5/69	0/70	0/69
10	17/69	5/66	2/69	0/66
30	16/67	14/68	2/67	0/68
30	11/68	14/67	4/68	1/67

* Lung alveolar-bronchial,

Exposure, 6 hrs/day, 5 days/week, 103 weeks"

According to Texaco, the obtained data "have not undergone review by the pathology working group of NTP."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible when EPA receives from NTP a copy of the draft technical report for peer review by Technical Report Peer Review Subcommittee of NTP's Board of Scientific Counselors. As in similar situations involving other previous TSCA Section 8(e) submissions, EPA should contact NTP to find out when NTP plans to release a formal report of this study.

Current Production and Use

A review of the production range (includes importation volumes) statistics for naphthalene (CAS No. 91-20-3), which is listed in the initial TSCA Chemical Substance Inventory, has shown that approximately 365 million to 1.55 billion pounds of this chemical were reported as manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

In its TSCA Section 8(e) submission, Texaco reported that the company manufactures naphthalene "as a high purity, low sulfur naphthalene of petroleum extraction." In addition, Texaco stated that the uses of naphthalene "may include insecticides, dyes, moth repellents, surfactants and leather tanning chemicals."

Comments/Recommendations

It should be noted that Part VII of EPA's Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978) provides a number of examples of the types of information that need not be reported to EPA under Section 8(e) of TSCA (i.e., information about which subject persons can automatically assume the Agency to be "adequately informed"). In addition to the examples cited in Part VII, subject persons can automatically assume, for the purposes of TSCA Section 8(e) reporting, that EPA has been adequately informed about substantial risk information contained in a formal publication or report released to the general public by an agency of the U.S. Government. It should be noted also that EPA's position on the Section 8(e)-reportability of results of NTP bioassays has been described previously (see EPA's "status report" prepared in response to TSCA Section 8(e) submission number 8EHQ-1282-0467). In summary, EPA's position on Section 8(e) as it relates to the results of NTP bioassays is as follows:

A subject person can assume automatically that EPA has been "adequately informed" about the results of an NTP carcinogenesis bioassay once the NTP formally releases copies of the draft technical report from that study for peer review by the Technical Report Peer Review Subcommittee of NTP's Board of Scientific Counselors. This assumption can be made because EPA's Office of Toxic Substances (OTS) routinely receives full copies of all draft NTP carcinogenesis biosassay technical reports formally released by NTP for peer review.

Therefore, if a subject company obtains (i.e., knows of or possesses) toxicologic information concerning an NTP bioassay and there has not been a formal public release of those findings by NTP (e.g., formal release of the draft technical report for peer review), the subject company should immediately consider the need to report the information to EPA under Section 8(e) of TSCA.

It should be noted that EPA has correctly received a number of TSCA Section 8(e) submissions (usually comprised of 1 to 2 pages) filed by companies that obtained toxicologic data from studies conducted by or for agencies of the U.S. Government that have not been published or released formally to the general public. In each of these cases, OTS has immediately initiated appropriate followup activities directly with the other Federal agency in order to minimize and, in most cases, eliminate further TSCA Section 8(e) reporting obligations on the part of the submitting company to provide such items as complete copies of supporting data or actual technical reports.

a) The Chemical Screening Branch will contact NTP to determine when the findings from NTP's bioassay on naphthalene will be formally released.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Texaco will be asked to describe the actions the company has taken or plans to take 1) to notify workers/others about the reported information, and 2) to reduce or eliminate exposure to naphthalene.

b) Upon EPA's receipt of the NTP report on naphthalene, the Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JAN 21 1988

SUBJECT: Status Report* 8EHQ-1287-0705

Approved: James F. Darr 1/26/88

FROM: David R. Williams, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The Monsanto Company provided a full copy of the final report of a 1-month inhalation study of diisopropylamine (DIPA) in rats. The cover letter to Monsanto's Section 8(e) submission presented the following information with regard to the conduct and results of the study:

> "In this study . . . four groups of 15 males and 15 female Sprague-Dawley rats per group were exposed for 6 hours per day (excluding weekends and holidays) to diisopropylamine (DIPA) at mean analytical concentrations of 0.0, 0.10, 0.60, and 2.00 milligrams per liter of air for a maximum of 23 exposures over a one-month period. Three high exposure level animals died during the study. Gross signs or irritation to [the] eyes and respiratory tract occurred in the mid and high exposure level animals. Ophthalmic examinations showed a dose-related corneal keratopathy. Decreased body weights were seen in both mid and high level animals. Increased red blood cell counts, hemoglobin and hematocrit measurements existed in the high level males and among mid and high exposure level females. Significantly lower white blood cell counts (due to reduced absolute numbers of lymphocytes) were present in males from all exposure levels.
>
> "Occurrences of decreased mean corpuscular volume, serum chloride, total protein, albumin and increased serum cholesterol all seemed to be directly associated to compound exposure. Thymic atrophy and seminal

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

> vesicle atrophy were also observed in high exposure animals. Pathology findings consistent with gross signs of irritation were inflammatory lesions in the nasal passages of all exposure groups and those in the trachea, lung and corneas of high exposure groups. Since lymphocytopenia in males and lesions in the cornea and nasal passages of both sexes occurred at the lowest exposure level (0.10 mg/l in air), a 'no-effect level' for DIPA could not be determined in this study."

In its submission, Monsanto noted that the "primary hazard from diisopropylamine is due to its marked irritancy to skin, eyes and mucosae."

Submission Evaluation

According to a number of secondary scientific literature sources, DIPA has been shown in acute animal studies to be irritating upon contact with skin and mucous membranes and moderately toxic when administered orally. Overall, however, the secondary literature sources consulted by EPA do not present any information on the systemic toxicity of DIPA resulting from long term exposure.

In Monsanto's 1-month inhalation study in male and female rats, the DIPA concentrations of 0.10, 0.60 and 2.00 mg/l air for 6 hours a day for a maximum of 23 exposure days over a one month period are equivalent to approximately 12, 72 and 240 mg/kg/day, respectively. Gross signs of irritation to the respiratory tract and eyes were observed in the animals in the mid and high DIPA dose groups; ophthalmic examinations revealed a dose-related corneal keratopathy. In addition, decreased body weights were observed at the mid and high DIPA dose levels. The adverse blood effects seen included increased red blood cell counts, hemoglogin and hematocrits in the high dose males and in the mid and high dose females. A decrease in white blood cells was seen in male rats at each DIPA exposure. The observed decrease in the mean corpuscular volume, serum chloride, total protein and albumin, and the increase in serum cholesterol also appear to be directly associated with exposure to DIPA. Further, thymic atrophy (males and females) and seminal vesicle atrophy (males) were seen in the high dose groups. Also, inflammatory lesions were found in the nasal passages in animals from all exposure groups and in the trachea, lung and corneas of the animals from the high exposure group.

Current Production and Use

A review of the production range (includes importation volumes) statistics for diisopropylamine (CAS No. 108-18-9), which is listed in the initial TSCA Chemical Substance Inventory, has shown that 0 to 1,000 pounds of this chemical were reported as manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s)

reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

According to the Condensed Chemical Dictionary (10th Edition), diisopropylamine is a volatile (boiling point 84.1°C) colorless liquid used as a catalyst and chemical intermediate.

In its Section 8(e) submission, Monsanto reported that the "Material Safety Data Sheet (MSDS) for diisopropylamine details the hazards of the chemical and the necessary protective measures which must be taken to control workplace exposure at or below acceptable levels (ACGIH/TLV: 5 ppm)." Finally, Monsanto stated that the company "no longer manufactures diisopropylamine."

Comments/Recommendations

The discussion pertains to the TSCA Section 8(e) reporting obligation of a company that obtains "new" information that reasonably supports a conclusion that a chemical substance or mixture that the subject company did, but does not any longer, manufacture, import, process or distribute presents a substantial risk of injury to health or the environment. A company that finds itself in this particular situation should be aware that although it may not be required technically to submit such information to EPA under Section 8(e) of TSCA, EPA believes that a timely formal submission of such information would fall clearly within the "spirit" of the Section 8(e) reporting provision. EPA believes also that, in many cases, such a report would be of great benefit to others who currently handle the subject chemical(s) and who can then initiate any warranted actions to reduce or eliminate health or environmental risks. Finally, the Agency believes that the timely formal submission of such risk-related information would be a demonstration of the reporting company's chemical stewardship practices.

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Monsanto will be asked to describe the nature and results, if available, of all studies (other than those reported already to the Agency or those published in the open scientific literature) about which Monsanto is aware or that Monsanto has conducted, is conducting or plans to conduct to determine the toxicity of diisopropylamine.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of diisopropylamine.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: FEB 19 1988

SUBJECT: Status Report* 8EHQ-1287-0706

Approved: MAR 15 1988

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

TO: Joseph J. Merenda, Director
Existing Chemical Assessment Division/OTS/OPTS

Submission Description

Via private counsel, Borg-Warner Chemicals, Inc. submitted the final report from a 4-month oral toxicity study of Weston XR 1532 in dogs. According to the submission, "Weston XR 1532 was the identification used by Borg-Warner in 1980 for a product now known as Ultranox 626 [(major component: bis(2,4-di-tert-butylphenyl)pentaerythritol diphosphite, CAS No. 26741-53-7)]." The "ABSTRACT" section of the submitted final report contains the following information regarding the conduct and results of this subchronic dog study:

> "This study . . . was designed to assess the toxicity of Weston XR 1532 when administered, via gelatin capsules, to Beagle dogs (4/sex/group) at dose levels of 0, 4, 12 and 40 mg/kg/day for 4 months.
>
> "One high dose female (4686) exhibited progressive fore and hind limb paralysis accompanied by decreasing body weight and food consumption and was sacrificed on Test Day 86. All of the other control and treated animals survived the duration of the study. The physical and neurological observations of these animals did not reveal any effects which could be attributed to the administration of the test material.
>
> "The mean body weights of the treated males were slightly greater than control prior to the initiation of dosing and throughout the 4 month treatment period. Mean food consumption values in the treated males were slightly lower than control during the treatment period. Mean body weight and food consumption values of the surviving treated females were unremarkable.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

> "A subacute, eosinophilic pneumonia was observed microscopically in four of eight high-dose animals, one of eight mid-dose animals and two of eight low-dose animals. This condition was not observed in any of the control animals. The etiology of these pulmonary lesions could not be determined.
>
> "Seven of [the] eight high-dose animals displayed degenerative myelin lesions. These lesions were confined to the high-dose group and were considered related to the administration of the test material. One animal (4686) displayed clinical manifestations of severe abnormalities of the axonal fibers and myelin.
>
> "Ophthalmology, hematology, clinical chemistry, urinalysis, absolute and relative organ weights and gross necropsy findings did not reveal any effects that could be attributed to the administration of Weston XR 1532."

Borg-Warner also submitted a Material Safety Data Sheet (MSDS) covering Ultranox 624 (the subject chemical alone), Ultranox 626 (the subject chemical containing approximately 0.1% by weight triisopropanolamine (TIPA; CAS No. 122-20-3)) and Ultranox 626A (a "compacted" form of Ultranox 626). With regard to acute toxicity of the subject product(s), the submitted MSDS reports an acute rat oral LD50 of 5.58 g/kg, an acute rat inhalation LC50 of >2 mg/l, and an acute rabbit dermal LD50 of >200 mg/kg; the MSDS reports also that an acute dermal study (species not given but is assumed to be rabbits) showed the product(s) to be irritating with some necrosis observed. In addition to citing the results of the subchronic oral dog study, the MSDS states that "rats fed for 90 days at 100, 300, or 1000 ppm showed no effects except some very slight to slight extramedullary hematopoiesis in the liver and spleen of the animals fed at the highest dose." The MSDS states also that "hens dosed from 0.8 to 6.8 g/kg once and then again 21 days later showed no signs of neurotoxicity." In addition, the MSDS states that no adverse behavioral, gross or histologic effects were seen in rats in a two year feeding study at dietary levels of 100 or 500 ppm. The MSDS states also that the test material was not teratogenic in rabbits dosed (route not specified; assumed to be oral) at 20, 50 or 200 mg/kg. Finally, the MSDS presents the following statements about neurotoxicity:

> "Animal studies have indicated in one test that the material is a neurotoxin at the high dose in dogs. Three other tests in other types of animals, including a 2 year study in rats, did not produce neurotoxicity. This material is considered to be a suspect neurotoxin at high levels of exposure. Symptoms of neurotoxicity can include weakness, staggered walk, tremors, or even paralysis."

In its submission, Borg-Warner provided the following information regarding the actions that the company took voluntarily to notify

customers about the preliminary/final results of the company's subchronic oral study in dogs:

> "As the result of a 'Dear Customer' letter . . . dated April 7, 1980, users were specifically advised of the interim evidence of neurotoxicity of Ultranox 626. This was followed by a second [Borg-Warner] letter dated February 6, 1981, which described the final results of the dog study as well as the results of a study in hens where no neurotoxicity was observed. . . . . Subsequently, all users received [Material Safety Data Sheets] disclosing the final results of the four-month feeding study in dogs. . . . . A neurotoxicity warning also appears on the label of each package of Ultranox 626. . . . ."

It should be noted also that a submitted Ultranox 626 product label carries the following precautionary statement:

WARNING

MAY CAUSE SKIN IRRITATION.

MAY AFFECT NERVOUS SYSTEM.

DO NOT GET IN EYES OR ON SKIN.

USE WITH ADEQUATE VENTILATION.

LABORATORY ANIMAL STUDIES INDICATED NEUROTOXIC EFFECT AT HIGH DOSE LEVELS.

In its TSCA Section 8(e) submission, Borg-Warner reported that 1) "the sole use of Ultranox 626 is as a stabilizer for plastic resins" and 2) "the product is compounded into mainly olefin polymers where it becomes encapsulated by the plastic material." The submission reports also that in order for this product to be commercially successful, Borg-Warner recognized the need for clearance by the U.S. Food and Drug Administration (FDA) for use of the product in food packaging materials. The submission presents the following background information with regard to Borg-Warner's request for and ultimate receipt of clearance by FDA for the product:

> "On September 17, 1979, Borg-Warner filed a Food Additive Petition (FAP) [with FDA] for the use of Ultranox 626 as a stabilizer in polymer systems. The petition number OB3478 was assigned by FDA. 46 Fed. Reg. 12332 (Feb. 13, 1981). As part of its review of FAP OB3478, a three-month oral toxicity study in non-rodent species was requested by FDA. Borg-Warner responded by commissioning the study in beagle dogs that is the subject of this submission. [According to the final report of this subchronic dog study, dosing

was begun on September 13, 1979.] The preliminary data from that study noted fore and hind limb paralysis accompanied by decreasing body weight loss in one [female] dog at the high dose (40 mg/kg) level. This finding prompted Borg-Warner to send [to] all of its customers a 'Dear Customer' letter dated April 7, 1980 . . . advising them of the interim neurotoxicity finding. Borg-Warner also decided at this time to extend the study for an additional thirty days.

"At the conclusion of the study, the single high dose female was the only animal to display clinical signs of central nervous system disorders. Seven of the eight high-dose animals were found to display degenerative myelin lesions, the only group to exhibit such lesions. The final report [of the 4-month study in dogs] was received by the company shortly after May 28, 1980, and submitted to FDA promptly. In granting the petition, FDA found the substance to be safe for use in food contact materials under Section 409 of the Federal Food, Drug and Cosmetic Act. 21 U.S.C. 348. The [FDA] regulation at 21 CFR Section 178.2010 was amended on November 20, 1981, to include Ultranox 626. 46 Fed. Reg. 57034. . . . ."

Borg-Warner's submission also presents several arguments believed by the company to support its contention that the subchronic oral dog study results were not required to be reported to EPA under Section 8(e) of TSCA. The following statements contained in the submission outline Borg-Warner's position in this matter:

- "The neurotoxicity data on Ultranox 626 would have long since been submitted to EPA -- either as a Section 8(e) notice or as an FYI [("For Your Information")] submission depending upon the decision of Borg-Warner's Risk Review Group -- had not Borg-Warner been advised by . . . [the EPA's TSCA Assistance Office (TAO)] in April or May 1980, and again as recently as December 7, 1987, that toxicology studies submitted to FDA did not have to be submitted to EPA under Section 8(e).

- "Consistent with the intent of [TSCA] Section 8(e), Borg-Warner has not suppressed the . . . [4-month oral toxicity study of Ultranox 626 in dogs]. Quite the contrary, it has been submitted to regulatory agencies in at least eight foreign countries, is in the public domain by virtue of its submission to FDA and the neurotoxic effect noted in the study are disclosed in the Material Safety Data Sheet (MSDS) sent to every purchaser when the product is sampled or sold.

- "The neurotoxicity of organophosphorus compounds is well-known and the data merely corroborate known information about these materials.

- o "Given the general knowledge of the toxicity of these compounds, there has never been any significant exposure to Ultranox 626 and, hence, no significant risk to man or the environment."

Borg-Warner's submission also raises a number of issues related to application of EPA's May 15, 1987 TSCA Sections 8, 12, and 13 "Enforcement Response Policy" (ERP) in this matter.

Submission Evaluation

In summary, Weston XR 1532 (now known as Ultranox 626), which contains bis(2,4-di-tert-butylphenyl)pentaerythritol diphosphite, was administered orally via gelatin capsules to Beagle dogs (4/sex/group) at doses of 4, 12 and 40 mg/kg/day for four months. The study assessed the potential neurotoxicity of the product by way of behavioral and neuropathological examinations.

A minimal battery of behavioral procedures was used to assess the effects of the test material. Behavioral signs of toxicity were observed in only one female and only at the highest dose. These signs included progressive forelimb and hindlimb paralysis, and decreased body weight and food consumption; no clinical observations were reported for the other animals in the study.

The neuropathological assessment was conducted on the following tissues: brain (3 sections), eye (with the optic nerve), sciatic nerve and spinal chord. In general, tissues were fixed in 10% neutral buffered formalin. Central nervous system tissues were cut at 10 microns and stained with hematoxylin and eosin and with luxol fast blue. Seven of the eight high dose animals displayed degenerative myelin lesions. There were no reported lesions at lower dose levels.

The study protocol used was adequate to assess the potential for neurotoxicity. Neurotoxicity was clearly observed at the highest dose level. However, the protocol was limited in its ability to adequately assess the extent of the damage or to determine the minimal effective dose. It is possible that effects would have been observed if additional doses between 12 and 40 mg/kg had also been tested. It is also possible that effects could have been observed if a more complete neuropathological assessment had been conducted. Phosphites can produce a different pattern of neuropathological endpoints compared to agents that produce an organophosphate induced delayed neuropathy (OPIDN; Veronesi et al., 1986; Veronesi and Dvergsten, 1987). For example, in the rodent model of OPIDN, the fasciculus gracilis is the earliest and most severely damaged tract; only after repeated exposures are the lateral and ventral columns of the cervical chord involved. In contrast, with some phosphites, the most vulnerable tracts are those located in the lateral and ventral columns with a sparing of the large diameter ascending tracts of the dorsal columns. If the neurological assessment of such a phosphite in the rat was restricted to the fasciculus gracilis, the extent of

the adverse effects would likely be lost. Similarly, it is possible that the areas examined in Borg-Warner's subchronic dog study did not adequately characterize the damage to the nervous system. Furthermore, it is possible that if more sophisticated neuropathological assessment procedures had been used (e.g., electron microscopy, use of plastic media or other specialized stains), other effects might have been observed.

The neurobehavioral procedures used, although adequate to assess neurotoxicity, were also limited in nature. The description of the procedures for behavioral assessment stated that they were limited to "behavior, movements, reactivity to stimuli, muscle tone." A clear description of these endpoints was not given. For example, what behavior was observed? Were the movements forced? What were the characteristics of the stimuli used? In addition, the discussion of the examination of different reflexes (e.g., righting, patellar) did not adequately describe how these observations were made (e.g., order, time after dosing). The autonomic signs examined were pupil size and secretions; other autonomic signs that have proven to be reliable and sensitive in other studies but were not included in the present dog study are piloerection, respiration, urination and vocalization. Although functional effects were observed in only one female in the high dose group, it cannot be excluded that the absence of functional effects in the other animals was due to the insensitivity of the neurobehavioral measures used. Several other important questions also arise with regard to the neurobehavioral examinations. For example, were these neurobehavioral examinations conducted on a "blind" basis? If different observers were used, was the inter-observer reliability controlled? If so, how? If these factors are not controlled appropriately, the power of the dog study to detect neurobehavioral problems could be adversely affected. The ability to detect neurobehavioral effects has been shown to be highly correlated to the test conditions employed (Reiter and MacPhail, 1979).

In conclusion with regard to the submitted subchronic dog study, neurotoxicity was observed at the high dose level and included degenerative myelin lesions in seven of the eight animals tested. Clinical symptoms of toxicity, which were reported in only one female at the highest dose level tested, included progressive forelimb and hindlimb paralysis, and decreasing body weight and food consumption; because more extensive neuropathological and behavioral examinations were not conducted, the possibility that other neurobehavioral/neuropathological effects occurred cannot be excluded. Considering that there was such a large gap between the 12 and 40 mg/kg/day dose levels, it is also possible that neurotoxicologic effects could have occurred at doses lower than 40 mg/kg/day. It is concluded, therefore, that the test material caused significant neurological effects at the highest dose level tested in this subchronic oral study in dogs.

EPA should request Borg-Warner to submit full copies of the final reports (including the actual experimental protocols, results of

gross and histopathological examinations, etc.) from the hen study, 90-day rat study and two-year rat study cited in the provided Ultranox 626 MSDS. The Agency may also want to request Borg-Warner to submit complete copies of some or all of the other studies cited in the MSDS.

Current Production and Use

A review of the production range (includes importation volumes) statistics for CAS No. 26741-53-7, which is listed in the initial TSCA Chemical Substance Inventory, has shown that no 1977 manufacture or importation of the chemical was reported or that all manufacturing and/or importation data submitted were claimed to be TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial Inventory and cannot be disclosed (Section 14(a) of TSCA; U.S.C. 2613(a)). All of the data submitted for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

According to the submission, during the time that Borg-Warner was seeking FDA approval of Ultranox 626 under the food additive regulations, Borg-Warner was working with prospective customers in establishing appropriate applications of the chemical. The submission states that "during this time, Borg-Warner sold limited quantities of Ultranox 626 for those few applications where customers did not demand an FDA clearance" and "sales in 1979 were about 10,000 pounds to only one customer." In addition, the submission states that "by 1980, sales had increased to 60,500 pounds to five customers." The submission states further that "traditionally, this product has been purchased by a relatively few customers who are well aware of the hazards associated with organophosphite materials."

In Appendix B of Borg-Warner's submission, the company provided the following additional information regarding the manufacture of and the potential for exposure to Ultranox 626:

> "Borg-Warner Chemicals is the USA's only manufacturer of the chemical substance identified as Ultranox 626 . . . The product is currently manufactured at one site in the United States. The sole commercial use of Ultranox 626 is as a stabilizer in polymer systems. Borg-Warner Chemicals exports approximately 30% of the Ultranox 626 it manufactures. The remaining 70% is used domestically by large resin manufacturers that compound the Ultranox 626 into mainly olefin polymers at which point the potential environmental and human exposure to Ultranox 626 is reduced to near zero. Accordingly, human and environmental exposure can be extremely well-defined as involving relatively few users, each sophisticated enough to be well aware of the potential for neurotoxicity of organophosphorus compounds. . . . .

"The number of Borg-Warner employees involved on a daily basis in [the] manufacturing [of] Ultranox 626 is approximately fourteen. Ultranox 626 is an essentially dust-free solid and is not readily absorbed through the skin; employees handling Ultranox 626 even without proper protection would not be expected to absorb a significant amount of the substance. The airborne concentration of Ultranox 626 to which employees might be exposed over an 8 hour period is less than 2 parts per million (ppm) (w/w). In order to inhale a quantity of Ultranox equivalent to 40 mg/kg body weight (the dose at which a neurotoxic effect was observed in the canine feeding study), an employee would need to be exposed to an airborne Ultranox 626 concentration of 210 ppm (w/w) over a period of 8 hours. ["Based on assumptions that a 70 kg worker inhales 10 cubic meters of air over 8 hours and that all inhaled Ultranox 626 would be retained."] . . . . [Note: The submitted Ultranox 626 Material Safety Data Sheet, recommends that exposure to Ultranox 626 be limited to 10 mg/m^3 air as an 8-hour time weighted average (TWA).]

"Plastic resins manufactured with Ultranox 626 are sold to molders for fabrication into articles. Ultranox 626 is typically encapsulated in such articles at a level of 300-500 ppm. The Food and Drug Administration (FDA), having reviewed the [dog] toxicity study that is the subject of this submission, has cleared Ultranox 626 for use in food-contact plastic materials at a level of up to 1000 ppm in olefin polymers and at levels up to 8600 ppm in polyvinyl chloride copolymers. . . . . In doing so, FDA confirmed that the use of Ultranox 626 in food packaging materials not only poses no significant risk, but that such use is safe. . . . ."

Comments/Recommendations

Although EPA acknowledges the actions taken by Borg-Warner to notify customers and others, it is EPA's initial position that the neurotoxicologic effects from the subchronic oral dog study should have been reported to EPA previously under Section 8(e), the substantial risk information reporting provision of TSCA. The following discussion provides the basis for EPA's position:

> Section 8(e) states that "any person who manufactures, [imports,] processes or distributes in commerce a chemical substance or mixture and who obtains [(i.e., knows of or possesses)] information which reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment shall immediately inform the [EPA] Administrator of such information unless such person has actual knowledge that the Administrator has been adequately informed of such information."

> The preface to Part V of EPA's TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978) explains that a "substantial risk of injury to health . . . is a risk of considerable concern because of (a) the seriousness of the effect . . . and (b) the fact or probability of the occurrence [of that serious effect]." With regard to the seriousness of the effect, Part V explains that EPA considers the types of health effects for which substantial risk information must be reported to include "any pattern of effects or evidence that the chemical substance can produce . . . toxic effects resulting in . . . serious or prolonged incapacitation." Information regarding these types of serious effects can be obtained either directly or inferred from designed studies (e.g., studies in animals) as described in Part VI of the Section 8(e) policy statement. Part VI explains also that a subject "person is not to delay reporting until he obtains conclusive information that a substantial risk exists, but is to immediately report any evidence that reasonably supports that conclusion."
>
> With regard to the "fact or probability of its [(i.e., the serious effect's)] occurrence" criterion, Part V of the Section 8(e) policy statement explains that certain types of adverse health effects (e.g., neurotoxicologic effects) are considered by EPA to be so serious that relatively little or no weight should be attached to the implicated chemical's exposure in determining whether a risk is substantial.

The following discussion addresses Borg-Warner's rationale (described previously; see Submission Description section of this status report) as to why the subchronic oral dog study results were not submitted previously to EPA under Section 8(e) of TSCA:

> Borg-Warner stated that the company sought and received (by phone from EPA's TSCA Assistance Office (TAO)) guidance regarding the TSCA Section 8(e)-reportability of information submitted to FDA. Although it is not possible to determine precisely the questions asked by Borg-Warner, the responses (if any) given by TAO in this matter or to whom Borg-Warner spoke, it is clear that EPA's TSCA Section 8(e) policy statement does not authorize reporting to other Federal agencies as a way to satisfy EPA's Section 8(e) reporting requirements. Part VII of the Section 8(e) policy statement explains that information need not be reported to EPA pursuant to Section 8(e) if the information has been reported already to EPA under another mandatory reporting provision of TSCA or some other authority administered by EPA. Further, EPA has made it clear that Part VII of the Section 8(e) policy statement does not exempt from

Section 8(e) reporting information submitted elsewhere under an authority administered by an agency other than EPA (see EPA's response to Comment 21 in Appendix B of the TSCA Section 8(e) policy statement which explains that until successful information exchange systems are in place between EPA and other Federal agencies and the policy statement is amended to exempt certain reports made to other specified Federal agencies, "substantial risk information must be reported directly to EPA.") (emphasis added)

Borg-Warner contends that the data from the company's subchronic oral dog study merely corroborate known information. While the Agency agrees that much is known about the neurotoxic properties of many organophosphorus compounds, the neurotoxicologic findings from Borg-Warner's dog study appear to be first and only neurotoxicologic findings to date for the subject plastic resin stabilizer. Further, Borg-Warner's understanding that Section 8(e) reporting is triggered upon receipt of new serious toxic effects information obtained from an animal study involving a different route of exposure is reflected in Borg-Warner's past TSCA Section 8(e) reporting practices. For example, on June 23, 1982, Borg-Warner submitted data on triphenyl phosphite "in accordance with Section 8(e) of the Toxic Substances Control Act" (Section 8(e) submission number 8EHQ-Ø682-Ø451 et seq). In this previous Section 8(e) notice, Borg-Warner stated that triphenyl phosphite (an organophosphite used primarily as a stabilizer in plastics) had been found to produce neurotoxic effects in chickens exposed to the chemical via the skin. In submitting these neurotoxicologic findings to EPA under Section 8(e) of TSCA, Borg-Warner reported that "it has been known for many years and reported in the open literature that triphenyl phosphite can produce neurotoxic effects in animals when taken orally." It should be noted, however, that Borg-Warner did not state nor imply that the company considered the submitted data on triphenyl phosphite to be merely corroborative and not subject to reporting to EPA under Section 8(e) of TSCA. In fact, Borg-Warner's triphenyl phosphite submission ends with the following statement: ". . . [Borg-Warner trusts] that this information fulfills [the Agency's TSCA Section 8(e)] reporting requirements."

With regard to Borg-Warner's contention that "there has never been any significant exposure to Ultranox 626 and, hence, no significant risk to man or the environment," Part V of the Section 8(e) policy statement makes it clear that in the case of new serious toxic effects information, little or no weight is to be given to exposure in deciding whether to submit new toxicity information to EPA under Section 8(e) of TSCA.

Based on the preceding discussion, it is EPA's initial position that the neurotoxicologic findings from Borg-Warner's subchronic oral study of Weston XR 1532 in dogs should have been submitted previously under Section 8(e) of TSCA; the fact that Borg-Warner provided this dog study to FDA for review and ultimate approval of Ultranox 626 for use in certain food packaging materials did not in any way relieve Borg-Warner of its obligation to report the observed neurotoxicologic effects to EPA under Section 8(e) of TSCA.

a) The Existing Chemical Assessment Division (ECAD/OTS) will ask Borg-Warner to submit any further information regarding Borg-Warner's rationale for not submitting the neurotoxicologic findings from the subchronic dog study at an earlier date under Section 8(e) of TSCA. Borg-Warner will be asked also to submit full copies of the final reports (including the actual experimental protocols, results of gross and histopathological examinations, results of any statistical analyses, etc.) from all studies (other than the subchronic oral study in Beagle dogs) that were cited in the submitted Ultranox 624/626/626A Material Safety Data Sheet.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Borg-Warner will be asked to describe the nature and results, if available, of all studies (other than those submitted already to EPA, those cited in the open scientific literature, or those cited in the provided Ultranox 624/626/626A MSDS) about which Borg-Warner is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of bis(2,4-di-tert-butylphenyl)-pentaerythritol diphosphite or products that contain the subject chemical substance.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

References

Veronesi, B., Padilla, S. and Newland, D.; Biochemical and neuropathological assessment of triphenyl phosphite in rats. Toxicol. Appl. Pharmacol. 83:203-210, 1986.

Veronesi, B. and Dvergsten, C.; Triphenyl phosphite neuropathy differs from organophosphorus-induced delayed neuropathy in rats. Neuropathology and Appl. Neurobiol. 13:193-208, 1987.

Reiter, L.W. and MacPhail, R.C.; Motor activity: A survey of methods with potential use in toxicity testing. Neurobehav. Toxicol. 1: Suppl. 1, 53-66, 1979.

NOTE: The reader's attention is directed to the following status report prepared by EPA in response to 8EHQ-0488-0706 Followup Response.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUN 24 1988

SUBJECT: Status Report* 8EHQ-0488-0706 FLWP

Approved: JUN 24 1988

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

TO: Joseph J. Merenda, Director
Existing Chemical Assessment Division/OTS/OPTS

Note

The reader's attention is directed first to the "Status Report" prepared by EPA following receipt of initial TSCA Section 8(e) submission number 8EHQ-1287-0706.

Submission Description

In 8EHQ-0488-0706 Followup Response, Borg-Warner Chemicals, Inc. submitted final reports from 16 toxicological studies conducted by or for Borg-Warner on a product containing bis(2,4-di-tert-butylphenyl)pentaerythritol diphosphite (CAS No. 26741-53-7) as the major component. This product, known at one time as Weston XR 1532, Weston XR 1452, Weston MDW-6140 or CDP-1106, is known presently as Ultranox 626. The following studies were contained in Borg-Warner's followup response:

- o 90-day oral toxicity study (rats);
- o two acute oral toxicity studies (chickens);
- o two primary dermal irritation studies (rabbits);
- o hypersensitivity study (guinea pigs);
- o two Ames Salmonella typhimurium mutagenicity studies;
- o acute inhalation LC50 study (rats); acute dermal irritation toxicity study (rabbits); skin corrosivity study (rabbits);
- o acute oral delayed neurotoxicity study (chickens);

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

- o 8-week bioaccumulation study (fish);
- o 2-year oral toxicity study (rats);
- o oral teratology study (rabbits);
- o 6-month oral toxicity study (rats);
- o oral (feeding) reproduction study (rats);
- o acute oral toxicity study (rats).

In its followup response, Borg-Warner reiterated its rationale as to why the neurotoxicological findings from the company's subchronic oral toxicity study of Weston XR 1532 in Beagle dogs were not submitted under Section 8(e) of TSCA. A discussion of this subchronic study and Borg-Warner's rationale can be found in the Submission Description and Comments/Recommendations sections of the status report prepared for 8EHQ-1287-0706 Initial.

Submission Evaluation

In general, the mammalian studies contained in Borg-Warner's followup response do not suggest that the subject product caused neurological changes. In evaluating these mammalian toxicity studies, however, the Agency has found that there are a number of problems associated with the design/interpretation of many of the submitted studies that can reduce the strength of the findings for assessing neurological effects. For example, some of the studies 1) did not utilize a positive control, 2) did not include any neuropathological examinations, and/or 3) did not contain a clear description of the neurobehavioral examination/assessment. These "negative" neurotoxicological findings do not in any way, however, alter the fact that clear, serious neurotoxicological effects were observed in Borg-Warner's subchronic oral toxicity study of the subject product in Beagle dogs. EPA's evaluation of the results of this subchronic oral study can be found in the Submission Evaluation section of the status report prepared for 8EHQ-1287-0706 Initial.

Based on a preliminary evaluation of the studies presented in Borg-Warner's followup response for toxic effects other than neurotoxic effects, the tested product does not appear to cause mutagenic, oncogenic or teratogenic effects; further, the product does not appear to bioaccumulate. With regard to the results of the reproduction study in rats (in which Weston XR 1452 was administered via the feed), Borg-Warner should be asked to supply the raw data from this study to EPA in order for the Agency to attempt to determine if the 20% reduction in fertility observed in the high dose (500 ppm) group is cause for concern.

Current Production and Use

Ultranox 626 is used as a stabilizer in polymer systems. Further information relating to production/use of this chemical can be found in the Current Production and Use section of the status report prepared by EPA in response to 8EHQ-1287-0706 Initial.

Comments/Recommendations

Although the results of the studies included in 8EHQ-0488-0706 Followup Response do not indicate any overt neurotoxicological effects for Borg-Warner's product known now as Ultranox 626, this does not alter the fact that serious neurotoxicological effects were observed in Borg-Warner's subchronic oral toxicity study in Beagle dogs. EPA has determined, therefore, that the serious neurotoxicological effects from Borg-Warner's subchronic oral study in Beagle dogs should have been submitted in a timely manner under Section 8(e) of TSCA. The basis for EPA's position on the Section 8(e)-applicability/reportability of the subject findings as well as EPA's comments on Borg-Warner's rationale can be found in the Comments/Recommendations section of the status report prepared for 8EHQ-1287-0706 Initial.

a) The Existing Chemical Assessment Division will inform Borg-Warner about EPA's determination that the neurotoxicological findings from the company's subchronic oral toxicity study in Beagle dogs should have been submitted to EPA in a timely manner under Section 8(e) of TSCA.

   Borg-Warner will be asked to submit complete copies of the raw data from the company's reproduction study of Weston XR 1452 in rats.

b) The Chemical Screening Branch will continue its review of the reported information in order to determine the need for further OTS assessment.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and OCM/OPTS/EPA; copies of this status report will be sent also to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: JAN - 5 1988

SUBJECT: Status Report* 8EHQ-1287-0707 S

Approved: James F. Darr 1/7/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD/OTS

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

Note

The submitting company has claimed its company name and the exact identity of the subject chemical to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will be requesting the submitting company to substantiate these TSCA CBI claims. In the "sanitized" version of this Section 8(e) submission, the company identified the subject chemical substance nonconfidentially as a "pyridinecarboxylate."

Submission Description

The submitting company provided the following information with regard to the conduct and preliminary results of an ongoing 2-week pilot feeding study of this pyridinecarboxylate in mice:

> "In this study, mice were administered diets containing 0, 200, 1000, or 5000 ppm [pyridinecarboxylate] for 2 weeks prior to sacrifice. At necropsy, liver foci were observed in one of three males and one of three females at both 1000 and 5000 ppm. Microscopic evaluation of these foci is not yet complete but liver foci are not commonly observed in animals of this age. The only other evidence of toxicity in this study are decreased weight gain and discolored livers at 5000 ppm."

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon EPA's receipt of a complete copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, etc.) from the ongoing study cited in the company's Section 8(e) submission.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Current Production and Use

In view of the submitter's TSCA CBI claims, no information with regard to TSCA Chemical Substance Inventory status of the subject chemical will appear in this status report.

Comments/Recommendations

In its Section 8(e) notice, the submitting company stated that, when completed, a copy of the final report from the company's ongoing 2-week feeding study of pyridinecarboxylate in mice will be forwarded to EPA.

a) The Chemical Screening Branch will ask the submitter to ensure that EPA receives a complete copy of the final report (including the actual experimental protocols, results of gross/histopathologic examinations, etc.) from the 2-week feeding study cited in the company's Section 8(e) notice.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity/exposure information, the submitting company will be asked to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported information, and 2) to reduce or eliminate exposure to this pyridinecarboxylate. In addition, the submitting company will be requested to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the published scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to this pyridinecarboxylate.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JAN - 5 1988

SUBJECT: Status Report* 8EHQ-1287-0708 S

Approved: James F. Darr 1/7/88

FROM: David R. Williams DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

Note

The submitting company has claimed its company name and the exact identity of the subject chemical to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will be requesting the submitting company to substantiate these TSCA CBI claims. In the "sanitized" version of this Section 8(e) notice, the company reported non-confidentially that the subject chemical is an "acetophenone oxime."

Submission Description

The submitting company provided the following information with regard to the conduct and preliminary results of an ongoing chronic oncogenicity study of this acetophenone oxime in mice:

> "Preliminary data from the 12 month sacrifice of 10 animals/sex from the mouse oncogenicity study with [acetophenone oxime revealed] an increase in liver tumors in the high dose males. No such tumors were observed in the females. The tumor incidence in the males was:

	[Acetophenone Oxime Dose Levels]					
	0	0.2	1	5	15	50/75*
hepatocellular adenoma	0	0	0	1	0	4
hepatocellular carcinoma	0	1	0	0	1	1

> * animals dosed [(route of administration not specified)] at 50 ppm for 6 months then changed to 75 ppm."

In providing these preliminary toxicologic findings to EPA under Section 8(e) of TSCA, the submitting company stated that the "results are not surprising since liver tumors have been reported in mice administered commercial chemicals of similar structure."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon EPA's receipt of a full copy of the final report (including the actual experimental protocol, results of gross and histopathological examinations, results of statistical analyses, etc.) from the mouse oncogenicity study cited in the submission. In the interim, the submitting company should be asked to keep EPA apprised of any further significant findings from the ongoing chronic study.

Current Production and Use

In view of the submitter's TSCA CBI claims, no information with regard to the TSCA Chemical Substance Inventory status of the subject chemical will appear in this status report.

Comments/Recommendations

In its submission, the company reported that, when completed, a copy of the final report of the company's mouse oncogenicity study of acetophenone oxime would be sent to EPA.

a) The Chemical Screening Branch will ask the submitter to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, results of gross/histopathologic examinations, results of statistical analyses, etc.) from the oncogenicity study cited in the company's Section 8(e) submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity/exposure information, the submitting company will be asked to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported information, and 2) to reduce or eliminate exposure to this acetophenone oxime. The submitting company will be asked also to describe the nature and results, if available, of all studies (other than those reported already to the Agency or those cited in the open scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to this acetophenone oxime.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: JAN 18 1988

SUBJECT: Status Report* 8EHQ-1287-0709 S

Approved: James F. Darr 1/21/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

Note (See Note on Page 3 of this Status Report)

The submitting company has claimed its company name and the trade names of the tested chemicals to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will be requesting the submitting company to substantiate these CBI claims. The exact identities and CAS Registry Numbers of the tested chemicals were not claimed to be TSCA CBI.

Submission Description

The submitting company provided the following summary information with regard to the conduct and preliminary findings of in vitro Ames Salmonella typhimurium (bacteria) mutagenicity assays conducted with and without exogenous metabolic activation:

		TEST RESULTS [**]			
	TEST STRAIN:	TA 100		TA 1535	
CHEMICAL NAME	ACTIVATION:	WITHOUT	WITH	WITHOUT	WITH
Oxirane, 2,2'-(3,7,7,11-tetramethyl-2,5,9,12-tetraoxatridecane-1,13-diyl)bis- (CAS No. 87257-05-4)		3.4	12.4	6.2	107.6
Poly(oxy-1,2-ethanediyl),α-hydro-ω-(oxiranylmethoxy)-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1) (CAS No. 52495-71-3)		3.6	12.1	2.8	125.6

[**] Fold Over Background

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

In providing this information to EPA under Section 8(e) of TSCA, the company stated that while bacterial strains TA 98, TA 1537 and TA 1538 were negative, "the primary source of concern is the somewhat unusual results showing responses >100 [fold over background] in one TA test strain [(TA 1535)] with activation." In addition, the submitter reported that "many other closely related substances are present in lesser quantities (due to the nature of the reaction process) as well as impurities." The submitter noted also that "because these products are made with epichlorohydrin, . . . [the company does] not know if the results are influenced by impurities." The submitter reported further that although epichlorohydrin may be present in the products at a concentration of approximately 0.5%, the company has "not been able to determine what effect would be expected if there were 50 ug of epichlorohydrin in a 10,000 ug product sample." The submitter also reported that analyses of the epichlorohydrin content of the tested products are underway. Finally, the company stated that the company plans "to purify the samples and rerun them to determine if impurities are having a significant effect."

Submission Evaluation

The provided data indicate that the subject chemicals are potent inducers of reverse mutations in prokaryotes under the conditions employed in the performed Ames assays. An EPA evaluation of the overall significance of the reported findings should be possible upon EPA's receipt of full copies of the final reports (including the actual experimental protocols, data, results of statistical analyses, etc.) from all studies (including analytical studies) that were cited in the company's TSCA Section 8(e) notice.

Current Production and Use

The subject chemicals are not listed in the computerized version of the non-confidential initial (1977) TSCA Chemical Substance Inventory. According to the submitter, these chemicals are currently in research and development (R&D). The company did not provide any information on the actual or intended use of the subject chemicals, nor was such use information located in the secondary literature sources consulted by EPA.

With regard to the potential for worker exposure to the tested chemicals, the submitter stated that although "people handling these products in . . . [the submitting company's] laboratories and other laboratories have been using suitable precautionary measures," the company is conducting a review of the current handling practices. The submitting company also reported that "in addition to the specific precautions advised, the presence of epichlorohydrin, reported on . . . [the Material Safety Data Sheets (MSDSs)] and risk assessment as an impurity but possible carcinogen, should prompt appropriate caution among those handling the material[s]." Finally, the submitter stated that "potential risk would be based on improper handling."

Comments/Recommendations

Although a positive *in vitro* genotoxicologic assay result, when considered alone, may not be sufficient to reasonably support a conclusion of substantial risk (as that term is defined in EPA's TSCA Section 8(e) policy document ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978)), EPA believes that such results are of value in assessing possible risks posed by exposure to chemical substances or mixtures. The Agency also believes that positive genotoxicity findings, when considered in combination with other pertinent information (e.g., knowledge of potential exposure to and/or high production of the subject chemical or mixture), would suggest the need, in many cases, to conduct further studies that are designed to better define the toxicologic properties of or exposure to the subject chemical(s). The results of such further testing should be considered also for submission to EPA pursuant to Section 8(e) of TSCA.

a) The Chemical Screening Branch will ask the submitting company to ensure that EPA receives complete copies of the final reports (including the actual experimental protocols, data, results of statistical analyses, etc.) from all studies (including analytical studies) cited in the company's TSCA Section 8(e) submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity/exposure data, the submitter will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those published in the open scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to the subject chemical substances.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemicals.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and RAB/ECAD/OTS/OPTS. In addition, copies of this status report will be provided to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

Note — As the result of a letter to the Agency dated May 13, 1988, the Henkel Corporation withdrew its TSCA CBI claim for the company's name.

James F. Darr 7/21/88

James F. Darr

DATE: JAN - 7 1988

SUBJECT: Status Report* 8EHQ-1287-0710

Approved: James F. Darr 1/11/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

Submission Description

Texaco Inc. provided summarized information regarding the conduct and preliminary results of an ongoing chronic mouse skin painting study of hydrodesulfurized light vacuum gas oil (CAS No. 64742-87-6) and hydrodesulfurized heavy vacuum gas oil (CAS No. 64742-86-5). It should be noted that in a previous Section 8(e) notice (8EHQ-0887-0687 et seq.), Texaco provided preliminary results of this same study, but only for the hydrodesulfurized heavy vacuum gas oil; the reader's attention is directed to the status report prepared for 8EHQ-0887-0687. Texaco's current Section 8(e) submission provides an update of the company's previously reported findings on hydrodesulfurized heavy vacuum gas oil and presents new data on hydrodesulfurized light vacuum gas oil. According to Texaco, the ongoing chronic study involves application of 50 ul of the test materials twice per week to the shaved backs of mice (50/group) with no attempt to remove the test materials from the skin at any time during the study. The following table reflects the interim findings as of approximately the 10th month of the ongoing study:

Test Group	No. of Animals Alive	Papillomas	Advanced Tumors
A	47	0	0
B	47	0	0
C	0	4	46
D	16	12	34
E	41	4	10

A: Negative Control (no treatment)
B: Negative Control (USP Mineral Oil)
C: Positive Control (Benzo(a)pyrene 0.05% in Acetone)
D: Hydrodesulfurized Heavy Vacuum Gas Oil (neat)
E: Hydrodesulfurized Light Vacuum Gas Oil cut back with 50(v)% USP Mineral Oil

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

According to Texaco, the results obtained to date in the study show that there is a significant increase in the incidence of papillomas and advanced tumors in mice exposed via the skin to benzo(a)pyrene (positive control), hydrodesulfurized light vacuum gas oil and hydrodesulfurized heavy vacuum gas oil when compared to either control group. In its previous Section 8(e) submission (8EHQ-Ø887-Ø687), Texaco reported that the latency of onset of tumorigenicity for the hydrodesulfurized heavy vacuum gas oil was considered to be short (i.e., 6 months). In the present notice, Texaco stated that the latency period (i.e., 1Ø months) observed for the hydrodesulfurized light vacuum gas oil as a 5Ø/5Ø mixture with USP mineral oil was considered by the company to be short as well.

Submission Evaluation

The submitted information indicates that hydrodesulfurized light and heavy vacuum gas oils possess oncogenic activity toward the skin of mice. An EPA evaluation of the overall significance of the reported findings should be possible upon EPA's receipt of a complete copy of the final report from this chronic mouse skin application study.

Current Production and Use

A review of the production range (includes importation volumes) statistics for hydrodesulfurized light vacuum gas oil (CAS No. 64742-87-6) and hydrodesulfurized heavy vacuum gas oil (CAS No. 64742-86-5), which are listed in EPA's initial TSCA Chemical Substance Inventory, showed that over 1 billion pounds and over 9 billion pounds, respectively, were reported as being manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All information reported for the initial TSCA Inventory, including the production range information, is subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (4Ø CFR 71Ø).

Appendix A of the printed TSCA Chemical Substance Inventory (1985 Edition) gives the following definition for the hydrodesulfurized light vacuum gas oil (CAS No. 64742-87-6):

> "A complex combination of hydrocarbons obtained from a catalytic hydrodesulfurization process. It consists of hydrocarbons having carbon numbers predominantly in the range of C13 through C3Ø and boiling in the range of approximately 23Ø°C to 45Ø°C (446°F to 842°F)."

Appendix A of the printed TSCA Chemical Substance Inventory (1985 Edition) gives the following definition for the hydrodesulfurized heavy vacuum gas oil (CAS No. 64742-86-5):

> "A complex combination of hydrocarbons obtained from a catalytic hydrodesulfurization process. It consists of hydrocarbons having carbon numbers predominantly in the range of C2Ø through C5Ø and boiling in the range of approximately 35Ø°C to 6ØØ°C (662°F to 1112°F). This stream is likely to contain 5 wt. % or more of 4- to 6-membered condensed ring aromatic hydrocarbons."

In the present TSCA Section 8(e) submission, Texaco reported that hydrodesulfurized light vacuum gas oil "is a non-isolated, site limited refinery process stream which is used as a feed to the catalytic cracking unit."

In the prior TSCA Section 8(e) notice (8EHQ-Ø887-Ø687), Texaco reported that hydrodesulfurized heavy vacuum gas oil "is a non-isolated, site limited refinery process stream which is used as a feed to the catalytic cracking unit or is recycled in the H-Oil process."

In addition, Texaco stated in both Section 8(e) submissions that "twelve shift personnel operate the [catalytic cracking] unit; however, exposure is limited since the unit is a closed system and closed sampling procedures are used. . . . ."

Comments/Recommendations

Texaco reiterated in the present Section 8(e) submission that the reported toxicologic findings will be included in the company's "hazard communication program and workers will be warned again of the potential for adverse health effects from skin contact from certain oils and refinery streams." In addition, Texaco stated that the company will 1) keep EPA apprised as further results from the mouse skin painting study are received, and 2) send a copy of the final report to EPA when that report is completed.

a) The Chemical Screening Branch has already asked Texaco to ensure that EPA receives a full copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, results of any statistical analyses, etc.) from the company's chronic mouse dermal application study.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure information, Texaco will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the published scientific literature) about which Texaco is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of the hydrodesulfurized light vacuum gas oil; Texaco was requested previously to respond to similar questions regarding the hydrodesulfurized heavy vacuum gas oil.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of these petroleum process streams.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JAN 11 1988

SUBJECT: Status Report* 8EHQ-1287-0711

Approved: James F. Darr 1/11/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

On behalf of the Amoco Chemical Company, the Amoco Corporation submitted the following summary information with regard to the conduct and preliminary results of animal studies designed to determine the respiratory sensitizing potential of pyromellitic dianhydride (PMDA; CAS No. 89-32-7) and the cross-reactivity between PMDA and trimellitic anhydride (TMA; CAS No. 552-30-7):

> "Two groups of ten male rats each were exposed to five exposures of 500 micrograms [(ug)] PMDA per cubic meter of air over a seven day period. [Note: The length of the five exposures was not given in the submission.] Following a two week rest period, one group was challenged with a single six hour dose of 500 ug/m^3 PMDA and the other group challenged with a single six hour dose of 500 ug/m^3 TMA. Animals were sacrificed and necropsied on the day after the challenge doses. Based on earlier work with TMA, an evaluation of lung effects was performed by removing the lungs at necropsy and counting (gross observation) the number of hemorrhagic foci on the lungs.
>
> "These studies indicate that PMDA, under the conditions employed, produced numbers of lung foci strongly indicative of respiratory sensitization. It was also found that a TMA challenge of rats exposed to PMDA produced lung foci similar to those produced following PMDA challenge.
>
> ". . .[Amoco interprets] these results to indicate that PMDA, at this concentration, produces a sensitizing effect in male rats. . . .[Amoco also has] evidence, from this work, that male rats exposed to PMDA react to TMA in a manner [that is] indicative of a sensitization reaction."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

In addition to reporting the preliminary experimental findings to EPA under Section 8(e), Amoco provided a copy of a PMDA Material Safety Data Sheet (MSDS) and product label that had been updated to reflect the results of the performed animal studies.

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon EPA's receipt of full copies of the final reports from all studies cited in the submission.

Current Production and Use

A review of the production range (includes importation volumes) statistics for trimellitic anhydride (CAS No. 552-30-7), which is listed in the initial TSCA Chemical Substance Inventory, showed that 0 to 1000 pounds of this chemical substance were reported as manufactured and/or imported in 1977. A review of the production range (includes importation volumes) statistics for pyromellitic dianhydride (CAS No. 89-32-7), which is listed in the initial TSCA Chemical Substance Inventory, showed that 0 to 3,000 pounds of this chemical substance were reported as manufactured and/or imported in 1977.

The above production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in EPA's initial TSCA Inventory Reporting Regulations (40 CFR 710).

According to the Condensed Chemical Dictionary (10th Edition), PMDA has the following applications: "curing agent for epoxy resins used in high temperature laminates, molds, and coatings; cross-linking agent for epoxy plasticizers in vinyls; alkyd resins; intermediate for pyromellitic acid. This publication also states that TMA has the following applications: "plasticizer for polyvinylchloride; alkyd coating resins; high temperature plastics; wire insulation; gaskets; automotive upholstery."

Comments/Recommendations

In addition to updating the PMDA MSDS and product label, Amoco reported that the company plans to conduct studies designed to determine PMDA dose-effect relationships.

It should be noted that EPA's Office of Toxic Substances (OTS) has received other Section 8(e) and "For Your Information" (FYI) notices on TMA. Prompted by a 1978 NIOSH "Current Intelligence Bulletin" describing severe respiratory problems in workers exposed to TMA, OTS prepared (in 1978) a draft Chemical Hazard Information Profile (CHIP) on TMA.

a) The Chemical Screening Branch will request Amoco to ensure that EPA receives complete copies of the final reports (including the actual experimental protocols, results of gross/histopathologic examinations, etc.) from all studies cited in the company's Section 8(e) submission on TMA and PMDA. In addition, Amoco will be asked to keep EPA apprised of significant findings from the planned studies designed to determine PMDA dose-effect relationships.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of TMA and/or PMDA.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JAN 21 1988

SUBJECT: Status Report* 8EHQ-0188-0712
8EHQ-0188-0712 SUPP

Approved: James F. Darr 1/27/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

Submission Description

In its initial Section 8(e) submission, the Koppers Company, Inc. provided the following information with regard to the conduct and preliminary results of a guinea pig dermal sensitization study of Sapstain Control Chemical NP-1:

> "Observations from the [performing] laboratory indicate that Sapstain Control Chemical NP-1 induced a skin sensitization response in guinea pigs following repeated topical exposure to a 0.6% aqueous solution. Challenge applications of 0.5% elicited a sensitization response in one of 20 test animals. No control animals developed a comparable response. Upon rechallenge, 10 of 20 test animals developed an enhanced response. Skin reactions observed at lower challenge concentrations, 0.25% and 0.125%, were suggestive of a dose-response relationship for sensitization but are not sufficient evidence for the induction of sensitization at dose concentrations.
>
> "Other observations reported by the laboratory were signs of marked to severe skin irritation following contact with [the] slightly diluted or undiluted test material.
>
> "Koppers is aware of the results of animal testing for sensitization conducted on the major components of this product by the manufacturers of these components. In each case, the testing was negative for the induction of sensitization."

In its initial submission, Koppers stated also that the company "has not received any reports of dermal sensitization from . . . [Koppers] employees engaged in the manufacture of Sapstain Control Chemical NP-1 or from . . . [Koppers] customers who use it or the alternate brandname product LH-25 [Preservative]."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

In its supplemental Section 8(e) notice (8EHQ-Ø188-Ø712 SUPP), Koppers reported that because the subject products are pesticides registered with EPA under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) with Koppers as the "registrant" (EPA Registration No. 453-297), all of the information contained in the company's initial Section 8(e) notice had been submitted on the same date to EPA's Office of Pesticide Programs (OPP/OPTS) under Section 6(a)(2), a mandatory reporting provision of FIFRA.

In the initial TSCA Section 8(e) notice, Koppers stated that "the results of acute oral and dermal lethality studies and primary eye and skin irritation studies on Sapstain Control Chemical NP-1 . . ." were submitted to the Agency under FIFRA in July, 1984.

Submission Evaluation

EPA's Office of Pesticide Programs will be evaluating the overall significance of the reported dermal sensitization findings for this registered pesticide.

Comments/Recommendations

Koppers reported that it "has initiated a review of the current NP-1/LH-25 product labels and material safety data sheets" and "these documents will be amended accordingly to afford warnings to . . . [Koppers] workers and customers who manufacture and use these products." In addition, Koppers stated that "in light of the negative reports of sensitization potential existing on the ingredients of Sapstain Control Chemical NP-1 and the absence of reports of sensitization in the workforce exposed to this product, Koppers Company will pursue additional investigations concerning . . . [the recent guinea pig dermal sensitization study findings for NP-1]." Finally, Koppers stated that the final report from this recent sensitization study would be forwarded to EPA in March, 1988.

It should be noted that the toxicologic information on Sapstain Control Chemical NP-1 did not have to be submitted to EPA under Section 8(e), the substantial risk information reporting provision of TSCA. According to Part VII of EPA's Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" March 16, 1978; 43 FR 11110), information does not need to be reported under Section 8(e) if the information "has been submitted in writing to EPA pursuant to mandatory reporting requirements under TSCA or any other authority administered by EPA (including the Federal Insecticide, Fungicide and Rodenticide Act [(FIFRA)] . . ."

a) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: JAN 29 1988

SUBJECT: Status Report* 8EHQ-0188-0713 Approved: James F. Darr 2/1/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The Dow Chemical Company provided summary information regarding the results of a 2-year mouse inhalation study of ethyl chloride (CAS No. 75-00-3) conducted by the National Toxicology Program (NTP). According to Dow, "this inhalation study has a single dose level, namely 15,000 ppm, of ethyl chloride, and . . . adenocarcinomas of the uterus have been observed in the exposed animals." In addition, Dow reported that to the best of the company's knowledge, "this study is currently under review within NTP and a draft report has not been issued [formally by NTP]."

Submission Evaluation

An evaluation of the significance of the reported findings should be possible upon EPA's receipt of further information from NTP regarding the conduct and results of this chronic bioassay. EPA should ask NTP when it plans to issue the draft technical report of this study for peer review by the Technical Report Peer Review Subcommittee of NTP's Board of Scientific Counselors.

Current Production and Use

A review of the production range (includes importation volumes) statistics for ethyl chloride (CAS No. 75-00-3), which is listed in the initial TSCA Chemical Substance Inventory, has shown that 411 million to 1.76 billion pounds of this chemical substance were reported as manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

The Condensed Chemical Dictionary (10th Edition), contains the following information pertaining to the uses of ethyl chloride: "manufacture of tetraethyl lead and ethylcellulose; anesthetic; organic synthesis; alkylating agent; refrigeration; analytical reagent; solvent for phosphorus, sulfur, fats, oils, resins and waxes; insecticides."

Comments/Recommendations

It should be noted that Part VII of EPA's Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978) provides a number of examples of the types of information that need not be reported to EPA under Section 8(e) of TSCA (i.e., information about which subject persons can automatically assume the Agency to be "adequately informed"). In addition to the examples cited in Part VII, subject persons can automatically assume, for the purposes of TSCA Section 8(e) reporting, that EPA has been adequately informed about substantial risk information contained in a formal publication or report released to the general public by an agency of the U.S. Government. It should be noted also that EPA's position on the Section 8(e)-reportability of results of NTP bioassays has been described previously (see EPA's "status report" prepared in response to TSCA Section 8(e) submission number 8EHQ-1282-0467). In summary, EPA's position on Section 8(e) as it relates to the results of NTP bioassays is as follows:

> A subject person can assume automatically that EPA has been "adequately informed" about the results of an NTP carcinogenesis bioassay once the NTP formally releases copies of the draft technical report from that study for peer review by the Technical Report Peer Review Subcommittee of NTP's Board of Scientific Counselors. This assumption can be made because EPA's Office of Toxic Substances (OTS) routinely receives full copies of all draft NTP carcinogenesis bioassay technical reports formally released by NTP for peer review.
>
> Therefore, if a subject company obtains (i.e., knows of or possesses) toxicologic information concerning an NTP bioassay and there has not been a formal public release of those findings by NTP (e.g., formal release of the draft technical report for peer review), the subject company should immediately consider the need to report the information to EPA under Section 8(e) of TSCA.

It should be noted that EPA has correctly received a number of TSCA Section 8(e) submissions (usually comprised of 1 to 2 pages) filed by companies that obtained toxicologic data from studies conducted by or for agencies of the U.S. Government that have not been published or released formally to the general public. In each of these cases, OTS has immediately initiated appropriate followup activities directly with the other Federal agency in

order to minimize and, in most cases, eliminate further TSCA Section 8(e) reporting obligations on the part of the submitting company to provide such items as complete copies of supporting data or actual technical reports.

It is important to note that ethyl chloride was listed in a TSCA Section 8(d) health and safety data reporting rule (May 1, 1987; 52 FR 16Ø22).

a) The Chemical Screening Branch will contact NTP in order to obtain further information regarding the conduct and results of NTP's 2-year inhalation bioassay of ethyl chloride in mice. In addition, the Chemical Screening Branch will ask NTP when NTP plans to issue the draft technical report from this study for peer review by the Technical Report Peer Review Subcommittee of NTP's Board of Scientific Counselors.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Dow will be asked to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported information, and 2) to reduce or eliminate exposure to ethyl chloride.

b) The Chemical Screening Branch will review the reported and other available information on ethyl chloride in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: MAR - 1 1988

David R. Williams for
Approved: James F. Darr
March 7, 1988

SUBJECT: Status Report* 8EHQ-0188-0714

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The Eastman Kodak Company provided the following information with regard to the conduct and results of a 4-week oral toxicity study of 2-bromo-3-methylbutanoic acid (CAS No. 565-74-2) in rats:

> "Groups of 5 male and 5 female rats were given daily gavage doses of 80, 250, or 800 mg/kg of the test compound dissolved in corn oil for five days per week over four weeks; a total of 22 doses were administered. The high dose proved lethal to 2/10 animals. All males in the 800 mg/kg dose group exhibited varying degrees of motor impairment after one or more doses during the first week of exposure. Abnormal clinical observations in affected males included weakness in the hindlimbs, decreased extension of the joints in the hindlimbs, and weakness in the tail. In addition, a hypotonic gait and waddling were observed. Spinal reflexes, superficial pain pathways, and bowel and bladder functions appeared to be unaffected. With continued dosing, the affected males showed some recovery from the motor impairment. Only very slight deficits were evident at the end of the study. No motor impairment was observed in females at any dose or in males at the two lower doses.
>
> "Preliminary microscopic examination of nervous system tissue from the high-dose males showed degeneration of the cerebellar granule cells, symmetrical foci of malacia or softening in the thalamus, and axonal degeneration in the dorsolateral and ventral or ventromedial funiculi."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Eastman Kodak also submitted the final results of a battery of previously conducted acute animal toxicity studies of the subject chemical. A provided internal corporate memorandum presents the following information regarding the conduct and results of these acute studies:

> "The approximate acute oral LD50 values for the rats were 884 mg/kg for males (95% Confidence Interval (C.I.) 669-1169 mg/kg) and 769 mg/kg for females (95% C.I. 583-1015 mg/kg). [Being a solid, the test article was liquified by warming to approximately 42°C prior to dosing.] Following oral gavage, the material was a severe gastric irritant causing necrosis of the stomach wall and damage to adjacent organs by leakage through the gastric wall. Based on the dose level required to produce toxicity, the material should be considered a slight to moderate toxicant by the oral route. The only apparent organ toxicity was to the stomach following direct contact with the test article.
>
> "Similarly, when the test article was placed in contact with the skin of rats at doses of 0.5, 1, 2, and 20 ml/kg, it caused significant necrosis of the skin and eschar formation. The test article is a solid, therefore prior to application to the skin, it was liquified by warming to 40°C. It was held against the skin for 24 hours under an occlusive wrap. Doses of 2 or 20 ml/kg were lethal to rats while doses of 0.5 or 1 ml/kg were not. A single male [rat] given a dose of 1 ml/kg developed weakness, prostration, dehydration, and a roughened hair coat, but gained a small amount of body weight and survived the two week observation period. In spite of skin necrosis at the application site, clinical signs potentially due to percutaneous absorption of the test article were not observed in the remaining rats (0.5 ml/kg and 1 ml/kg) and all rats gained weight during the observation period. The approximate dermal LD50 values were 1.41 ml/kg (95% C.I. 1.07-1.87 ml/kg) for both males and females.
>
> "To evaluate the irritant potency of the test article, 0.5 ml of the test article was placed against the skin of guinea pigs and held in place for 24 hours by an occlusive wrap. The test article was liquified by warming prior to application. The exposure resulted in necrosis and erosion at the application site after 24 hours and therefore the guinea pigs were euthanatized for humane reasons without further observation.
>
> "The test article was also tested for the potential to produce skin sensitization or a skin hypersensitivity reaction. Ten guinea pigs were induced with the test article in complete Freund's adjuvant and an equal number of animals received just the adjuvant. When the

> animals were rechallenged two weeks later by dermal application of the test article, 7 of the 10 animals induced with the test article had a slight dermal irritation reaction. Although the irritation response did not meet the criteria for categorization as a positive response, the presence of slight erythema in a majority of the induced animals indicates the test material may have a slight potential to cause human skin sensitization."

According to Eastman Kodak, 2-bromo-3-methylbutanoic acid exists with two different purities (i.e., approximately 95% pure and greater than 99% pure). Eastman Kodak stated that the lower grade product was the one tested, and, in the absence of data on the higher grade, the company assumes that the high grade has the same toxicologic properties as the low grade. Eastman Kodak stated also that both grades are considered to be "strong skin, eye, and respiratory tract irritants." Eastman Kodak reported further that both grades of the chemical are handled and labelled in the same manner. Finally, Eastman Kodak stated that it is "not aware of any adverse health effects associated with the manufacture or use of these materials."

Submission Evaluation

An EPA evaluation of the overall significance of the reported neurotoxicologic findings should be possible upon EPA's receipt of a complete copy of the final report of Eastman Kodak's 4-week oral toxicity study of 2-bromo-3-methylbutanoic acid in rats.

Current Production and Use

A review of the production range (includes importation volumes) statistics for 2-bromo-3-methylbutanoic acid (CAS No. 565-74-2), which is listed in the initial TSCA Chemical Substance Inventory, shows that 0 to 1000 pounds of this chemical were reported as manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

According to Eastman Kodak, the lower grade of 2-bromo-3-methylbutanoic acid "is produced in larger volume than the pure form, and is used as a site-limited intermediate; none of it appears in the final product." In addition, Eastman Kodak stated that "a small quantity of the more pure form is sold as a reagent for laboratory use." Eastman Kodak stated further that "potential employee exposure during manufacturing has been minimized by the use of company-supplied protective clothing, gloves, and appropriate NIOSH-approved respirators."

Comments/Recommendations

In its Section 8(e) notice, Eastman Kodak provided a copy of a Material Safety Data Sheet (MSDS) that has been revised to reflect the reported neurotoxicologic findings. In addition, Eastman Kodak stated that the 2-bromo-3-methylbutanoic acid product labels would be revised also to reflect the reported findings. Finally, Eastman Kodak stated that the company is "currently evaluating the need for further testing."

a) The Chemical Screening Branch will ask Eastman Kodak to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, results of gross/histopathologic examinations, results of statistical analyses, etc.) from the 4-week oral toxicity study cited in the company's submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Eastman Kodak will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Eastman Kodak is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to the subject chemical substance.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of 2-bromo-3-methylbutanoic acid.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: FEB 25 1988

SUBJECT: Status Report* 8EHQ-0288-0715

Approved: James F. Darr 3/1/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The CIBA-GEIGY Corporation provided final reports from a battery of in vitro genotoxicity assays of 2,2,6,6-tetramethylol cyclohexanol polyglycidyl ether (TK-10854). According to CIBA-GEIGY, positive results were obtained in an Ames Salmonella typhimurium (bacteria) mutagenicity assay, a point mutation assay in cultured V79 Chinese hamster cells and a chromosomal aberration assay in cultured human lymphocytes; negative results were reportedly obtained in Unscheduled DNA Synthesis (UDS) assays in cultured rat hepatocytes and cultured human fibroblasts.

Submission Evaluation

The subject chemical (TK-10854) was evaluated in the Ames assay in four Salmonella typhimurium tester strains (TA1535, TA1537, TA98 and TA100) using the standard plate incorporation assay protocol. [The] tests were conducted with or without exogenous metabolic activation (S9 mix derived from livers of Aroclor 1254-induced rats). At least 5 different concentrations of TK-10854 ranging from 20 to 5000 ug/plate were tested. The assay itself was conducted with an acceptable protocol and both the positive and negative controls responded appropriately during the study. Using this procedure, TK-10854 was found to produce reproducible dose-related responses in tester strains TA1535 and TA100 in the presence of the S9 mix. For example, in tester strain TA1535, a doubling of the number of background revertants was observed at 78 ug/plate and a 26-fold increase in background revertants was found at the highest concentration tested (i.e., 5000 ug/plate). Although a slight increase (i.e., 1.6-fold increase over background) in the number of revertant colonies occurred in TA1535 at

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

5000 ug/plate in the absence of exogenous metabolic activation, this result was neither reproducible nor dose-related, and thus, is not considered to be biologically significant. Based on the results of this bacterial mutagenicity study, TK-10854 produces primarily base-pair substitution mutations; the incorporation of liver activation appears to be required in order for TK-10854 to exert its mutagenic properties in this assay.

With regard to the gene mutation assay of TK-10854 in cultured V79 Chinese hamster cells, the procedures used to maintain the cultures for mutagenicity and the conditions for mutant selection are reasonably consistent with those presented in the published literature on this assay. However, there are departures in the cytotoxicity test, the conditions and sample size for mutant detection, and, of the greatest significance, in the use of a "default" spontaneous mutant frequency. In the cytotoxicity test, only 200 cells were exposed while $1X10^6$ cells were exposed in the mutagenicity test. The recommended procedure is to conduct the cytotoxicity test at the same cell density that is used in the mutagenicity test. The procedure used in this assay could result in the selection of concentrations that do not span the full range of toxicity (i.e., low cell density results in high test substance concentration on a per cell basis). In view of the fact that the results of the toxicity determination on the mutagenicity portion were not reported, it is not possible to verify that toxicity was or was not a function of cell density. For mutant selection, 4 dishes at $2.5X10^6$ cells/dish were incubated with either thioguanine (TG) or azaguanine (AG); the AG cells were supplemented with AG on the third day and split and fresh AG was added on the fourth day. Although this is generally a common procedure, it is usually recommended that 10 and 30 dishes be used for selection with TG and AG, respectively. The effect of this small sample size is apparent in the control data presented in the submitted final report. In the total of 16 dishes (4 each for TG and AG with and without exogenous metabolic activation), there were only 3 mutant colonies observed, for an average of 1 colony per five dishes. Assuming 100% cloning efficiency, this is an observed mutant frequency of $0.75X10^{-6}$. In the submitted report, however, the investigators state that the limit of sensitivity of the test (4 dishes per group) is $4X10^{-6}$ and the investigators use this value as a default value for any experimental frequency below this value. Because the investigators' decision analysis is based on a fold increase over controls, the effect of this procedure is that the factors shown in Table 2 through Table 5 of the submitted final report are 4 times too low. A recalculation of the ratio of treated versus control mutant frequency using the observed frequency value cited above results in a conclusion that the conditions for a positive result (as defined in the protocol) are fulfilled in all cases except for the group selected with AG without activation. This is in conflict with the single case (TG without activation) cited in the submitted report. It should be noted that even after making a correction for actual spontaneous mutant frequency, the magnitude of the response with treatment with TK-10854 is not

striking. Although the data relating to cloning efficiency were not included in the report, EPA assumes that cloning efficiency can be calculated because a "corrected" mutant count is provided in the report. Overall, while the study as conducted is not adequate to accurately characterize the potential of TK-10854 to induce gene mutations in cultured V79 cells, the submitted data do suggest that TK-10854 is capable of inducing gene mutations in the assay. The deficiencies of small sample size and use of a default spontaneous mutant frequency preclude a more definitive conclusion regarding the results of this particular assay.

TK-10854 was also assayed for its ability to induce chromosomal aberrations in cultured human peripheral blood lymphocytes. The cultures were treated both with and without exogenous metabolic activation. Dose-related increases were observed for a variety of aberration types including breaks, exchanges and fragments. The submitted final report states that TK-10854 is clastogenic; positive responses seen in cultures in the absence of metabolic activation suggest that the liver microsomes may be involved in detoxification of the parent compound. Basically, the assay was performed well; the assay was preceded by a cytotoxicity study and the highest doses tested were those that reduced the mitotic index by 50%. The cytostatic studies confirm the observation of increased toxicity in the absence of metabolic activation. Although there are two criticisms of this particular assay, neither criticism changes the overall conclusions. First, cells were treated with TK-10854 48 hours after the commencement of the culture period. At the 48 hour time point, the majority of the dividing cells are in first division and this represents an appropriate time for chemical treatment. Following the cessation of chemical treatment, the cells were cultured for an additional 43.5 hours; in the absence of mitotic delay, this would represent an additional 4 to 5 cell cycles. This protracted culture period could lead to an underestimation of the clastogenic effects of the tested chemical because most chromosomal aberrations are cytotoxic and many of the damaged cells would be lost after 1 to 2 cell cycles. Thus, if a shorter post-exposure culture period had been used, higher clastogenic responses may have been seen and TK-10854 doses that were judged to be negative may have been found to yield positive results. The second criticism relates to the classification of certain aberrations as "minutes" or "double minutes." It is not clear to EPA how these were distinguished from chromatid and isochromatid fragments, respectively. Again, neither of EPA's criticisms alter the qualitative evaluation that TK-10854 is clastogenic in cultured human lymphocytes inducing a variety of aberrations including breaks, fragments and exchanges.

Although TK-10854 was found to be inactive in the Unscheduled DNA Synthesis (UDS) assays using cultured rat hepatocytes and human fibroblasts, the study protocols may have been inadequate. In the rat hepatocyte study, cells were exposed for 5 hours to TK-10854; published recommendations (Mutation Research 123: 363-410; 1983) suggest that for those UDS assays conducted with hepatocytes, the exposure time should encompass 18 hours. In the human fibroblast

study, the cells were exposed to TK-1Ø854 for 5 hours only in the absence of exogenous metabolic activation; therefore, the study is considered to be incomplete because it would fail to detect chemicals requiring metabolic activation to exert their activity.

Current Production and Use

According to CIBA-GEIGY, the subject chemical "is a research and development [(R&D)] material intended primarily for weatherable liquid coatings." CIBA-GEIGY reported also that "only small quantities have been distributed to a few potential customers." In addition, CIBA-GEIGY reported that "once the product is used in its intended application, it becomes a highly cross-linked, high molecular weight, insoluble and inert material." CIBA-GEIGY reported further that worker exposure "should be minimal or nil" when the product is used by customers according to the following handling warnings/recommendations given in the product Material Safety Data Sheet (MSDS):

> "Wear impervious gloves. Wear splash-proof chemical goggles. Use NIOSH approved organic vapor cartridge respirator when vapor/mist exposure is likely. Wear appropriate protective equipment to avoid personal contact and exposure. Avoid breathing vapor, mist or spray. Wash thoroughly after handling."

Finally, CIBA-GEIGY reported that "there is no consumer exposure to the product."

Comments/Recommendations

CIBA-GEIGY reported that the company is 1) revising the MSDS to reflect the reported positive and negative genotoxicity findings, and 2) notifying in writing all customers who received samples of this R&D material about the reported findings.

Although a positive in vitro genotoxicologic assay result, when considered alone, may not be sufficient to reasonably support a conclusion of substantial risk (as that term is defined in EPA's TSCA Section 8(e) policy document ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978)), EPA believes that such results are of value in assessing possible risks posed by exposure to chemical substances or mixtures. The Agency also believes that positive genotoxicity findings, when considered in combination with other pertinent information (e.g., knowledge of potential exposure to and/or high production of the subject chemical or mixture), would suggest the need, in many cases, to conduct further studies that are designed to better define the toxicologic properties of or exposure to the subject chemical(s). The results of such further testing should be considered also for submission to EPA pursuant to Section 8(e) of TSCA.

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, CIBA-GEIGY will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which CIBA-GEIGY is aware or that CIBA-GEIGY has conducted, is conducting or plans to conduct to determine the toxicity of the subject chemical substance.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: FEB 16 1988

SUBJECT: Status Report* 8EHQ-0288-0716 S Approved: James F. Darr 2/17/88

FROM: David R. Williams DRW, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Note

The submitting company has claimed its company name and the exact identity of the subject chemical to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will be requesting the submitter to substantiate these TSCA CBI claims. In the "sanitized" version of this Section 8(e) notice, the submitting company identified the tested chemical substance non-confidentially as a "pyridinecarboxylate." It should be noted that Section 8(e) submission numbers 8EHQ-1287-0707 S and 8EHQ-0288-0717 S each contain information on a chemical substance identified non-confidentially as a pyridinecarboxylate.

Submission Description

In this Section 8(e) notice, the company provided the following information with regard to the conduct and preliminary findings from an ongoing pilot teratology study of a pyridinecarboxylate in rats:

> "In this study, the subject pyridinecarboxylate compound was administered by gavage to 6 groups of 7 female rats at dose levels of 0, 25, 50, 100, 200 and 400 mg/kg/day during gestation days 6-15. Surviving dams were sacrificed on gestation day 20. Fetuses were weighed, sexed and externally examined. . . . . The most notable finding was the dose related increase in fetal malformations at 100 and 200 mg/kg/day (no pregnant females survived at 400 mg/kg/day). These malformations consisted primarily of abdominal wall defects that occurred at an incidence much higher than seen historically, and were observed at dose levels which produced only minimal maternal toxicity."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Submission Evaluation

In its submission, the company reported that the final report of this pilot rat teratology study would be provided to the Agency when the report is completed. Upon EPA's receipt of that final report, EPA will evaluate the findings of this study as well as those presented in the final pilot teratology study report which is the subject of TSCA Section 8(e) submission 8EHQ-0288-0717 S. The reader's attention is directed to the status reports that have been prepared by EPA in response to 8EHQ-0288-0717 S and 8EHQ-1287-0707 S.

Current Production and Use

In view of the submitter's TSCA CBI claims, no information with regard to the TSCA Chemical Substance Inventory status of the subject pyridinecarboxylate will appear in this status report. In its submission, the company did report non-confidentially that this pyridinecarboxylate "is currently manufactured and used for [research and development (R&D)] purposes only."

Comments/Recommendations

a) The Chemical Screening Branch will ask the submitter to ensure that the Agency receives a complete copy of the final report (including the actual experimental protocol, results of gross/histopathological examinations, results of statistical analyses, etc.) from the pilot teratology study cited in this submission.

   In view of EPA's general interest in corporate actions that are taken on a voluntary basis in response to new-found chemical toxicity or exposure information, the submitting company will be requested to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported findings, and 2) to reduce or eliminate exposure to the subject pyridinecarboxylate. The submitter will be requested also to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of this pyridinecarboxylate.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA; copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: FEB 16 1988

SUBJECT: Status Report* 8EHQ-0288-0717 S Approved: James F. Darr 2/17/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Note

The submitting company has claimed its company name and the exact identity of the subject chemical to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will be requesting the submitter to substantiate these TSCA CBI claims. In the "sanitized" version of this Section 8(e) notice, the submitting company identified the tested chemical substance non-confidentially as a "pyridinecarboxylate." It should be noted that Section 8(e) submission numbers 8EHQ-1287-0707 S and 8EHQ-0288-0716 S each contain information on a chemical substance identified non-confidentially as a pyridinecarboxylate.

Submission Description

In this TSCA Section 8(e) notice, the company provided the final report of a pilot teratology study of a pyridinecarboxylate in rats. The submitter's cover letter presented the following information regarding the conduct and results of this study:

> "In this [pilot] study, the subject pyridinecarboxylate compound was administered by gavage to groups of six mated female rats during gestation days 6 through 15. Dose levels [administered] were 0, 100, 300, 600, 1000 and 2000 mg/kg/day. All females in the 600 mg/kg group and above died during the study. Maternal toxicity, including the deaths of two dams, also occurred at 300 mg/kg; there were no live implants in [the] surviving females. At 100 mg/kg/day, clear maternal toxicity was not observed. There were no external fetal abnormalities at the 100 mg/kg/day dose, but the mean body weight of female pups was significantly reduced. This body weight decrease is considered to be a borderline reproductive effect."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Submission Evaluation

An EPA evaluation of the reported findings will take place upon EPA's receipt of the final report of the pilot rat teratology study which was the subject of TSCA Section 8(e) submission 8EHQ-0288-0716 S. The submitter of this previous Section 8(e) notice stated that a copy of that pilot teratology study report would be provided to EPA when the report is completed. Upon EPA's receipt of that final report, the findings of both pilot teratology studies will be evaluated. The reader's attention is directed to the status reports that have been prepared by EPA in response to 8EHQ-0288-0716 S and 8EHQ-1287-0707 S.

Current Production and Use

In view of the submitter's TSCA CBI claims, no information with regard to the TSCA Chemical Substance Inventory status of the subject pyridinecarboxylate will appear in this status report. In its submission, the company reported non-confidentially that this pyridinecarboxylate "is currently manufactured and used for [research and development (R&D)] purposes only."

Comments/Recommendations

a) In view of EPA's general interest in corporate actions that are taken on a voluntary basis in response to new-found chemical toxicity/exposure data, the submitter will be asked to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported findings, and 2) to reduce or eliminate exposure to the subject pyridinecarboxylate. The submitting company will be asked also to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of this pyridinecarboxylate.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of this pyridinecarboxylate.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA; copies of this status report will be transmitted also to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: FEB 25 1988

SUBJECT: Status Report* 8EHQ-0288-0718

Approved: James F. Darr 3/1/88

FROM: David R. Williams, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The Dow Corning Corporation provided the final results from a recently conducted chronic Daphnia magna reproductive limit test of a mixture of polyethylene glycol sorbitan monolaurate (CAS No. 9005-64-5) and octamethylcyclotetrasiloxane (CAS No. 556-67-2). The "ABSTRACT" section of the submitted final report presents the following information regarding the conduct/results of the study:

> "This test was conducted to determine whether octamethylcyclotetrasiloxane (OMCTS) elicits any adverse response in Daphnia magna in the presence of an organic solvent, polyethylene glycol sorbitan monolaurate (PGSM), to prevent coalescence of the OMCTS. The test vessels were glass jars with Teflon-lined caps to reduce the loss of the volatile OMCTS. The test organisms were transferred to fresh solutions on a daily basis and once on the weekend.
>
> "Survival of the Daphnia magna during the first 48 hours of the test was excellent. However, survival of both test concentrations and the surfactant control deteriorated through the course of the study. Due to the differential survival between unamended controls and the surfactant controls, this test does not conclusively demonstrate an adverse effect of OMCTS in the absence of the surfactant.
>
> "The following [test] results were determined to be statistically significant. . . Day 7 survival of the daphnia exposed to 10 ppm PGSM/100 ppb OMCTS was significantly less than either control group. Survival of the daphnia exposed to 10 ppm PGSM/10 ppb OMCTS was reduced relative to controls by day 14. By the end of the test, the mortality rate in the surfactant control

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was significantly greater than that of [the] unamended controls and mortalities in vessels exposed to either level of OMCTS with PGSM were more than either control. Since the mortalities [observed] in the surfactant control occurred so late in the study, the survival rate as measured by total days survival was not significantly different between the controls. However, both levels of OMCTS with PGSM reduced survival by this measure.

"Reproduction, as measured by total number of young produced, was reduced from both controls at 10 ppm PGSM/100 ppb OMCTS. However, at 10 ppm PGSM/10 ppb OMCTS, there was not a significant reduction in young compared to surfactant controls.

"Statistical analysis of the reproduction data was also done to reduce the impact of premature death on total young by examining total young/total days survival. Only daphnia exposed to 10 ppm PGSM/100 ppb OMCTS showed reduced reproduction by this measure.

"A no observable effect level cannot be determined from this test, nor can the possibility of a synergistic effect between PGSM and OMCTS be eliminated. This study should be repeated with lower levels of PGSM and OMCTS."

Submission Evaluation

Immediately upon receipt of this TSCA Section 8(e) notice, the Chemical Screening Branch (CSB/ECAD) transmitted a full copy of the submission to the Test Rules Development Branch (TRDB/ECAD) for inclusion in the ongoing review of available toxicologic and exposure data on OMCTS. In 1984, OMCTS was designated by the Interagency Testing Committee (ITC; 15th List) for consideration of test rule development under Section 4 of TSCA. The proposed test rule on OMCTS was published by EPA on October 30, 1985 (50 FR 45123). OMCTS is also the subject of TSCA Section 8(a) and Section 8(d) information reporting rules published by EPA on November 28, 1984 (49 FR 46739 and 49 FR 46741, respectively).

Current Production and Use

Information on the manufacture and uses of OMCTS can be found in EPA's October 30, 1985 proposed test rule (see 50 FR 45123).

Comments/Recommendations

In its TSCA Section 8(e) submission, Dow Corning stated that the company had notified Dow Corning customers and silicone producers worldwide about the reported findings. Dow Corning stated also

that additional studies were being conducted to determine the reliability and importance of the submitted results. Dow Corning stated further that EPA would be apprised of any additional pertinent information. Finally, Dow Corning stated that the final report of the Daphnia magna reproduction limit test was also being submitted to EPA under Section 8(d) of TSCA.

The following discussion pertains to the relationship between TSCA Section 8(e) reporting and the reporting of studies "listed" under Section 8(d) of TSCA and those required to be conducted under Section 4 of TSCA:

> Part VII of EPA's TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" March 16, 1978; 43 FR 11110) explains that substantial risk information does not need to be submitted to EPA under Section 8(e) if the subject information has been submitted to EPA under another mandatory reporting requirement of TSCA or some other authority (e.g., Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)) administered by EPA. The purpose of this particular exemption is not to change substantially the Section 8(e) reporting obligation, but is designed merely to avoid requiring duplicative reporting except in those cases where reporting under the other authority does not or will not meet the timeliness requirements of Section 8(e). Further, if other mandatory reporting to EPA under an EPA-administered authority is incurred coincidental with a Section 8(e) reporting requirement and the subject information is reported to EPA within no more than 15 working days, the filing of a separate Section 8(e) report with EPA's Office of Toxic Substances would not be necessary.
>
> Therefore, a Section 8(e) reporting requirement would apply to any "substantial risk" information that is obtained during the conduct of any study "listed" under TSCA Section 8(d) as being underway or required to be conducted under Section 4 of TSCA unless the subject information is otherwise required formally to be submitted to EPA under those or other sections of TSCA. To date, a number of TSCA Section 8(e) submitters have correctly reported interim findings from studies "listed" under Section 8(d) of TSCA or those being conducted under Section 4 of TSCA. In such cases, the TSCA Section 8(e) reporting obligation was incurred before the information was required to be reported to the Agency under Section 8(d) or Section 4 of TSCA.

The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OW/EPA, OAR/EPA, ORD/EPA, OSWER/EPA, OPP/OPTS/EPA and TRDB/ECAD/OTS; copies of this status report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAR 22 1988

SUBJECT: Status Report* 8EHQ-0288-0719 Approved: James F. Darr 3/23/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The Olin Corporation provided a copy of the final report of an Ames Salmonella typhimurium (bacteria) mutagenicity assay of a chemical product known as "Chemical 400, Step 1" (2-[ethyl[3-methyl-4-(phenylazo)phenyl]amino]ethanol; CAS No. 68214-81-3). According to Olin, the tested material was mutagenic under both oxidative and reductive conditions. Under oxidative conditions, the product reportedly caused a positive response in bacterial strains TA 98 and TA 1538 in the presence of induced rat liver microsomes; under reductive conditions, the product reportedly caused a positive response in strains TA 98 and TA 1538 in the presence of uninduced hamster liver microsomes.

Submission Evaluation

The subject Ames assay was conducted with and without exogenous metabolic activation in the following bacterial strains: TA98, TA100, TA1535, TA1537 and TA1538. The metabolic activation was supplied by the S9 fraction of livers from rats treated before sacrifice with Aroclor 1254 for the nonspecific induction of liver enzymes and from the S9 fraction of livers from hamsters receiving no treatment prior to sacrifice. The use of uninduced hamster liver S9 in the Ames assay has been found in some cases to facilitate the reduction of azo compounds. The hamster liver activation is referred to in the submitted report as "reductive conditions" while the use of induced rat liver activation is referred to as "oxidative conditions."

The tests conducted without metabolic activation were uniformly negative. In the presence of metabolic activation, however, the subject chemical was found to be mutagenic for TA98 and TA1538 under both oxidative and reductive conditions. The test chemical appears to be less toxic under reductive conditions than it is under oxidative conditions. Under the reductive conditions, the

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

highest non-toxic dose was found to be 333 ug/plate while under the oxidative conditions the highest non-toxic dose was found to be 100 ug/plate. These are also the doses at which the maximum mutagenic response was observed. Under the reductive conditions, the maximum response was 2X background in strain TA98 and 2.3X background in strain TA1538. Under the oxidative conditions, the maximum response in TA98 was 3X background. In strain TA1538, which was tested twice under oxidative conditions, the maximum responses were 5.3X background (first test) and 2.5X background (second test). The differences found in these two tests are not considered to be outside the normal range of intralaboratory variation for this assay. Further, there does not appear to be any significant difference in response between the oxidative and reductive conditions. In conclusion, the subject chemical is considered to be mutagenic in the Ames assay when tested with metabolic activation derived from either Aroclor 1254-induced rat liver or uninduced hamster liver.

Current Production and Use

A review of the production range (includes importation volumes) statistics for CAS No. 68214-81-3, which is listed in the initial TSCA Chemical Substance Inventory, shows that no 1977 manufacture or importation of the chemical was reported or that all of the manufacturing and/or importation data reported were claimed as TSCA Confidential Business Information (CBI) by the person(s) reporting for the initial Inventory and cannot be disclosed (Section 14(a) of TSCA; U.S.C. 2613(a)). All of the data that were submitted for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

In its submission, Olin reported that the subject chemical is "an intermediate for the production of color developing agents used in photographic products." Olin reported also that the chemical "is used by Olin Hunt Specialty Products, Inc. of Rhode Island, a wholly owned subsidiary of Olin and is not sold to any other company nor is it an ingredient in any other final product."

Comments/Recommendations

In its submission, Olin stated that the company has "conducted a comprehensive review of employee work practices and engineering controls and assessment of employee exposure in the manufacturing area while employees (a) drum Chemical 400, Step 1, (b) isolate Chemical 400, Step 1, and (c) conduct other manufacturing activities." Olin stated also that "industrial hygiene recommendations were made, adopted and implemented for each of these manufacturing activities." Finally, Olin stated that "all management, manufacturing and occupational health employees of Olin have been informed of the . . . [reported mutagenicity findings as well as the] engineering controls and monitoring programs are in place to further control any possible exposure during manufacturing."

Although a positive in vitro genotoxicologic assay result, when considered alone, may not be sufficient to reasonably support a conclusion of substantial risk (as that term is defined in EPA's TSCA Section 8(e) policy document ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978)), EPA believes that such results are of value in assessing possible risks posed by exposure to chemical substances or mixtures. The Agency also believes that positive genotoxicity findings, when considered in combination with other pertinent information (e.g., knowledge of potential exposure to and/or high production of the subject chemical or mixture), would suggest the need, in many cases, to conduct further studies that are designed to better define the toxicologic properties of or exposure to the subject chemical(s). The results of such further testing should be considered also for submission to EPA pursuant to Section 8(e) of TSCA.

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Olin will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the published scientific literature) about which Olin is aware or that Olin has conducted, is conducting or plans to conduct to determine the toxicity of the subject chemical substance.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAR - 3 1988

SUBJECT: Status Report* 8EHQ-0288-0720

Approved: James F. Darr 3/3/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The General Electric Company provided data (see Table 1 attached) from a study conducted by the Institut Fresenius in West Germany to determine if polybrominated dibenzofurans (PBrDF) and/or polybrominated dibenzodioxins (PBrDD) were formed as the result of pyrolysis of a mixture containing polybutylene terephthalate resin (85%; CAS No. 30965-26-5), decabromodiphenyl ether flame retardant (11%; CAS No. 1163-19-5), antimony oxide synergist (2.7%; CAS No. 1309-64-4) and other unspecified constituent(s) (3%). According to General Electric, samples of this mixture were heated for 10 minutes at temperatures ranging from 200°C to 900°C and then subjected to gas chromatography/mass spectroscopy to quantify selected PBrDF and PBrDD isomer levels.

Submission Evaluation

The General Electric Company stated by phone on March 2, 1988, that the company was in the process of preparing a supplemental TSCA Section 8(e) notice containing further information regarding the reported analytical findings. According to General Electric, this supplemental Section 8(e) submission will be sent to EPA during the week of March 7-11, 1988.

It should be noted that on June 5, 1987 (52 FR 21412), the Agency published a final PBrDF/PBrDD testing and reporting rule under Sections 4 and 8 of TSCA; this rule was prepared by the Chemical Regulation Branch (CRB)/Exposure Evaluation Division (EED)/Office of Toxic Substances (OTS). In addition, it should be noted that based on a Chemical Hazard Information Profile (CHIP) prepared in 1986 by the Chemical Screening Branch on a number of brominated diphenyl ethers, the Risk Analysis Branch (RAB/ECAD/OTS) has been reviewing available toxicologic/exposure data on this class of chemical substances.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Comments/Recommendations

The following discussion pertains to the relationship between TSCA Section 8(e) reporting and 1) mandatory reporting of studies under Section 8(d) of TSCA, and 2) mandatory reporting of results of studies required to be conducted under Section 4 of TSCA:

> Part VII of EPA's TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" March 16, 1978; 43 FR 11110) explains that substantial risk information must be submitted to EPA under Section 8(e) of TSCA unless the subject information has been submitted to EPA under another mandatory reporting requirement of TSCA or some other authority administered by EPA. The purpose of this particular reporting exemption is not to change substantially the Section 8(e) reporting obligation, but is designed merely to avoid requiring duplicative reporting except in those cases where reporting under the other authority does not or will not meet the timeliness requirements of Section 8(e). Further, if other mandatory reporting to EPA under an EPA-administered authority is incurred coincidental with a Section 8(e) reporting requirement and the subject information is reported to EPA within 15 working days, the filing of a separate Section 8(e) report with EPA is not necessary.
>
> Therefore, a Section 8(e) reporting requirement would apply for example to any "substantial risk" information obtained during the conduct of any study "listed" under TSCA Section 8(d) as being underway or required to be conducted under Section 4 of TSCA unless the subject information is otherwise required formally to be submitted to EPA under those or other sections of TSCA. To date, a number of TSCA Section 8(e) submitters have correctly reported interim results of studies "listed" under Section 8(d) of TSCA or those being conducted under Section 4 of TSCA. In such cases, the TSCA Section 8(e) reporting obligation was incurred before the information was required to be reported to the Agency under Section 8(d) or Section 4 of TSCA.

Considering the preceding discussion and in view of the fact that EPA's TSCA Sections 4 and 8 PBrDD/PBrDF testing and reporting rule covers only manufacturers and importers of the chemical substances listed in that rule, General Electric, a processor but not a manufacturer or importer of decabromodiphenyl ether (which is a chemical listed in the rule), did not have any mandatory obligation to report the analytical findings to EPA under that rule. General Electric was correct, therefore, in making the decision to submit the analytical findings to the Agency pursuant to Section 8(e) of TSCA.

As was the case with General Electric's initial TSCA Section 8(e) submission, the Chemical Screening Branch will immediately send copies of General Electric's supplemental Section 8(e) submission to the Chemical Regulation Branch/EED/OTS, the Risk Analysis Branch/ECAD/OTS, other appropriate EPA Program Offices and other appropriate Federal agencies.

The Chemical Screening Branch will send this status report to NIOSH, OSHA, CPSC, FDA, NTP, OW/EPA, OAR/EPA, ORD/EPA, OSWER/EPA, OPP/OPTS/EPA, CRB/EED/OTS/OPTS/EPA and RAB/ECAD/OTS/OPTS/EPA. In addition, this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

Attachment: TABLE I

TABLE I

"Effects of Pyrolysis Temperatures
on
Polybutyleneterephthalate Resin Flame Retarded with Decabromodiphenylether/Sb_2O_3*
All in micrograms/kilogram (ppb)

	200°C	250°C	300°C	400°C	500°C	600°C	700°C	800°C	900°C
Br_4-PBrDF	n.d.	1,300,000	5,200,000	2,000,000	1,200,000	490,000	24,000	30	40
2,3,7,8-PBrDF	n.d.	66,000	150,000	64,000	120,000	19,000	400	5	n.d.
Br_5-PBrDF	n.d.	4,400,000	5,900,000	1,200,000	1,300,000	350,000	8,000	6	20
1,2,3,7,8-PBrDF	n.d.	n.d.	n.d.	n.d.		n.d.	n.d.	n.d.	n.d.
Br_6-PBrDF	36,000	2,600,000	2,200,000	900,000	670,000	100,000	3,400	n.d.	n.d.
1,2,3,4,7,8-PBrDF	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Br_7-PBrDF	140,000	140,000	n.d.	n.d.	50,000	3,100	90	n.d.	n.d.
Br_4-PBrDD			1,300	1,400	1,500	n.d.	n.d.	n.d.	n.d.
2,3,7,8-PBrDD			n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Br_5-PBrDD			320	340	3,600	1,100	50	n.d.	n.d.
1,2,4,7,8-PBrDD			n.d.	n.d.	1,000	n.d.	6	n.d.	n.d.
Br_6-PBrDD			n.d.	n.d.	5,200	900	10	n.d.	n.d.
1,2,3,4,7,8-PBrDD			n.d.	n.d.	n.d.	80	n.d.	n.d.	n.d.
Br_7-PBrDD			n.d.	n.d.	n.d.	40	n.d.	n.d.	n.d.

n.d. = not detectable

* Resin formulation: Polybutylene terephthalate, 85%; Decabromodiphenylether 11%; Antimony oxide, 2.7%; other, 3%"

DATE: MAR 22 1988

SUBJECT: Status Report* 8EHQ-0388-0721

Approved: David R. Williams Jr. James F. Darr

MAR 24 1988

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The Eastman Kodak Company submitted the following summarized information with regard to the conduct and results of a guinea pig skin sensitization study and an acute rat oral LD50 study of 4-methoxy-2-nitrophenylthiocyanate (CAS No. 59607-71-5):

> "A group of 10 guinea pigs was tested for skin sensitization using the method described in the [Organization for Economic Cooperation and Development (OECD)] Guideline for Testing of Chemicals: Skin Sensitization Guideline 406, Section 5. When animals which had been induced with the test article in Freund's adjuvant were challenged, strong erythema developed in nine of ten animals. The strong erythema persisted to the 48-hour observation point in six of the nine animals. The erythematous response was extensive. An area of necrosis was noted in one animal. No edema was seen in any of the animals at challenge. The intensity of the erythematous response and the area of skin over which the reaction occurred at challenge resulted in a strong positive classification.
>
> "As part of an acute oral LD50 study, 5 male rats were given a dose of 5000 mg/kg body weight of the test compound by gavage. Groups of 5 female rats were dosed at 1250, 2500, or 5000 mg/kg. At 5000 mg/kg, one male and four females died on Day 2. Treatment-related changes in rats dying within two days of treatment included hemorrhage of the glandular gastric mucosa, presence of the test compound in the gastrointestinal

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tract, and yellow discoloration of the facial and inguinal hair. Yellow discoloration of the inguinal hair was the only abnormality noted at necropsy of the one female surviving the 5000 mg/kg dose. No treatment-related changes were seen at scheduled necropsy in females at the two lower doses. The estimated LD50 in females was 3536 mg/kg.

"Since four of five male rats survived a dose of 5000 mg/kg, the LD50 was estimated at greater than 5000 mg/kg. Treatment-related changes in male rats which survived the 14-day observation period included small testes (four of four animals) and yellow discoloration of the inguinal hair (one of four animals). Treatment-related testicular changes noted in tissue from all four animals included decreased numbers of spermatogonia, spermatocytes, spermatids, and spermatozoa, and degenerating spermatids and spermatozoa. Body weight loss in males was significant during the first week after dosing, and inadequate nutritional intake is a confounding factor involved in interpretation of this study. Additional testing is being conducted on groups of male rats in order to determine the no-effect-level for the testicular changes. Preliminary findings from these additional investigations indicate that the acute oral LD50 in male rats may be lower than originally estimated. The LD50 will be revised, if necessary, and the no-effect-level for testicular effects will be addressed in the final report on the acute toxicity of this material. . . . ."

According to a submitted interim report on the acute toxicity of 4-methoxy-2-nitrophenylthiocyanate, the chemical was found to be slightly toxic (LD50 >2000 mg/kg) in an acute dermal study in rats, slightly irritating in an acute dermal study in guinea pigs, and slightly irritating in an acute eye study in rabbits.

Submission Evaluation

The provided acute toxicologic findings indicate that 4-methoxy-2-nitrophenylthiocyanate is slightly to moderately toxic by the oral route in rats. The treatment-related changes observed in the surviving male rats in this acute oral study included small testes, decreased spermatogonia, spermatocytes, spermatids, and spermatozoa as well as degenerating spermatids and spermatozoa. These changes suggest that the male reproductive system could be a potential target in long term studies conducted at lower doses of the subject chemical.

The submitted data indicate also that the chemical is slightly irritating to the skin of guinea pigs and slightly to moderately irritating to rabbit eyes. The guinea pig sensitization study results indicate that the chemical may have a high potential for skin sensitization in humans.

Current Production and Use

A review of the production range (includes importation volumes) statistics for 4-methoxy-2-nitrophenylthiocyanate (CAS No. 59607-71-5), which is listed in the initial TSCA Chemical Substance Inventory, has shown that no 1977 manufacture/importation of the chemical was reported or that all of the manufacturing and/or importation data reported were claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory and cannot be disclosed (Section 14(a) of TSCA; U.S.C. 2613(a)). All data submitted for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

In its Section 8(e) notice, Eastman Kodak provided the following information regarding the production of and the potential for exposure to 4-methoxy-2-nitrophenylthiocyanate:

> "This chemical is used as a site-limited intermediate in a photographic chemical. None of the intermediate is present in the final chemical. The intermediate was not manufactured in 1987 and, at present, there are no plans to manufacture it in 1988. . . . [Eastman Kodak is] not aware of any adverse health problems associated with its manufacture or its use to make the final product. After the initial synthesis, the chemical is handled damp. Potential employee exposure has been minimized during manufacture by the use of neoprene gloves, safety glasses, full face air-supplied respirators, safety shoes, and company supplied clothing. During use, employees are protected by neoprene gloves, disposable dust masks, safety glasses, company supplied clothing, and general and local exhaust. In future operations, employees will wear Tyvek coveralls over their company supplied clothing."

Comments/Recommendations

In addition to conducting additional studies to determine the no-observed-effect-level for the testicular toxicity found in rats, Eastman Kodak updated the 4-methoxy-2-nitrophenylthiocyanate Material Safety Data Sheet (MSDS) to reflect a potential for skin sensitization and testicular toxicity; a copy of this updated MSDS was included in the Eastman Kodak Company's Section 8(e) submission.

a) The Chemical Screening Branch will ask Eastman Kodak to ensure that EPA receives complete copies of the final reports (including the actual experimental protocols, results of gross and histopathological examinations, etc.) from the company's ongoing studies to determine the no-observed-effect-level for adverse testicular effects of 4-methoxy-2-nitrophenylthiocyanate.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Eastman Kodak will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Eastman Kodak is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of 4-methoxy-2-nitrophenylthiocyanate.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of 4-methoxy-2-nitrophenylthiocyanate.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: APR - 7 1988

SUBJECT: Status Report* 8EHQ-0288-0722

Approved: James F. Darr 4/12/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

Submission Description

The Boeing Company provided the results of an epidemiological investigation conducted by the company as a result of employee "concerns that women at Boeing's fabrication facility in Auburn, Washington, were experiencing a rate of miscarriage that was higher than expected." According to Boeing, the study "suggested that the rate of miscarriage in a selected employee group may be elevated; however, the small size of the study and the numerous confounding factors identified in the study made the results inconclusive." Boeing stated that "because this investigation suggested that the rate of miscarriage in the selected employee group may be elevated, . . . a further statistical analysis of the data collected during the initial investigation [was performed] to determine if [any] links to specific agents could be established." According to Boeing, this "followup analysis suggests a possible association between the rate of miscarriage and potential exposure to agents in the workplace." Boeing also stated, however, that "because of the small size of the group studied, and the multiple sources of potential bias that were identified, this [followup] analysis also provides only suggestive evidence of [an] association between the rate of miscarriage and workplace agents."

The "CONCLUSIONS" section of the submitted followup analysis presents the following information:

"The following conclusions can be drawn from the study:

1. The study does not conclusively establish that the overall rate of miscarriage in the organizations investigated is higher than that in the general population. However, the results do more to support than to refute the contention that [workers in] these organizations experience higher rates of miscarriage than does the general population.

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2. Exposure to . . . [a polymeric resin parting compound], to . . . [an epoxy resin adhesive film], and to heavy lifting are implicated by this study as being associated with the rate of miscarriage.

3. No single agent can be identified as the cause of miscarriage in this study.

"The 95% confidence interval [(CI)] for the rate of miscarriage in the study cohort is 15%-43%. This is inconsistent with those population-based studies in which the normal rate of miscarriage was estimated to be 10%-15%, but is consistent with those studies in which a normal rate of 15%-20% was found. Had the 95% confidence interval of this study included the entire range of estimates of the normal range, one could conclude that the rate of miscarriage in the target population did not exceed the normal. If the lower bound of the 95% confidence interval of the study exceeded 20%, one could conclude that the rate of miscarriage in the target population exceeded the normal. Since the results were intermediate, the conclusion must be intermediate.

"The question of cause and effect cannot be answered by this study. Of the five ["generally accepted"] criteria for inferring causality [i.e., strength of association, temporality, consistency of results, dose-response relationship, coherence]. . . only two are satisfied--a moderately strong association between the implicated agents and miscarriage was found [(strength of association criterion)] and the potential for exposure to these agents preceded the miscarriages in all cases [(temporality criterion)]. However, there are no other reports concerning the reproductive effects of the implicated agents and heavy lifting is generally thought not to be associated with miscarriage [(consistency of results criterion)]. There was no information collected whereby the dose-response relationship could be evaluated [(dose-response relationship criterion)], and the biologic plausibility of the relationship was not explored [(coherence criterion)]."

Submission Evaluation

Boeing's investigations demonstrate the difficulty involved in studying reproductive hazards in the workplace. Although it cannot be determined that any particular chemical exposure or process or workplace activity was the cause of miscarriages among the employees at this Boeing facility, the studies do signal the need for a more extensive examination of the rate of miscarriages at the facility and suggest the need for a monitoring program for workplace exposure to numerous chemicals. Considering that undiagnosed miscarriages may not have been reflected accurately by

employees' self-reported information, other indices of adverse reproductive effects (e.g., low birth weight) could be used as appropriate substitutes. Also, some emphasis in any further studies that are conducted by the company should be placed on the implicated polymeric resin parting compound and epoxy resin adhesive film as well as the components of those products.

Comments/Recommendations

In its submission, Boeing stated that in spite of the uncertainty of the reported epidemiologic findings, the company "is requiring employees in the work areas included in the study to wear protective gloves . . ."

a) In view of EPA's general interest in corporate actions that are taken on a voluntary basis in response to new chemical toxicity or exposure information, the Chemical Screening Branch will request Boeing to describe the nature and results, if and when available, of all other epidemiologic studies that Boeing has underway or plans to conduct to investigate adverse reproductive outcomes among employees at the Auburn, Washington facility.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the reported findings.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAR 14 1988

SUBJECT: Status Report* 8EHQ-0388-0723 Approved: James F. Darr 3/21/88

FROM: David R. Williams DRW, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The Monsanto Company reported that preliminary results from a number of acute toxicity studies of 6-methylpurine (CAS No. 2004-03-7) indicate that this chemical substance has an oral LD50 of <50 mg/kg, a dermal LD50 of about 200 mg/kg and is corrosive to the eyes; the animal species tested in these studies were not identified in the submission.

Submission Evaluation

It should be noted that chemicals having an oral LD50 value of less than 50 mg/kg are typically classified as being "extremely" toxic. An evaluation of the overall significance of the reported toxicologic findings should be possible upon the Agency's receipt of complete copies of the final reports from all of the studies cited in this submission.

Current Production and Use

6-Methylpurine was not found on the non-confidential computerized initial TSCA Chemical Substance Inventory. According to Monsanto, the company's "use of this purchased material is currently limited to small quantities for research and development (R&D) activities" and "as a result, Monsanto worker exposure to this R&D material (6-methylpurine) is extremely low, both in terms of [the] existing quantity (120 grams) and number of research people handling it (<5)."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Comments/Recommendations

In its submission, Monsanto stated that the company has labelled the subject chemical as a "Class B Poison" and "Corrosive" to the eyes. In addition, Monsanto stated that the company has advised its potentially exposed workers and the supplier of the chemical about the reported toxicologic findings.

a) The Chemical Screening Branch will request Monsanto to ensure that EPA receives complete copies of the final reports (including the actual experimental protocols, results of gross/histopathologic examinations, etc.) from all acute toxicity studies cited in the company's submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Monsanto will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Monsanto is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of 6-methylpurine.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: APR 12 1988

SUBJECT: Status Report* 8EHQ-0388-0724 S

Approved: James F. Darr 4/18/88

FROM: David R. Williams, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Note

The CIBA-GEIGY Corporation has claimed the exact identities of the subject chemical substances as TSCA Confidential Business Information (TSCA CBI); the Information Management Division (IMD/OTS) will be requesting the company to substantiate these confidentiality claims. In the "sanitized" version of this TSCA Section 8(e) submission, CIBA-GEIGY reported non-confidentially that the tested material is a "mixture of sterically hindered phenol derivatives." CIBA-GEIGY reported also that the major component accounts for approximately 86% of the mixture and the minor component accounts for approximately 8% of the mixture.

Submission Description

CIBA-GEIGY submitted the final report of a 28-day dietary feeding study of the subject mixture in rats. CIBA-GEIGY's cover letter presented the following information regarding the conduct and major results of this study:

> "A 28-day dietary administration study with rats was performed at feed levels of 0, 100, 500, 2500 and 12,000 ppm. Among other effects, signs of anemia (2,500 and 12,000 ppm groups), liver toxicity (100-12,000 ppm groups) and focal cell hypertrophy within the adenohypophysis with parallel thyroid follicle hypertrophy (500 - 12,000 ppm groups) were observed."

According to the "SUMMARY AND ASSESSMENT" portion of the provided final report, administration of the test material in the diet for 28 days "did not result in any deaths and only caused a minor disturbance in food intake and bodyweight gain of rats receiving 12,000 ppm."

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Submission Evaluation

The subject mixture was administered in the feed for 30 days to 5 rats/sex/group at doses of 0, 100, 500, 2500 and 12,000 ppm. This correlated with doses of 0, 9.94, 49.0, 250 and 1211 mg/kg/day in males and 0, 10.1, 47.1, 253 and 1102 mg/kg/day in females. Food consumption, body weight, clinical observations, hematology, biochemistry and pathology were examined.

No mortalities or adverse clinical findings were observed during the study. Body weight was slightly decreased at 12,000 ppm for both sexes, with the females showing a 4% decrease and the males a 7% decrease by week 4. By weeks 3 and 4, the females at 2500 and 12,000 ppm showed a 7% and 9% decrease, respectively, in food consumption from the controls. The males at the 12,000 ppm dose level exhibited a statistically significant 13% reduction in food consumption.

Hematology revealed a dose-related decrease in red blood cells for both sexes which was not statistically significant and a dose-related decrease in hemoglobin and hematocrit which was statistically significant for both sexes at 2500 and 12,000 ppm. The male rats showed a statistically significant decrease in reticulocytes at the highest dose level. These data suggest that the tested mixture may be adversely affecting the hematopoietic system and producing anemia.

The clinical chemistry results for both sexes indicated a dose-related increase in cholesterol, total protein and total globulin levels and a dose-related decrease in the albumin/globulin ratio. The values given for serum cholesterol, total protein, globulin and albumin/globulin ratio were statistically significant at 2500 and 12,000 ppm in both sexes. These values were also much more dramatically altered for females than for males. Although the alterations in these parameters are suggestive of a cholestatic type of liver injury, the remaining chemistry results do not support this premise. Both sexes showed a decrease in alkaline phosphatase levels instead of an increase as would be expected with a cholestatic type injury. Serum bilirubin levels would also be expected to be increased; however, none were examined. In addition, males showed a significantly decreased blood urea nitrogen at 12,000 ppm which may have been due, in part, to the 13% reduction in food consumption. Neither the alanine aminotransferase (GPT) nor the aspartate aminotransferase (GOT) levels were elevated at the highest doses. The GPT and GOT values were statistically significantly elevated at 500 ppm in males, but then proceeded to decrease with increasing dose.

Gross necropsy results showed a statistically significant dose-related increase in relative liver weight for the males at 500, 2500 and 12,000 ppm and for the females at all dose levels. Again, the values observed for females were markedly increased over those of the males. The females also exhibited a dose-related decrease in absolute and relative spleen weight.

The procedure section of the submitted final report listed a more than adequate number of tissues to be preserved and examined microscopically. However, the study results cover only a limited number of these tissues (i.e., liver, kidney, uterus, bladder, myocardium, adenohypophysis, thyroid and harderian gland). The primary treatment-related lesions that were presented appeared to involve the liver, thyroid and pituitary. Hypertrophy of the liver hepatocytes was present in all test animals at 2500 and 12,000 ppm. Minimal foci of liver cell necrosis was observed in 1/10 rats at 100 ppm, 2/10 at 500 ppm, 2/10 at 2500 ppm and 3/10 at 12,000 ppm. Electron microscopic examination of the hepatocytes from rats exposed to 12,000 ppm revealed some (no number given in the report) with intracytoplasmic inclusions consisting of lipid droplets and tubular elements of smooth endoplasmic reticulum. These intracytoplasmic inclusions may be associated with the accumulation of lipids in the hepatocytes or the liver. Histopathologic examination of the thyroid showed hypertrophy of the thyroid follicles in 1/10 rats at 100 ppm, 9/10 at 500 ppm, and 10/10 at 2500 and 12,000 ppm. Focal cell hypertrophy within the adenohypophysis was observed in 1/10 rats at 500 ppm and 5/10 at 2500 and 12,000 ppm; only males were observed to have lesions of the adenohypophysis.

Although the data from this study adequately demonstrate the toxicity of the subject mixture at the doses selected, the pattern or type of toxicity produced is unclear. For example, although the test material appears to be affecting the liver, the lack of biologically significant increases in serum GOT or GPT levels suggests that the constituents of the mixture are not producing direct toxicity to the liver. The markedly increased cholesterol, total protein and globulin levels suggest a cholestatic type injury; however, the alkaline phosphatase levels are notably decreased instead of increased and no bilirubin levels were examined. The possibility of fat accumulation within the liver may account for the hepatocellular hypertrophy but it is unlikely that this would produce the biochemical aberrations observed. Considering that elevated cholesterol levels have been associated with hypothyroid states, the effects of the mixture component(s) on the pituitary and thyroid may be as important as the effects on the liver.

In conclusion, administration of the subject mixture to rats at doses of from 9.94 to 1211 mg/kg/day in the feed for 30 days, resulted in adverse effects to the liver, pituitary, thyroid, and/or blood at each dose level tested.

Current Production and Use

In view of CIBA-GEIGY's TSCA CBI claims, no information with regard to the TSCA Chemical Substance Inventory status of the constituents of the tested mixture will appear in this status report.

CIBA-GEIGY provided the following non-confidential information concerning the company's activities with the subject mixture of sterically hindered phenol derivatives:

> "The company imported for research and development purposes approximately 50 gms of the subject material, all of which was used internally by [the] CIBA-GEIGY Corporation for technical performance evaluations. No material was distributed outside the company. The substance has been subsequently dropped from further consideration as a potential product. . . . .
>
> ". . . [The small amount of the mixture imported into the U.S.] was handled using prudent laboratory practices. There is no remaining inventory of the material in the U.S. . . ."

Comments/Recommendations

In addition to dropping from commercial consideration this mixture of sterically hindered phenol derivatives, CIBA-GEIGY reported that the company "will revise its Material Safety Data Sheet and notify its employees who worked with or handled the material of the new findings."

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, CIBA-GEIGY will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which CIBA-GEIGY is aware or that CIBA-GEIGY has conducted or is conducting to determine the toxicity of the subject mixture or its constituents.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of this mixture or its constituents.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: APR 12 1988

SUBJECT: Status Report* 8EHQ-0388-0725 Approved: James F. Darr 4/18/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

Submission Description

The CIBA-GEIGY Corporation submitted the following information with regard to the conduct and preliminary results of a chronic feeding study of the 1,2-ethanediyl-bis(oxy-2,1-ethanediyl) ester of 3-(1,1-dimethylethyl)-4-hydroxy-5-methyl-benzenepropanoic acid (CAS No. 36443-68-2) in rats:

> "[At the CIBA-GEIGY's parent company (CIBA-GEIGY Ltd. in Basel, Switzerland),] a 24-month feeding study was conducted in rats which received targeted doses of 0, 5, 15, 50 and 100 mg/kg/day. The results [(as received orally from the parent company)] apparently showed a disturbance of lipid metabolism and liver enzyme activities, indicative of liver toxicity, and an increased incidence of cystic dilatation or hyperplasia of the thyroid follicles in the 15 (males only), 50 and 100 mg/kg groups. In addition, an increased incidence of thyroid gland follicular adenomas and carcinomas were observed in the 50 (males only) and 100 mg/kg/day groups.
>
> "Due to the limited data currently available and the well known secondary mechanisms of thyroid tumor induction in the rat, . . . [CIBA-GEIGY is] not certain at this time whether this information is relevant to humans. . . . [The] parent company is presently considering the etiology of the thyroid effects. Since the [subject] chemical is not genotoxic, an epigenetic mechanism may have been responsible for the thyroid tumors. The company is considering investigating the possibility that liver hypertrophy, which is known to be an effect of this chemical, produced an imbalance of thyroid hormone levels resulting in secondary tumor development."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Submission Evaluation

In order to evaluate the overall significance of the reported toxicologic findings, CIBA-GEIGY should be asked to ensure that EPA receives a complete copy of the final report of the subject 24-month feeding study in rats.

Current Production and Use

Although the subject chemical substance was not located on the non-confidential computerized version of the initial TSCA Chemical Substance Inventory, the CAS Registry Number for this chemical (followed by a "P") was found in Volume I of the non-confidential printed TSCA Inventory (1985 Edition). According to introductory information given in Volume I, the "P" designation indicates that 1) the chemical substance was the subject of a TSCA Section 5 "Pre-Manufacture Notification" (PMN), and 2) EPA has received a "Notice of Commencement" (NOC) for the manufacture and/or importation of that chemical.

In its Section 8(e) notice, CIBA-GEIGY reported that the subject chemical substance, which is imported to the U.S. for use as a stabilizer for a number of polymers, "is still at an early stage of commercialization." CIBA-GEIGY also provided the following information about the potential for exposure to this chemical:

> "The current [Material Safety Data Sheet (MSDS)] and label already warn against undue exposure through swallowing, inhaling dust, eye contact, and repeated or prolonged skin contact. Exposure of industrial workers to CAS No. 36443-68-2 should, therefore, be minimal. The subject material is present in very low concentrations in the final polymer product(s), typically Ø.25 percent by weight or less. Since the substance is uniformly admixed throughout the polymer, the amount of stabilizer at the surface of any article containing it is extremely low. Dermal exposure to consumers is, therefore, negligible."

Comments/Recommendations

CIBA-GEIGY reported in its Section 8(e) submission that the company was 1) revising the subject chemical's MSDS to reflect the reported toxicologic findings, and 2) notifying all company employees and customers about these findings.

a) The Chemical Screening Branch will request CIBA-GEIGY to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, results of gross/histopathologic examinations, results of any statistical analyses, etc.) from the 24-month feeding study cited in the company's TSCA Section 8(e) submission.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, CIBA-GEIGY will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which CIBA-GEIGY is aware or that CIBA-GEIGY has conducted, is conducting or plans to conduct to determine the toxicity of the subject chemical substance.

b) As in the case of the initial submission, copies of all additional reported information will be transmitted to staff of the Chemical Control Division (CCD/OTS) which is responsible for the OTS New Chemicals Program. In addition, the Chemical Screening Branch will review all reported information in order to determine the need for further OTS assessment of the subject chemical.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and CCD/OTS/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: APR 14 1988

SUBJECT: Status Report* 8EHQ-0388-0726 Approved: James F. Darr 4/18/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The Hoechst Celanese Corporation provided the final report of a subchronic fertility study of p-tert-butylbenzoic acid (PTBBA; CAS No. 98-73-7) in male rats. The "Summary and Evaluation" section of the submitted final report presents the following information regarding the conduct and results of this study:

> " . . . p-t-Butylbenzoic acid was given to groups of 10 male Wistar rats each for 70 days prior to mating in concentrations of 20, 100 or 500 ppm mixed with the daily food. These concentrations corresponded to a daily substance intake of about 1.6, 7.9 or 41.0 mg/kg body weight. This was followed by mating attempts extending over a period of 7 days with two females each per male. The females were expected to produce offspring. The males were considered fertile when at least one of the two females became pregnant. Males which failed to prove their fertility were mated again 70 days after the end of the treatment. At the end of the test, the sex organs of the male animals were subjected to a histological examination.
>
> "The investigations have shown that the repeated administration of 20 ppm p-t-butylbenzoic acid did not lead to an impairment of the general state of health and of the fertility of the male animals.
>
> "After feeding 100 ppm, the fertility of a single male animal was impaired. Beyond that, the animals of this group were without pathological findings.
>
> "500 ppm led in all males to a slowing down of the weight gain and to an interference with the fertility.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

> "The fertility impairment observed in the animals treated with 100 and 500 ppm, however, [was] reversible within 70 days after the end of the treatment, although after 500 ppm, the weights of the testicles were still reduced and histological damage could be detected in some tubulus sections of the germinal epithelium.
>
> "The concluding autopsy produced, except for the slightly reduced testicular weights, no conspicuous findings in the animals treated with 500 ppm.
>
> "On the basis of these results, the "no effect level" for p-t-butylbenzoic acid with respect to its effect on the fertility of male rats is about 20 ppm. 100 ppm lies in the borderline area of tolerance."

In its submission, Hoechst Celanese stated that the subject study had been commissioned by the German Berufsgenossenschaft Chemie in Heidelberg, West Germany.

Submission Evaluation

Immediately upon receipt of this TSCA Section 8(e) notice, the Chemical Screening Branch transmitted a complete copy of the submission to the Risk Analysis Branch/ECAD for review in conjunction with other available PTBBA toxicity/exposure information including data received by EPA under TSCA Sections 8(a), 8(d) and 8(e) as well as on a "For Your Information" (FYI) basis. The TSCA Sections 8(a) and 8(d) data reporting rules for PTBBA (as well as p-tert-butylbenzaldehyde and p-tert-butyltoluene) were published by EPA on May 12, 1986 (51 FR 17336). In addition, the Chemical Screening Branch prepared (in 1982) "Chemical Hazard Information Profiles" (CHIPs) on PTBBA, p-tert-butylbenzaldehyde and p-tert-butyltoluene. Finally, it should be noted that EPA published (in 1985) a "Chemical Advisory" covering PTBBA, p-tert-butyltoluene and p-tert-butylbenzaldehyde.

Comments/Recommendations

In its Section 8(e) submission, Hoechst Celanese stated that the final report of this PTBBA study had been submitted already to EPA under Section 8(d) of TSCA; the following discussion pertains to the relationship between reporting under TSCA Section 8(e) and other reporting under TSCA or other authorities administered by the Agency:

> Part VII of EPA's TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" March 16, 1978; 43 FR 11110) explains that substantial risk information does not need to be submitted to EPA under Section 8(e) <u>if</u> the subject information has been submitted to EPA under another <u>mandatory</u> reporting requirement of TSCA or some other authority (e.g., Federal Insecticide, Fungicide

and Rodenticide Act (FIFRA)) administered by EPA. The purpose of this particular exemption is not to change substantially the Section 8(e) reporting obligation, but is designed merely to avoid requiring duplicative reporting except in those cases where reporting under the other authority does not or will not meet the timeliness requirements of Section 8(e). Further, if other mandatory reporting to EPA under an EPA-administered authority is incurred coincidental with a Section 8(e) reporting requirement and the subject information is reported to EPA within no more than 15 working days, the filing of a separate Section 8(e) report with EPA's Office of Toxic Substances would not be necessary.

The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OW/EPA, OAR/EPA, ORD/EPA, OSWER/EPA, OPP/OPTS/EPA and RAB/ECAD/OTS/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: APR 24 1988

SUBJECT: Status Report* 8EHQ-0488-0727

Approved: James F. Darr 4/26/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

Submission Description

The Amoco Corporation submitted the following summarized information regarding the conduct and preliminary results of a 28-day dermal toxicity study of intermediate catalytic cracked petroleum distillate (ICCD; CAS No. 64741-60-2) in rats:

> "The study was a 28-day dermal toxicity test with the following experimental design:
>
> > "Four groups of ten collared rats per sex were dosed dermally with 0.0, 0.2, 0.8, or 1.5 ml of ICCD per kilogram body weight. Dosing was [for] five days per week for four weeks. Following the exposure phase, the rats were killed and subjected to gross necropsy. Organ weights were [then] determined and a number of tissues were collected for histologic evaluation.
>
> "The following effects were observed:
>
> "1. Dose-dependent body weight decreases over time in both sexes;
>
> "2. Dose-dependent increases in absolute and relative liver weight in both sexes;
>
> "3. Dose-dependent decreases in absolute and relative ovary weights;
>
> "4. Thymic atrophy in both sexes at all dose levels;

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"5. Small ovaries in the Ø.8 ml/kg and 1.5 ml/kg dose groups; [and]

"6. Small uterus in [the] 1.5 ml/kg group rats."

In submitting this information to EPA, Amoco reported that the findings from the 28-day dermal study "indicate that ICCD can produce toxic effects at Ø.2 ml/kg and above, that these toxic effects include general or systemic toxicity (body weight loss), and that the thymus, liver, ovaries and uterus appear to be target organs for this substance." Amoco reported also that the observed toxic effects "appear to be similar to those observed following repeated dermal application of catalytic cracked clarified oil (CAS No. 64741-62-4)." In addition, Amoco stated that because "the boiling ranges of these two streams overlap, they will contain many of the same components including carbazole derivatives."

Submission Evaluation

Although no information was submitted regarding any clinical signs of toxicity or histopathological findings, the provided information does indicate that dermal exposure to ICCD may result in a wide variety of toxic effects including general toxicity, hepatotoxicity, immunotoxicity and reproductive system toxicity. Amoco should be asked to ensure that EPA receives a full copy of the final report (including the actual experimental protocol, results of gross and histopathological examinations, etc.) from the 28-day ICCD rat dermal toxicity study cited in the company's TSCA Section 8(e) submission.

Current Production and Use

A review of the production range (includes importation volumes) statistics for ICCD (CAS No. 64741-6Ø-2), which is listed in the initial TSCA Chemical Substance Inventory, has shown that over 1 billion pounds were reported as manufactured and/or imported in 1977. This production range information does not include any data claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any data that would compromise TSCA CBI. All of the data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (4Ø CFR 71Ø).

In its TSCA Section 8(e) submission, Amoco reported that "both ICCD and catalytic cracked clarified oils can be used as components in heavy fuels."

Comments/Recommendations

Amoco reported that because 1) the Material Safety Data Sheets (MSDSs) for ICCD and catalytic cracked clarified oil reflect the toxicity of the clarified oil, and 2) the toxic effects of these petroleum streams appear to be similar, "only minor modification to the MSDSs for these products appears necessary at this time." In addition, Amoco reported that copies of the updated MSDSs for these streams would be sent to EPA when the final report from the 28-day ICCD rat dermal study is submitted.

It should be noted that EPA's Office of Toxic Substances (OTS) has received many TSCA Section 8(e) and "For Your Information" (FYI) submissions on various petroleum process streams, including catalytic cracked clarified oil. It should be noted also that the Risk Analysis Branch (RAB/ECAD/OTS) staff is evaluating available toxicologic/exposure information on catalytic cracked clarified oil.

a) The Chemical Screening Branch will ask Amoco to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, results of gross and histopathological examinations, etc.) from the 28-day rat dermal toxicity study that was cited in the company's TSCA Section 8(e) submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Amoco will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Amoco is aware or that Amoco has conducted, is conducting or is planning to conduct to determine the toxicity of or the exposure to ICCD.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of ICCD.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and RAB/ECAD/OTS/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: APR 28 1988

SUBJECT: Status Report* 8EHQ-0488-0728

Approved: James F. Darr 4/29/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The Union Carbide Corporation provided the following information regarding a possible human anaphylactic reaction to polyethylene glycol-8000 (CAS No. 25322-68-3) "when taken orally in a complex pharmaceutical preparation."

> "The subject suffered a potentially life-threatening apparent anaphylactic reaction within a few minutes of taking a commercially available throat lozenge called Imposit. He was hospitalized in a state of circulatory shock with hypotension, but responded to standard treatment. He was subsequently subjected to intradermal sensitivity challenge testing with each of the individual constituents of Imposit (14 in all).
>
> "He exhibited a severe local reaction only to . . . [polyethylene glycol-8000]. It was also determined that 3 months before his apparent anaphylactic reaction he had a mild reaction to a dental paste (Ledermix) containing polyethylene glycols 400 and 3000 and [a] local anaesthetic. The patient has no other known allergies and has been well since the apparent episode of anaphylaxis.
>
> "The European manufacturer of Imposit (Maddaus) notes that it has sold over 10 million Imposit lozenges, but has received no other reports of [human] hypersensitivity reactions to the preparation. Additionally, extensive literature searches by Union Carbide has revealed a few cases of allergic contact dermatitis due to polyethylene glycols, but no reports of anaphylactic (Type I) hypersensitivity reactions."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

In providing this information under Section 8(e), Union Carbide stated that "in the nearly 50 years of worldwide sales of hundreds of millions of pounds of polyethylene glycol products, this is the first report of an anaphylactic reaction . . . [to Union Carbide's knowledge]." Union Carbide reported also that its TSCA Section 8(e) filing was "collated" from letters from the patient and [European] physician involved as well as a direct phone conversation between Union Carbide and that doctor.

Submission Evaluation

As stated in **Casarett and Doull's Toxicology** (3rd Edition, 1986), "Type I or anaphylactic reactions are mediated by homocytotropic antibodies (IgE in man). The Fc portion of IgE antibodies can bind to receptors on mast cells and basophils. If the antibody molecule then binds antigen, pharmacologically active amines such as slow-reacting substance of anaphylaxis and histamine are released from the mediator cell (e.g., mast cell, basophil). These agents result in vasodilation, edema, and generation of an inflammatory response. The main targets of this type of reaction are the gastrointestinal tract (food allergies), the skin (urticaria and atopic dermatitis), the respiratory system (rhinitis and asthma), and the vasculature (anaphylactic shock). These responses tend to occur quickly after rechallenge with an antigen to which the individual has been sensitized and are termed immediate hyper-sensitivity."

According to the information provided by Union Carbide, the affected individual exhibited a state of circulatory shock with hypotension; hospitalization and treatment reportedly resulted in recovery. Further, the patient's subsequent exposure to polyethylene glycol-8000 by intradermal sensitivity challenge testing confirmed this chemical substance as the causative agent. In view of the fact that no information concerning such serious reactions to polyethylene glycol-8000 has been located by Union Carbide or EPA, this particular occurrence of a Type I sensitivity reaction in a human appears to represent a truly idiosyncratic response.

Comments/Recommendations

a) The Chemical Screening Branch will ask Union Carbide to ensure that EPA is apprised of any further significant information regarding the reported case of anaphylaxis.

b) The Chemical Screening Branch will include the reported information in its ongoing review of other toxicologic and exposure data on a number of polyalkylene glycols.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: MAY - 4 1988

SUBJECT: Status Report* 8EHQ-0488-0729 S Approved: James F. Darr 5/2/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Note

The submitting company claimed its name and the exact identity of the subject chemical substance to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will be requesting the submitting company to substantiate these TSCA CBI claims. By phone, the submitting company identified the subject chemical non-confidentially as "ethyl sulfluramid."

Submission Description

The submitting company provided the following summary information with regard to the conduct and results of two 13-week studies of ethyl sulfluramid in beagle dogs:

> "A preliminary 13-week toxicity study . . . was conducted in beagle dogs with ethyl sulfluramid. ['Three groups of 4 male and 4 female dogs were initially exposed by either capsule or dietary admixture to dose levels of 100, 300 and 1000 mg/kg/day on a five day per week basis. An additional group of 4 male and 4 female beagles served as a control group.'] The doses [that were] selected for this test elicited unexpected toxicity and dose levels were reduced ['starting on day 9 of the study as follows: 100 to 50 mg/kg/day, 300 to 100 mg/kg/day, and 1000 to 300 mg/kg/day.'] Histopathological evaluations revealed an absence of sperm in the seminiferous tubules and epididymis for all treated male dogs (except one from the mid dose). Sperm production for control males was deemed normal for dogs of this age (approximately 7 to 8 months of age). This effect in treated dogs was considered as a maturational arrest of spermatogonia.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"Valid interpretation of this study was confounded by several factors. The test chemical was more toxic than [was] expected from earlier range-finding results and necessitated dose level reductions. The health and husbandry of the dogs may have added to the toxic stress exhibited by the animals. The male dogs were juveniles and the differences in sperm production may have been a reflection of the animals' age.

"A second study was conducted . . . to verify these results and to determine if these effects, if treatment related, were reversible. Mature (1.5 to 2 years of age) and maturing (6 months of age) dogs were repeatedly dosed with ethyl sulfluramid. ['Ten mature and ten maturing dogs were initially exposed via capsule to daily doses of 100 mg ethyl sulfluramid/kg body weight on a five day per week basis. Two mature and two maturing dogs served as controls. Clinical signs of toxicity were seen in both the mature and maturing dogs receiving ethyl sulfluramid. One mature dog was found dead on day 20 of the study. As a result of these observations, the dosing regimens for the mature and maturing dogs was modified . . . [as follows]:

Mature dogs

Weeks 1-3	Dosed with 100 mg/kg/day
Weeks 4-8	Dosing suspended
Weeks 9-13	Dosing with 50 mg/kg/day*
Weeks 14-16	Dosing suspended
Week 17	Dosing with 50 mg/kg/day
Weeks 18-32	Non-dosing recovery period*

* one dog was dosed Weeks 9-21; recovery was Weeks 22-33

Maturing dogs

Weeks 1-3	Dosed with 100 mg/kg/day
Week 4	Dosing suspended
Weeks 5-15	Dosed with 50 mg/kg/day
Weeks 16-32	Non-dosing recovery period

'During the first period in which dosing was suspended, mature dogs continued to show signs of toxicity. Two dogs were sacrificed in extremis on days 32 and 39, respectively. Another mature dog was found dead during week 13. No mortalities occurred in the maturing dogs treated with ethyl sulfluramid.'] A clearcut time-related decrease in sperm production was seen in the mature dogs with the effect occurring approximately 3

weeks after the first dose. Upon suspension of dosing, sperm production was essentially normal. These findings could not be verified in the maturing dogs due to the variability in sperm production for male dogs of this age.

"Unilateral castration was performed on all dogs at termination of the dosing period. Histological assessment of the testis and epididymis revealed reduced sperm production for the mature dogs and some of the maturing dogs. The remaining testis was removed and evaluated upon completion of the non-dosing recovery period. A general increase in sperm production was noted for both the mature and maturing dogs."

Submission Evaluation

The provided summary information indicates that sexually mature male dogs are more sensitive than sexually immature male dogs with regard to the adverse reproductive system effects of ethyl sulfluramid. In order for EPA to evaluate the overall significance of the reported findings, however, the submitting company should be requested to ensure that EPA receives full copies of the final reports (including the actual experimental protocols, results of gross and histopathologic examinations, etc.) from the two 13-week oral/feeding toxicity studies cited in the company's TSCA Section 8(e) notice.

Current Production and Use

In view of the submitter's TSCA CBI claims, no information with regard to the TSCA Chemical Substance Inventory status of the subject chemical will appear in this status report. In its TSCA Section 8(e) notice, the submitting company reported that "no quantities [of ethyl sulfluramid] have been distributed . . . for any purpose other than research and development, although an application for registration as a pesticide will be filed . . . [shortly with EPA's Office of Pesticide Programs (OPP/EPA) under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)]."

Comments/Recommendations

a) The Chemical Screening Branch will ask the submitting company to ensure that EPA receives complete copies of the final reports (including the actual experimental protocols, results of gross/histopathologic examinations, etc.) from the two 13-week oral/feeding studies cited in the company's TSCA Section 8(e) submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, the submitter will be asked to describe the actions the company has taken or plans to take 1) to notify workers and others about the

reported information, and 2) to reduce or eliminate exposure to ethyl sulfluramid. In addition, the submitter will be requested to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the published scientific literature) about which the company is aware or that the company has conducted (including the company's "earlier range-finding" studies), is conducting or plans to conduct to determine the toxicity of or the exposure to ethyl sulfluramid.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAY 11 1988

SUBJECT: Status Report* 8EHQ-0588-0730

Approved: James F. Darr 5/12/88

FROM: David R. Williams DRW, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The BASF Corporation submitted the following summary information regarding the conduct and preliminary results of 9-month feeding studies in rats with ethyl auramine, nitrate salt (C.I. Basic Yellow 37; CAS No. 43130-12-7) and auramine, hydrochloride salt (C.I. Basic Yellow 2; CAS No. 2465-27-2) performed by BASF's parent company (BASF AG in West Germany):

> "Groups of rats were administered 0, 1000 or 2000 ppm of ethyl auramine, nitrate salt in the feed for nine months. Animals were sacrificed at 3, 6 and 9 months for histopathological examination. Mean body weights and food intake were lower in the treated animals and increased activity of gamma-glutamyl transpeptidase was observed in liver homogenate. In addition, higher incidences of foci and altered hepatocytes were noted in the treated animals after 6 months and 9 months. At nine months, hyperplastic nodules were noted in two of 5 high dose males.
>
> "In the . . . [auramine hydrochloride] study, rats were administered 0, 300, 500, 1000, 1500 or 2000 ppm of the compound in the feed for nine months. [The] mean body weights and food intake were lower at all concentrations and a dose-related increased activity of gamma-glutamyl transpeptidase was noted in liver homogenate. Histopathology indicated increased incidences of foci and altered hepatocytes among treated animals. After nine months, hyperplastic nodules were seen in males at 1000 and 2000 ppm and hepatocellular carcinomas were observed in the high dose of 2000 ppm."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

In submitting these preliminary findings under Section 8(e), BASF stated that the results of these 9-month studies "indicate that [the nitrate salt of] ethyl auramine appears to exhibit the same pattern of effects on enzymes and liver pathology as auramine; however, . . . [the nitrate salt of ethyl auramine] appears to be quantitatively less potent than auramine." BASF reported also that the International Agency for Research on Cancer (IARC) "has concluded that commercial auramine is carcinogenic to mice and rats after oral administration and that there is sufficient evidence that the manufacture of auramine is associated with [an] increased risk of bladder cancer in humans."

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon the Agency's receipt of full copies of the final reports of the cited 9-month feeding studies of auramine hydrochloride and the nitrate salt of ethyl auramine.

For further information with regard to the IARC deliberations on auramine, the reader's attention is directed to the following IARC Monographs: Volume 1 (pages 69-73; 1972) and Supplement 7 (pages 118-119; 1987).

Current Production and Use

The nitrate salt of ethyl auramine (CAS No. 43130-12-7) is not listed in the non-confidential computerized version of the initial (1977) TSCA Chemical Substance Inventory.

A review of the production range (includes importation volumes) statistics for the hydrochloride salt of auramine (CAS No. 2465-27-2), which is listed in the initial TSCA Chemical Substance Inventory, showed that 140 thousand to 1.4 million pounds of this chemical substance were reported as manufactured and/or imported in 1977. This production range information does not include any data claimed as TSCA Confidential Business Information (CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any data that would compromise TSCA CBI. All of the information reported for the initial TSCA Inventory, including the production range information, is subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

In its TSCA Section 8(e) notice, the BASF Corporation stated that it "does not handle or market the nitrate salt of ethyl auramine; however, it does import or has imported the hydrochloride and acetate salts of ethyl auramine as well as the hydrochloride salt of auramine."

According to the **Condensed Chemical Dictionary** (10th Ed.), the uses of auramine hydrochloride are listed as follows: "Yellow dye for paper, textiles, leather; also an antiseptic; fungicide." No information on the use(s) of ethyl auramine or any of its salts was located in the secondary literature sources consulted by EPA.

Comments/Recommendations

BASF stated that although the company does not handle the nitrate salt of ethyl auramine, the reported results will be distributed to all employees and customers who handle/purchase products that contain other salts of ethyl auramine. In addition, BASF stated the company is updating the Material Safety Data Sheets (MSDSs) for these products.

a) The Chemical Screening Branch will ask BASF to ensure that EPA receives complete copies of the final reports (including the actual experimental protocols, results of gross and histopathological examinations, etc.) from the two 9-month feeding studies cited in the company's TSCA Section 8(e) submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, BASF will be asked to describe the actions the company has taken or plans to take to reduce or eliminate exposure to the various salts of auramine and ethyl auramine. In addition, BASF will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which BASF is aware or that BASF has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to such compounds.

b) In 1981, the Chemical Screening Branch prepared a Chemical Hazard Information Profile (CHIP) on auramine and its hydrochloride salt. Following a review of the final reports from the BASF 9-month feeding studies, the Chemical Screening Branch will consider updating and/or expanding the CHIP.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: MAY 31 1988

SUBJECT: Status Report* 8EHQ-0588-0731 S Approved: James F. Darr 6/3/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Note

The Dow Chemical Company has claimed the exact identity of the subject chemical to be TSCA Confidential Business Information (CBI); staff of the Information Management Division (IMD/OTS) will be requesting Dow to substantiate this CBI claim. In the "sanitized" version of the Section 8(e) submission, Dow reported non-confidentially that the subject chemical is a "substituted diphenyl ether."

Submission Description

Dow provided the following summarized information with regard to the conduct and preliminary results of an oral teratology study of a substituted diphenyl ether in rats:

> "Groups of 30 bred Fischer 344 rats were administered the substituted diphenyl ether in corn oil solution by oral gavage on days 6 through 15 of gestation at dose levels of 0, 0.25, 0.50, 1.0 or 7.5 mg/kg body weight/day. Each fetus was examined externally and at least 50% of the fetuses from each litter were examined for visceral alterations by the Staples technique. Results summarized below do not include skeletal examination of fetuses which is in progress.
>
> "Indications of maternal toxicity were evidenced by an increase in liver weights in high dose (7.5 mg/kg/day) females. Accompanying the maternal toxicity at the high dose was a significant decrease in fetal body weight. In addition, visceral examination revealed an increased incidence (not statistically significant) of

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

> a great vessel malformation in the high dose group. This [fetal] malformation involved a displacement of the ascending aortic arch which occurred in one fetus in the 1.0 mg/kg/day dose group and 3 fetuses in the 7.5 mg/kg/day dose group. Although the increased incidences of great vessel malformation were not statistically significant, the clustering of 3 fetuses from 3 different litters at the top dose level suggests a possible teratogenic response. . . . ."

Submission Evaluation

In order for EPA to evaluate the overall significance of the reported developmental toxicity, Dow should be asked to ensure that the Agency receives a complete copy of the final report from the oral teratology study cited in Dow's Section 8(e) submission.

It should be noted that the reported developmental toxicity information is quite similar to that reported to EPA previously under Section 8(e) on a chemical identified generically as a substituted diphenyl ether; the reader's attention is directed to the "status report" prepared by EPA in response to initial TSCA Section 8(e) submission number 8EHQ-0986-0623 S. It should be noted further that EPA has also received "For Your Information" (FYI) submissions on chemical substances identified generically as substituted diphenyl ethers (FYI-OTS-0286-0483 S et seq. and FYI-OTS-1087-0580 S et seq.). In addition, EPA has received Section 8(e) and FYI notices on brominated diphenyl ethers and the Chemical Screening Branch prepared (in late 1986) a "Chemical Hazard Information Profile" (CHIP) on a number of brominated diphenyl ethers; the Risk Analysis Branch (RAB/ECAD) is reviewing available toxicity/exposure data on brominated diphenyl ethers.

Current Production and Use

According to Dow, the subject substituted diphenyl ether "is at the research stage and is being evaluated as a pesticide."

Comments/Recommendations

In its Section 8(e) submission, Dow stated that in accordance with Dow's longstanding policy, the company is notifying relevant employees about the reported toxicologic findings.

a) The Chemical Screening Branch will ask Dow to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, results of any statistical analyses, etc.) from the oral teratology study cited in the company's TSCA Section 8(e) notice.

In addition, Dow will be asked to submit final reports (if available) from any pilot teratology studies of the subject chemical if such studies were conducted.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Dow will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Dow is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of this substituted diphenyl ether.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUN - 9 1988

SUBJECT: Status Report* 8EHQ-0588-0732

Approved: James F. Darr 6/14/88

FROM: David R. Williams DRW, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Note (See Note on Page 5 of this Status Report)

The submitting company has claimed its company name to be TSCA Confidential Business Information (TSCA CBI); the Information Management Division (IMD/OTS) will be requesting the submitting company to substantiate this TSCA CBI claim. In the "sanitized" version of this Section 8(e) notice, the submitter stated that the TSCA CBI claim involving company name is consistent with the claim associated with a TSCA Section 5 "Low Volume Exemption" (LVE-88-0020) submitted previously to the Agency on the subject chemical substance.

Submission Description

In its Section 8(e) notice, the submitting company provided the final results of an acute male guinea pig dermal toxicity study and an acute male and female rat oral toxicity study of 2-amino-5,6-dimethoxybenzothiazole (CAS No. 6294-52-6).

The "REMARKS" section of the submitted report on the guinea pig study provides the following information regarding the conduct and results of this acute study:

> "The test article was a slight skin irritant. A dose of 0.5 g was applied to the guinea pig abdomen, and an occlusive wrap was used to hold the material against the skin for 24 hours. Signs of irritation were restricted to slight erythema in three of five animals at the site of application. By 24 hours after termination of exposure, all animals appeared normal. All animals gained weight normally and no evidence of percutaneous absorption was noted."

The submitter's cover letter provides the following information regarding the conduct and results of the acute oral toxicity study in rats:

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"In the acute oral toxicity study [(in which 2-amino-5,6-dimethoxybenzothiazole was administered at single dose levels of 312, 625, 1250, 2500 and 5000 mg/kg body weight)], an estimated oral LD50 of 1165 mg/kg was obtained in both male and female rats. All animals receiving doses of 2500 mg/kg or more died before scheduled study termination. Doses of 625 or 1250 mg/kg were also lethal to a portion of the treated animals. Some animals from the latter two dose groups which survived developed swellings of the neck and face during the second week of the study. The swellings were located in the cervical lymph nodes and appeared to be abscesses. Materials obtained from three of the abscesses were cultured for anaerobes and aerobes. Bacteria that were isolated consisted predominantly of beta hemolytic streptococci (non-group A) which are normally found in the oral cavity of rats.

"The test article adversely affected the thymus and may have decreased the immune response of the test animals, but the precise nature of the toxic effect and the cause of [the] deaths following test article administration are not clear. Atrophy of the thymic cortex was observed in a majority of the rats that survived for at least twenty-four hours after exposure to doses $\geq$ 625 mg/kg. Atrophy of the thymus commonly occurs in animals given near lethal doses of many materials because of stress induced during the toxic response. Thus, [the] thymic atrophy is not totally unexpected. However, the occurrence of streptococcal abscesses in these animals is unusual. There are two possible explanations for the seemingly high rate of infection found in this study. The first is that near lethal doses of the test article severely stressed the animals resulting in lowered immune function and therefore infection. The second [explanation] is that the test article directly interfered with immune function resulting in infection. In either case, the test article was associated with infection only at doses which were lethal to some of the rats.

"At a dose level of 312 mg/kg, lethality and infection were not seen, even though [the] animals were housed on the same rack with infected animals."

Submission Evaluation

In the skin irritation study, 2-amino-5,6-dimethoxybenzothiazole (0.5 g moistened with water) was applied to presumably unabraded skin of the abdomen of 5 male Crl:(HA)BR Hartley guinea pigs. An occlusive wrap was used to hold the test material in place for 24 hours. According to a table in the final report, slight erythema at the application site was seen in 3/5 animals at 24/48 hours post-exposure; no skin reactions were seen 2 weeks post-exposure.

In the acute oral toxicity study, groups of 5 male and 5 female specific pathogen free (SPF) Crl:CD(SD)BR rats were administered by gavage a single dose of 2-amino-5,6-dimethoxybenzothiazole in 0.5% solution/suspension in guar gum at 312, 625, 1250, 2500 or 5000 mg/kg body weight. The animals were then observed daily for 14 days at which time surviving animals were sacrificed and subjected to necropsy. Dose-related clinical effects suggestive of neurotoxicity were most notable. The clinical signs included slight to severe weakness in animals from all 5 dose groups, prostration in most animals at the highest doses, vasodilation in all animals in the 3 highest dose groups, convulsions in 1 female at 1250 mg/kg and tremors in 1 male at 625 mg/kg. At the highest dose level, death occurred between a few hours and one day after dosing; at the lower doses, death occurred between 1 and 12 days post-exposure. The estimated oral LD50 is 1165 mg/kg for both males and females.

The treatment-related gross morphological changes observed in the animals that died shortly after dosing (i.e., within 24 hours) included one or more of the following effects: small spleens, red discoloration of the facial hair, red discoloration of the urine in the bladder, necrosis of the glandular/non-glandular gastric mucosa, and yellow discoloration of the inguinal hair. Although the cause of death is not known, the findings suggest that kidney damage, hemorrhage and erosion of the stomach are the possible causes.

Necropsy and histological examination of selected animals with delayed deaths or animals that survived the 14-day observation period showed one or more of the following treatment-related changes: atrophy of the thymic cortex, enlarged livers, enlarged spleens, pale kidneys, abscessation and enlargement of cervical lymph nodes, and adipose tissue atrophy. Again, the cause of death was not determined but was most likely due to impairment of organ systems such as the immune system, liver and kidney. No treatment related histopathological changes were observed in the animals from the lowest dose group (312 mg/kg).

It should be pointed out that the most notable and consistent effects observed in the animals that survived for at least 24 hours after oral exposure to 2-amino-5,6-dimethoxybenzothiazole at doses of greater than 625 mg/kg involved the immune system. In these animals, the thymus, spleen and lymph nodes were all affected; streptococcal abscesses were also found in most of these animals. These findings suggest that the observed infection was most likely due to impaired immune function.

In conclusion, based on the submitted toxicological information, 2-amino-5,6-dimethoxybenzothiazole may be classified as slightly irritating following acute dermal exposure and moderately toxic following acute oral exposure. It would be of interest to know if the submitting company plans to conduct a repeated exposure study (e.g., a 28-day study) in order to characterize better the toxicity profile of the subject chemical substance.

Immediately upon receipt of this TSCA Section 8(e) submission, the Chemical Screening Branch informed the Chemical Control Division (CCD/OTS); CCD is responsible for the administration of EPA's TSCA Section 5 "New Chemicals Program" (NCP).

Current Production and Use

In its TSCA Section 8(e) notice, the submitting company provided the following information regarding the use of and the potential for exposure to 2-amino-5,6-dimethoxybenzothiazole:

> "This chemical is used as a low volume site-limited intermediate. . . . [The company] is not aware of any adverse health problems associated with its manufacture or use to make the final product. The chemical was originally evaluated as health hazards unknown - avoid all contact. Based on the acute toxicity testing, employees will be required to wear company supplied clothing and gloves. In addition, employees working with the damp material will wear disposable dust masks while those working with the dry material will wear cartridge dust respirators or air-line respirators."

A "sanitized" (i.e., non-confidential) November 2, 1987 letter attached to the sanitized version of LVE-88-0020 (obtained from EPA's public TSCA files) presents the following information with regard to the general use of and the potential for exposure to 2-amino-5,6-dimethoxybenzothiazole as well as other chemicals for which LVEs were submitted (LVE-88-0019 and LVE-88-0021):

> "The [LVE] substances will be manufactured/used as site-limited intermediates in a new synthesis for chemicals already on the TSCA Inventory. All wastes containing the LVE substances will be collected and disposed of by incineration; therefore, . . . [the company expects] no releases to receiving bodies of water. Additionally, products distributed in commerce will not contain any of the LVE substances; therefore, there will be no consumer exposure to the substances."

Comments/Recommendations

In addition to the previously described actions taken to reduce or eliminate exposure to 2-amino-5,6-dimethoxybenzothiazole, the submitter reported that the Material Safety Data Sheet (MSDS) for this chemical has been updated to warn workers and others about possible immunotoxicity; a copy of this updated MSDS was provided by the company as part of its TSCA Section 8(e) notice. Finally, the company reported that it is considering the need for further toxicologic testing of 2-amino-5,6-dimethoxybenzothiazole.

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, the submitter will be

asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to 2-amino-5,6-dimethoxybenzothiazole. The submitter will be informed that EPA would be especially interested in the results of a multiple exposure toxicity study (e.g., a 28-day study) of 2-amino-5,6-dimethoxybenzothiazole.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of 2-amino-5,6-dimethoxybenzothiazole. As was the case for the submitter's initial TSCA Section 8(e) notice, the Chemical Screening Branch will immediately inform appropriate staff of the Chemical Control Division (CCD/OTS) about all incoming TSCA Section 8(e) data pertaining to the subject chemical.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and CCD/OTS/OPTS/EPA. In addition, copies of this status report will be provided to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

Note — In a letter to EPA dated July 11, 1988, the Eastman Kodak Company withdrew its TSCA CBI claim for company name.

David R. Williams for
James F. Darr
7/21/88

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUN 22 1988

SUBJECT: Status Report* 8EHQ-0588-0733
FYI-OTS-0288-0599

Approved: James F. Darr 6/22/88

FROM: David R. Williams, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

Under Section 8(e) of TSCA, the American Telephone and Telegraph Company (AT&T) provided a complete copy of the final report from a delayed dermal contact hypersensitivity study of "PD Makeup" (a palladium plating compound) in guinea pigs. According to AT&T, PD Makeup was the subject of a TSCA Section 5 "Pre-Manufacture Notification" (PMN No. P-88-445) filed previously by AT&T. It should be noted that in PMN No. P-88-445, AT&T has asserted TSCA Confidential Business Information (CBI) claims for 1) the exact chemical composition of PD Makeup, 2) information concerning portions of a mixture, and 3) certain process information.

The "SUMMARY" section of the final report submitted by AT&T under Section 8(e) presents the following information with regard to the conduct and results of the sensitization study as well as other studies designed to determine appropriate dose levels for that sensitization study.

> "In a preliminary dose-range-finding study, four animals, two per sex, were exposed to four concentrations of 1.0, 5.0, 10 and 20% of the test material in 80% ethanol. In two Secondary Irritation Screens, a total of four animals (one per sex per study) were exposed to concentrations of 30, 40, 50, 60, 70, 80, 90 and 100% of the test article in 80% ethanol. Based on the results of the dose-range-finding studies, the dose concentration chosen for induction and challenge [in the dermal sensitization study] was 100%.
>
> "[In the sensitization study,] PD Makeup . . . was dermally applied to twenty guinea pigs (ten males and ten females) for a total of three six-hour insult periods at a 100% concentration. An additional group

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

of five guinea pigs (three males and two females) was treated with 1-chloro-2,4-dinitrobenzene [(DCNB)] at a 0.3% concentration. The positive control group was treated for a total of three six-hour periods. A group of ten guinea pigs (five males and five females) was treated with 80% ethanol for a total of three six-hour insult periods. This group served as the negative control. Four naive guinea pigs (two males and two females) remained untreated until the challenge period.

"Thirteen days after the last induction period, the animals were challenged in the same manner at a naive site. Positive responses were elicited in all animals receiving the positive control article, 1-chloro-2,4-dinitrobenzene (DCNB). No responses were observed at 24 or 48 hours after challenge in the animals in the negative control group. One response was observed at 24 and 48 hours after challenge in the naive animals receiving the test article at a 100% concentration. Three positive responses were observed in the experimental animals at 24 hours after challenge. Six positive responses were observed in the experimental animals at 48 hours after challenge. Seven days after the primary challenge, the experimental animals and an additional group of four naive guinea pigs (two males and two females) were rechallenged at a naive site. Responses were observed at 24 and 48 hours after rechallenge in the naive animals receiving the test article at a 100% concentration. Four positive responses were observed in the experimental animals at 24 hours after rechallenge. Seven positive responses were observed in the experimental animals at 48 hours after rechallenge.

"Based upon the observations [that were] made in the Delayed Contact Hypersensitivity Study in Guinea Pigs, PD Makeup . . . when induced, challenged and re-challenged at a 100% concentration, caused delayed contact hypersensitivity in guinea pigs."

In providing the above toxicologic findings to EPA, AT&T directed the Agency's attention specifically to the symptomology and death of one of the guinea pigs in the sensitization study:

"Animal # 6455 showed decreased activity, decreased body tone, abnormal stance, abnormal gait, and dyspnea on April 23 and 24, and died on April 25, 1988. The animal had an initial weight of 323 grams but upon death weighed 243 grams. Death occurred during the rest period, after initial exposure but prior to the challenge phase of the study. Gross necropsy of this one animal - the only animal to die out of the twenty used in the study - showed multiple lesions throughout the cecum. This may have been due to exposure to . . .

> [PD Makeup], and/or stress on the animal resulting from the experimental conditions. The animal may have licked the area when the protective bandage was removed during the rest period and thus ingested some of the [test] material. Cecum lesions were not noted in the Acute Exposure Dermal Toxicity Study with PD Makeup . . . previously submitted to EPA [in conjuntion with PMN No. P-88-445]. No other animal showed this symptom complex during the study. It is therefore plausible that inadvertent exposure via the oral route occurred in this instance. Because of the small amount of material applied, the lack of similar pathological findings in other assays of this material (previously submitted to the Agency), and the fact that the physical symptoms displayed by the animal occurred shortly before death, this symptom complex is not considered to represent a neurotoxicity response."

It should be noted that in a recent (February 1988) "For Your Information" (FYI) submission (FYI-OTS-Ø288-Ø599), AT&T provided a complete copy of the final report from an acute rabbit dermal toxicity study of a palladium plating compound identified non-confidentially as "PD Replenisher." In submitting this final report, AT&T noted that PD Replenisher was the subject of PMN No. P-88-444. (At the time of EPA's receipt of this particular FYI submission, EPA's 9Ø-day review period for PMN No. P-88-444 had not ended.) The "SUMMARY" section of the submitted final report presented the following information with regard to the conduct and results of this acute rabbit dermal toxicity study of PD Replenisher:

> ". . . [PD Replenisher was applied in single doses of 8.Ø ml/kg to the shaved unabraded dorsal skin of 5 male and 5 female New Zealand white rabbits. The site of application was wrapped throughout the 24-hour exposure period. Following the 24-hour exposure period, the wraps were removed and the animals were observed for a 14-day period after which all surviving animals were sacrificed and necropsied.] Signs observed during the study included decreased activity, decreased muscle tone, abnormal gait, abnormal stance and prostration. A yellow-brown discoloration, [a] slight to moderate erythema and necrosis of the skin at [the] application site were observed during the course of the study. Three of ten rabbits [(one male and two females)] died during the study. Necropsy findings on these animals revealed multiple black lesions throughout the stomach, pale or discolored intestines and discolored cecums with multiple lesions. No visible lesions were observed in any of the remaining animals upon terminal necropsy.
>
> "Based upon the observations made . . ., the estimated dermal LD5Ø for PD Replenisher . . . was determined to be greater than 8.Ø ml/kg."

Submission Evaluation

Immediately upon receipt of FYI-OTS-0288-0599 and 8EHQ-0588-0733, the Chemical Screening Branch provided complete copies of these submissions to the Chemical Control Division (CCD/OTS) which is responsible for administering EPA's TSCA Section 5 "New Chemicals Program" (NCP).

Based on an initial review of the study submitted by AT&T under Section 8(e) of TSCA, PD Makeup appears to elicit delayed dermal contact hypersensitivity in guinea pigs when challenged with the test compound after an induction period. AT&T should be asked to describe the studies that the company has underway or plans to conduct to determine whether accidental ingestion of PD Makeup or PD Replenisher produced the behavioral signs and digestive tract lesions observed in the acute studies of these palladium plating compounds.

Current Production and Use

In its TSCA Section 8(e) and FYI submissions, AT&T provided the following information regarding the use of and the potential for exposure to PD Makeup or PD Replenisher:

> "This material, like all similar plating solutions, is used in a plating process which is fully enclosed and designed to avoid any loss of the plating compounds, which frequently, as in this case, contain precious metals. Moreover, the . . . [Material Safety Data Sheet (MSDS)] requires that individuals handling this substance wear gloves, goggles and protective overalls. Accordingly, dermal exposure, even under the worst conditions, will be minimal."

It should be noted that PD Replenisher and PD Makeup MSDSs were submitted to EPA with PMN No. P-88-444 and PMM No. P-88-445, respectively.

The sanitized (i.e., non-confidential) versions of PMN No. P-88-444 and PMN No. P-88-445 obtained from EPA's public document files state that PD Replenisher and PD Makeup are plating bath component solutions "for deposition of palladium on electronic component contacts." According to these PMNs, the palladium system is a replacement for gold cyanide plating systems.

Regarding the production volumes of PD Makeup and PD Replenisher, the sanitized versions of PMN No. P-88-444 and PMN No. P-88-445 state that past yearly production of these materials has been less than 1000 kg each and future production for each is not expected to be more than 1100 to 1500 kg per year.

Comments/Recommendations

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, AT&T will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the published scientific literature) about which AT&T is aware or that AT&T has conducted, is conducting or plans to conduct to determine the toxicity of PD Makeup and PD Replenisher.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of these palladium plating compounds.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and CCD/OTS/OPTS/EPA. In addition, copies of this status report will be provided to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUL - 7 1988

SUBJECT: Status Report* 8EHQ-0688-0734 S

Approved: James F. Darr 7/15/88

FROM: David R. Williams DRW, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Note

The submitting company has claimed its company name and the exact identity(ies) of the subject chemical(s) to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will be requesting the submitter to substantiate these TSCA CBI claims. It should be noted that in the "sanitized" (i.e., non-confidential) version of the Section 8(e) submission, the company stated that the test material was a "silane mixture." In addition, the company stated non-confidentially that a portion of the test material was the subject of a previous submission to the Agency under Section 5, the "Pre-Manufacture Notification" (PMN) provision of TSCA. The company-sanitized version of the Section 8(e) submission identified that PMN number as P-88-1168.

According to the company-sanitized version of P-88-1168 obtained from the Agency's public files, the PMN chemical was identified generically by the submitting company as a "modified aliphatic alicyclic polyester" intended for use as an "industrial coating component" with a reported production range of 212,000 to 248,000 kilograms/year. It should be noted also that the "DESCRIPTION OF ON-GOING HEALTH EFFECT TESTING" (the last page of the sanitized version of P-88-1168) provides the following information:

> "The subject of this notification has been submitted for toxicity testing at . . . [the company's] in-house toxicology laboratory. Tests to be performed include the following:
>
> 28-Day Repeated Inhalation on Final Product Containing the New Substance
>
> "The results and tests protocols will be forwarded [to the Agency] when the studies are complete."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Submission Description

In the sanitized version of the TSCA Section 8(e) submission, the company provided the following information regarding the conduct and preliminary findings from a 28-day inhalation study of the silane mixture in rats:

> "This silane mixture was the subject of a repeated, 28-day study, in which male and female Fischer 344 rats were exposed to target concentrations of 0, 25, 100, or 300 mg/m^3. The duration of the exposures was six hours a day, five days a week for four weeks. At the conclusion of the study, [the] animals were necropsied and subjected to an extensive histopathological evaluation. The relevant findings thus far from this investigation have revealed significant respiratory distress and the majority of the animals were necropsied in a moribund condition at the 300 mg/m^3 concentration. Additionally, during the final week of exposure, one male rat died in the 100 mg/m^3 exposure group. At necropsy, lungs were filled with fluid in these exposure groups. However, after a two-week recovery period, the [animals in the] 100 mg/m^3 exposure group showed weight gain which was normal and no gross pathology during necropsy. Animals exposed to 25 mg/m^3 resembled the control group with respect to in-life evaluations with the exception that females showed a decreased body weight gain during the fourth week of exposure [as] compared to the controls. Histopathology results are not available at this time. Finally, in a separate study, the sensory irritation response in S-W mice was evaluated. The RD50 ([i.e., the] concentration which caused a 50% decrease in respiratory rate) was found to be 700 mg/m^3."

Submission Evaluation

Immediately upon receipt of this Section 8(e) submission, the Chemical Screening Branch sent copies of the submission to the Chemical Control Division (CCD/OTS) for review and appropriate followup attention. The Chemical Control Division is responsible for administration of the Agency's TSCA Section 5 "New Chemicals Program" (NCP).

Current Production and Use

Considering the submitter's TSCA CBI claims, no information with regard to the TSCA Chemical Substance Inventory status of the subject chemical(s) will appear in this status report. In its Section 8(e) notice, the submitting company reported that the test "material was confined to . . . [the company's] research and development [(R&D)] and toxicology laboratories."

Comments/Recommendations

In its TSCA Section 8(e) submission, the company stated that upon completion and quality assurance review of the 28-day inhalation study, a copy of the final report of that study would be provided to the Agency. In addition, the submitter reported that although "no further work is scheduled for this [silane] mixture," any further information that may be obtained would be submitted to the Agency for review. Finally, the submitter reported that all employees who worked with the test material have been notified in writing.

a) The Chemical Screening Branch will ask the submitting company to ensure that the Agency receives a full copy of the final report (including the actual experimental protocols, results of gross/histopathological examinations, etc.) from the 28-day inhalation study cited in the company's Section 8(e) submission. In addition, the submitter will be asked to submit a complete copy of the final report of the RD50 study in S-W mice that was cited also in the company's Section 8(e) notice.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, the submitter will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which the company is aware or that the company has conducted that are designed to determine the toxicity of the test material.

b) As was the case with the initial Section 8(e) notice, the Chemical Screening Branch will immediately send all reported information to CCD/OTS staff for review and appropriate followup attention.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and CCD/OTS/OPTS/EPA. In addition, copies of this status report will be provided to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUL - 8 1988

SUBJECT: Status Report* 8EHQ-0688-0735

Approved: James F. Darr 7/12/88

FROM: David R. Williams DRW, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

Pursuant to Section 8(e) of TSCA, the Pennzoil Company provided a report concerning the detection of arsenic in samples from oil and gas operations in West Virginia. The following information regarding this detection is presented in the "EXECUTIVE SUMMARY" portion of the submitted report:

> ". . . [Following] a series of laboratory tests by a university and by its own technical staff, Pennzoil determined that natural gas samples from two of its production areas in West Virginia contained trace amounts of arsenic [(i.e., approximately 1 ug/l gas)].
>
> "There is reason to believe that the arsenic traces are organic in nature [(e.g., trimethyl arsine)] and as such constitute no health hazard during the production, gathering and distribution operations.
>
> ". . . [Pennzoil does] not know the level of arsenic exposure, if any, which would result from whatever arsenic may be converted to arsenic trioxide [(an inorganic arsenic compound)] during the combustion of the gas. Consequently, at this time . . . [the company is] unable to determine the precise nature of the health risk, if any, which prolonged exposure to the combusted gas/arsenic mix presents. . . . .
>
> "Also included in this report is information pertaining to arsenic which Pennzoil has found in produced water from certain crude oil production in West Virginia. Because of its potential relevance to West Virginia's NPDES permit program for produced water discharges, this information has been previously reported to the

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

> West Virginia Department of Natural Resources. All [of] the arsenic detected in the water samples is in the organic methylated form, mostly the trimethylated species. Concentrations ranged from very low levels (less than Ø.3 milligrams per liter (mg/l)) in water samples taken from wellheads to high levels (up to 388 mg/l) in [water] samples taken from oil storage tanks. The levels of arsenic observed in the wellhead samples are well within the concentrations for arsenic in produced water reported in the published literature. The produced water containing high levels of arsenic from [oil] storage tanks is being disposed of at a permitted disposal facility.
>
> "[Monitoring] data from the State of West Virginia show no exceedances of the drinking water standard or the ambient water quality standard (each is Ø.Ø5 mg/l) for inorganic arsenic anywhere in the state. Because of the relatively low toxicity of organic (particularly trimethylated) arsenic and the minimal exposure potential involved, as confirmed by the West Virginia drinking water supply and stream [monitoring] data, the information regarding arsenic in produced water clearly does not present a substantial risk to health or the environment."

Pennzoil also provided the following information about a worst-case analysis involving potential arsenic exposure in homes:

> "Based on a worst-case scenario, (conditions described below), . . . [Pennzoil] arrived at a calculated upper bound exposure level of 1 ug/m^3. This calculated exposure level must not, however, be used to calculate risk. To employ this already uncertain exposure level in calculating health risk would only compound the uncertainties. In order to obtain any reasonable degree of confidence, actual exposure measurements inside homes would be required. A more accurate estimate of the dose to humans can only be determined based on the exposure measurements, time spent inside the homes, and the amount of arsenic retained in the body.
>
> "The assumptions employed in . . . [Pennzoil's] calculation of [an] exposure level of 1 ug/m^3 are:
>
> Concentration of arsenic in gas = 1 ug/l
>
> Volume of home (85Ø sq. ft. equivalent) = 2ØØ m^3
>
> Natural gas consumption rate = 3 m^3/day
>
> Number of air changes in home/day = 15
>
> Exposure time = 24 hours/day

"The [preceding] calculations further assumed that none of the combustion products were vented to the outside, but rather that they were exhausted to the interior of the home."

Submission Evaluation

The assumptions used by Pennzoil in their worst-case exposure assessment raise a number of concerns. While the values used for home volume and air changes per day are reasonably conservative, a natural gas consumption rate of 3 m^3 per day is far below the 5.5 m^3 per day calculated from the data in the U.S. Department of Energy Residential Energy Consumption Survey (DOE/EIA-Ø321/1(82). In addition, the use of 1 ug/l arsenic in natural gas does not appear to be consistent with the actual sampling data contained in the company's submission (e.g., arsenic concentrations ranged from .17 to 63 ug/l with values predominantly in the 1 to 6 ug/l range). Even if one assumes the 63 ug/l value to be unreliable, employing some of the other values gives rise to theoretical output concentrations in the home of over 4 ug/m^3. It should be noted that this theoretical concentration exceeds the National Institute of Occupational Safety and Health (NIOSH) Recommended Exposure Limit (REL) of 2 ug/m^3 for arsenic in the workplace.

With regard to the provided water data, Pennzoil's report shows that arsenic concentrations in produced water that is released to surface waters are in excess of the Ø.Ø5 mg/l inorganic arsenic standard in the West Virginia Water Quality Criteria. Pennzoil does not appear to perceive this to be a problem because 1) the arsenic in the produced water is most likely in an organic form (and therefore less toxic than inorganic forms), and 2) the water quality tests for West Virginia's streams and water supplies do not indicate exceedances of the standard. It should be noted, however, that although Pennzoil assumes that the arsenic in the produced water is in a less toxic form (e.g., trimethyl arsine) and assumes further that this form will persist, EPA believes that it is possible that the trimethyl arsine could be partially oxidized to the inorganic form in surface waters. Considering the fact that Pennzoil does not know the exact species of arsenic present in the produced water, it is possible that a species of arsenic of greater concern is already present or could form upon release to surface waters. It should be noted also that the Safe Drinking Water Act (SDWA) standard of Ø.Ø5 mg/l at the tap is applicable to all forms of arsenic and not just to inorganic arsenic. Finally, the fact that West Virginia water quality data do not show exceedances for arsenic is not relevant except for samples collected from those streams or surface waters that receive produced water.

An additional point of concern is the possibility that liquids in the gas transmission/distribution pipelines may contain arsenic. Typically, natural gas pipelines contain liquids consisting of organic compounds (mainly alkanes) condensed from the natural gas stream, water, and contaminants introduced into the pipeline from

outside sources (e.g., addition of anti-corrosion agents; fluids entering as the result of leaking compressor seals). Pipeline liquids move with the gas throughout a pipeline system and tend to collect in low-lying areas of the pipeline and at points in the pipeline where pressure changes occur. The line must be cleaned out ("pigged") periodically to prevent pipeline corrosion and/or damage to the compressors. The points of liquid removal ("pig receivers" and "pig launchers") are typically located at compressor stations and at low-lying areas along the pipeline right-of-way. Further, "pigging" operations for some pipeline systems involve collection and disposal of thousands of gallons of liquids. In addition, some pipelines vent the natural gas directly to the atmosphere during compressor start-up operations. Such venting may occur as often as daily during peak-use seasons and may involve coincidental release and dispersion of pipeline liquids over a large area.

Finally, it should be noted that in November 1987, the Agency for Toxic Substances and Disease Registry (ATSDR), in collaboration with EPA, published a DRAFT "Toxicological Profile for Arsenic." According to the draft document, requests for copies of this profile should be sent to:

Office of External Affairs
Agency for Toxic Substances
and Disease Registry
Chamblee 28 South
1600 Clifton Road
Atlanta,GA 30333

Comments/Recommendations

Immediately upon receipt, the Chemical Screening Branch provided complete copies of Pennzoil's Section 8(e) submission to EPA's Office of Water (OW), Office of Air and Radiation (OAR), Office of Research and Development (ORD), Office of Solid Waste and Emergency Response (OSWER), EPA's Region III Office (located in Philadelphia, PA), the Department of Energy (DOE), the Consumer Product Safety Commission (CPSC), the National Institute for Occupational Safety and Health (NIOSH), and the Occupational Safety and Health Administration (OSHA); copies of Pennzoil's Section 8(e) notice were also sent immediately to the Exposure Evaluation Division (EED/OTS) and Regional Risk Guidance Staff (RRGS) in the Existing Chemical Assessment Division (ECAD/OTS).

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure data, Pennzoil will be asked to describe the actions the company has taken or plans to take to notify workers and others about the reported information. In addition, Pennzoil will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA)

about which Pennzoil is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine human or environmental exposure to arsenic in any form resulting from production and distribution of natural gas.

b) In conjunction with other OTS Divisions, the Chemical Screening Branch will review the reported information to determine the need for further OTS assessment. The Chemical Screening Branch will send Pennzoil's response to all EPA Offices and other Federal agencies that received Pennzoil's initial TSCA Section 8(e) notice.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, DOE, OW/EPA, OSWER/EPA, OAR/EPA, ORD/EPA, EPA's Region III Office, EED/OTS and RRGS/ECAD/OTS. In addition, copies of this status report will be provided to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUL -7 1988

SUBJECT: Status Report* 8EHQ-0688-0736 Approved: James F. Darr 7/8/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The Reilly Tar & Chemical Corporation submitted the following information with regard to several workplace incidents involving 2-amino-5-chloropyridine (CAS No. 1072-98-6):

> "The first incident occurred on April 30, 1988 during the reprocessing of the above product. Reprocessing involved washing the product with water then spinning the water off in an electric centrifuge. The affected employee was involved in the operation for his entire shift (12 hours). While showering prior to leaving work, the employee noticed that his skin was slightly blue in color. At that time, he also reported that for the last four hours of his shift he had felt light-headed and nauseated, but thought he was coming down with the flu. He was sent to a local hospital where he stayed overnight for observation. He returned to work on his next shift. At least one other employee was working in the area on a different process at this time and suffered no apparent ill effects.
>
> "At the time of the incident, the affected employee was wearing the protective equipment specified in the run-sheet for this product, which included the following: Tyvek (non-porous) coveralls with hood, nitrile latex gloves, Tyvek foot coverings, chemical goggles, and half-face chemical cartridge respirator. The individual did not recall any specific contact with the product with the exception of a small amount he noticed on his wrists which he washed off. After this incident, the protective equipment requirements were modified to include protective sleeve cuffs, and [a] full-face respirator with supplied air. In addition, the cuffs at the wrist were to be taped.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"On May 19, 1988, the same individual and another chemical operator were involved in sweeping the floor and cleaning the area where the product had been dried and drummed. Both operators were wearing the required protective equipment. After 2-3 hours of doing this, at approximately 1330 hours, the previously affected individual reported to the first aid room. He was having difficulty breathing, had a bluish caste to his skin, and numbness of his extremities. He was given oxygen, an ambulance was summoned, and he was admitted to the hospital. He was released from the hospital on May 20. His co-worker was also sent to the hospital for a blood test as a precautionary measure, although she was not experiencing any of the symptoms seen in the first individual.

"This, in addition to the fact that the product had been manufactured previously without incident, led . . . [Reilly] to believe that the individual in question had heightened sensitivity to the product. A decision was made to continue the clean-up by hosing down the area with water using the same protective equipment, but employing the buddy-system to complete the job. Two chemical operators alternated on the clean-up until 2020 hours when it was noticed that one of the operators was beginning to turn blue about the ears, hands, and toes. He was sent to the hospital for observation and subsequently released at 2400 hours [on] the same evening. The other operator was unaffected.

"At 2100 hours, a third operator who had been working with the material on the previous shift reported for work. He stated that he had passed out while at home and still had a headache. He was sent to the hospital for observation."

Reilly reported also that the company has taken the following actions as a result of the incidents described above:

"1. The drummed product has been isolated and will remain so until a written release is received from the customer. The customer has been notified about the problems experienced at this site with this chemical.

"2. The material safety data sheet [(MSDS)] has been revised to reflect the new information on this product. The labels will be revised prior to shipment.

"3. The drying room where these incidents occurred has been decontaminated using a jet spray device operated by an individual in a fully encapsulated suit.

"4. The supplied-air system has been thoroughly inspected to ensure that it was not in some way responsible for the incidents. No problems were detected.

"5. The results of any medical tests have been requested through Reilly's insurance carrier, American International Adjustment Company, Inc. As of this time, Reilly has not yet received the results.

"6. A review of the protective equipment, specifically the coveralls and gloves specified for use with this product and related products, is in progress.

"7. Reilly will not manufacture this product again until such time that all [of] the safety concerns and questions have been satisfactorily addressed and answered."

Submission Evaluation

The symptoms (cyanosis, light-headedness to passing out, nausea and headaches) observed in the affected workers are typical of acute toxic methemoglobinemia. This condition is quite serious and can be life-threatening. In view of the fact that methemoglobinemia is known to be induced by certain aromatic amines (e.g., aniline), it is very possible that exposure to 2-amino-5-chloropyridine, which is an aromatic amine, caused the symptoms observed in and/or reported by the workers. It would be of interest to know if the affected workers' blood was tested to determine methemoglobin levels and NADH-Diaphorase enzyme activity levels; the results of these two tests would help in determining if the workers were suffering from acute toxic methemoglobinemia.

Current Production and Use

The subject chemical, 2-amino-5-chloropyridine (CAS No. 1Ø72-98-6), was not found in the non-confidential computerized or printed versions of the initial TSCA Chemical Substance Inventory. The submitter did not provide any information about the production volume or use(s) of the subject chemical substance nor was such information located in the secondary literature sources consulted by the Agency.

Comments/Recommendations

It should be noted that the Office of Toxic Substances (OTS) has received TSCA Section 8(e) notices on other pyridine derivatives. In 1982, the Chemical Screening Branch/ECAD/OTS prepared Chemical Hazard Information Profiles (CHIPs) on 2-methyl-, 3-methyl- and 4-methylpyridine; these particular pyridine derivatives are the subject of a Section 8(d) health and safety data reporting rule.

It should be noted further that pyridine itself was recommended by the Interagency Testing Committee (ITC) for testing under Section 4 of TSCA; pyridine is the subject of TSCA Section 8(a) and Section 8(d) information reporting rules. Finally, it should be noted that EPA has received a number of TSCA Section 8(e) and "For Your Information" (FYI) submissions on aromatic amines; a number of aromatic amines are the subject of TSCA Section 4 test rules as well as TSCA Section 8(a) and 8(d) information gathering rules.

a) The Chemical Screening Branch will request Reilly to ensure that the Agency is kept abreast of the company's ongoing investigation of the reported incidents. In addition, Reilly will be requested to submit, if/when available, the results of all clinical studies of the affected workers, especially the results of tests that would help to determine if the workers were suffering from acute toxic methemoglobinemia.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Reilly will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Reilly is aware or that Reilly has conducted, is conducting or plans to conduct that are designed to determine the toxicity of or the exposure to 2-amino-5-chloropyridine.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and IMD/OTS/OPTS/EPA. In addition, copies of this status report will be provided to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUL 15 1988

SUBJECT: Status Report* 8EHQ-0688-0737

Approved: James F. Darr 7/15/88

FROM: David R. Williams DRW, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

On behalf of the Antimony Oxide Industry Association (AOIA) member companies (M&T Chemicals; AMSPEC Chemical; ASARCO Incorporated; Laurel Industries, Inc.; and ANZON, Inc.), an outside counsel submitted the final report of a genotoxicity study of antimony trichloride (CAS No. 10025-91-9) administered to groups of Swiss mice in single oral doses of 0.5, 1.0 or 1.5 g/kg body weight. According to the cover letter, the animals were sacrificed at 24, 48 or 72 hours post-administration and the spleen cells were then analyzed for DNA damage and repair. The cover letter states that the results of this in vivo study show that the high dose of antimony trichloride "produced DNA damage in spleen cells and reduced their ability to repair other DNA damage produced later by UV irradiation." The cover letter also provides the following points to be considered in reviewing the reported findings:

> "1. The methodology used, while suitable for investigation of chemical damage to DNA, is not normally employed for measuring mutagenic activity. Direct damage to DNA does not necessarily imply that mutations are produced. Damage which is either cell-lethal or repaired by error-free repair systems will have no mutational consequence.
>
> "2. DNA damage may simply be one manifestation of gross toxicity if the high dosage employed in this study was generally toxic. This seems quite possible because the oral LD50 of . . . [antimony trichloride] to the rat is 525 mg/kg. The [submitted final] report gives no information on the systemic toxicity of the dosages employed, and the mice may have been generally sick.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

> "3. The dosing vehicle used [in the mouse genotoxicity study] was a 50% DMSO solution. This material is known to greatly increase the passage of many chemicals through biological membranes, and may have produced a degree of absorption quite unlike what would be expected following any possible human exposure."

The cover letter states further that the hypothesis that damaged DNA may not result in mutation is supported by published data showing that antimony trichloride, antimony pentachloride and antimony trioxide "caused DNA damage to the bacterium B. subtilis but induced no mutation in E. coli or S. typhimurium . . ."

Finally, the cover letter presents the following information with regard to the AOIA's ongoing chronic study of antimony trioxide, a chemical designated by the Interagency Testing Committee (ITC) for testing consideration under Section 4 of TSCA:

> "AOIA is currently sponsoring a two-year inhalation study of antimony trioxide in Fischer 344 rats as part of a [TSCA Section 4-associated] voluntary test program with EPA. 48 Fed Reg. 39979 (September 2, 1983). The rats were exposed to airborne concentrations of 0.05, 0.5 or 5.0 mg/m^3 for a period of one year and are now in a one-year recovery period. A final report of the study will be available in 1989. . . . ."

Submission Evaluation

The submitted data show that antimony trichloride does induce DNA damage in spleen cells of treated mice. This damage is manifested as DNA fragmentation, reduced replicative DNA synthesis and a reduced ability of cells to repair gamma-irradiation induced DNA damage.

It should be noted that in general there is a higher level of concern for those agents that have been shown to interact with DNA to produce detectable damage than for those for which no such evidence exists. While it is plausible that agents that interact with DNA to produce detectable damage may be carcinogenic when tested in vivo, a direct cause/effect relationship has not been established for cancer induction and the types of DNA damage observed in the submitted study.

Current Production and Use

A review of the production range (includes importation volumes) statistics for antimony trichloride (CAS No. 10025-91-9), which is listed in the initial TSCA Chemical Substance Inventory, has shown that 122 thousand to 1.22 million pounds of this chemical were reported as manufactured and/or imported in 1977. This production range information does not include any information claimed to be TSCA Confidential Business Information (CBI) by the

person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

According to the Condensed Chemical Dictionary (10th Edition), antimony trichloride has the following uses: "[production of] antimony salts; bronzing iron; mordant; manufacturing lakes [in dyestuff technology]; chlorinating agent in organic synthesis; pharmaceuticals; fireproofing textiles; analytical reagent."

Comments/Recommendations

When considered alone, positive genotoxicologic findings such as those presented in this submission may not be sufficient to offer reasonable support for a conclusion of substantial risk as that term is defined in the Agency's March 16, 1978 TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110). However, it should be noted that EPA does believe that such results are of value in assessing possible risks posed by exposure to chemical substances or mixtures. The Agency also believes that positive genotoxicity findings, when considered in combination with other pertinent information (e.g., knowledge of potential exposure to and/or high production of the subject chemical or mixture), would suggest the need, in many cases, to conduct further studies that are designed to better define the toxicologic properties of or exposure to the subject chemical(s). The results of such further testing should be considered also for submission to EPA pursuant to Section 8(e) of TSCA.

It should be noted that EPA's Office of Toxic Substances (OTS) has published TSCA Section 8(a) and Section 8(d) information reporting rules on antimony trioxide. Further, OTS has received a number of TSCA Section 8(e) and "For Your Information" (FYI) submissions on antimony compounds, including antimony trioxide. The Chemical Screening Branch prepared (in 1981) a "Chemical Hazard Information Profile" (CHIP) on antimony trioxide.

a) The Chemical Screening Branch will transmit copies of this status report to AOIA and ask AOIA to send copies of the report to their member companies.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure data, AOIA will be requested to describe the nature and results, if available, of all studies (other than those reported already to EPA or those published in the open scientific literature) about which AOIA member companies are aware or that AOIA member companies have conducted, are conducting or plan to conduct to determine the toxicity of antimony trichloride.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUN 29 1988

SUBJECT: Status Report* 8EHQ-0688-0738

Approved: James F. Darr 7/1/88

FROM: David R. Williams DRW, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The Mobay Corporation submitted the final reports from oral teratology/toxicity studies of alpha-[2-(4-chlorophenyl)ethyl]-alpha-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol (HWG 1608; CAS No. 107534-96-3) in mice and rabbits; these studies were conducted by/for Mobay's parent company (Bayer AG) located in West Germany. The reports of the mouse studies are in German with English translations of the study summaries only.

The following information with regard to the conduct and results of the first mouse study is presented in the English summary:

> "25 sperm-positive NMRI mice per group received HWG 1608 daily on days 6 through 15 of gestation by oral doses of 0, 10, 30 and 100 mg/kg body weight.
>
> "The pregnant females were observed for body weight, appearance, and behavior. The fetuses obtained on the 18th day of gestation by Cesarean-section were tested for embryotoxicity by determining their body weight as well as by exterior and interior morphological changes.
>
> "No deaths occurred. Indications of a maternal toxicity were not apparent.
>
> "No indications of embryotoxicity or teratogenicity of HWG 1608 were seen in the 10 mg/kg/bw dose per day group.
>
> "Starting at dose levels of 30 mg/kg/day, fetotoxic effects (stunted growth) were seen. In addition, increased numbers of terata [(e.g., cleft palate)] were seen in the 100 mg/kg body weight group which are regarded as [test] substance related.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"This investigation showed that 10 mg/kg body weight of HWG 1608 administered orally [to pregnant mice] did not produce embryotoxicity or fetotoxicity. 30 mg/kg body weight and higher doses produced fetotoxicity and 100 mg/kg body weight was teratogenic."

The following information with regard to conduct and results is presented in the English summary of a followup toxicity study of the subject chemical in mice:

"Because there was no indication of maternal toxicity evident in . . . [the previously described study] with doses up to 100 mg/kg body weight, a second study . . . was conducted.

"Ten sperm-positive NMRI mice per group received HWG 1608 daily on days 6 through 15 of gestation in oral doses of 0, 10, 20, 30 and 100 mg/kg body weight.

"The dams were observed for body weight, appearance and behavior.

"On the 16th day of gestation, the animals were sacrificed and blood was drawn from half the animals for hematological and clinical/chemical testing. Liver weight determinations and histopathological studies were done on the remaining half.

"No deaths occurred. Body weights of dams were not affected.

"Beginning at dose level 10 mg/kg body weight, the activities of the transaminases AST and ALT in the plasma were higher than those of the controls. Significant differences were noted at 10 mg/kg body weight (ALT) and at 30 mg/kg body weight (AST and ALT). In the 30 mg/kg body weight groups, the hematocrit values and the mean erythrocyte volumes (MCV - Mean Corpuscular Volumes) were decreased. Triglycerides in the livers of the 100 mg/kg group were significantly increased.

"Organ weights were not significantly changed, however, the liver weights of all dosed animals were clearly higher than in the control group. HE-stained paraffin slides showed cytoplasmic vacuoles in [the] liver cells in all animals of the 100 mg/kg group. These livers contained increased lipids, which was seen clearly on the ORO-stained frozen slides. In comparison to the control group, the fat content of the livers in the 20 mg/kg body weight and 30 mg/kg body weight groups was slightly increased, but this effect was not seen in the 10 mg/kg group.

"In conclusion, doses starting at 10 mg/kg body weight are regarded as slightly maternally toxic and at 30 mg/kg are regarded as clearly maternally toxic."

The following information with regard to the conduct and results of the oral embryotoxicity/teratogenicity study in rabbits is presented in the "**SUMMARY**" section of the submitted final report:

"The purpose of this . . . study was to assess the effects of HWG 1608 TECHNICAL on embryonic and fetal development when administered by oral gavage once daily to mated female rabbits (Kfm: CHINCHILLA, hybrids, SPF Quality) from day 6 through 18 post coitum at dose levels of . . . [0 (vehicle control), 10, 30 or 100 mg/kg body weight/day].

"Each group consisted of 16 mated female rabbits. The doses . . . [selected were based on an oral dose range-finding study in rabbits] (RCC Project 074068)."

"Distilled water with 0.5% Cremophor EL . . . was used as the vehicle for the test article in the dose groups and was administered as the control article to the females of the Control group. A standard dose volume of 4 ml/kg body weight, with a daily adjustment to the actual body weight, was used.

"On day 28 post coitum, the females were sacrificed and the fetuses removed by Cesarean-section. The examination of the females/dams and fetuses was performed in accordance with international recommendations. All [of the] parameters recorded were evaluated and reported.

"From this study, the following results were obtained:

- There were no mortalities, behavioral changes or necropsy findings (including liver weights) in the mated females considered to be related to treatment with HWG 1608 TECHNICAL. One female at 100 mg/kg died during the treatment period - this death was attributed to intubation error.

- Evaluation of the food consumption data resulted in a slight reduction during the treatment period in the dams of the high dose group (100 mg/kg). Mean body weight gain relative to day 0 post coitum showed statistically significant differences from the Control value on most days between days 7 and 25 post coitum.

- The mean post-implantation loss in the high dose group (100 mg/kg) was increased and significantly different from that of the vehicle control group. No further differences in the mean reproduction data were noted which could be attributed to treatment . . .

- External examination of fetuses resulted in eight (8.9%) fetuses with malformations at the high dose level (100 mg/kg). Peromelia of the left or right foreleg was noted in five fetuses and malrotation of the right hindlimb together with an enlarged fontanelle, agenesis of a few claws or palatoschisis were found respectively, in a further three fetuses.

- The abnormal findings noted during [the] internal examination of the fetuses (skeletal examination and examination of fetal heads by [the] Wilson technique) did not change the malformation rate because findings were noted only in the fetuses which were found to be malformed already at external examination.

- Evaluation of the mean body weights of fetuses showed a 6% reduction (not statistically significant) at the high dose level (100 mg/kg).

- The examination of the stage of skeletal development resulted in a slightly increased percentage of non-ossified phalangeal nuclei in the high dose group (100 mg/kg) fetuses. This finding was considered to be the consequence of a slightly delayed maturation associated with the slightly reduced mean body weight of the fetuses."

Submission Evaluation

Copies of the submitted German reports have been transmitted to the Health and Environmental Review Division (HERD/OTS) and forwarded for translation. An Agency evaluation of the overall significance of the reported findings, including the rabbit study findings, should be possible upon receipt of those translations.

Current Production and Use

The subject chemical was not located in the non-confidential computerized or printed versions of the initial TSCA Chemical Substance Inventory.

According to Mobay's TSCA Section 8(e) submission, HWG 1608 "is an experimental pesticide being evaluated by Mobay for possible use as a fungicide." Mobay reported also that this chemical "has been used and distributed solely for the purpose of research and development [(R&D)]." With regard to exposure, Mobay stated that "the potential for exposure to this [R&D] substance provides a very limited risk because the levels to which humans are exposed are low." Mobay reported further that "the safety factor for workers under expected exposure conditions is approximately 600, based on studies with similar products."

Comments/Recommendations

In its Section 8(e) notice, Mobay stated that its employees and those persons to whom Mobay distributed the subject chemical are being advised of the reported findings.

a) The Chemical Screening Branch will ask Mobay to submit a complete copy of the final report from the oral dose range-finding study ("RCC Project 074068") cited in the "**SUMMARY**" section of the provided final report from the oral embryotoxicity/teratogenicity study of HWG 1608 in rabbits.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Mobay will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Mobay is aware or that Mobay has conducted, is conducting or plans to conduct that are designed to define the toxicity of the subject chemical.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUL -7 1988

SUBJECT: Status Report* 8EHQ-0688-0739

Approved: David R. Williams for
James F. Darr 7/19/88

FROM: Jacqueline T. Favella for David R. Williams
David R. Williams, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The Eastman Kodak Company provided a report pertaining to the acute toxicity of propyl cyanoacetate (CAS No. 14447-15-5) in laboratory animals. Eastman Kodak's cover letter 1) states that the report was "submitted because of adverse neurological effects observed during an acute oral toxicity test" in rats, and 2) provides the following information with regard to the conduct and results of this particular study as well as other acute studies of propyl cyanoacetate:

> "Groups of 5 male and 5 female rats were given 1250, 2500, or 5000 mg/kg body weight of the test compound in a single oral gavage dose . . ." At 5000 mg/kg, nine of ten animals died or were euthanatized within two days of dosing. Treatment-related abnormalities seen at necropsy in animals dying prior to study termination included evidence of severe gastrointestinal irritation and evidence of leakage of the test chemical through the stomach wall. Two of [the] three animals that survived to day 2 exhibited functional abnormalities and degenerative lesions in the brain related to cerebral neurovascular damage. Neurological abnormalities included evidence of both sensory and motor deficits such as lack of response to sound or tail pinch, vigorous spontaneous head search movements, retropulsion, and hypotonic gait in the hind limbs.
>
> "At 2500 mg/kg, one female developed weakness, ataxia, and tremors and died on the day of dosing. As at the high-dose level, lethality was associated with severe gastrointestinal irritation. All other animals survived the scheduled observation period. The only abnormal clinical sign was slight weakness on the day of dosing. No treatment-related changes were observed at necropsy, but three rats (one male and two females

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

including the one which died on the day of dosing) had microscopic lesions in the brain which were similar to those seen at the 5000 mg/kg dose level. At 2500 mg/kg, brain lesions were generally less extensive than those seen at 5000 mg/kg.

"The 1250 mg/kg dose level was the no-observed-adverse-effect level (NOAEL). At this dose level, rats showed no mortality or abnormal clinical signs, they gained weight normally, and did not have either necropsy or neurohistological lesions.

"Other data which are included in this [Section 8(e)] submission include a dermal toxicity study [in rats], a dermal irritation study [in guinea pigs], an eye irritation study [in rabbits], and a skin sensitization study [in guinea pigs]. When applied to the skin, the test article had an estimated acute lethal dose of greater than 20 ml/kg for rats and did not produce abnormal clinical signs. The test article was a slight skin irritant [in guinea pigs], producing only transient erythema at the site of its application, and it was not a skin sensitizer [in guinea pigs]. When placed in the [rabbit] eye, the test article produced variable responses indicative of slight to strong irritation. Immediate irrigation of the eye following exposure to the test article was beneficial and significantly reduced the irritation caused by the test article.

"In summary, the test article produced functional and morphological evidence of central nervous system damage at high oral doses which were also associated with gastrointestinal damage. The NOAEL for oral toxicity was 1250 mg/kg. High dermal doses of the test article did not result in similar effects. The test article was not a skin sensitizer and was only a slight skin irritant, but it may cause strong eye irritation if not promptly washed out of the eye."

In addition to the findings discussed above, Eastman Kodak also submitted a propyl cyanoacetate Material Safety Data Sheet (MSDS) that had been updated to include a warning concerning potential neurotoxicity.

Submission Evaluation

The provided data indicate that the acute oral administration of propyl cyanoacetate to rats caused dose-related neurotoxicity as evidenced by behavioral changes and histopathological changes in the nervous system. Although a NOAEL of 1250 mg/kg was reported for this acute study, a lower NOAEL could have been found if 1) a more complete neurobehavioral assessment had been performed, or 2) a repeated (e.g., 28-day) exposure study had been conducted.

Current Production and Use

Propyl cyanoacetate (CAS No. 14447-15-5) was not located in the non-confidential computerized or printed versions of the initial TSCA Chemical Substance Inventory. In its Section 8(e) notice, Eastman Kodak provided the following information with regard to the manufacture and use of, as well as the potential for exposure to, the subject chemical substance:

> "This chemical has been manufactured only as a non-isolated intermediate that is completely consumed in the manufacture of a photographic dye. Approximately 4000 kg of the intermediate is produced per year. None of the intermediate is expected to be present in the final dye. No employee exposure is anticipated since the reaction is carried out in a totally enclosed vessel. . . . [Eastman Kodak is] not aware of any adverse health problems associated with production or use of this material."

Comments/Recommendations

In addition to updating the propyl cyanoacetate MSDS to include a neurotoxicity warning, Eastman Kodak stated that additional toxicological studies of this chemical are being considered.

a) The Chemical Screening Branch will ask Eastman Kodak to submit a complete copy of the final report (including the actual experimental protocol, results of gross and histopathological examinations, etc.) from the acute oral study cited in the company's initial submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Eastman Kodak will be asked to describe the nature and results, if available, of all studies (other than those submitted already to EPA or those cited in the open scientific literature) about which Eastman Kodak is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of propyl cyanoacetate. Eastman Kodak will be informed that EPA would be interested especially in the results of a repeated exposure (e.g., a 28-day) study of this chemical.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUL 25 1988

SUBJECT: Status Report* 8EHQ-0688-0740 S

Approved: David R. Williams for James F. Darr 7/27/88

FROM: Jacqueline Fawcett for David R. Williams, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Note

The Eastman Kodak Company has claimed the exact identity of the subject chemical to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will ask Eastman Kodak to substantiate this CBI claim. In the "sanitized" (i.e., non-confidential) version of this Section 8(e) notice, the chemical is identified as a "substituted thiazinohydrazine."

Submission Description

Eastman Kodak provided the following information about the conduct and results of an acute oral toxicity study in rats:

> "Groups of 5 male and 5 female rats were given [0, 625,] 1250, 2500 or 5000 mg/kg body weight of the test compound in a single gavage dose as part of an acute oral toxicity study. All [of the] animals receiving 2500 mg/kg or more of the test compound developed convulsions within 30 minutes of dosing and died before scheduled study termination. At 1250 mg/kg, 7/10 animals developed convulsions; 4/5 females died within 2.5 hours of administration of the test compound. All remaining animals in the 1250 mg/kg dose group survived and gained weight normally. At 625 mg/kg, all animals survived and no abnormal clinical signs were observed.
>
> "No significant lesions were observed at necropsy of animals dying following convulsions or in those which survived the 14-day observation period."

Eastman Kodak reported also that a 28-day gavage study of the subject chemical is in progress and involves doses of 100, 300 or 1000 mg/kg body weight. According to Eastman Kodak, preliminary results of this study "indicate that convulsions and mortality occurred at 1000 mg/kg but were not seen at [the] lower doses."

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In addition, Eastman Kodak submitted the following information about the conduct and results of an acute skin toxicity study in rats, an acute skin irritation study in guinea pigs, a skin sensitization study in guinea pigs and an acute eye irritation study in rabbits:

> "When applied to the skin, the test article had an estimated acute lethal dose of greater than 2000 mg/kg for rats and did not produce abnormal clinical signs. The test article was not a skin irritant, producing no signs of irritation at the site of its application, and it was not a skin sensitizer. When placed in the eye, the test article produced only slight irritation."

Submission Evaluation

The submitted data provide strong evidence that the test compound may produce neurotoxicity. Convulsions were observed in both a dose- and time-dependent manner. The rapidity of onset of the convulsions provides evidence that the effect may be mediated via the nervous system. Further, these effects are consistent with those reported for other hydrazine-like compounds (the reader's attention is directed to the "Status Report" that was prepared by EPA in response to a TSCA Section 8(e) submission on 3-methyl-2-benzothiazolinone hydrazone hydrochloride (8EHQ-0287-0654)). It should be noted that the submitted information also indicates a sex-related difference, i.e., the females died at lower doses and generally earlier than males. It must be pointed out, however, that the information contained in the present submission is not adequate to characterize fully the potential for neurotoxicity. For example, effects at the lower doses might have been observed if more sensitive procedures had been employed (e.g., kindling or electrophysiology). Furthermore, acute level effects may differ quantitatively and qualitatively from repeated exposure effects. The results of the ongoing 28-day study should help characterize the neurotoxic potential of the subject chemical substance.

It should be noted that although Eastman Kodak stated that "no [other] significant lesions were observed at necropsy of animals dying following convulsions or in those which survived the 14-day observation period," the acute oral toxicity report presents the following information about one male in the 625 mg/kg dose group:

> "Only small testes from Rat 383 (625 mg/kg) were processed for microscopic evaluation. Findings included atrophic spermatogenic epithelium with [an] absence of spermatozoa and spermatids, and [a] reduced number of spermatocytes, but a normal number of spermatogonia."

Although these adverse reproductive effects were not viewed by Eastman Kodak to be treatment-related (because "similar lesions occasionally occur in untreated control animals and testicular atrophy was not observed at the next higher dose level (1250 mg/kg)"), EPA is concerned for the following reasons:

1) Because histopathological examinations do not appear to have been performed on any other animals in the study, it cannot be ruled out that similar microscopic changes did not occur in the other male rats in the 625 mg/kg dose group. Further, the early deaths in the higher dose groups would minimize the probability that such effects would have time to occur. It should be noted also that testicular atrophy was not reported for any animals in the concurrent control group.

2) Not all toxicological effects are necessarily dose-related. For example, biphasic dose-response curves are often found for certain classes of chemicals (e.g., depressants).

3) Adverse reproductive effects have been seen in studies of other hydrazine-like compounds (e.g., procarbazine).

The submitter's ongoing 28-day study should help in determining the potential of the subject chemical substance to cause adverse male reproductive system effects.

Current Production and Use

In view of the Eastman Kodak Company's CBI claim, no information regarding the TSCA Inventory status of this substituted thiazinohydrazine will appear in this report.

In its TSCA Section 8(e) submission, Eastman Kodak provided the following information with regard to the company's production/use of and the potential for workplace exposure to this substituted thiazinohydrazine:

> "This compound is a . . . [research and development (R&D)] chemical being pursued as an early intermediate in a multistep synthesis. None of the R&D chemical is expected to be in the later intermediates. . . . [The company is] not aware of any adverse health problems associated with its use. Employees are required to wear company supplied clothing when working with chemicals. Because [the toxicologic] testing is incomplete, employees are also being required to wear Tyvek suits and air-line respirators when working with the damp or dry material."

Comments/Recommendations

In addition to conducting a 28-day gavage study to further define the toxicity of this substituted thiazinohydrazine, Eastman Kodak reported that the company is considering the need for additional toxicity studies on this chemical. Also, Eastman Kodak provided the current substituted thiazinohydrazine Material Safety Data Sheet (MSDS) that contains a warning about the potential for "adverse neurological effects."

a) The Chemical Screening Branch will ask Eastman Kodak to submit a complete copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, etc.) from the acute oral toxicity study cited in the company's TSCA Section 8(e) submission. Eastman Kodak will be asked also to ensure that EPA receives a complete copy of the final report of the company's ongoing 28-day gavage study of this substituted thiazinohydrazine in rats.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Eastman Kodak will be asked to describe the nature and results, as available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Eastman Kodak is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of the subject chemical substance.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of this substituted thiazinohydrazine.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUL 15 1988

SUBJECT: Status Report* DEW 8EHQ-0788-0741 Approved: James F. Darr 7/20/88

FROM: David R. Williams, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

On behalf of its member companies, the International Isocyanate Institute, Inc. (III) provided the following information with regard to the conduct and preliminary findings from a two-year inhalation study of polymeric diphenyl methylene diisocyanate (MDI) in rats being performed for III by the CIVO Institutes, Zeist, The Netherlands:

> "Male and female rats (Cpb:WU, Wistar Random), 60/sex/level, were exposed for 6 hours/day, 5 days/week for two years to an atmosphere of respirable polymeric MDI (CAS No. 9016-87-9) aerosol. Aerosol concentrations for this study were 0, 0.2, 1.0, and 6 mg/m^3 and were selected based on subchronic studies. An interim sacrifice of a satellite group of 10 additional rats/sex/level was performed at week 52. Animals under study were evaluated using clinical chemistry, hematological, urine analysis, gross and histopathologic procedures.
>
> "Due to . . . [the physical characteristics of the test material], it was not possible to generate a vapor atmosphere of MDI high enough to carry out a meaningful study. Therefore, an aerosol atmosphere was used. The aerosol atmosphere consisted of particles of which 95% were less than 5 um in diameter. Polymeric MDI was chosen as the test substance as it is the most widely used MDI-based product.
>
> "In preliminary studies in rats, the toxicity of MDI was confined to the respiratory tract where it caused irritation at levels of 4 mg/m^3 and above.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"In the animals [that were] killed after one year of exposure, those exposed to 6 mg/m^3 showed signs of irritation in the nose and lungs and some accumulation of a yellow material in the lungs. At 1 mg/m^3, there were some indications of minor irritation. No effects were observed at Ø.2 mg/m^3.

"Examination of the rats killed after two years of exposure showed that the irritation of the nose and lungs and the accumulation of the yellow material in the lungs continued in the rats exposed to 6 mg/m^3. In the rats exposed to 1 mg/m^3, similar, but lesser, changes were observed. Again, no effects were seen at Ø.2 mg/m^3.

"The overall tumor incidence, the incidence of malignant tumors, the incidence of benign tumors and the number of tumor-bearing animals did not show [any] differences between the high exposure group and control group. However, when considering individual organs, there was a statistically significant increase in benign tumors of the lung (adenoma) in 6 of the 6Ø male rats exposed to 6 mg/m^3. Four of 59 female rats exposed to 6 mg/m^3 and 1 of 6Ø female rats exposed to 1 mg/m^3 also had a similar benign tumor in their lungs, but neither was statistically significant. In addition, 1 of 6Ø male rats exposed to 6 mg/m^3 showed a malignant tumor in its lungs (adenocarcinoma). The presence of a variety of non-neoplastic changes in the lungs, including accumulation of yellow material, indicates the tumors occurred concurrently with irritation of the lungs."

In its Section 8(e) notice, III stated that the association 1) is a non-profit organization comprised of producers of MDI and/or toluene diisocyanate (TDI) "in the Americas, Europe and the Far East," and 2) "was formed in 1972 to promote and further the interests of the public, the users and the manufacturers of TDI and MDI in the safe use of these diisocyanates."

Submission Evaluation

Immediately upon receipt of this TSCA Section 8(e) submission, the Chemical Screening Branch sent a copy of the notice to the Risk Analysis Branch (RAB/ECAD/OTS) for inclusion in the ongoing review of MDI (including polymeric MDI) and other diisocyanates (e.g., TDI). The Chemical Screening Branch will request III to keep EPA apprised of any further significant findings from the two-year inhalation study of polymeric MDI that was cited in the submission.

It should be noted that in 1984, the Chemical Screening Branch prepared "Chemical Hazard Information Profiles" (CHIPs) on MDI (including polymeric MDI) and TDI. These CHIPs contain readily available toxicity and exposure information (as of 1984) on these chemical substances (persons wishing to obtain copies of these CHIPs should contact the TSCA Assistance Office (TAO/OTS) at (202) 554-1404 or write to the TSCA Assistance Office (TS-799), Office of Toxic Substances, U.S. Environmental Protection Agency, 401 "M" Street, S.W., Washington, D.C. 20460). Further, TDI and MDI (including polymeric MDI) are subject of TSCA Section 8(d) and 8(c) information gathering rules. Finally, it should be noted that the Interagency Testing Committee (ITC) has designated hexamethylene diisocyanate (HDI) for testing under Section 4 of TSCA; HDI is also the subject of TSCA Section 8(a) and 8(d) information gathering rules.

Comments/Recommendations

In its Section 8(e) notice, III stated that its member companies were being informed about the reported toxicological findings.

a) The Chemical Screening Branch will request III to ensure that the Agency is apprised about all further significant findings from the two-year inhalation study of polymeric MDI that was cited in III's Section 8(e) submission. The Chemical Screening Branch will forward all reported information to RAB/ECAD for inclusion in the ongoing evaluation of MDI and other diisocyanates.

b) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OW/EPA, OSWER/EPA, OAR/EPA, ORD/EPA, OPP/EPA, RAB/ECAD/OTS and TRDB/ECAD/OTS; copies of this status report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUL 21 1988

SUBJECT: Status Report* 8EHQ-0788-0742

Approved: James F. Darr 7/27/88

FROM: David R. DRW Williams, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The Atlantic Richfield Company (ARCO) submitted a final report from a U.S. Department of Transportation (D.O.T.) rabbit skin corrosivity study of an undiluted emulsifiable metal-working oil product (F-82) and asked that the information be "processed in accordance with EPA's substantial risk [information handling] procedures." In the cover letter to its submission, ARCO stated that 1) the tested product has a pH of 8.4, and 2) "emulsifiable metal-working fluids (or soluble cutting oils), similar to this test product, are petroleum lube/water/additive mixtures designed to be used in a much diluted state [(i.e., water:product dilution ratio of at least 10:1 prior to use)]." ARCO did not submit any information with regard to the exact identity and amount of each constituent of the tested product. ARCO's cover letter presents the following information about the conduct and results of the skin corrosivity study:

> ". . . [Six New Zealand White] rabbits (2.0 to 4.0 kg) had 0.5 ml of this product applied [undiluted] to their shaved backs at four intact skin sites for each rabbit. A gauze patch was placed over each site and securely taped in place. The entire trunk of the animal was then wrapped with impervious non-reactive rubberized material and securely taped in place. After 4 hours, the sheeting and patches were removed and each site was observed and scored for the appearance of irritation and/or corrosion. The sites were scored according to the techniques of Draize, and the skin evaluated for ulceration and necrosis, or any evidence of tissue destruction. The test sites were then washed to prevent further exposure. Additional skin observations were made at 24 and 48 hours after application of the product. Based on the scores obtained and the eschar noted, this product was designated as corrosive to [the] skin. . . . ."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

In its Section 8(e) submission, ARCO reported that because the tested product is diluted at least 10:1 with water before use, the "skin irritation/corrosivity potential is proportionately reduced in the actual workplace." ARCO reported also that the current Material Safety Data Sheet (MSDS) and label "warn that this product 'may cause skin irritation and sensitization' and to 'avoid prolonged and/or repeated skin contact and wash thoroughly after handling' [the product]." According to ARCO, such warnings and precautions "might explain why there have never been any employee or customer complaints associated with . . . [the product's] manufacture or use."

Submission Evaluation

In order for EPA to conduct a proper evaluation of the submitted findings, ARCO should be asked to report the exact identity and amount of each constituent of the tested product. Further, it would be of interest to know the results of other toxicological studies on the product or its constituents.

Current Production and Use

In general, metal-working fluids (known also as cutting/grinding fluids) are applied to cutting tools to aid in machine operation by serving as lubricants and/or coolants and by washing away metal chips. It should be noted that the Agency 1) has received a number of TSCA Section 8(e) notices on metal-working fluids, and 2) has issued **"Chemical Advisories"** outlining the potential risks that are posed by exposure to metal-working fluids containing amines or nitrites. Interested persons can obtain copies of these **"Chemical Advisories"** by contacting the TSCA Assistance Office at (202) 554-1404 or by writing to: TSCA Assistance Office (TS-799), Office of Toxic Substances, U.S. Environmental Protection Agency, 401 "M" Street, S.W., Washington, D.C. 20460.

Comments/Recommendations

In its Section 8(e) submission, ARCO stated that the company has taken the following risk reduction-related actions involving the tested product:

> "In addition to updating the [product's] current MSDS and precautionary label to reflect . . . [the reported findings], ARCO is informing both workers and customers of the potential hazards of this product. A D.O.T. 'Corrosive' material placard will be attached to all containers and bills of lading appropriately marked with the 'Corrosive Liquid, N.O.S.' shipping name and UN identification number. These communications will reinforce the necessity of proper skin protection when handling this product."

Based on a preliminary review of the provided information, it does not appear that the reported findings warranted submission to EPA under Section 8(e), the "substantial risk" information reporting provision of TSCA. ARCO's rationale for reporting this information under Section 8(e) of TSCA may become more apparent upon EPA's receipt/review of further information from ARCO about 1) the constituents of the tested product, and 2) the results of other toxicological studies conducted on this product and its constituents.

a) The Chemical Screening Branch will ask ARCO to report the exact chemical identity (including the CAS Registry Number, if known) and amount of each constituent of the tested product.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, ARCO will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which ARCO is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of the subject product or its constituents.

b) The Chemical Screening Branch will review the reported data in order to determine the need for further OTS assessment of the tested product or its constituents.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: AUG 16 1988

SUBJECT: Status Report* 8EHQ-0788-0743

Approved: James F. Darr 8/22/88

FROM: David R. Williams, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

DRW

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

Submission Description

The Procter & Gamble Company submitted the final report from an in vitro L5178Y TK+/- Mouse Lymphoma Mutagenesis Assay on Color Index (C.I.) Acid Red #1 (CAS No. 3734-67-6). The "Summary" section of the provided report presents the following information regarding the conduct and results of this genotoxicity study:

> ". . . [C.I. Acid Red #1 was tested in this assay] in the presence and absence of Aroclor induced rat liver S9. The non-activated cultures selected for cloning were treated with [C.I. Acid Red #1] doses of 4902 to 368 ug/ml and exhibited Total Growths from 86% to 134%. The S9 activated cultures selected for cloning were treated with [C.I. Acid Red #1] doses of 3000 to 225 ug/ml which produced from 18% to 98% Total Growths.
>
> "None of the non-activated cultures that were cloned exhibited a mutant frequency which was at least twice the mean mutant frequency of the solvent controls. A dose dependent response was not noted in the treated cultures. Three of the S9 activated cultures (3000, 2250, and 1688 ug/ml) that were cloned exhibited mutant frequencies which were significantly greater than the mean mutant frequency of the solvent controls. The Total Growths of the positive cultures ranged from 18% to 72%. A dose dependent response was noted in the treated cultures. No apparent increase in small mutant colonies was observed.
>
> "The results indicate that, under the conditions of these mutagenicity tests, . . . [C.I. Acid Red #1] was positive in the presence but negative in the absence of exogenous metabolic activation."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

According to Procter & Gamble, two published scientific papers reported that C.I. Acid Red #1 is weakly mutagenic in bacteria (E. coli and S. typhimurium) with exogenous metabolic activation, negative in yeast gene conversion and Drosophila (fruit fly) mutagenicity tests and negative in an unpublished carcinogenicity study (species not specified). Copies of these scientific papers were provided by Procter & Gamble in its submission.

Submission Evaluation

C.I. Acid Red #1 was tested in the L5178Y TK+/- Mouse Lymphoma Mutagenesis Assay both with and without exogenous metabolic activation using Aroclor 1254-induced rat liver S9. The chemical was not cytotoxic under non-activation conditions. Therefore, the non-activated cultures were dosed at 368 to 4902 ug/ml, which is considered adequately high for a non-toxic chemical substance. Total growths for the non-activated cultures ranged from 86% to 134%. The activated cultures were dosed at 225 to 3000 ug/ml. Due to severe cytotoxicity, however, the first activated assay was repeated and only the results from the second activated assay were presented in the submitted report.

Under non-activated conditions, there were no increases in the mutant frequency versus concurrent solvent (water) controls. With activation, however, three C.I. Acid Red #1 dose levels demonstrated dose responsive significant increases in mutant frequencies. The total growths for activated cultures showing positive responses were 18% to 72%. The concurrent positive controls demonstrated appropriate responses. No apparent increase in small colonies was observed which indicates that the positive responses were probably not due to clastogenic (i.e., chromosome-damaging) activity.

In conclusion, the submitted data show that C.I. Acid Red #1 induces gene mutations in cultured mammalian cells with, but not without, exogenous metabolic activation.

Current Production and Use

A review of the production range (includes importation volumes) statistics for C.I. Acid Red #1 (CAS No. 3734-67-6), which is listed in the initial TSCA Chemical Substance Inventory, has shown that 20 thousand to 202 thousand pounds of this chemical substance were reported as being manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All information reported for the initial TSCA Inventory, including the production range information, is subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

According to the **COLOUR INDEX** (3rd Edition), C.I. Acid Red #1 is a monoazo dye known also as C.I. Food Red #10; uses of this dye are reported to include the coloring of fibers (wool, silk and nylon), foods, drugs, cosmetics, inks, paper, plastics, pigments, soaps and wood stains. According to information presented in the publications submitted by Procter & Gamble, the subject dye was and may still be approved in the U.K. for use as a food colorant; U.S. Food and Drug Administration (FDA) staff reported by phone that this dye has not been approved for use in foods, drugs, cosmetics or medical devices in the U.S. Finally, Procter & Gamble reported in its submission that the company is using C.I. Acid Red #1 for research and development (R&D) purposes and that the company "has no commercial activities associated with this material."

Comments/Recommendations

Procter & Gamble reported that "the results and implications of the [submitted] mouse lymphoma study were reviewed promptly with all appropriate R&D personnel, and they were reminded about the safe handling of all research chemicals." Also, Procter & Gamble stated that the company is "currently conducting an additional assay (in vitro cytogenetics using Chinese hamster ovarian cells) . . ." Procter & Gamble reported that the results of this cytogenetics assay will be sent to EPA as soon as they are available.

Although a positive in vitro genotoxicologic assay result, when considered alone, may not be sufficient to reasonably support a conclusion of substantial risk (as that term is defined in EPA's TSCA Section 8(e) policy document ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978)), EPA believes that such results are of value in assessing possible risks posed by exposure to chemical substances or mixtures. The Agency also believes that positive genotoxicity findings, when considered in combination with other pertinent information (e.g., knowledge of potential exposure to and/or high production of the subject chemical or mixture), would suggest the need, in many cases, to conduct further studies that are designed to better define the toxicologic properties of or exposure to the subject chemical(s). The results of such further testing should be considered also for submission to EPA pursuant to Section 8(e) of TSCA.

a) The Chemical Screening Branch will ask Procter & Gamble to ensure that the Agency receives a full copy of the final report (including actual experimental protocol, data, results of any statistical analyses, etc.) from the company's ongoing in vitro cytogenetics assay of C.I. Acid Red #1.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Procter & Gamble will

be requested to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Procter & Gamble is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of C.I. Acid Red #1.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: SEP 13 1988

SUBJECT: Status Report* 8EHQ-0788-0744 S

Approved: James F. Darr 9/15/88

FROM: David R. Williams, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The Mobil Research and Development Corporation provided summary information about the conduct and results of studies designed to investigate "the toxicity of a generic jet engine oil and one of its components, tricresyl phosphate (TCP [CAS No. 1330-78-5])." It should be noted that TCP is a mixture of the ortho-, meta-, and para- isomers of TCP. According to the submitting company, the tested jet engine oil "contained certain additive components at concentrations representative of a cross section of those in commercial production." The submitter provided the following information regarding these studies:

> ". . . [The Mobil Research and Development Corporation] research showed that repeated [skin] applications of the generic jet engine oil containing 3% TCP (one dermal application/day, 5 days/week, for 90 days) to male and female Sprague-Dawley rats decreased the activities of both serum and erythrocyte cholinesterase. . . A follow-up study, designed to identify the component causing cholinesterase inhibition, showed that the TCP additive was entirely responsible. . ." An additional acute study, performed in male Long-Evans rats, showed that single . . . [oral or dermal doses of TCP or tri-ortho-cresyl phosphate (TOCP; CAS No. 78-30-8)] inhibited both serum cholinesterase and brain neuropathy target esterase (neurotoxic esterase; NTE). . . Inhibition of NTE is highly correlated with induction of organophosphorus induced delayed neurotoxicity (OPIDN). Surprisingly, there was very little difference between the activities of TCP and TOCP; the TCP manufacturer's product safety information sheet indicated that [the] TOCP content is less than 0.1%."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

". . . [The Mobil Research and Development Corporation has been] under the impression that a commonly held opinion is that TCP with TOCP levels below 1% is not neurotoxic. . . .[The company's] results indicate that the TOCP level in TCP is not a reliable predictor of potential neurotoxicity."

"Four batches of the TCP additive used in the tests . . . and three other TCP samples also were evaluated for acute cholinesterase and NTE inhibition . . . All showed significant inhibitory effects that, on repeated administration, would be expected to result in neurotoxicity. All materials were derived from cresylic acids produced as a byproduct of petroleum refining. Other commercially available TCPs are prepared from synthetically derived materials, which can provide better control of the content of potentially neurotoxic components.

"A thorough literature review . . . [appended to the company's submission] revealed that the neurotoxic properties of commercial TCP are known, but that there is confusion over the appropriateness of using the TOCP level as an indicator of neurotoxic potential. . . . ."

Immediately upon receipt of this TSCA Section 8(e) submission, the Chemical Screening Branch sent copies of the submission to staff of the Test Rules Development Branch (TRDB/ECAD/OTS) for inclusion in their ongoing review of available toxicologic and exposure data on TCP, TOCP and other aryl phosphates. The aryl phosphates category was designated by the Interagency Testing Committee (ITC) for testing consideration under Section 4 of TSCA. In addition, EPA has published TSCA Section 8(a) and 8(d) information gathering rules on TCP, TOCP as well as other aryl phosphates.

Submission Evaluation

The submitted data indicate that subchronic dermal application of a generic jet engine oil containing 3% TCP to rats produced a significant inhibition of erythrocyte and serum cholinesterase activity levels relative to controls. The submitted data also indicate that 1) a single oral dose of TCP to rats produced a significant (83%) NTE inhibition and a significant (82%) serum cholinesterase inhibition, and 2) a single TCP dose applied dermally to rats resulted in a significant (55%) NTE inhibition and a significant (65%) serum cholinesterase inhibition. The doses of TCP required to produce the acute effects in rats were approximately 2.Ø g/kg for both the dermal and oral routes of administration. It should be noted that 2.Ø g/kg of TOCP produced generally a comparable amount of inhibition of the NTE and cholinesterase levels.

Overall, the submitted summarized data indicate that TCP can produce neurochemical effects (inhibition of cholinesterase and NTE levels) comparable to those produced by TOCP. Considering that NTE inhibition is predictive of OPIDN, the submitted results indicate further that TCP may also produce OPIDN. In the past, the primary concern for mixtures of TCP isomers has focussed on the concentration of TOCP in the TCP isomer mixture based on the assumption that TCP isomer mixtures with TOCP levels below 1% were not neurotoxic.

The submitted data also open the question of which species is the most appropriate to study OPIDN. Until recently, it has been argued that the hen is the best animal model for evaluating OPIDN because other species (e.g., the rat) were thought to be more resistant to the neurotoxic effects of organophosphates (OPs). However, recent published studies have shown that the rat is sensitive to OPs and should be considered as a viable species for testing OPIDN-like effects. The data contained in the present submission support the use of the rat for such testing.

The Mobil Research and Development Corporation should be asked to ensure that EPA receives a complete copy of the final report from each study cited in the cover letter to the company's submission. In addition, the company should be asked to submit a copy of the Material Safety Data Sheet (MSDS) for the commercial TCP product that reportedly produced "NTE inhibition after large single oral doses in hens." This particular MSDS was cited in ATTACHMENT I (TCP literature review section) of the company's submission.

Current Production and Use

A review of the production range (includes importation volumes) statistics for TCP (CAS No. 1330-78-5), which is listed in the initial TSCA Chemical Substance Inventory, has shown that 100 thousand to 1 million pounds were reported as manufactured and/or imported in 1977. This production range information does not include any information that was claimed as TSCA Confidential Business Information (CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise CBI. All of the information reported for the initial TSCA Inventory, including the production range data, is subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

In its submission, the Mobil Research and Development Corporation reported that "TCP is used as an anti-wear agent in jet engine oils, and is required to meet both military and commercial jet engine builders' specifications." The company stated also that TCP "is used as a minor component (< or = 2%) in certain mineral oil based lubricants." Finally, the company stated that "certain fire resistant hydraulic fluids are based on 100% TCP, some of which are synthetically derived."

According to the **Condensed Chemical Dictionary** (10th Edition), tricresyl phosphate (mixture of o-, m- and p- isomers) has the following uses: "Plasticizer for polyvinyl chloride, polystyrene, nitrocellulose; fire retardant for plastics; air filter medium; solvent mixtures; waterproofing; additive to extreme pressure lubricants; hydraulic fluid; heat exchange medium."

Comments/Recommendations

In its submission, the Mobil Research and Development Corporation stated that although the company is "unaware of any neurotoxic effects on humans having been caused by exposure to jet engine oils in their intended application," the company is revising product labels/MSDSs in order to inform workers and customers about the submitted toxicological findings. In addition, the company reported that copies of the submission were sent to the U.S. Occupational Safety and Health Administration (OSHA), to other TCP users and suppliers, and to a number of industry trade associations (including the American Petroleum Institute (API)).

a) The Chemical Screening Branch will request the Mobil Research and Development Corporation to submit a full copy of the final report (including the actual experimental protocol, results of any gross/histopathological examinations, results of statistical analyses, etc.) from each study that was cited in the cover letter to the submission. The company will be requested also to provide to EPA a complete copy of the MSDS for the commercial TCP product that reportedly produced "NTE inhibition after large oral doses to hens." This MSDS was cited in the last paragraph of ATTACHMENT I (TCP literature review) in the company's submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, the Mobil Research and Development Corporation will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the neurotoxicologic properties of TCP or any products (e.g., jet engine oil) containing TCP.

b) As in the case of the initial Section 8(e) submission, the Chemical Screening Branch will immediately send all additional reported information to TRDB/ECAD/OTS. The Chemical Screening Branch will also review the reported information in order to determine the need for further OTS assessment of any chemical substance(s)/product(s) not already being evaluated within OTS.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and TRDB/ECAD/OTS/OPTS/EPA. In addition, copies of this status report will be provided to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: AUG 16 1988

SUBJECT: Status Report* 8EHQ-0788-0745 S

Approved: James F. Darr 8/22/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Note

The CIBA-GEIGY Corporation has claimed the exact identity of the subject chemical as TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will be requesting CIBA-GEIGY to substantiate this CBI claim. In the "sanitized" (i.e., non-confidential) version of CIBA-GEIGY's submission, the subject chemical is identified generically as a "carbomonocyclic aminobutyrolactone."

Submission Description

CIBA-GEIGY submitted the following information regarding the conduct and interim results of a two-year dietary oncogenicity and chronic toxicity study of the subject chemical in rats:

> "The dose levels for the two-year dietary oncogenicity and chronic toxicity study are 0, 20, 100, 2500 and 5000 ppm. Microscopic findings in interim sacrifice animals after one year on study indicate an increased incidence of hepatocellular adenomas and carcinomas in males at the 5000 ppm dose level. Liver hypertrophy was noted in both males and females at the 2500 and 5000 ppm dose levels."

According to CIBA-GEIGY, this two-year study is being "conducted in toxicology laboratories of Research and Consulting Company AG, Basel, Switzerland."

Submission Evaluation

Based on the submitted interim sacrifice data, this chemical does appear to possess some degree of oncogenic activity in rats. An evaluation of the overall significance of the reported findings

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

should be possible upon EPA's receipt of information from future interim sacrifices and a full copy of the final report (including the actual experimental protocol, results of gross/histopathologic examinations, results of statistical analyses, etc.) from this ongoing two-year study.

Current Production and Use

In view of CIBA-GEIGY's TSCA CBI claim, no information regarding the TSCA Inventory status of the subject chemical substance will appear in this report. According to CIBA-GEIGY, the subject chemical is "a research and development compound being evaluated solely for pesticidal purposes." CIBA-GEIGY also stated that "these evaluations for pesticidal purposes are being conducted under the supervision of technically qualified personnel, [who are] knowledgeable in handling potentially hazardous chemicals."

Comments/Recommendations

In its Section 8(e) notice, CIBA-GEIGY reported that in response to the submitted preliminary findings, the company is updating the subject chemical's Material Safety Data Sheet (MSDS) to state that the "compound may cause cancer in laboratory animals."

a) The Chemical Screening Branch will ask CIBA-GEIGY to ensure that 1) EPA is kept abreast of the results of future interim sacrifices from the ongoing two-year study, and 2) EPA receives a complete copy of the final report (including the actual experimental protocol, the results of gross and histopathologic examinations, the results of any statistical analyses performed, etc.) from that two-year study.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, CIBA-GEIGY will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which CIBA-GEIGY is aware or that CIBA-GEIGY has conducted, is conducting or plans to conduct that are designed to determine the toxicological properties of the subject chemical substance.

b) The Chemical Screening Branch will review the reported information to determine the need for further OTS assessment of this carbomonocyclic aminobutyrolactone.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: SEP 13 1988

SUBJECT: Status Report* 8EHQ-0888-0746 Approved: James F. Darr 9/15/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The Monsanto Company provided the following information regarding the conduct and preliminary results of a single oral dose level teratology study of 4-aminodiphenylamine (4-ADPA; CAS No. 101-54-2) in Sprague-Dawley rats:

> ". . . [Monsanto] recently received unaudited tabular data . . . for a single [dose level] rat teratology study consisting of one [25-member] group dosed with 4-ADPA and a [25-member] control group. The 4-ADPA was administered by gavage at 150 mg/kg[/day] in corn oil. [(The submitted information does not indicate on which days of gestation the 4-ADPA was administered.)] The data show significant maternal toxicity, embryotoxicity (i.e., increased resorptions) and developmental effects in the fetal population, including gross external and internal malformations. Several of the malformations were well in excess of what could be considered spontaneous occurrences, and they are considered [to be] related to treatment. Additional visceral and skeletal evaluations of the fetuses are in progress. . . . .
>
> "It is important to note that these preliminary observations differ substantially from [the] published results of teratogenicity testing of 4-ADPA used as a component of hair dyes (Picciano, et al., Drug & Chem. Toxicol. 7:167, 1984). According to the published report, 4-ADPA in propylene glycol failed to produce developmental effects or terata when given by gavage to Sprague-Dawley rats (the same strain used in the study being reported [herein by Monsanto] to the Agency) at dosages up to 200 mg/kg.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

> "The reason for the dramatic differences in biological response between the two studies is not known. The material used in . . . [Monsanto's] study was analyzed before and after the teratology study and [was] shown to be stable. The stability of the 4-ADPA used in the published study was not stated."

The following "ABSTRACT" is from the Picciano article cited by Monsanto in its TSCA Section 8(e) submission:

> "The oxidative dye . . . [4-ADPA (also known as N-phenyl-p-phenylenediamine)] was evaluated for teratogenic potential. The dye was administered by gavage to [groups of 12] pregnant Sprague-Dawley rats at dose levels of 50, 100, and 200 mg/kg on gestation days six through fifteen. No signs of toxicity were observed during the treatment period. A significant reduction in mean maternal body weight gain was noted during treatment at the high dose level of 200 mg/kg. The test material did not produce embryotoxic nor fetal toxic effects at the dose levels utilized. Evaluation of fetal external, visceral, and skeletal anomalies revealed no statistically significant differences between dye treated and [the propylene glycol vehicle] control groups. Oral exposure of dams to the positive control, Vitamin A, resulted in a significant increase in the number of litters with fetuses having external, visceral and skeletal anomalies."

It should be noted also that the "INTRODUCTION" section of the Picciano paper stated that a National Cancer Institute (NCI) two-year carcinogenesis bioassay of 4-ADPA "administered in the feed to [Fischer 344] rats and [B6C3F1] mice revealed that the dye was not carcinogenic to either species [(DHEW Publication No. (NIH) 78-1332)]." According to staff at the National Toxicology Program (NTP), 4-ADPA was tested by NTP in a number of *in vitro* genotoxicity studies; the results of these studies were reported to be mixed.

Submission Evaluation

The submitted data indicate that 4-ADPA when administered orally to pregnant Sprague-Dawley rats at a dose of 150 mg/kg/day for an unknown number of days during gestation produced maternal and developmental toxicities.

With regard to adverse maternal effects, the mean maternal body weight was strikingly lower for the 4-ADPA-treated animals than control animals on day 11, and at all later measurements. The maternal weight gain was depressed beginning in the interval of gestation day 6 to day 11 (presumably treatment commenced on day 6) continuing through the end of the study (including the interval between days 15 and 20. In a standard developmental toxicity

study this latter interval covers the time period after treatment ceases). There were also corresponding decreases observed for maternal food consumption.

Most striking among the litter parameters was a decrease in mean fetal weight from 3.42 g to 1.94 g in the treated animals. Among the external abnormalities that occurred at elevated frequencies among the fetuses from the 4-ADPA-treated animals were: edema, "flexure," shortened digits (forepaws), and reduced number of digits (fore- and hind-paws). The overall frequency of external malformations was found to be 0% for the control fetuses and 21% of the fetuses in 39% of the litters in the 4-ADPA-treated group. Categorized as "external variations" were "areas of subcutaneous discoloration on [the] snout" (hematoma?) and a glassy or shiny appearance. These particular variations were reportedly observed at a frequency of 21% of the fetuses in 52% of the 4-ADPA-treated litters compared to 0% for the controls.

The internal malformations and variations that occurred at high frequencies in treated relative to control fetuses included: "aortic arch vessels appear to be reversed," abnormal position of the heart vessels, presence of additional aortic arch vessels, descending aorta to the right side of the heart, absence of the pulmonary arteries, absence of the innominate artery, absence of the ductus arteriosus, absence of the postcaval lobe of the lung, small kidneys, ectopic ovaries, undescended testes, and distended ureters. Overall, the heart and great vessels appeared to be the most seriously affected by treatment with 4-ADPA.

The reason(s) for the dramatic difference between the results of the Monsanto and Picciano studies may become apparent upon EPA's receipt and review of a full copy of the final report (including the actual experimental protocol, results of gross/histopathological examinations, results of statistical analyses, etc.) from Monsanto's study. In submitting this final report to the Agency, Monsanto should be asked to ensure that all terminology used in the report is defined clearly. For example, it is not entirely clear what is meant by "flexure" and "areas of subcutaneous discoloration on [the] snout" as those terms are used in the initial submission. In addition, Monsanto should be asked if the company is planning to conduct a developmental toxicity study in Sprague-Dawley rats exposed orally to 4-ADPA at doses of 150 mg/kg/day and below.

Current Production and Use

A review of the production range (includes importation volumes) statistics for 4-ADPA (CAS No. 101-54-2), which is listed in the initial TSCA Chemical Substance Inventory, showed that between 10 thousand to 100 thousand pounds of this chemical were reported as manufactured and/or imported in 1977. This production range data does not include any data claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial

TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

In its submission, Monsanto provided the following information regarding the manufacture/use of 4-ADPA:

> "Monsanto manufactures . . . 4-ADPA . . . primarily as a non-isolated intermediate which is further converted to substituted p-phenylenediamines, which are used as antioxidants. Smaller amounts [of 4-ADPA] are sold in bulk to other producers of p-phenylenediamines."

According to the "INTRODUCTION" section of the Picciano paper, 4-ADPA "is listed as an ingredient of oxidative hair dyes" and "is used in the manufacture of several dyes and dye reagents."

According to the **Colour Index** (Third Edition), 4-ADPA is known by a number of names, including C.I. Oxidation Base 2, C.I. Azoic Diazo Component 22, C.I. Developer 15, C.I. 76085, C.I. 37240 and Diphenyl Black.

In its TSCA Section 8(e) submission, Monsanto also provided the following information concerning the potential for workplace exposure to 4-ADPA at Monsanto:

> "Monsanto manufactures 4-ADPA in a closed system and much of it is converted without being isolated. Thus, potential exposures to the few employees involved are low and contact with 4-ADPA is minimal in normal operations. Potential for exposures can be greater during sampling or maintenance work or in preparing bulk shipments. Protective equipment is required in . . . [Monsanto's] operations if it is considered that airborne concentrations [of 4-ADPA] could exceed 0.1 mg/m^3 (TWA) or if there is potential for skin contact. The airborne limits and limitation of skin contact are derived, by analogy, from the standards (PEL,TLV) established for p-phenylenediamine and are based upon the sensitization properties of that chemical. Thus . . . [Monsanto] previously adopted 0.1 mg/m^3 as a workplace exposure guideline."

Comments/Recommendations

Monsanto reported that its "employees and customers are being notified directly regarding these preliminary findings." Also, Monsanto stated that it is initiating a review of "work practices, labeling, safety data sheets and other company literature on . . . [4-ADPA] with a view to revising them if necessary."

It should be noted that immediately upon receipt of this TSCA Section 8(e) submission, the Chemical Screening Branch sent a copy of the submission to the U.S. Food and Drug Administration (FDA) for review and appropriate followup attention.

a) The Chemical Screening Branch will request Monsanto to ensure that the Agency receives a complete copy of the final report (including the actual experimental protocol, results of gross and histological examinations, results of any statistical analyses performed, etc.) from Monsanto's single oral dose level teratology study of 4-ADPA in pregnant Sprague-Dawley rats. Monsanto will be asked also to ensure that all terminology used in the submitted report is defined clearly.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure data, Monsanto will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the published scientific literature) about which Monsanto is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of 4-ADPA. Monsanto will be informed that the Agency would be interested especially in the results of a developmental toxicity study in Sprague-Dawley rats exposed orally to 4-ADPA at doses of 150 mg/kg/day and below.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of 4-ADPA.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: SEP 23 1988

SUBJECT: Status Report* 8EHQ-0888-0747

Approved: James F. Darr 9/27/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The CIBA-GEIGY Corporation provided the following information regarding the conduct and results of 49-day and 90-day feeding studies of 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)-phenol (Tinuvin 320; CAS No. 3846-71-7) in rats:

> "In the short-term [49-day] test [in which 2 groups of 30 (15 male/15 female) rats were exposed to Tinuvin 320 in the feed at dose levels of either 0 and 2000 ppm], decreased growth rate, food consumption, and food efficiency occurred at the 2000 ppm feeding level, whereas water intake was not affected. Relative weights of livers and kidneys were increased. Moreover, the livers were discolored and showed severe pathological changes [(i.e., 'hypertrophy and necrosis of hepatic parenchyma and proliferation of bile ducts')]. Gross and microscopic examination of the kidneys were essentially negative."
>
> "The primary effects produced during . . . [the 90-day subchronic feeding study] of Tinuvin 320 were lesions of the kidney and liver. After feeding [0,] 100, 200, 400, 800 and 1600 ppm to [6 groups of 20 (10 male/10 female) rats] for 90 days, all males . . . had enlargement and discoloration of the liver and kidneys. Upon gross examination, multiple tiny foci of necrosis were occasionally visible on the livers of the males in the 800 and 1600 ppm groups. Single cell necrosis and hypertrophy of the parenchymal cells were observed in the livers of all males and females in the 400, 800 and 1600 ppm groups. The hepatic damage increased with dose with the top dose causing numerous necrotic hepatocytes (occasionally foci of necrosis were present) and slight proliferation of bile ducts with necrosis of the epithelian lining of the larger bile ducts. Toxic tubular nephrosis was found for males (200, 400, 800 and 1600 ppm groups) and females (800 and 1600 ppm groups)."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Submission Evaluation

In the 49-day feeding study, the Tinuvin 320-dosed animals showed decreased growth rate, decreased food intake, decreased food efficiency (i.e., digestive efficiency), increased liver weights, increased kidney weights and morphological abnormalities of the liver. Specifically, these hepatic changes were hypertrophy and necrosis of the hepatic parenchyma and proliferation of the bile duct. With regard to kidney toxicity, the performed histologic examination did not reveal any morphological differences between the Tinuvin 320-dosed rats and the control rats.

In the 90-day study, distinct growth depression occurred for the male rats at the two highest Tinuvin 320 dose levels (800 ppm and 1600 ppm); growth depression occurred also in the females but was less pronounced. At the lower feeding levels, the body weights of the males were lower, but not significantly lower, than the controls. Food consumption and food efficiency were similar except at 800 ppm and 1600 ppm. At these feeding levels, food consumption and food efficiency were decreased in both sexes, although only during the first two weeks of this 90-day feeding study.

An altered blood profile was observed in the 90-day feeding study. Specifically, hemoglobin content, packed cell volume and number of erythrocytes were decreased in all Tinuvin 320-dosed male rats. These effects were also evident in the female rats in the two highest dose level groups (800 ppm and 1600 ppm). The packed cell volume was found to be decreased in females receiving 200 ppm and 400 ppm Tinuvin 320. At 100 ppm, the blood profile for the female rats was comparable to the controls.

In both sexes in the 90-day study, the average liver and kidney weights were increased at all Tinuvin 320 dose levels, except in females in the 100 ppm and 200 ppm dose groups. Additionally, spleen, thymus, pituitary and adrenal weights were decreased in female rats in the 1600 ppm dose group. Microscopic examination of the livers revealed distinct hepatic damage in all male rats at all Tinuvin 320 dose levels and in female rats at the three highest dose levels (i.e., 400 ppm, 800 ppm and 1600 ppm). The hepatic damage consisted of necrosis of individual liver cells, homogenous cytoplasm of hepatocytes occasionally containing yellowish-green bi-refringent slightly PAS-positive pigment granules. The appearance of such yellowish-green pigmented granules indicates an abnormal accumulation of bilirubin in the hepatocytes. The observed liver damage increased in severity with increasing Tinuvin 320 dose levels. Microscopically, the kidney toxicity was evidenced by tubular nephrosis found at 200 ppm and above in the male rats and at 800 ppm and 1600 ppm in the female rats.

Overall, the observed target organ effects caused by Tinuvin 320 are consistent with those reported in other benzotriazole-based chemical toxicity studies that have been evaluated to date by the

Office of Toxic Substances (OTS). (The reader's attention is directed to the second paragraph in the Comments/Recommendations section of this status report.)

Current Production and Use

A review of the production range (includes importation volumes) statistics for CAS No. 3846-71-7, which is listed in the initial TSCA Chemical Substance Inventory, showed that 1,000 to 10,000 pounds were reported as imported in 1977. This production range information does not include any data that were claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

In its submission, CIBA-GEIGY provided the following information concerning the importation, use and sale of Tinuvin 320:

> "Tinuvin 320 is a benzotriazole-type ultraviolet [(UV)] light absorber used for stabilizing polymers. It is not currently sold in the United States, nor has it been for the past several years. Tinuvin 320 is not manufactured in the United States. This product, which is not being actively promoted, was last imported in 1984. As a result of a comprehensive [CIBA-GEIGY] inventory cleanup in 1985, in which inactive products were either disposed of or shipped back to [CIBA-GEIGY's parent company in Basel,] Switzerland, . . . no remaining stock of Tinuvin 320 [is] in inventory [in the U.S.]."

CIBA-GEIGY reported, however, that although Tinuvin 320 is not being sold or distributed in the United States at the present time, the company has "some expectations of having a potential customer [for Tinuvin 320] in 1989."

Comments/Recommendations

CIBA-GEIGY reported that because there may be a new customer for Tinuvin 320 in 1989, the product's Material Safety Data Sheet (MSDS) and label are being updated to reflect the reported toxicological findings. In addition, CIBA-GEIGY reported that the company is informing its "laboratory employees and warehouse personnel of these new findings through written communications and, possibly, personal meetings."

It should be noted that EPA has received a number of Section 8(e) and "For Your Information" (FYI) notices on benzotriazole-based UV light stabilizers. Also, the Chemical Screening Branch is in the process of preparing a "Chemical Hazard Information Profile" (CHIP) on benzotriazole-based UV light stabilizers; a CHIP on piperidinyl-based UV light stabilizers is in preparation as well.

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, CIBA-GEIGY will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which CIBA-GEIGY is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of or the exposure to Tinuvin 320.

b) Staff of the Chemical Screening Branch will ensure that any relevant reported information on Tinuvin 320 is included in the benzotriazole-based UV light stabilizers CHIP now in preparation.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: OCT 20 1988

SUBJECT: Status Report* 8EHQ-0988-0748

Approved: James F. Darr 10/21/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The CIBA-GEIGY Corporation provided the final results of 49-day and 90-day feeding studies of 2-(2H-benzotriazol-2-yl)-4,6-bis-(1,1-dimethylpropyl)phenol (Tinuvin 328; CAS No. 25973-55-1) in rats and a 90-day feeding study of Tinuvin 328 in dogs. The submitter's cover letter presents the following information with regard to the conduct and results of these studies:

> "During the 49- and 90-day oral study with rats . . . , animals were fed diets containing 0, 100, 200, 400, 800 and 1600 ppm (90-days) or 2000 ppm (49-days) of [the] Tinuvin 328. The primary findings centered on renal and hepatic toxicity. In brief, toxic tubular nephrosis and foci of hepatic necrosis were observed in the 800 and 1600 ppm groups. A more limited degree of hepatic damage was observed down to the 100 ppm group. . . . .
>
> "During the 90-day dog study . . . , dogs received 0, 15, 30, 60, 120 and 240 mg/kg doses of Tinuvin 328. One animal died in the 240 mg/kg group. The primary effect was liver toxicity with fatty changes/fatty degeneration and monocellular necrosis, fibrosis and inflammation occurring at doses $\geq$60 mg/kg. Certain liver effects, however, were seen in the 15 mg/kg group which included increased liver enzyme levels (SGPT, SGOT & SAP), serum bilirubin levels and fatty changes in the Kupffer cells. Other major effects seen in this study include fatty changes in the renal glomeruli ($\geq$30 mg/kg), abnormal spermiogenesis/atrophy of tubules ($\geq$60 mg/kg), atrophy of the prostate ($\geq$30 mg/kg) and atrophy of the uterus ($\geq$60 mg/kg). . . . ."

CIBA-GEIGY also submitted the final results from two additional 90-day studies in rats; the cover letter presents the following information about the conduct and results of these studies:

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

> "Tinuvin 328 was added to the diet at concentrations of 0, 100, 250, 500, 750 and 1000 ppm during a 90-day rat study . . . The primary finding concerned increased liver and kidney weights, and increased serum alkaline phosphatase; however, there were no histopathological correlates to these organ weight changes. . . . .
>
> "Tinuvin 328 was administered to rats in feed at a concentration of 1000 ppm during a 13-week study . . . While there were no histopathological changes, the primary finding indicated liver damage: increased liver weight with increased liver enzyme levels (SGPT, SGOT & SAP). . . . ."

In its submission, CIBA-GEIGY reported that the final reports from these studies had been obtained recently from CIBA-GEIGY's parent company, CIBA-GEIGY Ltd. located in Basel, Switzerland.

Submission Evaluation

In the 49-day feeding study in rats, Tinuvin 328 at a dose of 2000 ppm caused liver discoloration and "severe" hepatic damage in both sexes. According to the provided pathology report, the livers of the treated animals were distinctly enlarged (i.e., an increase in liver weight) and were of a greenish-drab color. The microscopic examination of the livers revealed overtly enlarged parenchymal cells with homogeneous, eosinophilic cytoplasm and nuclei varying greatly in size and shape as well as in quantity of chromatin. In addition, large eosinophilic droplets and a few yellowish-green pigment granules (most likely bilirubin) were reportedly found occasionally in the cytoplasm of the parenchymal cells. Necrosis of individual hepatocytes and, in some livers, a slight proliferation of bile duct epithelium was seen. Although no kidney lesions were reportedly found, there was an increase in relative kidney weight ($P<0.01$) in both sexes in the Tinuvin 328-treated groups. Further, the relative testicular weights were found to be slightly higher than controls but the difference was not statistically significant.

In the 90-day rat feeding study involving Tinuvin 328 dose levels of 100, 200, 400, 800 and 1600 ppm, decreased body weights and food efficiency were reportedly observed only at the 1600 ppm feeding level. The submitted final report provides the following additional information with regard to other findings from this study:

> "Hemoglobin content and packed cell volume showed a dose related decrease at [feeding] levels of 200 ppm and above. Glucose-6-phosphatase activity in the livers was increased at all levels, the lowest level (100 ppm) included. Relative weights of [the] livers, kidneys and thyroids were increased, the effect on the livers being significant already at the lowest level.

> "Gross examination at week 14 [of this 90-day study] revealed enlargement and discoloration of livers at all dose levels in males. Livers of females and kidneys of males and females showed distinct enlargement and discoloration only at the 800 and 1600 ppm feeding level. Microscopically, hepatic damage was observed at all levels in males and females. Signs of toxic tubular nephrosis were present in kidneys of males at the 800 and 1600 ppm feeding level[s]."

In the 90-day study in Beagle dogs (3/sex/group), Tinuvin 328 was administered in the feed at dose levels of 15, 30, 60, 120 or 240 mg/kg. One (1) dog in the high dose group (240 mg/kg) died in the 8th week of the study. Depression of food consumption and loss of body weight were observed in the higher dose groups; the major finding in the two highest dose groups was an "icterus" or jaundice. It should be noted that this particular effect may have been accompanied by anemia because there was a decrease in number of erythrocytes, decreased packed cell volume, decreased mean corpuscular hemoglobin concentration, "shrivelled" erythrocytes and anisocytosis (i.e., an excessive size variation of erythrocytes). The anisocytosis was evident in the 30 mg/kg dose group as well as in the two highest dose groups.

Further with regard to the 90-day dog study, the testes of the animals in the higher Tinuvin 328 dose groups showed altered spermiogenesis and atrophy of the tubules. Testicular changes were evident also in one dog in the 30 mg/kg dose group. Atrophy was evident in the prostate gland of several dogs in the higher dose groups as well as in one dog in the 30 mg/kg dose group. In the female dogs, atrophy of the uterine wall was observed in the 60 mg/kg dose groups and higher. In the liver at most Tinuvin 328 dose levels, there were fatty changes in the hepatocytes and Kupffer cells, protein globules in the cytoplasm, brownish-yellow pigmentation in the hepatocytes and Kupffer cells, Kupffer cell hyperplasia, monocellular necrosis of hepatocytes, fibrosis and signs of inflammation. Some of these adverse effects were seen at the lowest dose level (15 mg/kg). Compound-related atrophy of the cortex of lymph nodes was observed as were changes in the spleen at the 30 mg/kg dose level and above.

Regarding the 90-day study in which rats (15/sex/group) received Tinuvin 328 dose levels of 100, 250, 500, 750 and 1000 ppm in the diet, 7 animals died but not in a dose-related manner (1 female at 1000 ppm, 1 male at 750 ppm, 2 males at 500 ppm, 1 male at 100 ppm and 2 control males). According to the submitted report, an acute respiratory infection was believed to have been responsible for these deaths. In general, the liver and kidney weights in the Tinuvin 328-exposed males and females were higher than in the control animals. As for hematological findings, urine analysis, gross pathologic findings in spleen and microscopic pathology, the submitted study report states that there were no differences in these parameters between the Tinuvin 328-treated and control rats.

With regard to the 90-day (13-week) feeding study in which rats received Tinuvin 328 at a dose of 1000 ppm, another target organ (i.e., the heart) was identified. According to the submitted summary report (none of the actual data from the study were provided), Tinuvin 328 caused distinctly enlarged ($P \leq 0.01$) heart, liver, kidneys and gonads as well as a significant increase in SGPT, SGOT and alkaline phosphatase activities. The provided summary states also that histological examinations failed to reveal any pathologic organ changes that were attributable to administration of the subject chemical.

It should be noted that a number of benzotriazole-based chemical toxicity studies have been evaluated to date by EPA's Office of Toxic Substances (OTS). (The reader's attention is directed to the second paragraph in the Comments/Recommendations section of this status report.) There is a consistency in the types of effects that have been observed in these studies, which have been mainly repeated oral short-term (28- or 49-day) studies in rats. These effects include death, decreased size and/or weight of the seminal vesicles, decreased splenic weight, decreased thymic weight, focal liver hemorrhages, liver necrosis, dose-related increased liver weight, hepatic discoloration, increased kidney weight and renal tubular degeneration. A previously received 90-day benzotriazole-based chemical feeding study also demonstrated similar effects as well as an altered blood profile (decreased hemoglobin content, decreased packed cell volume and decreased number of erythrocytes). The current TSCA Section 8(e) notice concerning Tinuvin 328 demonstrates further consistency with this toxicological profile based on studies conducted both in rats and dogs; the current TSCA Section 8(e) submission also identifies the heart as yet another target organ.

Current Production and Use

A review of the production range (includes importation volumes) statistics for CAS No. 25973-55-1, which is listed in the initial TSCA Chemical Substance Inventory, has shown that 210 thousand to 2.1 million pounds were reported as imported in 1977. This production range information does not include any information that was claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the data that have been reported for the initial TSCA Inventory, including the production range data, are subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

In its TSCA Section 8(e) submission, CIBA-GEIGY reported that Tinuvin 328 "is a benzotriazole-type ultraviolet [(UV)] light absorber used primarily for stabilizing polymers and coatings." In addition, CIBA-GEIGY submitted the following information with regard to the potential for worker and end user exposure to Tinuvin 328:

"Any dermal and inhalation exposure to this product which may occur during transfer and blending operations can be controlled by local exhaust or other engineering controls, or by the use of personal protective equipment, including impervious gloves and dust respirators.

"Low use concentrations are employed (~Ø.5%) and, once incorporated into the polymer or coating, the product remains physically encapsulated therein, virtually precluding exposure to the end user."

Comments/Recommendations

In the cover letter to its TSCA Section 8(e) notice, CIBA-GEIGY reported that the Tinuvin 328 Material Safety Data Sheet (MSDS) and label are being updated to reflect the reported toxicological findings. In addition, CIBA-GEIGY reported that the company is informing its customers by letter about the submitted findings. Finally, CIBA-GEIGY reported that the company is notifying its "plant and laboratory personnel of the new findings through written communication and/or personal meetings."

It should be noted that EPA has received a number of Section 8(e) and "For Your Information" (FYI) notices on benzotriazole-based UV light stabilizers. Also, the Chemical Screening Branch is in the process of preparing a "Chemical Hazard Information Profile" (CHIP) on benzotriazole-based UV light stabilizers; a CHIP on piperidinyl-based UV light stabilizers is in preparation as well.

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, CIBA-GEIGY will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which CIBA-GEIGY is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of or the exposure to Tinuvin 328.

b) Staff of the Chemical Screening Branch will ensure that any relevant reported information on Tinuvin 328 is included in the benzotriazole-based UV light stabilizers CHIP now in preparation.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: SEP 28 1988

SUBJECT: Status Report* 8EHQ-0988-0749 S

Approved: James F. Darr 9/28/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Note

The submitting company claimed its name and the exact identity of the subject chemical substance to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will be requesting the submitter to substantiate these TSCA CBI claims. In the "sanitized" (i.e., non-confidential) version of its Section 8(e) notice, the submitter stated that the subject chemical is an "alkyl pyridine" that is "currently manufactured exclusively for [research and development (R&D)] purposes."

Submission Description

In its Section 8(e) submission, the submitting company provided the following summary information with regard to the conduct and preliminary results of a pilot teratology study of the subject alkyl pyridine in rats:

> "In this study, [the alkyl pyridine] was administered by gavage to 6 groups of 8 mated female rats at dose levels of 0, 25, 50, 100, 200 and 400 mg/kg/day during gestation days 6 - 15. Surviving dams were sacrificed on gestation day 20. Fetuses were removed, weighed, sexed and examined for possible external malformations.
>
> "Three of eight females at 400 mg/kg/day died during the study. All of the remaining high dose animals and most of the animals at 200 mg/kg/day exhibited at least a moderate degree of weight loss and/or decreased weight gain during at least part of the gestation period. There were no viable fetuses in the surviving dams at 400 mg/kg/day. Fetal weights were decreased at

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

200 mg/kg/day. In addition, 17 fetuses from 4 litters at 200 mg/kg/day exhibited a number of external malformations. These malformations included a variety of tail defects, distended abdomens (apparently from enlarged and malpositioned livers), cleft palate and umbilical hernia. No indication of maternal or developmental toxicity was noted at 100 mg/kg/day."

The submitting company stated that upon completion of the final report from this pilot teratology study, a copy of that report would be provided to EPA.

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon the Agency's receipt of a full copy of the final report (including the actual experimental protocol, results of gross/histopathological examinations, results of statistical analyses, etc.) from the teratologic study cited in the company's TSCA Section 8(e) submission.

Current Production and Use

In view of the submitter's TSCA CBI claims, no information with regard to the initial TSCA Chemical Substance Inventory status of the subject chemical will appear in this status report.

Comments/Recommendations

a) The Chemical Screening Branch will ask the submitting company to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, results of gross/histopathological examinations, results of any statistical analyses, etc.) from the teratology study that was cited in the company's TSCA Section 8(e) submission.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure data, the submitter will be asked to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported information, and 2) to reduce or eliminate exposure to the subject chemical. The company will be requested also to describe the nature and results, if available, of all studies (other than those reported already to EPA or those published in the scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine either the toxicity of or the exposure to the subject chemical.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: SEP 28 1988

SUBJECT: Status Report* 8EHQ-0988-0750 S Approved: James F. Darr 9/28/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Note

The submitting company claimed its name and the exact identity of the subject chemical substance to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will ask the company to substantiate these TSCA CBI claims. In the "sanitized" (i.e., non-confidential) version of the TSCA Section 8(e) notice, the submitting company reported that the subject chemical substance is a "heterocyclic aryl amide" that is being produced solely by the company for the purpose of research and development (R&D).

Submission Description

The submitting company provided the following information about the conduct and preliminary results of a pilot teratology study of this heterocyclic aryl amide in rats:

> "In this study, [the subject chemical substance] was administered by gavage to 6 groups of 8 mated female rats at dose levels of 0, 75, 150, 250, 500 and 1000 mg/kg/day during gestation days 6-15. Surviving dams were sacrificed on gestation day 20. Fetuses were removed, weighed, sexed and examined for possible external malformations.
>
> "No maternal mortality occurred during the study. However, dams at 1000 and 500 mg/kg/day exhibited mean weight losses of 8 grams and 1 gram, respectively, during gestation days 6-9 (as compared to a mean weight gain of 5 grams in the controls). Mean weight gain from gestation days 9-12 was normal at 500 mg/kg/day but lower than controls at 1000 mg/kg/day. Mean fetal

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

weights appeared to be slightly decreased relative to control at 1000 mg/kg/day but [were] comparable to control at the other dose levels. One fetus each from four litters at 1000 mg/kg/day exhibited a thread-like tail. One fetus each at 75 and 500 mg/kg/day exhibited microphthalmia. All of these defects are observed occasionally in control animals and it cannot be determined whether or not the defects observed in this study were related to treatment."

The submitting company stated that a copy of the final report from this pilot teratology study would be transmitted to EPA as soon as the report is completed.

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon EPA's receipt of a full copy of the final report (including the actual experimental protocol, results of gross and histopathological examinations, results of statistical analyses, etc.) from the oral teratology study cited in the company's Section 8(e) notice.

Current Production and Use

In light of the submitting company's CBI claims, no information about the initial TSCA Chemical Substance Inventory status of the subject chemical will appear in this status report.

Comments/Recommendations

a) The Chemical Screening Branch will ask the submitter to ensure that the Agency receives a complete copy of the final report (including the actual experimental protocol, results of gross/histopathological examinations, results of statistical analyses, etc.) from the pilot teratology study that was cited in the company's TSCA Section 8(e) submission.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, the submitter will be asked to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported information, and 2) to reduce or eliminate exposure to the subject chemical. In addition, the company will be requested to describe the nature and results, if available, of all studies (other than those reported already to the Agency or those that have been published in the scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine either the toxicity of or the exposure to the subject chemical substance.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: SEP 28 1988

SUBJECT: Status Report* 8EHQ-0988-0751 S

Approved: James F. Darr 9/29/88

FROM: David R. Williams DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Note

The submitting company has claimed its company name and the exact identity of the subject chemical to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will be asking the submitting company to substantiate these TSCA CBI claims. In the "sanitized" (i.e., non-confidential) version of its Section 8(e) submission, the company reported that the subject chemical substance was a "diaryl ether." In addition, the company reported non-confidentially that this chemical is currently being manufactured by the company solely for research and development (R&D).

Submission Description

The submitting company provided the following summary regarding the conduct and preliminary results of a pilot teratology study of this diaryl ether in rats:

> ". . .[The subject chemical] was administered by gavage to 6 groups of 8 mated female rats at dose levels of 0, 50, 100, 200, 400 and 600 mg/kg/day during gestation days 6-15. Surviving dams were sacrificed on gestation day 20. Fetuses were removed, weighed, sexed and examined for possible external malformations.
>
> "Maternal death occurred in 3/8 and 8/8 animals at 400 and 600 mg/kg/day, respectively. Decreased maternal body weight gain and clinical signs of toxicity were noted at 200 mg/kg/day. No live fetuses were found in the survivors at 400 mg/kg/day. An increase in early resorptions and a decrease in fetal weights were noted at 200 mg/kg/day. No external malformations were observed in any group. No maternal or developmental toxicity was noted at or below 100 mg/kg/day."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

In its TSCA Section 8(e) submission, the company stated that EPA would receive a copy of the final report of this teratology study as soon as that report is available.

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon the Agency's receipt of a full copy of the final report (including the actual experimental protocol, results of gross/histopathological examinations, results of all statistical analyses, etc.) from the oral teratology study cited in this TSCA Section 8(e) notice.

Current Production and Use

Considering the submitting company's TSCA CBI claims, this status report will not contain any information concerning the initial TSCA Chemical Substance Inventory status of the subject chemical.

Comments/Recommendations

a) The Chemical Screening Branch will ask the submitting company to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, results of gross/histopathological examinations, results of statistical analyses, etc.) from the teratologic study cited in the company's Section 8(e) submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity/exposure data, the submitter will be asked to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported information, and 2) to reduce or eliminate exposure to the subject chemical. In addition, the company will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those that have been published in the scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine either the toxicity of or the exposure to this diaryl ether.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: SEP 29 1988

SUBJECT: Status Report* 8EHQ-0988-0752 S

Approved: James F. Darr 9/30/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Note

The 3M Company claimed the exact identity of the subject chemical substance to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will be requesting 3M to substantiate this TSCA CBI claim. In the "sanitized" (i.e., non-confidential) version of its TSCA Section 8(e) submission, 3M stated that the subject chemical was an "inorganic fiber with [a] diameter [of] less than one micron and length ranging from less than 5 microns to greater than 100 microns."

Submission Description

3M reported that "aqueous suspensions of [inorganic fiber] sample were deposited in the lungs of albino rats by intratracheal insufflation" and "after six months the lungs were fixed in 10% formalin, stained (hematoxylin and eosin) and examined by light microscope." According to 3M, verbal reports received by the company indicate that "all samples caused pulmonary fibrosis to one degree or another." Finally, 3M stated that a copy of the final report from this study would be submitted to the Agency when that report becomes available.

Immediately upon receipt of this TSCA Section 8(e) submission, the Chemical Screening Branch provided copies of the submission to staff of the Chemical Control Division (CCD/OTS) for inclusion in the ongoing OTS review of available toxicological and exposure data on a number of man-made and naturally-occurring fibers.

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon EPA's receipt of a full copy of the final report (including the actual experimental protocol, the results of gross/histopathological examinations, the results of statistical analyses, etc.) from the intratracheal insufflation study cited in the company's TSCA Section 8(e) submission.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Current Production and Use

In view of 3M's TSCA CBI claim, no information about the initial TSCA Chemical Substance Inventory status of this inorganic fiber will appear in this status report.

In its TSCA Section 8(e) submission, 3M provided the following non-confidential information concerning the manufacture of and the potential for exposure to this inorganic fiber:

> "This [inorganic fiber] is a research and development [(R&D)] material. About 1,000 kg have been manufactured in a closed process. During manufacture, exposure may occur with transfer or shutdown and clean-up during which personnel use high efficiency filter respirators. No airborne fibers have been detected (<.001 fibers/cc). Approximately 200 potential customers have been sampled with quantities of less than 10 grams each and two customers have received kilogram quantities. The latter and all future recipients will be advised of these [toxicological] findings and that 3M has an exposure guideline of 0.2 fibers per cubic centimeter [(cc)], time weighted average [(TWA)]. They will also be advised to use high efficiency filter respirators and local exhaust ventilation."

Comments/Recommendations

It should be noted that the Office to Toxic Substances (OTS) has received a number of TSCA Section 8(e) and "For Your Information" (FYI) submissions on a variety of naturally-occurring and man-made fibers.

a) The Chemical Screening Branch will ask the 3M Company to ensure that the Agency receives a complete copy of the final report (including the actual experimental protocol, results of gross/histopathological examinations, results of any statistical analyses, etc.) from the cited intratracheal insufflation study.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity/exposure data, 3M will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the scientific literature) about which 3M is aware or that 3M has conducted, is conducting or plans to conduct that are designed to determine either the toxicity of or the exposure to these inorganic fibers.

b) The Chemical Screening Branch will immediately provide copies of all reported information to the CCD/OTS for review and appropriate followup attention.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OW/EPA, OSWER/EPA, OAR/EPA, ORD/EPA, CCD/OTS and RAB/ECAD/OTS; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: SEP 29 1988

SUBJECT: Status Report* 8EHQ-Ø988-Ø753 S Approved: James F. Darr 9/30/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Note

The Hoechst Celanese Corporation has claimed the exact identity of the subject chemical substance as TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will be requesting the company to substantiate this CBI claim. In the "sanitized" (i.e., non-confidential) version of its TSCA Section 8(e) notice, Hoechst Celanese stated that the subject chemical was a "substituted indoleninium salt." In addition, Hoechst Celanese reported non-confidentially that the chemical substance had been the subject of a "Premanufacture Notification" (PMN No. P-88-1Ø19) submitted to EPA under Section 5 of TSCA.

Submission Description

The Hoechst Celanese Corporation submitted the final report of an acute eye irritation study of the subject chemical in rabbits. The submitter's cover letter provides the following information regarding the conduct and results of this toxicologic study:

> "Three rabbits each received 1ØØ mg of the test material in one eye. Within one hour, two of the rabbits had died and no irritation evaluation was performed. The third rabbit was evaluated after one hour and substantial irritative effects on the cornea, iris and conjunctiva were noted. This rabbit died within four hours."

Submission Evaluation

Immediately upon receipt of this TSCA Section 8(e) submission, the Chemical Screening Branch sent copies of the notice to the Chemical Control Division (CCD/OTS) for review and appropriate followup attention; CCD is responsible for administering EPA's TSCA Section 5 "New Chemicals Program" (NCP).

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Current Production and Use

In its TSCA Section 8(e) submission, Hoechst Celanese reported that this substituted indoleninium salt "is not in the public TSCA Chemical Substance Inventory" and "has not been imported to the U.S. for commercial purposes." Finally, Hoechst Celanese reported that a "Notice of Commencement" (NOC) for this chemical has not as yet been sent by the company to EPA.

The sanitized version of PMN No. P-88-1019 provides the following information about the use of this substituted indoleninium salt:

> "This PMN substance is a cationic dyestuff used for the coloration of acrylic fibers. A solution of the dyestuff in dimethyl formamide [(DMF)] is prepared and introduced into the fiber as a DMF solution."

The sanitized version of PMN No. P-88-1019 also reports that the projected importation range for the subject chemical substance is 5,000 to 10,000 kilograms per year.

Comments/Recommendations

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Hoechst Celanese will be asked to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported information, and 2) to reduce or eliminate exposure to this substituted indoleninium salt. Also, Hoechst Celanese will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those that have been published in the scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine either the toxicity of or the exposure to the subject chemical substance.

b) As in the case of the initial Section 8(e) notice, the Chemical Screening Branch will immediately send copies of the reported information to CCD/OTS for review and appropriate followup attention.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OW/EPA, OSWER/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and CCD/OTS; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: SEP 30 1988

SUBJECT: Status Report* 8EHQ-0988-0754

Approved: James F. Darr 9/30/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Note

In this fully non-confidential TSCA Section 8(e) submission, the American Cyanamid Company reported that the subject chemical substance (2-amino-2,3-dimethylbutanenitrile (hereinafter termed "aminonitrile"); CAS No. 13893-53-3) had been the subject of a "Premanufacturing Notification" (PMN No. P-83-603) submitted previously to EPA under Section 5 of TSCA. In addition, the company reported that a TSCA Section 5(e) Consent Order is in effect for the subject chemical.

Submission Description

In its Section 8(e) submission, American Cyanamid provided the following information with regard to the conduct and preliminary results of an acute inhalation study of the subject aminonitrile as a 60% solution in toluene:

> "Groups of 5 male and 5 female Sprague-Dawley rats were exposed to [aminonitrile/toluene] vapors for one hour. Concentrations of aminonitrile were measured analytically by gas chromatography. In the first exposure, rats were exposed to 169 ppm aminonitrile in the presence of 21 ppm [hydrogen cyanide (HCN)], a degradation product of aminonitrile, for one hour. All ten animals were dead at the conclusion of the one-hour exposure. In a second exposure, rats were exposed to 100 ppm aminonitrile in the presence of 11 ppm HCN. Six of the 10 animals were dead at the conclusion of the one-hour exposure. Symptoms of intoxication included dyspnea, hypoactivity and prostration prior to death. Although the 14-day post-exposure observation period is still continuing for the 100 ppm exposure group, there have been only two further deaths observed. Neither death appeared to result from delayed systemic toxicity."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

In its TSCA Section 8(e) notice, American Cyanamid also provided the following summary of toxicologic findings submitted thus far to EPA by the company:

> "Data previously reported to the Agency indicate that 2-amino-2,3-dimethylbutanenitrile of greater than 95% purity . . . is moderately toxic by ingestion and highly toxic by single skin application or ocular instillation. The acute oral LD50 in male and female albino rats is 83 mg/kg. The acute dermal LD50 in rabbits is 23 mg/kg. The instillation of aminonitrile (89 mg) into the eyes of rabbits resulted in the deaths of five of the six animals tested.
>
> "A 28-day rat dermal toxicity study was conducted on aminonitrile to evaluate if this chemical, like other nitriles, was neurotoxic. Aminonitrile when administered dermally at 0, 3, 10 or 30 mg/kg produced no overt signs of neurotoxicity. Skin irritation was observed at the application site in the 10 and 30 mg/kg dose groups. The No Observed Effect Level [(NOEL)] was 3 mg/kg.
>
> "Aminonitrile was not mutagenic in S. typhimurium (TA 98, TA 100, TA 1535, TA 1537) or E. coli WP-2uvrA in the presence or absence of Aroclor 1254-induced rat liver S-9."

American Cyanamid reported in its Section 8(e) notice that the company was submitting the acute inhalation data "because test information on the inhalation hazard of aminonitrile was heretofore unavailable." In addition, American Cyanamid reported that the submitted inhalation data "confirm that aminonitrile, like other aliphatic nitriles, is an acute inhalation hazard ([see] Table 1 [below]):

Table 1

Nitrile	Inhalation Result
Lactonitrile [1]	LCLO 4 hour/rat = 125 ppm
Malononitrile [2]	LC50 2 hour/rat = 57 ppm
Glycolonitrile [3]	LC50 8 hour/rat = 27 ppm"

[1] 2-hydroxypropanenitrile (CAS No. 78-97-7)

[2] propanedinitrile (CAS No. 109-77-3)

[3] hydroxyacetonitrile (CAS No. 107-16-4)

American Cyanamid stated that a copy of the final report from the company's acute inhalation study would be submitted to EPA when that report is completed.

Submission Evaluation

Immediately upon receipt of this TSCA Section 8(e) submission, the Chemical Screening Branch sent copies of the submission to staff of the Chemical Control Division (CCD/OTS) for review and followup attention; CCD is responsible for the administration of EPA's TSCA Section 5 "New Chemicals Program" (NCP).

Current Production and Use

In its TSCA Section 8(e) submission, American Cyanamid provided the following information regarding the production/use of and the potential for exposure to the subject chemical:

> "Aminonitrile is made and processed in a closed system. Wherever there is a possibility of exposure, American Cyanamid Company is currently handling aminonitrile as an inhalation hazard. . . .[The company's] procedure for handling the material specifies that the following protective equipment must be worn when the possibility of exposure exists:
>
> > "Positive pressure, full facepiece, air-supplied respirator, total encapsulating SARANEX-coated Tyvek suit with ultrasonic sealed seams, or butyl rubber suit. Gloves must be of butyl rubber or Viton. Boots must be butyl rubber or made from a heavy nitrile/PVC combination.
>
> "Engineering, industrial hygiene and environmental controls minimize risk during manufacture.
>
> "Since the aminonitrile is solely an intermediate for the production of a class of herbicides of very low toxicity and is not sold as an article of commerce or transferred to any contract manufacturer, there is a low potential for exposure of humans or the environment."

Comments/Recommendations

a) American Cyanamid will be asked to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, the results of gross and histopathological examinations, the results of any statistical analyses, etc.) from the acute inhalation study cited in the company's Section 8(e) notice. In addition, the company will be asked to describe the nature and results, if available, of all studies (other

than those reported already to the Agency) about which the company is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of the subject chemical.

b) Immediately upon receipt, the Chemical Screening Branch will send copies of the reported information to CCD/OTS for review and appropriate followup attention.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OW/EPA, OSWER/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and CCD/OTS; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: OCT 24 1988

SUBJECT: Status Report* 8EHQ-1088-0755 Approved: James F. Darr 10/25/88

FROM: David R. Williams DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

Eli Lilly and Company submitted the following information with regard to an incident that occurred during the preparation of a pesticide formulation containing monolinuron, a chemical that was imported on September 9, 1988 by Eli Lilly (in conjunction with Schering, A.G.) from Hoechst A.G. in West Germany:

> "On the evening of September 14, 1988, three male employees of the Van Diest Supply Company, Box 610, Webster City, Iowa 50595 reported symptoms [that were] compatible with hypoxia while preparing the pesticide formulation. Two of the men were diagnosed as having methemoglobinemia. They were hospitalized overnight for supplemental oxygen and observation and were discharged the following day, asymptomatic. The third man was observed as an outpatient for approximately an hour on the same evening (9/14/88) and [was] discharged asymptomatic.
>
> "This pesticide formulation contains:
>
> N'-(4-chlorophenyl)-N-methoxy-N-methyl urea
> (CAS No. 1746-81-2) Common name: monolinuron
>
> N-ethyl-N-(2-methyl-2-propenyl)-2,6-dinitro-4-
> (trifluoromethyl)benzenamine
> (CAS No. 55283-68-6) Common name: ethalfluralin
>
> Inerts: Speswhite (clay) [CAS No. 1332-58-7**]
> Polyfon H [CAS No. 8061-51-6**]
> Sellogen HR [CAS No. 1322-93-6**]
> Hi-Sil 233 [CAS No. 63231-67-4**]
>
> [** Non-confidential CAS Registry Numbers reported by Eli Lilly via telephone on October 14, 1988]

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

> "During the process, the materials were processed in an airmill and a hammermill to reduce 45 percent of the particles to below 5 microns and 0.5 percent to below 1 micron."

In reporting this information to EPA under Section 8(e) of TSCA, Eli Lilly submitted copies of two scientific articles reporting that monolinuron was implicated as the cause of methemoglobinemia in humans. Eli Lilly stated that based on these articles, the effects observed in the Van Diest workers "may have been due to the monolinuron." Eli Lilly stated also that Eli Lilly "has not seen this effect [(i.e., methemoglobinemia)] with ethalfluralin." Further, Eli Lilly provided a copy of a February 20, 1987 Hoechst A.G. Safety Data Sheet for monolinuron (trade name: Aresin) which provides the following information on the mammalian toxicity of monolinuron:

> "Acute oral toxicity (LD50): 1800 mg/kg (rat)
> Literature: WHO
> Acute dermal toxicity (LD50): >1500 mg/kg (female rat)
> Primary dermal irritation: non-irritant (rabbit)
> Primary eye irritation: non-irritant (rabbit eye)"

Eli Lilly and Company stated that the Elanco Products Company (a division of Eli Lilly and Company) had provided the subject information to EPA's Office of Pesticide Programs (OPP) pursuant to Section 6(a)(2) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA); Eli Lilly's TSCA Section 8(e) submission contained a copy of Elanco's FIFRA Section 6(a)(2) notification letter which referenced the following:

> "SONALAN (ETHALFLURALIN) TECHNICAL
> EPA REG. NO. 1471-144"

It should be noted that immediately upon receipt of this TSCA Section 8(e) submission, the Chemical Screening Branch transmitted a full copy of the submission to EPA's Office of Pesticide Programs for review and appropriate followup attention under FIFRA.

Submission Evaluation

The company's suspicion that monolinuron is the agent responsible for the observed adverse effects in the Van Diest Supply Company workers has some merit in that 1) methemoglobinemia has not been seen by the company with ethalfluralin, and 2) the published medical literature cites a number of animal studies and human incidents in which monolinuron caused or was suspected as having caused methemoglobinemia and/or sulfhemoglobinemia.

The significance of the blood effects observed in the workers lies in the associated pathophysiology. Methemoglobin is hemoglobin in which the iron has been oxidized. Methemoglobin is

being formed continuously in normal red blood cells (in the absence of exogenous oxidizing drugs or toxins) and is reduced continuously to hemoglobin. In normal red cells (in man) under steady state conditions, the methemoglobin level does not exceed 2% of the total hemoglobin content. A methemoglobin level in excess of 1.5 g/100 ml (10% of total hemoglobin) leads to visible cyanosis. If methemoglobin exceeds 35% of the total hemoglobin content, headache and dyspnea may occur, while methemoglobin levels over 70% are lethal. Methemoglobinemia can develop when red blood cells are exposed to excess oxidant drugs or toxins or when the red cells are congenitally deficient in NADH diaphorase (the enzyme that catalyzes the reduction of methemoglobin back to hemoglobin).

Sulfhemoglobinemia is associated with a condition in which the blood contains a poorly characterized hemoglobin derivative with a characteristic absorption spectrum that distinguishes it from methemoglobin. This condition can be produced in vivo by various oxidant drugs including sulfonamides, phenacetin and acetanilid. Unlike methemoglobin, sulfhemoglobin cannot be converted back to hemoglobin. When sulfhemoglobin is formed, it persists until the red cells containing the chemical are destroyed.

Current Production and Use

A review of the production range (includes importation volumes) statistics for monolinuron (CAS No. 1746-81-2) showed that 2 million to 20 million pounds of this chemical were reported as manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI.

A review of the production range (includes importation volumes) statistics for ethalfluralin (CAS No. 55283-68-6), which is also listed in the initial TSCA Chemical Substance Inventory, showed that no 1977 manufacture/importation of the chemical was reported or that all of the manufacturing and/or importation data reported were claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial Inventory and cannot be disclosed (Section 14(a) of TSCA; U.S.C. 2613(a)).

All of the information submitted for the initial TSCA Chemical Substance Inventory, including the reported production range information, is subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

In its TSCA Section 8(e) submission, Eli Lilly stated that the subject pesticide product was being formulated for export.

Comments/Recommendations

It is important to note that Part VII of EPA's March 16, 1978 TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk". 43 FR 11110) explains that information would not need to be reported to EPA under Section 8(e) of TSCA if the subject information "has been submitted in writing to EPA pursuant to mandatory reporting requirements under TSCA or any other authority administered by EPA (including the Federal Insecticide, Fungicide and Rodenticide Act . . ." In other words, if Elanco was not required to report the subject information to EPA under Section 6(a)(2) of FIFRA, then Eli Lilly was correct in submitting the information to the Agency under Section 8(e) of TSCA.

a) The Chemical Screening Branch will ask Eli Lilly to ensure that EPA is kept abreast of any further health- or exposure-related developments that arise from the reported incident.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance(s).

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA; copies of this status report will be sent also to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: OCT 26 1988

SUBJECT: Status Report* 8EHQ-1088-0756

Approved: James F. Darr 10/27/88

FROM: David R. Williams DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The CIBA-GEIGY Corporation submitted the final reports from two 90-day feeding studies of 2-(5-chloro-2H-benzotriazol-2-yl)-4,6-bis-(1,1-dimethylethyl)phenol (Tinuvin 327; CAS No. 3864-99-1) in rats. The following information with regard to the conduct and results of these subchronic studies was presented in CIBA-GEIGY's cover letter:

> "During a 90-day feeding study in rats, Tinuvin 327, at a dietary concentration of 2,000 - 50,000 ppm, produced distinct hepatic damage: scattered necrotic liver cells and, in some cases, foci of necrosis. There were also signs of anemia in these animals. . . . .
>
> "During . . . [another 90-day] feeding study, increased liver weight and isolated cell necrosis in the liver were observed in the 100 and 200 ppm groups. . . . ."

In its submission, CIBA-GEIGY reported that the final reports from these studies had been obtained recently from CIBA-GEIGY's parent company, CIBA-GEIGY Ltd. located in Basel, Switzerland.

Submission Evaluation

In the 90-day feeding study involving Tinuvin 327 dose levels of 2,000 to 50,000 ppm in the daily diet of rats, "distinct" liver damage evidenced by necrotic hepatic cells (and foci of necrosis in some cases) and signs of anemia were observed in the male rats. In addition, this 90-day feeding study also showed that the pancreas of the male rats had lesions. It is important to

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

recognize that the formation of many digestive enzymes and the regulation of carbohydrate metabolism are among the functions of the pancreas. Further, conditions that impair normal functions of the pancreas usually evoke signs or symptoms when far advanced because there is a large reserve for both endocrine and exocrine functions. In the other 90-day feeding study of Tinuvin 327, decreased hemoglobin content and packed cell volume, increased liver, kidney and thyroid weights, and isolated liver cell necrosis were observed in the male rats only.

It should be noted that a number of benzotriazole-based chemical toxicity studies have been evaluated to date by EPA's Office of Toxic Substances (OTS). (The reader's attention is directed to the second paragraph in the Comments/Recommendations section of this status report.) There is a consistency in the types of effects that have been observed in these studies, which have been mainly repeated oral short-term (28- or 49-day) studies in rats. These effects include death, decreased size and/or weight of the seminal vesicles, decreased splenic weight, decreased thymic weight, focal liver hemorrhages, liver necrosis, dose-related increased liver weight, hepatic discoloration, increased kidney weight and renal tubular degeneration. In a previously received TSCA Section 8(e) notice (8EHQ-0888-0747) on a 90-day feeding study of another benzotriazole-based chemical (Tinuvin 320), similar toxicologic effects as well as an altered blood profile (decreased hemoglobin content, decreased packed cell volume and decreased number of erythrocytes) were observed. The present TSCA Section 8(e) submission on Tinuvin 327 as well as another recent TSCA Section 8(e) submission (8EHQ-0988-0748 concerning Tinuvin 328) demonstrate further consistency with this overall toxicological profile and also identify the heart (in the case of Tinuvin 328) and the pancreas (in the case of Tinuvin 327) as other target organs.

Current Production and Use

A review of the production range (includes importation volumes) statistics for CAS No. 3864-99-1, which is listed in the initial TSCA Chemical Substance Inventory, has shown that 10 thousand to 100 thousand pounds were reported as manufactured in 1977. This production range information does not include any data that were claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any data that would compromise TSCA CBI. All of the data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

In its TSCA Section 8(e) submission, CIBA-GEIGY reported that Tinuvin 327 "is a benzotriazole-type ultraviolet [(UV)] light absorber used primarily for stabilizing plastics and polymer coatings." CIBA-GEIGY also submitted the following information on the potential for worker and end user exposure to Tinuvin 327:

"Any dermal and inhalation exposure to this product which may occur during transfer and blending operations can be controlled by local exhaust or other engineering controls, or by the use of personal protective equipment, including impervious gloves and dust respirators.

"Low use concentrations are employed (approximately Ø.5%) and, once incorporated into the polymer or coating, the product remains physically encapsulated therein, virtually precluding exposure to the end user."

Comments/Recommendations

In its TSCA Section 8(e) submission, CIBA-GEIGY stated that the Tinuvin 328 Material Safety Data Sheet (MSDS) and product label were being updated to reflect the reported toxicologic findings. In addition, CIBA-GEIGY reported that the company is 1) informing its Tinuvin 327 customers "in accordance with the notification requirements of the OSHA Hazard Communication Standard (29 CFR 1910.1200)," and 2) notifying CIBA-GEIGY workers via the revised MSDS and "the company's OSHA Hazard Communication Program."

It should be noted that EPA has received a number of Section 8(e) and "For Your Information" (FYI) notices on benzotriazole-based UV light stabilizers. Also, the Chemical Screening Branch is in the process of preparing a "Chemical Hazard Information Profile" (CHIP) on benzotriazole-based UV light stabilizers; a CHIP on piperidinyl-based UV light stabilizers is in preparation as well.

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, CIBA-GEIGY will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which CIBA-GEIGY is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of Tinuvin 327.

b) Staff of the Chemical Screening Branch will ensure that all relevant reported information on Tinuvin 327 is included in the benzotriazole-based UV light stabilizers CHIP now in preparation.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: NOV - 3 1988

SUBJECT: Status Report* 8EHQ-1088-0757

Approved: James F. Darr 11/7/88

FROM: David R. Williams, Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The CIBA-GEIGY Corporation provided the final report of a 28-day oral (gavage) toxicity study of 1-[bis(2-hydroxyethyl)amino]-3-(4-isononylphenoxy)-2-propanol (CAS No. unknown) in rats. The submitter's cover letter presents the following information with regard to the conduct and results of this study:

> "During a 28-day toxicity study, rats received oral doses of 0, 10, 50, and 300 mg/kg/day. Liver and spleen damage were observed at 300 mg/kg in male and female rats. The effects included slight necrosis of the centrilobular region of the liver and there was moderate to marked atrophy of the splenic white pulp. Mortality, ataxia, and partial motor paralysis were observed for males in the 300 mg/kg group. These effects were not seen at 50 mg/kg. . . . ."

CIBA-GEIGY reported also that the subject chemical is "corrosive to eyes and is also a skin sensitizer."

Submission Evaluation

In this 28-day toxicity study, the subject chemical substance was administered to 5 albino rats/sex/group at doses of 0, 10, 50 and 300 mg/kg/day by gavage and the animals were then evaluated for mortality, clinical signs, body weight gain, hematology, clinical chemistry, gross pathology and histopathology.

Three of 5 male rats at 300 mg/kg/day died between days 13 - 16. A fourth male in the same dose group was found moribund on day 17. There were no other mortalities in any of the other groups in the study. Adverse clinical signs such a ocular discharge, salivation, labored breathing, hypoactivity, ataxia, and/or

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paresis (i.e., partial paralysis) were observed in some but not all of the male rats in the highest dose group (300 mg/kg/day); some of these signs were seen but only infrequently in the high dose female rats. Although these clinical signs were not observed in the animals in any other groups in the study, some of these antemortem signs (as well as certain other clinical signs (e.g., tremors, sedation, ataxia) reportedly observed during an acute oral dose range-finding study in rats) do suggest that the test chemical may produce neurotoxicologic effects.

Body weight gains were statistically significantly reduced for both sexes at the 300 mg/kg/day dose level, with the male and female body weights being 35% and 12%, respectively, below those of the control animals. The weight gain for animals at the lower dose levels was comparable to those of the controls.

The hematology results were confusing in that the males showed a dose-related decrease in total white blood cells (WBCs) but an increased level of specific WBC types (neutrophils, monocytes, eosinophils). Furthermore, the female rats showed a similar increase in specific WBC types and the more logical increase in total WBCs. (There is some question as to whether the male total WBC counts could have been reversed.) In general, however, this occurrence may not be that critical because the total WBC counts are well within normal physiological range for rats and hence, may not be of any biological significance.

The biochemical analyses that were performed showed increased levels of serum cholesterol, aspartate aminotransferase (GOT) and alanine aminotransferase (GPT) and decreased levels of alkaline phosphatase (Alp) for males in the 300 mg/kg/day group. These results may not be valid, however, because the values were derived from only the one remaining male rat in the 300 mg/kg/day dose group. The females, on the other hand, showed definite dose-related increases in serum cholesterol and globulin; dose-related decreases were noted also in the albumin/globulin ratio. The females also exhibited significantly increased GOT and GPT levels and significantly decreased Alp levels at 300 mg/kg/day. These alterations in biochemical parameters are strong indicators of hepatocellular injury.

The major finding at necropsy was a significant dose-related increase in absolute and relative liver weights in rats in the 50 and 300 mg/kg/day dose groups. The relative liver weights at 300 mg/kg/day were 1.5 to 2 times those of the controls. The males also had increased relative kidney and testes weights at 300 mg/kg/day. The females showed definite dose-related increases in the relative weights of the kidney, brain, heart and adrenals which were statistically significant at 300 mg/kg/day.

The histopathological examination provided microscopic evidence to support the meaning of the observed alterations in biochemical parameters and organ weights. At 300 mg/kg/day, 4/5 males and 5/5 females exhibited centrilobular necrosis and cytoplasmic

vacuolization of the liver. Hepatocellular hypertrophy was present in 3/5 females at 300 mg/kg/day. All (5/5) females at 300 mg/kg/day exhibited cytoplasmic vacuolization of the renal tubules and 1/5 males at 300 mg/kg/day showed dilatation and casts in the renal tubules. Phagocytic cells were found to be present in the spleens of both sexes and atrophy of the splenic white pulp occurred in 4/5 males at 300 mg/kg/day. No treatment-related histopathologic effects were evident at the lower doses.

Although the final report "Summary" states that 10 mg/kg/day was determined to be the no-observed-adverse-effect-level (NOAEL) for the subject chemical in this 28-day oral toxicity study in rats, EPA suggests that 10 mg/kg/day be considered the lowest-observed-adverse-effect-level (LOAEL) based on the following rationale. The primary toxic effects of the tested chemical substance appear to occur in the liver. Although the serum biochemistry values and organ weights in the animals in the 10 mg/kg/day dose groups did not differ statistically from those of the controls, there was a definite linear dose-related increase in these parameters beginning at 10 mg/kg/day; such increases are indicative of hepatocellular injury.

Current Production and Use

CIBA-GEIGY provided the following information with regard to the importation/use of the subject chemical:

> "It is an imported research and development [(R&D)] material used as a corrosion inhibitor for lubricants. To date, approximately 1.8 kg of this material has been imported into the U.S. for laboratory testing and limited distribution to one customer for R&D testing (a total of 0.28 kg). Approximately 0.9 kg still remains in . . . [CIBA-GEIGY's] laboratory.

CIBA-GEIGY also provided the following information concerning the potential for exposure to the subject chemical:

"a) Exposure is minimal since very little material has been imported.

"b) This is a research and development material. It has been used only by or under the direct supervision of a technically qualified individual(s).

"c) Distribution has been limited to one customer in very small quantities.

"d) The material is corrosive to eyes and is also a skin sensitizer. It is labeled accordingly. Therefore, dermal exposure is already avoided or minimized by anyone handling the material by the use of impervious gloves and chemical goggles as recommended in . . . [the company's] Material Safety Data Sheet [(MSDS)].

"e) The product is a viscous liquid of low vapor pressure (2.2×10^{-8} torr at 25°C). Inhalation exposure is thus of limited concern.

"f) The product has been discontinued from further development in the U.S. for technical reasons."

Comments/Recommendations

In addition to discontinuing its activities with the subject chemical, CIBA-GEIGY reported that the company is 1) revising the product MSDS to reflect the submitted toxicologic findings, and 2) informing CIBA-GEIGY laboratory workers and the customer in writing about those findings.

a) The Chemical Screening Branch will ask CIBA-GEIGY to submit full copies of the final reports (including the actual experimental protocols, results of gross and histopathological examinations, results of statistical analyses, etc.) from 1) the acute rat oral dose range-finding study that was cited in the final report of the submitted 28-day oral study, and 2) the dermal sensitization and eye irritation studies that were cited in the cover letter to the company's Section 8(e) notice.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, CIBA-GEIGY will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which CIBA-GEIGY is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of the subject chemical.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: OCT 27 1988

SUBJECT: Status Report* 8EHQ-1088-0758 S

Approved: James F. Darr 10/27/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

Valent U.S.A. Corporation has claimed the exact identities of the four (4) subject chemical substances as TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS)will be requesting Valent U.S.A. to substantiate these CBI claims. In the "sanitized" (i.e., non-confidential) version of its Section 8(e) notice, Valent U.S.A. provided the following generic names for these chemicals: Substituted Phthalimide I, Substituted Phthalimide II, Substituted Phthalimide III, and Substituted Cyclohexenone.

Submission Description

Valent U.S.A. (a joint venture of Chevron Chemical Co. and Sumitomo Chemical Co. created in order to develop and market agricultural pesticides in the U.S.) provided the following summarized information regarding the conduct and preliminary results of several toxicologic studies of the subject chemicals:

> "In a series of teratogenicity screening studies, compounds Substituted Phthalimides II and III and the Substituted Cyclohexenone showed varying degrees of teratogenic potential in the rat. [According to the provided information, Substituted Phthalimides II and III caused ventricle septal defects and wavy ribs, while the Substituted Cyclohexenone caused omphalocele and anomalies of the vertebral bodies.] None of the subject chemicals showed teratogenic potential in the rabbit.

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"Compounds Substituted Phthalimides I, II and III produced a positive mutagenic response in an in vitro chromosomal aberration test (CHO-K1) in the presence of S-9 activation. These chemicals did not show mutagenic potential in an in vivo mouse micronucleus test or in the Ames Test.

"Compound Substituted Phthalimide I was shown to be a very strong skin sensitizer in the guinea pig."

Submission Evaluation

An EPA evaluation of the overall significance of the reported toxicologic findings should be possible upon the Agency's receipt of full copies of the final reports from all studies cited in the company's TSCA Section 8(e) notice.

Current Production and Use

Valent U.S.A. reported non-confidentially that these chemicals are "experimental" and are being "imported from Sumitomo in Japan exclusively for pesticidal efficacy [testing] . . ." According to Valent U.S.A., the company plans to apply for an Experimental Use Permit (EUP) under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) if the results of these efficacy tests "show promise."

In its submission, Valent U.S.A. also stated non-confidentially that there is no "undue hazard to persons handling the chemicals" because "the amounts involved are small, testing is conducted under the direct supervision of professionals trained in the use of hazardous chemicals and distribution is very limited."

Comments/Recommendations

Valent U.S.A. stated non-confidentially that the company is 1) revising the Material Safety Data Sheets (MSDSs) for the subject chemicals to reflect the reported toxicological findings, 2) advising persons who handle the chemicals about the submitted findings, and 3) reminding persons who work with the chemicals to "utilize proper handling procedures."

a) The Chemical Screening Branch will ask Valent U.S.A. to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, results of gross and histopathological examinations, results of any statistical analyses, etc.) from each study that was cited in the company's Section 8(e) submission.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Valent U.S.A. will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Valent U.S.A. is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of the subject chemical substances.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemicals.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: OCT 27 1988

SUBJECT: Status Report* 8EHQ-1088-0759

Approved: James F. Darr 10/27/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

E. I. DuPont de Nemours & Company, Inc. submitted a status report summarizing initial findings of an ongoing groundwater monitoring study being performed by DuPont at its Spruance facility located in Richmond, VA. According to DuPont, a number of chemicals, including trichlorofluoromethane (TCFM; CAS No. 75-69-4), chloroform (CAS No. 67-66-3), hexamethylphosphoramide (HMPA; CAS No. 680-31-9) and carbon disulfide (CAS No. 75-15-0), were detected in the groundwater samples taken.

In its submission, DuPont stated that this groundwater monitoring study was being conducted "under consent order entered with the State of Virginia" and was "initiated as the result of the discovery that trichlorofluoromethane (TCFM) had been released from a manufacturing unit into the ground and had apparently reached the groundwater in an undetermined amount." According to DuPont, this TCFM release was reported to the National Response Center (NRC) by telephone on November 14, 1986 and was reviewed by the Virginia State Water Control Board and Chesterfield County authorities on November 25, 1986. DuPont reported that under the consent order, it was agreed that Dupont would "investigate the possibility of contaminants in the groundwater present in concentrations above 10 ppb in addition to the TCFM that was released." DuPont reported further that the company has 1) kept the State of Virginia abreast of the company's efforts throughout preliminary data collection, and 2) presented a comprehensive review of the preliminary analytical data to the Virginia State Water Control Board on October 5, 1988.

DuPont provided EPA with the following summarized information regarding the conduct and results of the company's monitoring studies:

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"The nature and extent of the contamination at the site was investigated in four quarterly sampling events over the course of a year. Samples were obtained from on-site monitoring wells and from [the] nearby surface waters (Grindall Creek; the James River). All samples were analyzed for U.S. EPA Priority Pollutant Volatile Organic compounds. No organic or inorganic contaminants attributable to operations at the facility were found in any of the surface water samples. Most of the priority pollutant volatile organic constituents were not detected in any of the groundwater samples. ['Priority pollutant metals were not generally found in the groundwater samples. However, concentrations of zinc (ppm range) were associated with low pH (5 or below) wherever there was a measurement of both pH and zinc concentration. The monitoring record for the bedrock well locations (7 wells) is not as extensive as in shallower wells. Two bedrock wells near the James River were analyzed for volatile organics and HMPA; the remainder for priority pollutants only. No contamination was detected west of Grindall Creek and in wells nearest the James River. Acetone was found in two wells in the main plant area (2,600 and 1,500 ppb); chloroform at one well (11 ppb). Low levels of zinc (3.4 ppm) and low ppb levels of arsenic, beryllium, chromium, [methylethylketone (MEK)], phenol, phthalate and carbon disulfide were found in one well in the main plant area (total concentration of organics (excluding acetone) of 174 ppb).'] However, trichlorofluoromethane, chloroform, carbon disulfide and hexamethylphosphoramide (HMPA) were detected in [the] groundwater samples taken. HMPA has not been used at the site since 1982."

DuPont provided the following information specifically regarding the detection of TCFM, chloroform and HMPA:

"o TCFM: The preliminary findings show that the concentration of TCFM in groundwater in the western half of the site range from <10 ppb to >1000 ppm. The contamination is distributed in two plumes: (1) one plume extends east beyond the property boundary (the full easterly extent currently not quantified); and (2) the second plume extends to the southern boundary of the facility in a south south-eastern direction.

"o Chloroform: Concentrations of chloroform in groundwater range from <10 ppb to >10 ppm. The contamination is distributed in two plumes: (1) one plume extends north-easterly across the site boundary; and (2) the second plume extends to the southern boundary of the facility in a south south-eastern direction. [DuPont believes the] patterns of TCFM and chloroform contamination to be generally consistent with prior plant use.

"o HMPA: Concentrations of HMPA in groundwater range from <10 ppb to >100 ppm. The contamination is distributed in two plumes extending southeast and northeast, respectively, and in an area in the northwest corner of the plant. Highest HMPA concentrations (>100 ppm) were detected adjacent to the site of primary past usage. Monitoring wells immediately to the west of the James River show HMPA concentrations of approximately 100 ppb. HMPA has not been detected in the James River (5 ppb limit of detection). The pattern of HMPA contamination in the plume extending northeast is consistent with origin in an on-site landfill. The source of HMPA at the northwest corner of the plant is currently unknown but may have originated from a past spill. The source of the HMPA in the plume extending southeast is believed [to be] consistent with the prior use of the solvent in the manufacturing area."

DuPont also provided the following information about the possible impact(s) of this groundwater contamination on the James River:

> ". . . [DuPont believes] that, while no contaminants attributable to the Spruance facility were detected in the James River during this investigation, the James River is the probable discharge zone for HMPA, chloroform and TCFM. ['It is likely that HMPA originating in the site landfill area is discharging to the river; TCFM and chloroform plumes may also have reached the river northeast of the Spruance facility.'] The concentrations of these three compounds in groundwater discharging to the river are likely to increase for a number of years. Very gross approximations of transport rates using current levels of contaminants suggest that maximum concentrations [of these contaminants] will be attained at the river in 20 to 30 years. ['These same gross approximations suggest that, averaged across the entire zone of river discharge, maximum concentrations of TCFM, HMPA and chloroform in groundwater will be on the order of 100,000 ppb, 20,000 ppb and 5,000 ppb, respectively.'] Assuming complete and instantaneous mixing of the contaminated groundwater with the river, calculated maximum concentrations of TCFM, HMPA and chloroform in the river are (within an order of magnitude) 50, 5 and 1 ppb, respectively. The calculated maximum concentrations at average annual flow are (within an order of magnitude) 5, 0.5 and 0.1 ppb, respectively."

Comments/Recommendations

DuPont stated that although it "has not, at this time, determined potential human exposure to the groundwater" nor has the company "made a hazard assessment of the chemicals found . . .," DuPont

"will continue to closely coordinate with the State of Virginia to assure that further efforts to quantify and assess the problem, and to develop and implement an appropriate remediation strategy, can be effected expeditiously in an environmentally sound manner."

It should be noted that most, if not all, of the detected chemical substances have been or are currently the subject of data gathering, assessment and/or rules promulgated under the many environmental protection authorities administered by EPA. Therefore, immediately upon receipt of this TSCA Section 8(e) submission, the Chemical Screening Branch transmitted full copies of the notice to EPA's Region III Office (Philadelphia, PA), the Office of Water (OW/EPA), the Office of Groundwater Protection (OGWP/OW/EPA), the Office of Solid Waste and Emergency Response (OSWER/EPA), the Office of Air and Radiation (OAR/EPA) and the Exposure Evaluation Division (EED/OTS/OPTS/EPA); complete copies of the submission were sent also to the Chemical Control Division (CCD/OTS/OPTS/EPA) for inclusion in the ongoing review of chlorofluorocarbons (CFCs) and chlorinated solvents, and to the Test Rules Development Branch (TRDB/ECAD/OTS/OPTS/EPA) and the Risk Analysis Branch (RAB/ECAD/OTS/OPTS/EPA) for inclusion in their ongoing reviews of several of the detected chemicals (e.g., MEK, phthalates).

a) The Chemical Screening Branch will ask DuPont to ensure that EPA is apprised of any new health impact-related or exposure-related findings from the company's ongoing groundwater monitoring efforts at this Virginia plant site and surrounding area.

b) The Chemical Screening Branch will distribute copies of all reported information to appropriate EPA offices.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, EPA's Region III Office, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, EED and CCD/OTS/OPTS/EPA, and RAB and TRDB/ECAD/OTS/OPTS/EPA; copies of this status report will be sent also to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: NOV - 8 1988

SUBJECT: Status Report* 8EHQ-1088-0760 S Approved: James F. Darr 11/9/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Note

The submitting company has claimed its company name and the exact identity of the subject chemical to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will be asking the company to substantiate these TSCA CBI claims. The submitting company reported non-confidentially by phone on October 18, 1988 that the subject chemical substance is an "alkyl heterocyclic nitrogen compound."

Submission Description

The submitting company provided the following summary information regarding the conduct and preliminary results of a two-year skin application study of this alkyl heterocyclic nitrogen compound in rats:

> "In this study, the test article was applied daily to the shaved skin of the dorsum of four groups of Wistar rats at an application rate of 2 ml/kg in concentrations of 0 (control), 1%, 2.5% or 5% in isopropanol for 104 weeks. Control rats were treated with [the] vehicle (isopropanol) only. A total of eighteen squamous cell carcinomas were diagnosed in the treated rats (males and females combined) compared to none in the control group. Other neoplastic and non-neoplastic lesions recorded in the study were within the range of morphological alterations commonly diagnosed in rats of this age and strain."

The submitting company also provided the following information with regard to the results of other toxicological studies that have been conducted with the subject chemical substance:

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"A dermal two-year bioassay of the subject chemical has also been conducted in mice. No carcinogenic effect was observed in the long-term mouse study. . . . . Furthermore, five mutagenicity studies . . . were also negative. Acute and subchronic dermal [application] studies, including a twelve month study in monkeys, a six month study in rats, and teratogenicity studies in mice and rabbits were also conducted on the subject chemical. No significant systemic effects were found in any of these studies."

Submission Evaluation

According to a submitted draft pathology report, in addition to the squamous cell carcinomas of the skin of rats in the 2-year dermal application study, there were squamous cell carcinomas reportedly found in the posterior portion of the nasal cavity of the male rats (1 in the low dose group, 3 in the mid dose group and 2 in the high dose group) but not in the females or in the isopropanol controls. (NOTE: Immediately upon receipt of this TSCA Section 8(e) submission, the Chemical Screening Branch sent a copy of the submission to the Test Rules Development Branch (TRDB/ECAD/OTS) for inclusion in their ongoing evaluation of available toxicologic and exposure information on isopropanol. Isopropanol was designated by the Interagency Testing Committee (ITC) for testing under Section 4 of TSCA and is the subject of TSCA Section 8(a) and 8(d) information gathering rules.)

An EPA evaluation of the overall significance of the reported findings should be possible upon the Agency's receipt of a full copy of the final report from the company's 2-year bioassay in rats. Further, the submitter should be asked to provide to EPA full copies of the final reports from all other company studies that were cited in this Section 8(e) submission.

Current Production and Use

In view of the submitter's TSCA CBI claims, no information with regard to the TSCA Chemical Substance Inventory status or use of the subject chemical will appear in this status report. The submitter did report non-confidentially, however, that the chemical "is not being produced in commercial quantities."

Comments/Recommendations

In its TSCA Section 8(e) notice, the company reported that it has informed its customers about the submitted toxicologic findings.

a) The Chemical Screening Branch will ask the submitting company to ensure that EPA receives a full copy of the final report (including the actual experimental protocol, results of gross/histopathological examinations, results of any statistical analyses, etc.) from each company study cited in the submission.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, the submitter will be asked to describe the actions the company has taken or plans to take 1) to notify its own workers about the reported information, and 2) to reduce or eliminate exposure to the subject chemical. In addition, the submitting company will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of this alkyl heterocyclic nitrogen compound.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of this alkyl heterocyclic nitrogen compound. As in the case of the initial submission, all reported information pertaining to isopropanol will be sent immediately by the Chemical Screening Branch to the Test Rule Development Branch for inclusion in their ongoing review of isopropanol.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA and TRDB/ECAD/OTS/OPTS/EPA. In addition, copies of this status report will be provided to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: NOV 10 1988

SUBJECT: Status Report* 8EHQ-1088-0761 INIT
8EHQ-1088-0761 SUPPs

Approved: James F. Darr 11/10/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

Gelman Sciences reported that it has obtained data showing the presence of 1,4-dioxane (CAS No. 123-91-1) in automotive/truck engine coolants. In addition, the company reported that on the basis of these data, as well as other data showing the presence of 1,4-dioxane in air, soil and groundwater, the company believes this chemical substance to be widespread in the environment.

According to tabularized data provided by Gelman from a study conducted on a number of new and used foreign and domestic car and truck coolants of various ages, the concentrations of 1,4-dioxane ranged between 10 and 22,000 parts per billion (ppb). The provided table also showed that 1,4-dioxane was found in concentrations of 100 to 3400 ppb in "off-the-shelf" automotive engine coolants. Further, Gelman reported that concentrations of 1,4-dioxane detected in "radiator boil-over pools" at a number of rest areas in Michigan ranged from <10 ppb to over 2,000 ppb.

In its submissions, Gelman also provided a 122-page draft "Health and Environmental Effects Assessment for 1,4-Dioxane" prepared for the company by an environmental toxicology consultant, as well as two German articles on cosmetic preparations (particulary shampoos and bath preparations) found to contain 1,4-dioxane.

Gelman also provided an October 13, 1988 newspaper article that reports that the Michigan Department of Natural Resources (DNR) "has charged Gelman Sciences with polluting soil, surface water and groundwater [with 1,4-dioxane] near the company's plant . . . [outside Ann Arbor, Michigan]." The article states that the Michigan DNR is "suing Gelman to restore the groundwater to its original purity." According to the submitted article, Gelman claimed that based on already available information on sources of 1,4-dioxane exposure as well as the company's analytical studies showing the presence of 1,4-dioxane in engine coolants and boil-over pools at rest stops, "'the government and other individuals'

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e). the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

may be polluting drinking water with the same chemical solvent the company is charged with releasing into the environment." The provided article states further that at a recent Michigan state hearing "to consider changes to Michigan rules governing public water supply [('the state standard for safe levels of 1,4-dioxane in drinking water is 2 parts per billion')], a Gelman Sciences attorney claimed that the state has ignored the potential for groundwater contamination from puddles of antifreeze in the parking lots of rest areas along Michigan highways." The article reports also that Gelman's attorney in this matter stated that the company's automotive/truck coolant and highway rest-stop monitoring data show that "'. . . every service station, garage, parking lot and rest-stop as well as homes in the state [are] possible sources of 1,4-dioxane contamination.'" The article reports further, however, that "the state's leading attorney in its case against Gelman Sciences said the claims by the company have no bearing on the [1,4-dioxane] contamination around the [company's] plant site . . ." The article also reports that an official with Michigan DNR stated that the DNR was "'aware of the potential for contamination from 1,4-dioxane in antifreeze prior to the Gelman study.'"

Finally, Gelman submitted an October 20, 1988 news release in which Gelman announced that the company had prevailed in a lawsuit filed against the Michigan DNR that pertained to the DNR's review and evaluation of the Gelman plant site prior to publishing an assigned priority ranking for response action(s). According to the news release, Gelman had charged in its lawsuit that "(1) the DNR failed to promulgate rules necessary to carry out Act 307 (the Michigan Environmental Response Act-MERA)," and "(2) the DNR did not provide Gelman Sciences with a reasonable and meaningful public hearing and opportunity to comment on . . . [the DNR's most recent ranking of the Gelman plant site] as required by MERA."

Comments/Recommendations

EPA has received a number of TSCA Section 8(e) and "For Your Information" (FYI) submissions on 1,4-dioxane and the Chemical Screening Branch prepared a "Chemical Hazard Information Profile" (CHIP) on this chemical in 1979. In addition, it should be noted that like many polyethylene glycols, 1,4-dioxane (an anhydride of diethylene glycol) can produce toxic effects in the human kidney and liver. A characteristic nephrosis of the kidney tubules (hydropic degeneration) with an associated liver cell necrosis can occur regardless of the route of 1,4-dioxane exposure (oral, inhalation and/or dermal). Further, the **Fourth Annual Report on Carcinogens** (National Toxicology Program (NTP) 85-002; 1985) provides the following information regarding the carcinogenicity of 1,4-dioxane in laboratory animals:

> "There is sufficient evidence for the carcinogenicity of 1,4-dioxane in experimental animals.[218] 1,4-Dioxane administered in drinking water is carcinogenic in rats

and guinea pigs. It produced cancers of the nasal cavity and liver in rats and tumors of the liver and gall bladder in guinea pigs. It was also active as a promoter in a two-stage skin carcinogenesis study in mice.[219] In a drinking water study, results were positive for rats and mice. [220] "

Finally, it should be noted that pursuant to Section 110 of the Superfund Amendments and Reauthorization Act (SARA), the Agency for Toxic Substances and Disease Registry (ATSDR), in collaboration with EPA, will be preparing a "Toxicological Profile" for 1,4-dioxane. Information on the availability of SARA Section 110 profiles can be obtained from: Office of External Affairs, Agency for Toxic Substances and Disease Registry, Chamblee 28 South, 1600 Clifton Road, Atlanta, Georgia 30333.

Immediately upon receipt of this Section 8(e) submission, the Chemical Screening Branch sent copies of the provided information to NIOSH, OSHA, CPSC, OW/EPA, OSWER/EPA, OAR/EPA, and to the Regional Risk Guidance Staff (RRGS/ECAD/OTS/OPTS/EPA) for transmittal to EPA's Regional Offices. In addition, copies of the submitted information was provided immediately to staff of the Exposure Evaluation Division (EED/OTS/OPTS/EPA) for review.

a) The Chemical Screening Branch will request Gelman to submit complete copies of the actual protocols/methods used by the company to analyze for 1,4-dioxane.

b) The Chemical Screening Branch will continue to review the reported information in order to determine the need for further OTS assessment of 1,4-dioxane.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OW/EPA, OSWER/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA, RRGS/ECAD/OTS/OPTS/EPA and EED/OTS/OPTS/EPA; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

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[218] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. 292 pp. Lyon, France: IARC, 1982, pp. 121-122.

[219] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 11. 306 pp. Lyon, France: IARC, 1976, pp. 247-256.

[220] National Cancer Institute. Bioassay of 1,4-Dioxane for Possible Carcinogenicity. Technical Report Series No. 80. DHEW Publication No. (NIH)78-1330. 108 pp. Bethesda, Maryland. 1978.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: NOV - 9 1988

SUBJECT: Status Report* 8EHQ-1088-0762

Approved: James F. Darr 11/10/88

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Screening Branch/ECAD

TO: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

Submission Description

The Amoco Corporation provided the following summary information regarding the conduct and results of an acute inhalation study of 1-octanol vapor in rats:

> "Two exposures to 1-octanol were performed using two groups of 10 rats (5 males and 5 females) each. The rats were exposed via inhalation to 1-octanol vapor for either one hour at 6,400 mg/m^3 or for four hours at 5,600 mg/m^3. The 1-octanol was heated to 300°C and the animals were exposed to the resulting vapors. The rats were held for up to seven days, sacrificed, and the lungs [were] removed and processed for histological examination.
>
> "Three of [the] ten rats exposed to 1-octanol (5,600 mg/m^3) for four hours died within two days following the exposure.
>
> "Microscopic examination of the lungs of [the] exposed animals was conducted. No microscopic abnormalities were seen at any of the sacrifice periods in the lungs of the animals exposed to 1-octanol [vapor] for one hour (6,400 mg/m^3), with the exception of minimal alveolar hemorrhage in one of the exposed males. However, several treatment-related lesions were present in the lungs of the animals exposed to 1-octanol [vapor] for four hours (5,600 mg/m^3). These [lesions] included bronchial epithelial necrosis, alveolar edema, accumulation of alveolar macrophages, congestion, alveolar

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

hemorrhage, bronchial epithelial regeneration, and alveolar epithelial hyperplasia. Severe epithelial necrosis was seen in the bronchi of all lung lobes, while alveolar edema and alveolar macrophage accumulation were either diffuse or multifocal in distribution and generally of mild severity. No necrosis of the bronchiolar or alveolar epithelium was observed.

"The incidence of lung lesions (sexes combined) in the 4-hour exposure animals in relation to the day of death or post-exposure sacrifice was as follows:

LESION	DAY 1	DAY 2	DAY 5	DAY 6
Alveolar edema	2/2	3/3	Ø/2	3/3
Accumulation of alveolar macrophages	2/2	3/3	2/2	3/3
Bronchial epithelial necrosis	2/2	3/3	1/2	Ø/3
Bronchial epithelial regeneration	Ø/2	Ø/3	2/2	3/3
Congestion	Ø/2	3/3	Ø/2	Ø/3
Alveolar hemorrhage	1/2	Ø/3	Ø/2	1/3
Alveolar epithelial hyperplasia	Ø/2	Ø/3	Ø/2	1/3

"Examination of these data indicated that the initial lung lesion following [the 4-hour] 1-octanol [vapor] exposure consisted of necrosis of the bronchial epithelium with alveolar edema and [an] accumulation of alveolar macrophages. These changes were generally seen one to two days after exposure. The predominant lesions seen five and six days post-exposure were regeneration of the bronchial epithelium and residual alveolar edema with multifocal alveolar macrophage accumulation. The epithelial regeneration and macrophage accumulation are indicative of reparative and resolution processes, respectively: the regenerative epithelium replaced the necrotic epithelium and the macrophages removed the residual edema."

In its submission, Amoco provided the following information with regard to the company's interpretation of the reported findings:

". . . [Amoco interprets] these results to indicate that exposure to very high concentrations of 1-octanol vapor for an extended period of time is capable of producing temporary lung damage. However, to produce the vapors used in this study, it was necessary to heat the sample to approximately 300°C (the boiling point of 1-octanol is 196°C). Given that the boiling point of 1-octanol is so high, the potential for human exposure to the massive concentrations used in this study is unlikely. Also, in rats an exposure of greater than one hour was required to produce the effects seen; it is also unlikely that humans would be exposed for such a long duration."

Submission Evaluation

Despite the fact that the 1-octanol had to be heated to 300°C to generate the vapors, the submitted data indicate that a 4-hour exposure to 5600 mg/m^3 in rats resulted in bronchial epithelial necrosis, alveolar edema, accumulation of alveolar macrophages, congestion, alveolar hemorrhage, alveolar epithelial hyperplasia and bronchial epithelial regeneration. Although the submitting company interpreted the study findings to indicate "temporary" lung damage from exposure to high concentrations of 1-octanol for an extended period of time, EPA cannot agree that the toxicologic concern for this chemical can be dismissed. While EPA agrees that a high temperature was required to generate the vapors for an acute exposure, no information was submitted that predicts or alludes to a lack of chronic toxicity when there is long term exposure to lower levels of 1-octanol. Further, EPA's concern for chronic toxicity is not mitigated to any great degree by the observed post-exposure regenerative/reparative activity.

It should be noted that the **Registry of Toxic Effects of Chemical Substances** (RTECS) reports that 1-octanol is a mild irritant when applied to the skin of rabbits (500 mg) and has been shown to be moderately toxic when administered orally to mice (LD50 of 1790 mg/kg), but does not present any information with regard to the mammalian toxicity of 1-octanol via inhalation.

Current Production and Use

A review of the production range (includes importation volumes) statistics for 1-octanol (CAS No. 111-87-5), which is listed in the initial TSCA Chemical Substance Inventory, has shown that 11 million to 60 million pounds were reported as manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any data that would compromise TSCA CBI. All data reported for the initial TSCA Inventory, including production range data, are subject to the limitations in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

The **Condensed Chemical Dictionary** (10th Edition), presents the following information regarding the uses of 1-octanol:

> "Perfumery; cosmetics; organic synthesis; solvent; manufacture of high-boiling esters; antifoaming agent; flavoring agent."

Comments/Recommendations

a) The Chemical Screening Branch will ask Amoco to submit a full copy of the final report (including the actual experimental protocol, results of gross/histopathologic examinations, results of statistical analyses, etc.) from the cited acute inhalation toxicity study in rats.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Amoco will be asked to describe the actions the company has taken or plans to take to notify workers and others about the reported information. In addition, Amoco will be requested to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Amoco is aware or that Amoco has conducted, is conducting or plans to conduct that are designed to determine the toxicity of 1-octanol.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of 1-octanol.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: DEC 8 1988

SUBJECT: Status Report* 8EHQ-1088-0763 S INIT
8EHQ-1088-0763 S SUPP Approved: 12/9/88

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

The Union Carbide Corporation claimed the exact identity of the subject chemical to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will review all Union Carbide correspondence relating to substantiation of this CBI claim. In the "sanitized" version of this submission, Union Carbide stated non-confidentially that the subject chemical is an "alkylaminocarbonyl-substituted thiadiazole sulfonamide" with the following internal designation: "UC77179."

Submission Description

Union Carbide provided the final reports from 14-day and 90-day dietary feeding studies of UC77179 in rats and mice. The submitter's cover letter provides the following information with regard to the conduct and results of these studies:

"Rat Study

"In a preliminary study, UC77179 was administered to male and female Fischer 344 rats [(10/sex/group)] for 2 weeks at dietary concentrations of 0.0, 0.2, 0.4, 0.8, 1.6, or 3.2% (0, 2000, 4000, 8000, 16000, or 32000 ppm). Food uptake and body weights were reduced in a dose-related manner for all treatment groups. Mortality occurred in the males consuming 3.2% (8/10) and 1.6% (4/10) UC77179 and in females (6/10) in the high dose group. Death may have resulted from severely depressed food uptake.

"In a subsequent 90-day study, male and female Fischer 344 rats [(30/sex/group)] were fed diets containing 0.0, 0.015, 0.03, 0.06, 0.12, or 0.24% (0, 150, 300, 600, 1200, 2400 ppm) UC77179. Food uptake and body weights were depressed in [the] males from the 0.24,

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Ø.12 and Ø.Ø6% UC77179 groups. Food uptake was reduced for females at these same dietary concentrations. Body weights for the females were significantly decreased in a dose-related manner for all but the low dose group. Treatment-related water consumption increases were observed for all groups in both sexes. Corresponding changes in urinalysis measurements including increased urine volume, decreased specific gravity and decreased protein concentrations were recorded. Other clinical pathology alterations included a macrocytic anemia in the high dose males and at all treatment levels for the females. In addition, a dose-related increase in serum chloride concentration was observed for both sexes. Microscopic changes were seen in the kidneys of the animals in the Ø.24 and Ø.12% UC77179 groups. These [pathological] changes included mineralization of the renal pelvis with associated hyperplasia of the transitional epithelium. Thyroid adenomas were also observed in 3 of 3Ø male rats exposed to Ø.24% UC77179 for 9Ø days. Microscopic examinations on tissues from rats fed lower concentrations of UC77179 were not conducted.

"Mouse Study

"In a preliminary two-week study, six groups of B6C3F1 mice (1Ø mice/sex/group) were fed diets containing UC77179 at concentrations of Ø.Ø, Ø.2Ø, Ø.4Ø, Ø.8Ø, 1.6Ø, or 3.2Ø% for 14-days. The parameters measured were: clinical observations, body weight, organ weight (heart, lungs, liver, kidneys, testes, and brain) and gross pathologic examination. For the highest dose group, mortality occurred at a rate of 8Ø% for both sexes. [The] clinical signs for animals in the high dose groups included lethargy, tremors, unkempt fur, abdominal-urogenital wetness, and coldness to touch. Time to death was approximately 5-to-6 days for both sexes. Depressions in body weight and food consumption were observed at UC77179 [dietary] concentrations of Ø.8Ø% and greater for males, and at Ø.4Ø% and greater for females. Observed organ weight differences may have been a manifestation of [the] body weight loss. No treatment-related gross lesions were apparent at necropsy.

"In the 9Ø-day study, UC77179 was incorporated in the diet of B6C3F1 mice (3Ø mice/sex/group) at concentrations of Ø.Ø, Ø.Ø15, Ø.Ø3, Ø.Ø6, Ø.12, or Ø.24%. The Ø.Ø% and Ø.12% groups contained ten additional mice per sex that served as recovery groups maintained on [a] control diet for an additional four weeks. Body weight gain was reduced for males in the three highest dosage groups and [for] females at the two highest concentrations of UC77179 after 9Ø days. Clinical alterations were restricted to hyperchloremia for females in all

> [UC77179] treatment groups after 90 days. There was no treatment-related mortality. A no observable effect level [(NOEL)] of 0.03% was established."

In its submission, Union Carbide stated that upon receipt of the toxicologic findings from the 90-day UC77179 feeding study in rats, "all further studies with the chemical were abandoned" including the concurrent 90-day feeding study in mice that was cited previously. According to Union Carbide, "there were no pathological examinations done on tissue from the [90-day] study in mice."

In its submission, Union Carbide stated also that "rats appear to be much more sensitive than primates to the thyroid alterations induced by sulfonamides and other goitrogens" and cited several scientific articles and EPA documents on the observation and/or interpretation (e.g., "threshold" phenomena) of toxic effects (including certain oncogenic effects) induced by aromatic amines including sulfonamides.

In a supplemental TSCA Section 8(e) submission, Union Carbide provided the final reports from a variety of in vitro and in vivo genotoxicity studies of UC77179. According to the cover letter from this supplemental submission, UC77179 caused gene mutations in an Ames Salmonella typhimurium (bacterial) assay and produced chromosomal damage in cultured Chinese Hamster Ovary (CHO) cells; UC77179 was reportedly negative in a Forward Gene Mutation Assay in cultured CHO cells, a DNA Repair Assay in cultured rat hepatocytes, and an in vivo Bone Marrow Cytogenetics Assay in rats.

Finally, Union Carbide stated in its initial TSCA Section 8(e) notice that "there are other acute toxicity data available for UC77179" that were developed during the company's R&D activities with this chemical, "none of which is indicative of substantial risk."

Submission Evaluation

Overall, the major toxic effects induced by the subject chemical after 90 days or less of dietary exposure appear to be thyroid tumors, mineralization of the renal pelvis and macrocytic anemia. It should be noted that although many sulfonamide-containing compounds have been shown to exhibit antithyroid activity, this activity is considered generally to be weak. Further, it could be anticipated that the thiadiazole moiety would produce similar effects considering that both aminothiazole and aminotriazole have been reported to cause antithyroid effects. With regard to tumor induction, however, the scientific literature indicates that a number of sulfonamide-containing chemicals when tested for oncogenic effects induced bladder tumors and not thyroid tumors. Most interestingly, 2-p-methoxybenzenesulfonamido-1,3,4-thiadiazole, which contains sulfonamide and thiadiazole moieties, induced bladder tumors but not thyroid tumors in rats within 18 months at concentrations as low as 0.6% in the diet.

The observed adverse kidney effects are most likely due to the sulfonamide portion of the subject chemical. Many sulfonamide-containing compounds have been shown to cause direct damage to the kidneys and N-acetylsulfonamide is known to precipitate in the kidneys.

Many thiadiazole-containing compounds are effective hypoglycemic agents; such a biologic activity could account for the clinical signs (lethargy, tremors, coldness to touch) observed in the exposed animals, especially those at the higher doses.

Considering that many sulfonamide-containing compounds have been shown to cause hematopoietic disorders (including anemia), the macrocytic anemia detected in the submitter's 90-day study in rats may have been due to a direct effect of the subject chemical on the blood cells. It is also possible that the observed anemia was secondary to kidney damage or adverse effects on the thyroid.

EPA has the following comments on Union Carbide's interpretation of the findings from the performed studies. First, the Agency disagrees with the statement that the deaths observed in the 14-day rat study may have resulted from the "severely depressed food intake." It is important to note that the time to death was 12-13 days for the male and female rats. EPA believes that this time frame is much too short for the rats to have died from starvation alone. This is especially true when one considers that the rats were showing toxic signs/symptoms (e.g., lethargy, tremors).

Second, EPA disagrees that a NOEL was established in the 90-day mouse study. It is an EPA scientific policy that a NOEL cannot be established without a complete histopathologic examination; such an examination was not conducted for the 90-day mouse study because it was terminated immediately after the company learned of the effects seen in the 90-day rat study. It is also important to point out that the only tissues examined microscopically from the 90-day rat study were those from animals in the two highest UC77179 dose groups (0.12% and 0.24%).

Third, EPA believes that on the basis of the provided data, the observance of thyroid adenomas in 3/30 high-dose group rats after only 90-days of exposure is both biologically and statistically significant. An analysis of control Fischer 344 rats in long-term biossays conducted by the National Toxicology Program (NTP) shows that the incidence of this type of tumor in this strain of rat is rare (22/2320 animals) even after two years of age.

Finally, EPA believes that the submitter's statements concerning EPA's interpretation of and policy toward thyroid tumor induction in experimental animals are incorrect. It is not EPA's present risk assessment policy to assume automatically that thyroid tumor induction (even when a tested chemical substance or mixture that adversely affects the thyroid is involved) represents a threshold phenomenon. A threshold can be ascribed only after all available evidence demonstrates conclusively that a chemical substance or

mixture that induces thyroid tumors acts solely by interfering with those hormones regulating the thyroid. Further, it should be noted that EPA does not believe that the present Section 8(e) submission presents any real evidence regarding the mechanism(s) of action by which UC77179 induced thyroid tumors in rats.

With regard to the submitted genotoxicity studies, the Agency is in agreement with the stated conclusions. UC77179 was found to be a direct acting mutagen (i.e., the chemical did not require exogenous metabolic activation) in an Ames Salmonella typhimurium (bacteria) assay and clastogenic (i.e., chromosome breaking) in cultured Chinese Hamster Ovary (CHO) cells in the presence of exogenous metabolic activation; UC77179 was found to be negative in the in vitro CHO cell Forward Gene Mutation Assay, the rat hepatocyte primary culture/DNA Repair Assay and the in vivo Bone Marrow Cytogenetics Assay in rats. Overall, however, the positive results in two of the performed studies do indicate that UC77179 has some degree of mutagenic potential.

Current Production and Use

Union Carbide reported non-confidentially that UC77179, which "was being studied as a possible candidate pesticide," has not been assigned a Chemical Abstract Service (CAS) Registry Number and is not on the TSCA Chemical Substance Inventory. With regard to the potential for exposure to UC77179, Union Carbide reported that during the research and development (R&D) activities with this chemical, "stringent handling and exposure protection and precautionary practices were required to be followed . . . "

Comments/Recommendations

It is very important to note that even though a threshold for tumor formation may be suspected and/or ultimately established for a chemical substance or mixture during formal risk assessment procedures, such threshold considerations should have no bearing on a respondent's TSCA Section 8(e)-applicability/reportability decisions. The reader's attention is directed to the Agency's TSCA Section 8(e) policy document ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978) which explains that immediately reportable "substantial risk" information includes any new evidence (e.g., evidence from an animal study) that offers reasonable support for a conclusion that a TSCA-covered chemical substance or mixture (including a chemical substance or mixture at the research and development stage) is capable of producing cancer.

a) The Chemical Screening Branch will ask Union Carbide to describe the nature and results of all studies (other than those reported in detail already to the Agency or those cited in the published scientific literature) about which Union Carbide is aware or that the company has conducted to determine the toxicity of UC77179.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of this alkylaminocarbonyl-substituted thiadiazole sulfonamide.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: DEC 12 1988

SUBJECT: Status Report* 8EHQ-1088-0764 S
FYI-OTS-1088-0645 S

Approved: 12/14/88

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

The Union Carbide Corporation has claimed the exact identities of the subject chemical substances to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will review all incoming correspondence regarding Union Carbide's substantiation of its CBI claims. In the "sanitized" versions of the Section 8(e) and FYI notices, the following non-confidential generic names were provided for three of the subject chemicals: "tolylcycloalkenyl substituted alkyl ester" (UC55248), "xylyl-cycloalkenyl substituted alkyl ester" (UC55304), and "cyanoalkyl phosphorodithioate" (UC70480). By phone, Union Carbide provided the following non-confidential generic name for a fourth chemical substance: "tolylcycloalkenyl substituted phosphorothioate ester" (UC63152).

Submission Description

In its TSCA Section 8(e) submission, Union Carbide submitted the final reports from teratologic studies of UC55248 (rabbits and rats), UC55304 (rats), and UC63152 (rats) as well as the final report from a "Chernoff Assay" of UC55248 (mice and rats); these studies had been conducted for Union Carbide by outside contract laboratories. In its "For Your Information" (FYI) submission (FYI-OTS-1088-0645 S), Union Carbide submitted final reports from teratologic studies of UC55248 and UC70480 in rats; these studies were conducted by Union Carbide at its own testing facility. Finally, Union Carbide provided (in its Section 8(e) submission) copies of two internal Union Carbide documents comparing the conduct and assessing the results of the UC55248 teratologic studies that had been conducted inside and outside Union Carbide.

In the cover letter to its Section 8(e) submission, Union Carbide provided the following information with regard to the conduct and results of the studies conducted with UC55248:

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"In the range-finding teratology study in rabbits. . . [dosed orally by gavage at doses of 50, 130, 320, 800 and 2000 mg/kg/day on days 6-27 of gestation, the contract laboratory] reported slight signs of maternal and embryo toxicity at 320 mg/kg/day. In the [second contractor-performed] teratology study in rats. . ., UC55248 administered in the diet at 50, 130, and 320 mg/kg/day [on days 6-19 of gestation for those females scheduled for Cesarean section and continuing from day 0-21 of lactation for the females scheduled to deliver pups for observation] apparently caused an increased incidence of total malformations, primarily bent ribs and tail abnormalities. The [contract laboratory's final] report concludes: 'Treatment with UC55248 induced a teratogenic response in Charles River COBS CD rats when administered in the diet at a dose level of 50 mg/kg/day or greater.' [In the third contractor-performed teratology study, UC55248, UC55304 or UC63152 was administered via the feed to pregnant rats at doses of 320 mg/kg/day (UC55248), 5, 130 or 320 mg/kg/day (UC55304) and 8, 20 or 50 mg/kg/day (UC63152) on days 6-19 of gestation.] . . . [With regard to UC55248, the contractor] reported increases only in bent ribs and variations reflecting incomplete skeletal ossification, but no teratogenic effects: 'In the absence of additional malformations, these data were considered [to be] indicative of a retardation in fetal development and not a teratogenic effect.' . . . [With regard to the Chernoff Assay of UC55248, the contractor's final report states that 'UC55248 produced extreme toxicity resulting in morbidity and mortality in CD-1 mouse dams exposed to 1,500.0 or 4,500.0 mg/kg/day, po [(gavage)], on gd [(gestation days)] 6-15. Exposure to UC55248 at 50.0 or 100.0 mg/kg/day, po, on gd 6-15 resulted in no evidence of maternal, fetal or neonatal mortality or toxicity in CD-1 mice. Exposure to UC55248 at 160.0 or 320.0 mg/kg/day, po, in CD rats on gd 6-19 produced evidence of maternal and transient neonatal toxicity.'"

Further with regard to UC55248, the FYI submission cover letter presents the following information about the conduct and results of a rat teratology study of UC55248 conducted by Union Carbide at its own testing laboratory:

"In this study [(which was conducted with UC55248 at dietary dose levels of 0, 8, 20, 50, 130, or 320 mg/kg/day on gestation days 6-20)], a statistically significant ($p < 0.05$) reduction in fetal body weight per litter at 20.0 and 8.0 mg/kg/day (two lowest doses) was observed in the absence of statistically significant maternal toxicity. The fetal weights at these doses were 94-95% of the control values; the maternal weight gain for the gestation period (gd 0-20 - dosed feed was available on gd 6-20) was also 93-95% of the control

> value, but maternal weight gain depression was not statistically significantly different (due to more variability for maternal weights versus fetal weights). Fetal weights were also reduced, to a greater extent, at higher doses so the effect is clearly dose related.
>
> "There were also caudal and anal defects [observed] in the fetuses at doses (130.0 and 320.0 mg/kg/day - two highest doses) which also produced maternal toxicity. The incidence of the fetal defects was not significantly increased, but these defects are not typical of those observed in control [Charles River COBS] CD rats. They are also not typical of rats exposed in utero to a number of different agents causing maternal toxicity and other indications of developmental toxicity such as reduced fetal weight, . . . [as cited in reviews found in the published scientific literature]."

In the cover letter to its Section 8(e) submission, Union Carbide provided the following summary information with regard to the conduct and results of the contract laboratory's teratology study of UC55304:

> ". . . [As cited previously,] UC55304 was administered in the diet of pregnant Charles River COBS CD rats at 50, 130, and 320 mg/kg/day [on days 6-19 of gestation]. . . . [The contractor] reported that UC55304 'caused a dose-related trend in maternal toxicity at the 130 and 320 mg/kg/day levels.' In addition, . . .[the contractor] reported that 'UC55304 was fetotoxic at 50 mg/kg/day and teratogenic at 130 and 320 mg/kg/day.'"

The "SYNOPSIS" section of the submitted final report from the contract laboratory's teratology study of UC55248, UC55304 and UC63152 via the feed in rats presents the following information with regard to UC63152:

> "In contrast to . . . [UC55248 and UC55304], UC63152 caused marked maternal toxicity at the highest dosage level (50 mg/kg/day) but had no definite effect on any of the Cesarean section parameters or on the occurrence of malformations or variations at any dosage level. Nine high dose rats died from gestation days 17 to 21. Many of the rats which died had erosions and black or brown material in the stomach. [The] mean maternal body weights and mean maternal food consumption in the high dose group were both moderately reduced relative to the control group. A slight body weight inhibition and a reduction in food consumption were the only test article effects present at the 20 mg/kg/day [dosage] level. In conclusion, . . . test article UC63152 had no teratogenic effect at dosage levels of 50 mg/kg/day and less."

The cover letter to Union Carbide's FYI submission presents the following information regarding the conduct and results of an internally conducted Union Carbide teratologic study in which UC70480 was administered to pregnant Charles River COBS CD rats by gavage at doses of 0.0, 5.0, 17.5 or 35.0 mg/kg/day on gestation days 6-15:

> "This [oral teratologic] study provides evidence of reduced fetal ossification at a dose (5.0 mg/kg/day-the lowest dose) which did not result in demonstrable maternal toxicity. . . . . This evidence of feto-toxicity was not associated with any reductions in fetal body weight or any other indication of develop-mental toxicity and no evidence of teratogenicity. There were no dose-related increases in fetal mal-formations. The incidence of litters with one or more fetuses with any malformations, categorized as total malformations, was increased at 17.5 mg/kg/day, but not at 35.0 mg/kg/day, and was not accompanied by any increase in the incidence of individual, or pooled external, visceral (including craniofacial) or skeletal malformations. This finding [was] not considered [to be] treatment related."

With regard to interpreting the results of the submitted teratological studies, Union Carbide provided the following information in the cover letter to the company's Section 8(e) submission:

> "Two of . . . [the tested] chemicals, UC55248 and UC55304, have identical chemical structures, except that the latter [(UC55304)] contains an additional methyl group. Under the test conditions, both com-pounds readily liberate 2-ethylhexanoic acid [(CAS No. 149-57-5)], a chemical which has produced teratogenic response[s] in laboratory animals.
>
> "The sponsoring scientists conclude that the fetal effects observed in the studies on UC55248 and UC55304 are attributable to the liberation of 2-ethylhexanoic acid under [the] test conditions. This conclusion is consistent with the fact that UC63152, which is chemi-cally similar to [both] UC55248 and UC55304 but does not contain or liberate 2-ethylhexanoic acid, did not produce teratogenic responses in an identical con-current test in the same [contract] laboratory."
>
> [NOTE: The reader's attention is directed to the first paragraph of the Comments/Recommendations section of this status report for information with regard to the ongoing assessment/testing-related activities for 2-ethylhexanoic acid (2-EHA) in EPA's Office of Toxic Substances (OTS).]

Finally, Union Carbide stated in its Section 8(e) submission that one of the submitted internal Union Carbide documents compares the conduct/results of the UC55248 teratology studies performed inside and outside Union Carbide. Union Carbide reported that this particular corporate document notes that "because of the maternal toxicity, UC55248 could not be termed a teratogen, according to . . . [the criteria published in 1975 by Staples and Wilson in Chapter 4 ("Definition of Teratogenesis and Teratogen") of Methods for Detection of Environmental Agents that Produce Congenital Defects (Editors: T. Shephard, J. Miller, M. Marois; North Holland Publishing Company; 1975)]." Union Carbide noted also, however, that because the malformations observed in the UC55248 studies "are not usually seen in studies where there is maternal and/or fetal toxicity," the submitted internal corporate report states that 'UC55248 produced these malformations not just in the presence of, but in addition to, maternal and other fetal toxicity.'"

Regarding the other submitted internal Union Carbide document, the company reported that although this document "notes the difficulties in interpreting the results of the various studies," the document "concludes that UC55248 appears to cause caudal and anal defects."

Submission Evaluation

The following review does not include a detailed section on study conduct for each individual study submitted. The reader should assume, therefore, that a study was conducted using a generally accepted protocol unless noted otherwise. The general study design for a standard teratology (developmental toxicity) study is as follows: groups of pregnant animals (usually, one control and three treated) are administered the test agent or vehicle over the major period of organogenesis (usually days 6-15 of gestation for rodents and 6-18 for rabbits). The standard number of pregnant animals per group is 20 rodents and 12 rabbits. In a range-finding study, more dose levels are added with fewer animals included per group. The pregnant animals are examined daily for clinical signs and are weighed periodically; food consumption is also measured periodically. The pregnant animals are sacrificed just prior to term and subjected to necropsy. The uterus is excised, usually weighed, and the following parameters are assessed: number of implantation sites, number of resorptions, number of live/dead fetuses, number of corpora lutea, fetal body weight and sex ratio. All fetuses are examined for external malformations or variations. A portion of the fetuses are examined for visceral malformations/variations and the remaining fetuses are examined for skeletal malformations/variations. In a range-finding study, only a limited number of parameters are evaluated at the time of sacrifice and the fetuses are not examined for visceral and skeletal effects.

The general study design for a "Chernoff Assay" (i.e., Chernoff/Kavlock Assay (Preliminary Developmental Toxicity Screen)) is

similar to the standard teratology study up until the point of sacrifice. Instead of sacrificing the pregnant animals prior to term, in a Chernoff/Kavlock Assay, the animals are allowed to deliver their offspring and the only measurements made usually are weighing and counting the offspring on the day of birth (day 1 postnatally) and day 4 postnatally.

REVIEW OF RESULTS FOR UC7Ø48Ø

In the submitted UC7Ø48Ø study, there were no treatment-related effects on maternal body weight and body weight gain. There was an increased incidence of perioral wetness in the 17.5 and 35 mg/kg/day groups. At sacrifice there were no treatment-related differences in maternal body weight, corrected body weight (body weight minus gravid uterine weight), gravid uterine weight or absolute or relative liver weight.

With regard to developmental effects, there was no effect on the number of corpora lutea per dam, the total number of live/dead implantations per litter, pre- and post-implantation loss, sex ratio or fetal body weight. Further, there were no dose-related differences in the incidence of external or visceral malformations/variations or skeletal malformations. However, there was a dose-related statistically significant increase in the incidence of skeletal variations across all treatment groups, largely in the form of reduced ossification. In addition, there was a statistically significant increase in the total malformations at 17.5 mg/kg/day, but not 35 mg/kg/day; this may be due to slight, non-dose-related increases in the incidence of certain external and visceral malformations.

REVIEW OF RESULTS FOR UC63152

Each group in the performed study consisted of 2Ø mated females, all of which which were sacrificed on gestation day 2Ø. The control and high dose groups included an additional 1Ø mated females that were allowed to deliver and the offspring were maintained for 4 weeks postweaning. The test article was administered in the diet from day 6 through day 19 of gestation.

With regard to maternal effects, 9 rats died between days 17 and 21 of gestation. Prior to death, the animals were emaciated, pale, inactive and cool to the touch. At necropsy, these animals had black/brown material in and erosions of the stomach. There was a dose-related decrease in maternal body weight and food consumption (i.e., there was a significant decrease at 5Ø mg/kg/day and a slight decrease at 2Ø mg/kg/day). There were significant decreases in corrected body weight at 2Ø and 5Ø mg/kg/day.

In terms of developmental effects, there were no treatment-related effects on parameters evaluated at the time of Caesarean section nor were there any treatment-related effects on the incidence of malformations and variations.

With regard to postnatal effects, 4 dams delivered 51 pups, 2 of which were nonviable and 3 died by day 21. In addition, one pup had loss of righting reflex. Further, there was a slight decrease in litter weight on days Ø and 7 postnatally.

REVIEW OF RESULTS FOR UC55304

As in the case of the study on UC63152, each group in the UC55304 study consisted of 2Ø mated females which were all sacrificed on day 2Ø of gestation. The control and high dose groups included an additional 1Ø mated females which were allowed to deliver and the offspring were maintained for 4 weeks postweaning. The test agent was administered in the diet from day 6-19 of gestation.

With regard to maternal effects, there was an increased incidence of clinical signs (hair loss; red or black anogenital staining) in the 32Ø mg/kg/day group. There was a dose-related decrease in in body weight, body weight gain and corrected body weight in the 13Ø and 32Ø mg/kg/day groups. In addition, there was a slight reduction in maternal body weight during the period of days Ø-7 postnatally; however, these data were based on only two animals. Further, there was a dose-related decrease in food consumption in the 13Ø and 32Ø mg/kg/day groups.

In terms of developmental effects, at 32Ø mg/kg/day, 13 out of 17 gravid dams had total litter loss (resorptions or dead fetuses). Consequently there was a significant increase in postimplantation loss and a significant decrease in the number of live fetuses. Most of the deaths occurred as early resorptions. The exposure to 13Ø mg/kg/day had a similar but less severe effect. Although postimplantation loss and number of live fetuses were markedly different from control values, the values were not statistically different. Unlike the high dose group, total litter losses did not occur at 13Ø mg/kg/day. Further, there was a dose-related decrease in fetal body weight with all treatment group values being lower than the historical control range; however, only the mid and high dose groups were found to be statistically significantly different from the concurrent control values. The mean numbers of corpora lutea and total implantation sites were comparable across all groups. In addition, there was a dose-related increase in the number of fetuses and litters with fetuses with bent ribs in all treatment groups and all values were higher than those of the historical controls. All of the litters in the high dose group were affected. In the 5Ø mg/kg/day group, one fetus had bent bones and another a tail anomaly, while at 13Ø and 32Ø mg/kg/day, there was a dose-related increase in the incidence of several malformations. These included anasarca, gastroschisis, malpositioned limbs, bent tail, vertebral anomalies, fused ribs, and sternoschisis. Nearly all incidences were beyond those of the historical control ranges. All of the litters in the high dose exhibited bent ribs, bent bones, anasarca and gastroschisis. Although the sample size in the high dose group was small, as a result of the high in utero mortality, the high incidence of malformed fetuses (85.7%) and litters (1ØØ%) indicate that the

data have biological significance and are not likely to be due merely to chance. All treated groups exhibited a moderate to marked increase in the number of fetuses and litters with fetuses with reduced skeletal ossification. The bones most frequently involved were the sternebrae, vertebrae, pubis, and skull bones. Although there was not always a dose-related effect, these effects are viewed as being biologically significant and the reductions in ossification are undoubtedly treatment-related.

With regard to postnatal effects, there were only 2 dams that produced a total of 6 pups. Of the 6, 2 were nonviable at birth and 2 died the day after birth. One of the nonviable pups had gastroschisis. No body weight comparisons were made on the surviving 2 pups.

REVIEW OF RESULTS FOR UC55248

This section relates to the findings from the 3 standard studies and the Chernoff/Kavlock Assay (all conducted in the rat), the Chernoff/Kavlock Assay conducted in the mouse, and the range-finding study conducted in the rabbit.

RABBIT

With regard to the range-finding study in rabbits, each dose group consisted of 5 artificially inseminated rabbits. Exposure occurred during days 6-27 of gestation. Four animals in the 2000 mg/kg/day group and 2 animals in the 800 mg/kg/day group died; in addition, one animal in the 800 mg/kg/day group was sacrificed in extremis. Prior to death, these animals were emaciated and displayed reduced activity and anogenital matting of the fur, and had reduced fecal material. At necropsy, there was evidence of gastrointestinal irritation in 2 animals each in the 800 and 2000 mg/kg/day groups. Two additional animals in the 800 mg/kg/day group aborted and displayed clinical signs. At both the 800 and 2000 mg/kg/day levels, there was marked maternal body weight loss prior to death or abortion. There were no treatment related maternal effects at the levels of 320 mg/kg/day and lower.

Regarding developmental effects, the following values were found to be comparable across the 50, 130 and 320 mg/kg/day groups: number of live fetuses, total implantations, and number of corpora lutea. The single dam in the 800 mg/kg/day group that had to be sacrificed and one dam in the 320 mg/kg/day group had whole litter resorptions. There were 4 early resorptions of 6 total implantations in one dam in the 130 mg/kg/day group.

MICE

In terms of maternal effects, all of the mice exposed to 1500 or 4500 mg/kg/day were moribund or dead by the first or second day of treatment and were sacrificed. There were no statistically significant maternal effects for the animals exposed to 50 or 100 mg/kg/day.

With regard to developmental effects, there were no statistically significant effects on the number of implantation sites, number of live pups, or mean pup body weight on days 1 or 4 postnatally, or on percent of prenatal or postnatal loss in the 50 and 100 mg/kg/day groups.

RATS (4 studies)

In terms of maternal effects, there was no maternal mortality. There was reduced body weight, body weight gain, and food consumption at 130 and 320 mg/kg/day. In addition, the study that was conducted by Union Carbide's laboratory showed such decreases at 50 mg/kg/day. Gravid uterine weight was reduced at 130 and 320 mg/kg/day.

With regard to developmental effects in general, there was no effect on number of corpora lutea, total implantations, number of live fetuses, or sex ratio. There was a statistically significant reduction in fetal body weights found at all treatment levels. The Union Carbide laboratory reported a reduction in crown-rump length in all treated groups, as well. There was an increased incidence of malformations in all treatment groups. The incidence of bent ribs was increased at all dose levels (statistically significantly in Union Carbide's laboratory study) and the incidence of caudal and anal defects was increased in both the 130 and 320 mg/kg/day groups. The bent ribs and caudal/anal defects, while not always statistically significantly increased, were markedly above those of historical control values and were observed in three different studies conducted by two different laboratories. Therefore, the findings are considered by EPA to be biologically significant. In addition, there were significant reductions in skeletal ossification at all dose levels. Further, it should be noted that Union Carbide's laboratory study showed a significant increase in the incidence of several soft tissue variations, specifically ecchymosis of the cranial region (significant at 320 mg/kg/day) and bi-lobed apex of the heart (significant at both 130 and 320 mg/kg/day).

With regard to postnatal effects, in the Chernoff/Kavlock assay, there was a dose-related increase in the mean gestational length with the value from the 320 mg/kg/day group being significantly higher than that of control animals. In the contractor's second study, there was a dose-related increase in length of gestation but it did not reach statistical significance due possibly to the small number of animals (3-4) per group. In all three of the postnatal studies, pup body weights were significantly reduced at birth at levels of 130 mg/kg/day and greater. In the contractor's second study, the pup body weights remained significantly reduced throughout lactation and for four weeks postweaning in the 130 and 320 mg/kg/day dose groups. In the contractor's third study, pup body weights were decreased prior to weaning but were found to be comparable to those of the control animals after weaning. In the Chernoff/Kavlock Assay, body weights were significantly decreased only for the female pups and only at 160 but not 320

mg/kg/day on day 4 postnatally (the only time other than the day of birth that pup body weights were measured). The contractor's second study showed a significant reduction in pup survival index on day 4 postnatally for the 320 mg/kg/day group.

OVERALL DISCUSSION

In reviewing the submitted studies, it became clear to EPA that there are many areas that need further discussion other than the presentation/evaluation of the results of the studies supplied.

SUMMARY OF THE DATA

Overall, the submitted data show that 1) UC55248 and UC55304 are maternally and developmentally toxic, 2) UC63152 is maternally toxic but not developmentally toxic, and 3) UC70480 is developmentally toxic but not maternally toxic, although there was an increased incidence of perioral wetness observed in the maternal animal. Considering that this was the only finding, it was not considered biologically significant enough to characterize this chemical (UC70480) as causing maternal toxicity.

Based on various data from the submitted studies, the lowest-observed-adverse-effect-levels (LOAELs) and the no-observed-adverse-effect-levels (NOAELs) for each chemical are listed in the following table. It should be noted that data from the Chernoff/Kavlock Assay were not used to establish any NOAELs because only a limited number of end points are evaluated in that particular study; the study is designed merely to help prioritize chemicals for further testing and is not designed to provide "hard and fast" values for use in formal risk assessment.

	Maternal Toxicity (mg/kg/day)		Developmental Toxicity (mg/kg/day)	
Chemical	LOAEL	NOAEL	LOAEL	NOAEL
UC55248	50	NE*	50	NE
UC55304	130	50	50	NE
UC63152	20	8	>50	50
UC70480	>35	35	5	NE

*NE: Not Established

The data on UC55304, UC63152, and UC70480 were all derived from one study each and in one species each. On the other hand, the data on UC55248 were derived from two standard teratology studies

conducted in the rat performed at two different laboratories, one teratology study in the rat conducted at only a single high dose level, one Chernoff/Kavlock Assay conducted in the rat and mouse and one range-finding teratology study conducted in the rabbit. As a Union Carbide scientist noted in great detail in one of the submitted internal company documents, there is great concordance in the findings among the rat studies, regardless of study design and site of study. This serves to increase the confidence EPA has in the submitted data.

MATERNAL TOXICITY AND DEVELOPMENTAL TOXICITY

Over the years, there has been continued debate with regard to the role of maternal toxicity on developmental toxicity. There are a number of individuals who have taken the position that if a chemical is developmentally toxic at a maternally toxic dose, the substance should not be considered a developmental toxicant. It is EPA's position, however, that developmental effects cannot be dismissed as being secondary to maternal toxicity. Furthermore, currently available information is inadequate to allow one to assume that developmental effects at maternally toxic doses result only from maternal toxicity. In support of EPA's position in this matter, it should be noted that numerous studies have been conducted in which there was severe maternal toxicity and yet there was no evidence of developmental toxicity. In fact, the submitted study on UC63152 illustrates this point very well. Although 9/20 mated rats died at the high UC63152 dose, and there were significant effects on body weight at the mid and high dose levels, there were no treatment-related effects observed for 1) any developmental parameters evaluated at the time of Caesarean section, or 2) the incidence of fetal malformations/variations.

DIFFERENCES IN INTERPRETATION OF FINDINGS

In the studies conducted with UC55248, there was much discussion on the question of whether bent ribs should be classified as variations or malformations. (In two of the submitted studies, bent ribs are referred to as malformations, in another study, they are referred to as variations, and in still another study, they are referred to as both malformations and "deviations.") The point remains, however, that this particular end point was seen in three different studies and in a dose-related manner. Further, it does not matter whether bent rib is classified as a variation or a malformation because EPA regards both variations and malformations as signs of developmental toxicity. This point also comes into play in interpreting the results of the submitted study on UC70480 where the only adverse effect observed was a significant increase in the incidence of variations, specifically decreased skeletal ossification. The FYI submission cover letter refers to this finding as an indicator of fetal toxicity and goes on to state there was no evidence of teratogenicity. EPA, on the other hand, believes that no distinction should be made between teratogenicity and fetotoxicity; rather, EPA regards these as subsets of the broad term of developmental toxicity.

DEVELOPMENTAL TOXICITY DUE TO 2-ETHYLHEXANOIC ACID

In the cover letter to the Section 8(e) submission, it is stated that the sponsors concluded that the developmental effects of UC55248 and UC553Ø4 are due to the liberation of 2-ethylhexanoic acid, a demonstrated developmental toxicant. In addition, this cover letter states that UC63152, which is structurally similar to UC55248 and UC553Ø4 but does not contain nor liberate 2-ethylhexanoic acid, does not produce "teratogenic responses." The specific developmental effects caused by UC55248 and UC553Ø4 are different than those seen in studies submitted thus far to the Agency on 2-ethylhexanoic acid; however, a different strain of rat was used in those studies. In addition, it is important to note that the effects caused by UC55248 and UC553Ø4 while similar in some respects, were quite different in others. Therefore, it is difficult for EPA to agree that 2-ethylhexanoic acid alone is responsible for the observed effects; the possibility remains that the parent compounds and/or other metabolites may be the putative developmental toxicant(s). It is also interesting to note that, in the Chernoff/Kavlock Assay, the length of gestation was significantly increased for UC55248. Of the several hundred chemicals that have been tested in this assay to date, the only other chemicals shown to increase the length of gestation are valproic acid (2-propyl pentanoic acid) and 2-ethylhexanoic acid.

Current Production and Use

In its TSCA Section 8(e) and FYI submissions, Union Carbide reported non-confidentially that UC55248 (the tolylcycloalkenyl substituted alkyl ester), UC553Ø4 (the xylylcycloalkenyl substituted alkyl ester), UC7Ø48Ø (the cyanoalkyl phosphorodithioate) and UC63152 were experimental pesticide chemicals. In addition, Union Carbide reported non-confidentially that UC55248, UC553Ø4 and UC7Ø48Ø do not have CAS numbers and are not listed on the TSCA Chemical Substance Inventory. Union Carbide did not provide any non-confidential information pertaining to the TSCA Inventory status of UC63152.

Comments/Recommendations

It is important to note that the Test Rules Development Branch and the Risk Analysis Branch (TRDB and RAB/ECAD/OTS/OPTS/EPA) have been reviewing available toxicologic and exposure data on 2-ethylhexanoic acid (2-EHA), a chemical substance recommended by the Interagency Testing Committee (ITC) for testing pursuant to Section 4 of TSCA. Further, EPA has published TSCA Section 8(a) and 8(d) information gathering rules on 2-EHA. Also, EPA has received a number of TSCA Section 8(e) and FYI notices on 2-EHA.

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Union Carbide will be asked to describe the actions the company has taken or plans to take 1) to notify workers and others about the

reported findings, and 2) to reduce/eliminate exposure to the subject chemical substances. Union Carbide will be asked also to describe the nature and results, if available, of all studies (other than those reported already to the Agency or those cited in the published scientific literature) about which Union Carbide is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of the subject chemical substances.

b) Staff of the Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemicals.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OW/EPA, OSWER/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA, and TRDB and RAB/ECAD/OTS/OPTS/EPA; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: DEC 19 1988

SUBJECT: Status Report* 8EHQ-1188-0765 S Approved: 12/19/88

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

The submitting company has claimed its company name and the exact identity of the subject chemical to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will review all incoming correspondence relating to the company's substantiation of these CBI claims. In the "sanitized" version of the submission, the company stated non-confidentially that the subject chemical substance is an "aryl oxime."

Submission Description

The submitting company provided the following information with regard to the conduct and preliminary results of a "pilot" oral teratology study of this aryl oxime in rats:

> "In this study, the aryl oxime was administered by gavage to 6 groups of mated female rats at dose levels of 0, 75, 150, 250, 500 and 1000 mg/kg/day during gestation days 6-15. Surviving dams were sacrificed on gestation day 20. Fetuses were removed, weighed, sexed and examined for possible external malformations.
>
> "All 8 animals at 1000 mg/kg/day and 1/8 animals at 500 mg/kg/day died during the study. Maternal weight gain was substantially decreased at 500 and 250 mg/kg/day and slightly decreased at 150 mg/kg/day. There were no viable fetuses in the living dams at 500 mg/kg/day. An increase in post-implantation loss and a decrease in fetal weights were noted at $\geq$150 mg/kg/day. In addition 3 fetuses from 2 litters at 250 mg/kg/day exhibited rare limb defects (short legs, short and/or missing fingers). These defects were observed in fetuses that were extremely light in weight but the reduced fetal weight is not believed to have contributed to the defects."

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Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon EPA's receipt of a full copy of the final report from the oral "pilot" teratology study cited in the company's submission. In the interim, however, it should be noted that the submitted summary information, which includes several data tables, does provide evidence for the maternal and developmental toxicity of this aryl oxime.

All maternal animals in the highest dose (1000 mg/kg/day) group died before the end of the study. Although only one animal died at the next highest dose (500 mg/kg/day), no animals at this dose level produced any viable fetuses. At 250 mg/kg/day, 6/8 maternal animals did have viable fetuses. A trend for decreased maternal weight gain with increasing dose was apparent at all dose levels and statistical significance was reached for overall changes and for several specific time intervals at 250 and 500 mg/kg/day.

In the 150, 250 and 500 mg/kg/day dose groups, there were trends for dose-dependent decreases in fetal viability and increases in early resorptions and post-implantation loss. At the two higher doses (250 and 500 mg/kg/day), the early resorptions and post-implantation loss represented statistically significant changes. Fetal weights were significantly reduced at 150 and 250 mg/kg/day with a trend extending to the 75 mg/kg/day dose group; as stated previously, there were no live fetuses in the 500 and 1000 mg/kg/day groups.

External malformations were seen in 3 fetuses from 2 litters at 250 mg/kg/day. These external malformations included micromelia, brachydactyly, microphthalmia and/or anophthalmia, adactyly and open eye lid(s). As expected for a typical "pilot" teratology study, no examination appears to have been performed for fetal soft tissue or skeletal abnormalities.

Current Production and Use

In view of the submitter's TSCA CBI claims, no information with regard to the TSCA Chemical Substance Inventory status or use(s) of the subject chemical will appear in this status report. The submitter reported non-confidentially, however, that this aryl oxime "is currently being manufactured and used exclusively for R&D [(research and development)] purposes."

Comments/Recommendations

a) The Chemical Screening Branch will ask the submitter to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, results of gross and histopathological examinations, results of any statistical analyses, etc.) from the "pilot" oral teratology study in rats that was cited in the company's Section 8(e) submission.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, the submitter will be asked to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported information, and 2) to reduce or eliminate exposure to this aryl oxime. In addition, the submitter will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of this aryl oxime.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: DEC 19 1988

SUBJECT: Status Report* 8EHQ-1188-0766 S Approved: JDK 12/19/88

FROM: James F. Darr, Section Head James F. Darr
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

The submitting company has claimed its company name and the exact identity of the subject chemical to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will review all incoming correspondence concerning the company's substantiation of these TSCA CBI claims. In the "sanitized" version of the submission, the company stated non-confidentially that the subject chemical is a "heteroaryl alkyl ether."

Submission Description

The submitting company provided the following information with regard to the conduct and preliminary results of a "pilot" oral teratology study of this heteroaryl alkyl ether in rats:

> "In this [teratology] study, the heteroaryl alkyl ether was administered by gavage to 6 groups of mated female rats at dose levels of 0, 50, 100, 150, 250, and 450 mg/kg/day during gestation days 6-15. Surviving dams were sacrificed on gestation day 20. [The] fetuses were removed, weighed, sexed and examined for possible external malformations.
>
> "Three of eight females at 450 mg/kg/day died during the study and there were no viable fetuses in the surviving animals. Decreased maternal weight gain and an increase in post-implantation loss was observed at dose levels $\geq$ 100 mg/kg/day. Fetal weights were reduced in all treated groups. External malformations were also noted in all treated groups. The defects observed at the higher dose levels included umbilical hernias and omphalocele."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon EPA's receipt of a complete copy of the final report from the oral "pilot" teratology study cited in the company's TSCA Section 8(e) submission. In the interim, however, it must be noted that the submitted summary information, which includes a number of data tables, does provide evidence for the maternal and developmental toxicity of this heteroaryl alkyl ether.

In the high dose group (450 mg/kg/day), 4 maternal animals died or were sacrificed in a moribund condition prior to scheduled necropsy. Of the 4 remaining animals, none had any viable fetuses. Further, there were statistically significant decreases in gestational weight gain for maternal animals at 100, 150, 250 and 450 mg/kg/day.

The number of viable fetuses per litter was inversely related to dose. These decreases were statistically significant at all doses except the lowest dose (50 mg/kg/day). In addition, there were corresponding dose-dependent increases in early and late resorptions as well as post-implantation loss. The frequencies of both the early resorptions and post-implantation loss were statistically significant at the 3 highest dose levels (i.e., 150, 250 and 450 mg/kg/day). Further, the fetal weights were significantly ($p<0.01$) reduced from control values at all doses tested except the high dose (as there were no viable fetuses in the high dose group).

Several types of external fetal abnormalities were observed, most notably umbilical herniation of the intestines and omphalocele. The frequencies of umbilical herniation at different doses were as follows: 2 fetuses from 2 litters at 100 mg/kg/day, 1 fetus from 1 litter at 150 mg/kg/day, and 2 fetuses from 2 litters at 250 mg/kg/day. Omphalocele was observed in 2 fetuses from 1 litter at 100 mg/kg/day, 9 fetuses from 5 litters at 150 mg/kg/day (statistically significant at $p<0.05$), and 4 fetuses from 3 litters at 250 mg/kg/day. As expected for a typical "pilot" teratology study, no examination appears to have been conducted for fetal soft tissue or skeletal abnormalities.

Current Production and Use

In view of the submitter's TSCA CBI claims, no information about the TSCA Chemical Substance Inventory status or use(s) of this heteroaryl alkyl ether will appear in this status report. The submitting company reported non-confidentially, however, that this heteroaryl alkyl ether "is currently being manufactured exclusively for R&D [(research and development)] purposes."

Comments/Recommendations

a) The Chemical Screening Branch will ask the submitter to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, the results of gross/histopathological examinations, the results of statistical analyses, etc.) from the "pilot" oral teratology study in rats cited in the company's TSCA Section 8(e) submission.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, the submitter will be asked to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported information, and 2) to reduce or eliminate exposure to this heteroaryl alkyl ether. In addition, the submitter will be asked to describe the nature and results, if available, of all studies (other than those reported already to the Agency or those cited in the open scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of this heteroaryl alkyl ether.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: DEC 19 1988

SUBJECT: Status Report* 8EHQ-1188-0767 S

Approved: JDK 12/19/88

FROM: James F. Darr, Section Head James F. Darr
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

The submitting company has claimed its company name and the exact identity of the subject chemical to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will be reviewing all incoming correspondence from the submitting company regarding substantiation of these CBI claims. In the "sanitized" version of its Section 8(e) notice, the submitting company stated non-confidentially that the subject chemical is a "haloalkyl heterocycle."

Submission Description

The submitting company provided the following information with regard to the conduct and preliminary results of a "pilot" oral teratology study of this haloalkyl heterocycle in rats:

> "In this [teratology] study, the haloalkyl heterocycle was administered by gavage to 6 groups of mated female rats at dose levels of 0, 50, 100, 200, 400 and 800 mg/kg/day during gestation days 6-15. Surviving dams were sacrificed on gestation day 20. [The] fetuses were removed, weighed, sexed and examined for possible external malformations.
>
> "All eight females at 800 mg/kg/day died during the study. No maternal mortality occurred at 400 mg/kg/day but dams at this level exhibited significant weight loss and/or reduced weight gain. No maternal toxicity was evident at 200 mg/kg/day.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

"Post-implantation loss was moderately increased at 200 mg/kg/day and substantially increased at 400 mg/kg/day. Reduced fetal weights were also evident at both of these dose levels. Umbilical hernias were noted in one fetus at 100 mg/kg/day and 8 fetuses (4 litters) at 200 mg/kg/day. The 10 viable fetuses at 400 mg/kg/day did not exhibit any external malformations."

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon EPA's receipt of a complete copy of the final report from the oral "pilot" teratology study cited in the company's submission. In the interim, however, it should be noted that the submitted summary information, which includes several data tables, does provide evidence for the maternal and developmental toxicity of this haloalkyl heterocycle.

All maternal animals treated with 800 mg/kg/day died during the study. Although all maternal animals in the 400 mg/kg/day dose group survived, they had significant weight loss or reductions in weight gain. No apparent maternal toxicity was observed after treatment with doses of $\leq$200 mg/kg/day.

At 400 mg/kg/day, only 1 dam produced viable fetuses; 3 animals at this dose were nongravid and 4 had resorptions. At 200 mg/kg/day, there was a statistically significant ($p<0.05$) decrease in mean fetal weight. In addition, post-implantation loss was found to be increased among the litters at 200 mg/kg/day (a mean of 2.4/litter as opposed to 1.0/litter in the controls).

At 200 mg/kg/day, 8 fetuses from 4 litters were found to have umbilical herniation of the intestines. This same defect was seen in 1 fetus at the next lowest dose (100 mg/kg/day) but not in any of the control or low dose (50 mg/kg/day) fetuses. As expected for a typical "pilot" teratology study, no examination appears to have been performed for fetal soft tissue or skeletal abnormalities.

Current Production and Use

In view of the submitter's TSCA CBI claims, no information about the TSCA Chemical Substance Inventory status or use(s) of this haloalkyl heterocycle will appear in this status report. The submitter stated non-confidentially, however, that this haloalkyl heterocycle "is currently being manufactured exclusively for R&D [(research and development)] purposes."

Comments/Recommendations

a) The Chemical Screening Branch will ask the submitter to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, the results of gross and histopathological examinations, the results of statistical analyses, etc.) from the "pilot" oral teratology study in rats that was cited in the company's TSCA Section 8(e) submission.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, the submitter will be asked to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported information, and 2) to reduce or eliminate exposure to this haloalkyl heterocycle. In addition, the submitter will be asked to describe the nature and results, if available, of all studies (other than those reported already to the Agency or those cited in the open scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of this haloalkyl heterocycle.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: DEC 29 1988

SUBJECT: Status Report* 8EHQ-1188-0768 S Approved: Barbara Cotton

DEC 29 1988

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

The Eastman Kodak Company has claimed the exact identity of the subject chemical to be TSCA Confidential Business Information (TSCA CBI); the Information Management Division (IMD/OTS) will be reviewing all incoming correspondence pertaining to the company's substantiation of this CBI claim. According to the "sanitized" (i.e., non-confidential) version of the Section 8(e) submission, the subject chemical is an "inorganic potassium halide complex."

Submission Description

The Eastman Kodak Company provided the final report of an acute oral toxicity study of this inorganic potassium halide complex in rats. The company's cover letter presents the following information with regard to the conduct and results of the study:

> "In an acute oral toxicity study, estimated oral LD50 values of 769 mg/kg and 544 mg/kg were obtained in male and female rats, respectively. All animals receiving doses of 1250 mg/kg or more died before scheduled study termination. A dose of 625 mg/kg was also lethal to a portion of the treated animals.
>
> "At the 1250 mg/kg dose level, gross treatment-related changes in [those] animals dying within three days of treatment included hemorrhage, edema, and necrosis of the glandular gastric mucosa, green contents in the small intestines and cecum, pale kidneys, enlarged and discolored livers, and yellow discoloration of the inguinal hair. [The] microscopic lesions in the kidneys

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

included diffuse necrosis of the proximal convoluted epithelium, granular and epithelial casts in the proximal and distal tubules, and granular casts in the glomerulus (females only). Microscopic liver lesions included diffuse necrosis, hemorrhage (males only), and lipoid degeneration (males only) of the centrilobular or mid-zonal hepatocytes.

"At 612 mg/kg, [the] gross treatment-related changes seen in one or more animals dying within three days of treatment included hemorrhage in the glandular gastric mucosa, yellow, enlarged, mottled livers, dark, enlarged adrenal glands, and hydroperitoneum in the abdominal cavity. Microscopic liver lesions included diffuse necrosis, hemorrhage, and lipoid degeneration of the centrilobular or mid-zonal hepatocytes. Lesions of the adrenal glands, seen in one female [rat] only, included diffuse necrosis and hemorrhage in the zona fasciculata. No kidney lesions were observed. Treatment-related changes in the four males and two females which survived the 14-day observation period consisted of pale (2/4 males, 1/2 females) and enlarged (1/2 females) kidneys.

"The only treatment-related change in the 312 and 156 mg/kg dose groups consisted of pale kidneys in one 312 mg/kg male. All animals in these two groups survived the 14-day observation period.

"Animals in the 625 and 312 mg/kg dose groups which had gross treatment-related lesions and which survived the 14-day observation period showed regeneration of the proximal convoluted tubule epithelium."

In its submission, Eastman Kodak also provided the final results of an acute dermal toxicity study in rats, an acute dermal irritation study in rabbits, an acute eye irritation study in rabbits and a dermal sensitization study in guinea pigs. The submitted cover letter provides the following information regarding the results of these additional acute toxicity studies:

"When applied to the skin, the test article had an estimated acute lethal dose of greater than 2000 mg/kg for rats and did not produce abnormal clinical signs. The test article was, at most, a slight skin irritant [in rabbits], and it was not a skin sensitizer [in guinea pigs]. When placed in the [rabbit] eye, the test article produced strong irritation. Immediate irrigation of the eye following exposure to the test article was beneficial and significantly reduced the irritation."

Eastman Kodak also provided the following information summarizing the results of all of the submitted acute toxicity studies:

"In summary, the test article produced liver and kidney damage at moderate to high oral doses which were also associated with gastric damage. High dermal doses of the test article did not result in similar effects. The test article was not a skin sensitizer and was only a slight skin irritant, but it may cause strong eye irritant if not promptly washed out of the eye."

Submission Evaluation

Based on the reported acute rat oral LD5Ø values of 769 mg/kg (males) and 544 mg/kg (females), the subject chemical would be classified as being moderately toxic. Of particular concern in the submitted acute oral toxicity study are the adverse effects on the kidney, liver and adrenal glands. The oral administration of 612 mg/kg resulted in hemorrhage in the glandular mucosa, enlarged, mottled livers and dark, enlarged adrenal glands. Microscopically, the observed liver lesions included diffuse necrosis, hemorrhage and lipoid degeneration of the centrilobular or midzonal hepatocytes. These effects were seen in one or more of the animals that died during the study. It should be noted also that although no adverse kidney effects were observed in any 612 mg/kg dose group animals that died during the study, such effects were found in surviving animals from that dose group (pale kidneys in 2/4 males and 1/2 females; enlarged kidneys in 1/2 females). All animals receiving 312 or 156 mg/kg survived until study termination and only 1 male (in the 312 mg/kg group) was found to have treatment-related effects (pale kidneys). In addition, it should be noted that although proximal convoluted tubule epithelial regeneration was observed in the animals that survived the 312 and 625 mg/kg dose levels in this acute oral study, EPA's overall concern for kidney toxicity is not mitigated. While it is quite beneficial for EPA to know that repair can occur following kidney injury caused by acute exposure, there is no currently available evidence that consecutive short-term exposures or a long-term exposure would yield similar regenerative activity. Until such evidence is presented, EPA's concern for kidney toxicity remains.

With regard to the other reported toxicity studies, the subject chemical appears to be a slight skin irritant, a non-sensitizer and a strong ocular irritant.

Current Production and Use

In view of the submitter's TSCA CBI claim, no information with regard to the TSCA Chemical Substance Inventory status or use(s) of the subject chemical will appear in this status report. In its Section 8(e) submission, Eastman Kodak provided the following non-confidential information concerning the manufacture of and the potential for workplace exposure to this inorganic potassium halide complex:

"This substance has been synthesized and used only in small quantities for research and development purposes. It is being evaluated for potential limited (less than 1Ø kg/yr) use in the manufacturing operations within the company. . . .[The Eastman Kodak Company is] not aware of any adverse health problems associated with its manufacture or its use to make the final product. The chemical was originally evaluated as health hazards unknown. Such a rating is accompanied by a statement to avoid all contact. Based on the acute toxicity testing, employees will be required to wear company-supplied clothing, gloves, and safety glasses when working with this material. A hood, glove box, or vented enclosure will be used to weigh out material."

Comments/Recommendations

In its submission, Eastman Kodak reported non-confidentially that the company 1) is considering the need for further toxicological testing of the subject chemical, and 2) has updated the Material Safety Data Sheet (MSDS) to reflect the reported acute toxicity findings. A non-confidential version of this updated MSDS was included in Eastman Kodak's submission.

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity/exposure data, Eastman Kodak will be asked to describe the nature and results, when available, of all studies (other than those reported already to EPA) that the company conducts to determine the toxicity of this organic potassium halide complex.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OW/EPA, OSWER/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: DEC 9 1988

SUBJECT: Status Report* 8EHQ-1188-0769

Approved: 12/9/88

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB/ECAD

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The CIBA-GEIGY Corporation provided a written followup report concerning an incident that occurred in late October 1988, and involved a release of polychlorinated biphenyl (PCB; CAS No. 1336-36-3) oil (44% Aroclor 1260) from a transformer at the company's plant site in Toms River, New Jersey. According to CIBA-GEIGY, the release occurred "after an unrelated electrical fire in the proximity" of the transformer and was reported by phone and/or in writing under a number of mandatory State and Federal authorities (including CERCLA (i.e., "Superfund") and Section 8(e) of TSCA) "before the amount and extent of the PCB leakage were fully known." CIBA-GEIGY stated further that the release was determined later to have involved less than one (1) gallon of PCB oil and "occurred at the ceramic bushings that had apparently gotten hot from the heat of the electrical fire and cracked when subjected to cold water used to put out the fire." CIBA-GEIGY stated also that "some" of the PCB oil "mixed with a large volume of standing water which resulted from fighting the unrelated electrical fire." CIBA-GEIGY stated further that although "there was no environmental release outside of the plant," . . . "a small amount of PCB-contaminated water entered the process wastewater sewer line which leads to the plant's wastewater treatment facility." CIBA-GEIGY reported that an appropriate notice was given to the New Jersey Department of Environmental Protection (NJDEP) under the conditions of a NJDEP-issued permit. With regard to clean-up, CIBA-GEIGY reported that the contamination was contained and cleaned up by the next day by a contractor and arrangements were made by CIBA-GEIGY for "proper disposal of all PCB wastes."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

With regard to required reporting of this PCB-related incident, CIBA-GEIGY noted that the quantity of PCBs released was determined ultimately to be less than the ten (1Ø) pound "Reportable Quantity" (RQ) that would trigger a mandatory phone report to the National Response Center (NRC) pursuant to Section 3Ø2 of CERCLA. Further with regard to required reporting of this PCB release, CIBA-GEIGY stated that in "in retrospect, . . . this incident should not have been reported under TSCA Section 8(e) because:

"1. The quantity [of PCBs] spilled was minor;

"2. The PCB release was promptly contained and cleaned up;

"3. There was no environmental release outside of the plant. . . . .; [and]

"4. Appropriate Federal, [New Jersey] State and local authorities were notified."

Finally, the CIBA-GEIGY Corporation re-emphasized the fact that "the PCB transformer was not involved in the electrical fire."

Comments/Recommendations

Considering various criteria including but not limited to the reported amount, pattern and extent of this PCB release, it is EPA's initial opinion that this incident did not warrant formal reporting to EPA as an "Emergency Incident of Environmental Contamination" (EIEC) under Section 8(e) of TSCA. It should be noted, however, that EPA's opinion in this matter is based solely on the summary information provided in writing by CIBA-GEIGY and does not take into account any other information that may have been considered by CIBA-GEIGY on a prospective basis (e.g., as this PCB-related incident was occurring) in deciding to report the incident under Section 8(e) of TSCA. For further information on the reporting of EIECs under TSCA Section 8(e), the reader's attention is directed to Part V(c) of EPA's March 16, 1978 TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110). In addition, it should be noted that Part VII of the Section 8(e) policy statement explains that information need not be submitted under Section 8(e) of TSCA if the information has been reported to EPA pursuant to mandatory reporting requirements under TSCA or any other authority that is administered by EPA (e.g., CERCLA).

The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, OSWER/EPA, OW/EPA, OAR/EPA, EPA Region II and CRB/EED/OTS/OPTS/EPA; copies of this status report will be sent also to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: DEC 23 1988

SUBJECT: Status Report* 8EHQ-1188-0770 S Approved: JDK 12/23/88

FROM: James F. Darr, Section Head James F. Darr
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

The submitting company has claimed its company name and the exact identity of the subject chemical to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will review all incoming correspondence relating to the company's substantiation of these CBI claims. In the "sanitized" version of its Section 8(e) notice, the company stated non-confidentially that the subject chemical is a "heterocyclic acetal."

Submission Description

The submitting company provided the following information about the conduct and preliminary results of a "pilot" oral teratology study of this heterocyclic acetal in rats:

> "In this [teratological] study, the heterocyclic acetal was administered by gavage to 6 groups of mated female rats at dose levels of 0, 50, 150, 250, 500 and 1000 mg/kg/day during gestation days 6-15. Surviving dams were sacrificed on gestation day 20. Fetuses were removed, weighed, sexed and examined for possible external malformations.
>
> "The only maternal death in this study was a single animal at 50 mg/kg/day. Substantial weight loss occurred during gestation days 6-9 in dams at 1000 mg/kg/day. Slight losses in weight during days 6-9 were noted in dams from the 250 and 500 mg/kg/day groups. A slight, but not statistically significant, increase in post-implantation loss, and early resorptions and a moderate decrease in fetal weight were noted at 1000 mg/kg/day. External malformations were noted in 1 fetus from the control and 250 mg/kg/day groups and in 2 fetuses from the 1000 mg/kg/day group."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon EPA's receipt of a full copy of the final report from the oral "pilot" teratology study cited in the submission. In the interim, it should be noted that the submitted summary information, which included several data tables, does provide evidence for the maternal and developmental toxicity of this heterocyclic acetal.

Only 1 maternal animal died prior to scheduled sacrifice; this was in the 50 mg/kg/day group. Two animals were non-gravid (1 in the 50 mg/kg/day group and 1 in the 150 mg/kg/day group. Treatment with the heterocyclic acetal had a substantial effect on the maternal body weight gain. Over gestation days 6-9, animals in the 3 highest dose groups (250, 500 and 1000 mg/kg/day groups) lost weight. These changes were statistically significant (to the $p<0.05$ or 0.01 level). Reduced body weight gain over the entire gestation period, or just over the treatment period, was statistically significant ($p<0.01$) only at 1000 mg/kg/day.

There were no clear treatment-related increases observed in the frequencies of any specific or total external abnormalities. An increased frequency of early resorption (3.2X controls) and an increased frequency of post-implantation loss (3.8X controls) was observed at 1000 mg/kg/day. The mean fetal weight for the 1000 mg/kg/day group was reduced from controls by 0.7 grams. Although none of these changes were reported as statistically significant, it is not clear from the submitted information that statistical analyses were performed on the fetal data.

It should be noted that the lowest dose group (50 mg/kg/day) does appear to be anomalous. This particular dose group had fewer viable fetuses/litter, fewer implantation sites and higher pre-implantation loss than any of the other dose groups. Based on the provided summary information, these deviations from control values do not appear to be related to treatment.

In summary, maternal toxicity was clearly demonstrated after treatment with the test article at doses of 250, 500 and 1000 mg/kg/day. This maternal toxicity was evidenced by statistically significant reductions in weight gain. Developmental toxicity at a dose of 1000 mg/kg/day was evidenced by increased resorption and by fetal growth retardation. As expected for a typical "pilot" teratology study, no examination appears to have been performed for fetal soft tissue or skeletal abnormalities.

Current Production and Use

In view of the company's CBI claims, no information on the TSCA Chemical Substance Inventory status or use(s) of the heterocyclic acetal appears in this status report; the company did report non-confidentially, however, that the chemical is "being manufactured exclusively for R&D [(research and development)] purposes."

Comments/Recommendations

a) The Chemical Screening Branch will ask the submitting company to ensure that the Agency receives a full copy of the final report (including the actual experimental protocol, results of gross/histopathological examinations, results of any statistical analyses, etc.) from the "pilot" oral teratology study in rats cited in the company's TSCA Section 8(e) submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, the submitter will be asked to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported information, and 2) to reduce or eliminate exposure to this heterocyclic acetal. In addition, the submitter will be asked to describe the nature and results, if available, of all studies (other than those reported already to the Agency or those cited in the open scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of this heterocyclic acetal.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: DEC 23 1988

SUBJECT: Status Report* 8EHQ-1188-0771 S Approved: 12/23/88

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

The submitting company has claimed its company name and the exact identity of the subject chemical to be TSCA Confidential Business Information (CBI); the Information Management Division (IMD/OTS) will be reviewing all incoming correspondence pertaining to the company's substantiation of these CBI claims. In the "sanitized" version of its Section 8(e) submission, the company stated non-confidentially that this chemical is an "alkyl aryl ether."

Submission Description

The submitting company provided the following information with regard to the conduct and preliminary results of a "pilot" oral teratology study of this alkyl aryl ether in rats:

> "In this [teratology] study, the alkyl aryl ether was administered by gavage to 6 groups of mated female rats at dose levels of 0, 50, 125, 250, 500 and 1000 mg/kg/day during gestation days 6-15. Surviving dams were sacrificed on gestation day 20 . . . [and the] fetuses were removed, weighed, sexed and examined for possible external malformations.
>
> "Two of the eight animals at 1000 mg/kg/day died during the study. Substantial reductions in maternal weight gain were evident at 250 mg/kg/day. Maternal weight gain appeared to be slightly reduced at 125 mg/kg/day as well. No viable fetuses were produced at 500 or 1000 mg/kg/day. Substantially increased post-implantation loss was also evident at 125 and 250 mg/kg/day. Mean fetal weight was also decreased at these latter 2 dose levels. A single fetus at 125 mg/kg/day exhibited several external malformations. However, this fetus was extremely light and came from a mother which exhibited substantially decreased weight gain."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon EPA's receipt of a complete copy of the final report from the oral "pilot" teratology study cited in the company's submission. In the interim, however, it should be noted that the submitted summary information, which included a number of data tables, does provide evidence for the maternal and developmental toxicity of this alkyl aryl ether.

Two maternal animals died in the highest dose group (1000 mg/kg/day) before scheduled necropsy. One of these animals was non-gravid. Two animals at 250 mg/kg/day and 1 each at 125 and 500 mg/kg/day were non-gravid as well. Statistically significant ($p<0.01$) decrements in weight gain over the entire gestation period were observed in the 250, 500 and 1000 mg/kg/day dose groups. A trend for decreasing weight gain with increasing dose could be identified even at the 2 lower dose groups (50 and 125 mg/kg/day).

There was a clear and striking reduction in fetal viability with increasing dose. The control litters averaged 14.4 fetuses, the 50 mg/kg/day litters averaged 14.0 fetuses, the 125 mg/kg/day litters averaged 10.0 fetuses, the 250 mg/kg/day litters averaged 4.2 fetuses and there were no fetuses in either the 500 or 1000 mg/kg/day dose groups. There were no late resorptions in any dose group, hence all post-implantation loss was due to early resorption. The frequency of post-implantation loss increased with increasing dose; a dose-dependent trend was evident even at the lowest dose (50 mg/kg/day). The frequencies of implantation sites, corpora lutea and pre-implantation loss did not appear to have been affected by treatment with the test article. The mean fetal weights were reduced from control values by about 1 gram for the 125 and 250 mg/kg/day dose groups. It should be noted that it is not clear from the submitted information that any statistical analyses were performed on the fetal data. Only 1 fetus (from the 125 mg/kg/day dose group) was reported to have external malformations.

In summary, clear evidence of maternal toxicity was provided by statistically significant decreases in gestational weight gain at the 3 highest dose levels (250, 500 and 1000 mg/kg/day). The dose-dependent trend for decreased weight gain was evident for the 2 lowest dose levels (50 and 135 mg/kg/day). Developmental toxicity was seen at all dose levels, including the lowest dose level (50 mg/kg/day). Developmental toxicity was evidenced by increased fetal toxicity and by fetal growth retardation. As expected for a typical "pilot" teratology study, no examination appears to have been performed for fetal soft tissue or skeletal abnormalities.

Current Production and Use

In view of the submitter's TSCA CBI claims, no information about the TSCA Chemical Substance Inventory status or use(s) of this alkyl aryl ether will appear in this status report. The company did report non-confidentially, however, that the subject chemical "is currently being manufactured exclusively for R&D [(research and development)] purposes."

Comments/Recommendations

a) The Chemical Screening Branch will ask the submitting company to ensure that the Agency receives a full copy of the final report (including the actual experimental protocol, results of gross/histopathological examinations, results of any statistical analyses, etc.) from the "pilot" oral teratology study in rats cited in the company's TSCA Section 8(e) submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, the submitter will be asked to describe the actions the company has taken or plans to take 1) to notify workers and others about the reported information, and 2) to reduce or eliminate exposure to this alkyl aryl ether. In addition, the submitter will be asked to describe the nature and results, if available, of all studies (other than those reported already to the Agency or those cited in the open scientific literature) about which the company is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of this alkyl aryl ether.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: JAN - 4 1989

SUBJECT: Status Report* 8EHQ-1188-0772 Approved: JDK 1/4/89

FROM: James F. Darr, Section Head James F Darr
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Hoechst Celanese Corporation provided the following summary information regarding the conduct and preliminary results of a mortality study of workers at the company's Celriver cellulose triacetate (CAS No. 9012-09-3) fiber production plant located in Rock Hill, South Carolina:

> "A cohort of 1,271 employees who worked in the preparation and/or extrusion departments for at least three months between January 1, 1954 and June 1, 1977 was followed through September 1, 1986. Four deaths due to cancer of the liver and biliary passages were reported. Less than one (0.69) was expected. The standardized mortality ratio [(SMR)] was 5.8 with a 95% Confidence Interval [(CI)] of 1.8 to 14. All [of] the deaths from liver or biliary tract cancer occurred among people with greater than 10 years employment who died at least 20 years after they were hired. The observed deaths for all causes were 123, with 121 expected, and deaths for all malignant neoplasms were 28, with 33 expected.
>
> "The current preliminary status of this [mortality] study is typical of cohort studies with small populations which are still relatively early in a potential latency period. The diagnoses from the death certificates require verification before final conclusions can be drawn and a final report issued. Followup of the cohort will be continued."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

In its submission, Hoechst Celanese reported that this study "is an extension of . . . [an] earlier study of workers at the . . . [cellulose] triacetate plant (Ott et al., Scandinavian Journal of Work Environment and Health, 1983)." Hoechst Celanese stated also that methylene chloride (CAS No. 75-09-2) exposure had been the "motivating factor" for this earlier study. Finally, Hoechst Celanese stated that the [cellulose] triacetate fiber production process at the company's Rock Hill, South Carolina facility was "shut down in 1986."

Submission Evaluation

The present Section 8(e) notice pertains to a followup of an original cohort of 1,271 workers exposed to methylene chloride; the results of this initial study were published by Ott et al. in 1983. The original study consisted of all workers employed for longer than 3 months in the cellulose triacetate production and extrusion areas of the Rock Hill, South Carolina plant where there was exposure to methylene chloride as well as acetone. The "exposed" group was compared to a "referent" group of workers at another fiber production plant where there was exposure only to acetone (CAS No. 67-64-1). The findings from this original cohort study were statistically significant risks for "all causes" of mortality, diseases of the circulatory system and all "external causes" for white males among the exposed group. No differences in risk were detected among white females and there was no elevation overall in cancer deaths.

The present Section 8(e) submission adds 10 years of followup to the original cohort and reports excess liver and biliary tract cancer deaths among the exposed cohort. No other individual causes of death were cited, and the overall mortality and total cancer deaths were reported to be not statistically elevated.

The original (1983) cohort study had a number of problems that should be considered when evaluating the conclusions of that earlier study as well as the results reported in the present TSCA Section 8(e) submission. The original study had a maximum of 22 years of followup; however, 55% of the exposed group left employment between 1954 and 1977 (the original study dates were from January 1, 1954 to June 1, 1977), and the vital status could not be ascertained on 18% of this group. The referent group (i.e., those workers exposed to acetone only) had 29% of its workers leave employment between 1954 and 1977 and 12% were lost for further followup. Although the present study adds another 10 years of followup, the submitted summary does not present any additional information on the vital status ascertainment for the exposed or referent groups.

A number of differences exist between the exposed and referent populations. The sex and race distributions between the two groups were different in that the exposed cohort had more women (57% versus 26% in the referent group) and more non-whites (13% versus <1% in the referent group). The referent group had more

white males (73% versus 38% in the exposed group). In the original study, non-white females were not analyzed because no deaths occurred among the 108 non-white females (105 exposed, 5 referent). In addition, the white males in the referent group were younger than those in the exposed group. Also, there are geographic differences between the exposed and referent plant sites; the referent plant site is located in a mountainous, rural area while the exposed plant site is in a flat, urban area.

Although the primary focus of the first study was cardiovascular disease deaths, total mortality, cancer deaths and deaths from external causes were also reviewed. Overall, the general mortality of the exposed and referent groups was similar to the mortality experience of the general U.S. population; however, excess deaths due to external causes were observed in each sex-race group for both the exposed and referent cohorts. None of these excess deaths appeared to be related to methylene chloride or acetone exposures. Further, there were only 7 cancer deaths each in the exposed and referent groups; this number of cancer deaths is similar to the expected values although the white males in the referent group had much lower observed cancer deaths (5 versus 10 expected).

In the followup cohort study, which is the subject of the present TSCA Section 8(e) submission and encompasses the time period from June 1977 to September 1, 1986, overall mortality was found to be similar to the general U.S. population (Standard Mortality Ratio (SMR)=102) and total deaths from all malignant neoplasms was 28 with 33 expected. Of interest is the fact that the "healthy worker effect" does not seem to be operating in the exposed cohort. It should be noted that it is not unusual to find SMR values in the 80's for a group of workers; such values reflect a healthier population than the general U.S. population.

In the present submission, there were 4 deaths due to cancer of the liver and biliary passages reported for the workers in the exposed cohort. This number of deaths is significantly different than 0.69, the expected number of deaths for this cause ($p<0.05$; 95% Confidence Interval (CI) of 1.8 to 14). The submitter notes that all deaths occurred in people who worked for more than 10 years at the exposed plant and who died at least 20 years after they were hired. All of these liver and biliary cancer deaths occurred in the post-1977 10-year followup period.

The submitter did not specify sex or race differences in cancer mortality and no information was given on cancer deaths in the referent group. Further, the submitter did not provide any information about followup ascertainment or enumerate other types of malignant neoplasms found. Also, considering that the original study classified chemical exposure in areas within the plants as being low, intermediate or high, it would be of interest to know the exposures that were associated with the workers who died of liver and biliary tract cancer despite the fact that the low number of deaths precludes intensive analysis.

It is difficult to evaluate the meaning of the reported excess deaths without more information on the followup status, the experience of the referent group and the sex-race distribution of the liver and biliary tract cancer deaths.

Comments/Recommendations

Considering the potential impact of the reported findings on previous and ongoing Agency assessments of methylene chloride as well as natural and man-made fibers, the Chemical Screening Branch immediately sent full copies of the incoming Section 8(e) submission to the Test Rules Development Branch (TRDB/ECAD/OTS), Risk Analysis Branch (RAB/ECAD/OTS), Health and Environmental Review Division (HERD/OTS), Chemical Control Division (CCD/OTS), Exposure Evaluation Division (EED/OTS) and Carcinogen Assessment Group (CAG/ORD). Further, the reader's attention is directed to the "Health Assessment Document for Dichloromethane (Methylene Chloride) - Final Report" published in March 1985 by EPA's Office of Health and Environmental Assessment (OHEA/ORD). It should be noted also that under Section 110 of the Superfund Amendments and Reauthorization Act (SARA), the Agency for Toxic Substances and Disease Registry (ATSDR), in collaboration with EPA, is in the process of preparing "Toxicological Profiles" on a number of chemical substances, including methylene chloride. Information on the public availability of SARA 110 chemical profiles can be obtained from: Office of External Affairs, Chamblee 28 South, 1600 Clifton Road, Atlanta, Georgia 30333.

a) The Chemical Screening Branch will ask Hoechst Celanese to ensure that EPA receives a full copy of the final report (including protocols, data, all statistical analyses, etc.) from the company's ongoing followup study. In addition, the company will be asked to keep EPA apprised of any further significant findings from that ongoing followup study.

b) Staff of the Chemical Screening Branch will review and distribute the reported information to appropriate EPA offices and other agencies.

c) The Chemical Screening Branch will send copies of this status report to NIOSH; OSHA; CPSC; FDA; NTP; ATSDR; OW/EPA; OSWER/EPA; OAR/EPA; ORD/EPA; OPP/OPTS/EPA; CCD, HERD and EED/OTS; RAB and TRDB/ECAD/OTS; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: DEC 19 1988

SUBJECT: Status Report* 8EHQ-1288-0773 Approved: 12/20/88

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Amoco Oil Company provided the following summary information with regard to the conduct and preliminary results of a study designed to determine the tumor promotion potential in mice for Resid Hydroprocessing Unit (RHU) Middle Distillate:

> "Groups of 30 male mice received a single dermal application of either 50 ul acetone or 50 ul of a 1 mg/ml (w/v) solution of 9,10-dimethyl-1,2-benzanthracene (DMBA) in acetone. The initiated mice were rested for two weeks and then treated via dermal application twice weekly for 25 weeks with 50 ul of [the] undiluted Resid Hydroprocessing Unit (RHU) Middle Distillate. A third group [of mice], initiated with DMBA, received sham promotion treatment (i.e., identical treatment but without any test article). All study groups were terminated after 28 weeks on test. All [of the] mice underwent gross necropsy, and the application site skin and associated masses were collected, fixed, stained, and examined microscopically.
>
> "These studies indicate that RHU Middle Distillate possessed tumor promotion potential. Tumor incidence of RHU Middle Distillate was significantly increased in the DMBA-initiated/test article-promoted group (8/30) compared to the acetone-initiated controls (0/30) and DMBA-initiated sham controls (0/30). The tumors were squamous cell papillomas and one keratoacanthoma. Tumor latencies were also significantly shortened in the DMBA-initiated/test article-promoted group. . . . [Amoco interprets] these results to indicate that RHU Middle Distillate has the potential to promote skin tumors."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Submission Evaluation

Although Amoco interprets the reported positive findings to mean that RHU Middle Distillate is a tumor promoter, this type of study alone is insufficient to determine if RHU Middle Distillate is only promoting the DMBA-initiated cells or if RHU Middle Distillate itself is initiating. Further, despite the fact that only benign tumors were reportedly found, the length of the study may have been too short (i.e., 28 weeks) to allow the detection of malignant tumors; it is also possible that the dosage employed was too low. Amoco should be asked to ensure that EPA receives a full copy of the final report from this study. In addition, it would be of interest to know if Amoco is conducting or plans to conduct a study in which RHU Middle Distillate serves as the potential initiator.

Current Production and Use

Amoco reported non-confidentially by phone that the CAS Registry Number for the company's RHU Middle Distillate is 64741-76-Ø.

Appendix A of the first printed edition of the Agency's initial TSCA Chemical Substance Inventory reports that CAS No. 64741-76-Ø refers to heavy hydrocracked petroleum distillates and identifies this material as follows:

> "A complex combination of hydrocarbons from the distillation of the products from a hydrocracking process. It consists predominantly of saturated hydrocarbons having carbon numbers in the range of C_{15} through C_{25}, and boiling in the range of approximately 260°C to 400°C (500°F to 752°F)."

Although the "[CAS] REGISTRY NUMBER UPDATE" section of Volume I of the 1985 Edition of the printed TSCA Inventory reports that CAS No. 64741-76-Ø is no longer listed in the TSCA Inventory, staff of the Information Management Division (IMD/OTS) stated that 1) the deletion of CAS No. 64741-76-Ø was inadvertent, and 2) CAS No. 64741-76-Ø is still in the TSCA Inventory.

A review of the production range (includes importation volumes) statistics for CAS No. 64741-76-Ø, which is listed in the initial TSCA Chemical Substance Inventory, showed that over 1 billion pounds were reported as manufactured and/or imported in 1977. This production range information does not include any data claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the information reported for the initial TSCA Inventory, including the production range information, is subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

Amoco did not submit any information with regard to the current production or use(s) of the tested material nor was such information located in the secondary literature sources searched by EPA.

Comments/Recommendations

In its submission, Amoco reported that the RHU Middle Distillate Material Safety Data Sheet (MSDS) and product label are being revised to reflect the results of the company's tumor promotion study.

EPA's Office of Toxic Substances has received and evaluated many TSCA Section 8(e) and "For Your Information" (FYI) submissions containing toxicologic and/or exposure information on a wide variety of coal-, shale- and petroleum-derived oil products, process streams, and/or waste materials.

a) The Chemical Screening Branch will request Amoco to ensure that EPA receives a full copy of the final report (including the actual experimental protocol, results of gross and histopathological examinations, results of statistical analyses, etc.) from the tumor promotion study cited in the submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Amoco will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Amoco is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity (especially the tumor initiation potential) of or the exposure to RHU Middle Distillate.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of RHU Middle Distillate.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: DEC 21 1988

SUBJECT: Status Report* 8EHQ-1288-0774 Approved: 12/21/88

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Amoco Oil Company provided the following summary information with regard to the conduct and preliminary results of a study designed to determine the tumor initiation potential in mice for Resid Hydroprocessing Unit (RHU) Light Vacuum Gas Oil:

> "Groups of 30 male mice were treated dermally once a day [(number of days not specified)] with 50 ul of Resid Hydroprocessing Unit (RHU) Light Vacuum Gas Oil. The exposed mice, along with 60 sham control mice, were rested for two weeks and then dosed twice weekly for 25 weeks with 50 ul (0.1 mg/ml) of phorbol-12-myristate-13-acetate (PMA) in acetone as a promoter. All study groups were terminated after 28 weeks on test. All mice underwent gross necropsy, and the application site skin and associated masses were collected, fixed, stained, and examined microscopically.
>
> "These studies indicate that RHU Light Vacuum Gas Oil possessed initiation tumorigenic potential. Tumor incidence of RHU Light Vacuum Gas Oil (21/30) was significantly increased compared to sham controls (8/60), and tumor latency (17.4 weeks) was significantly different from sham controls (23.1 weeks). All [of the] induced tumors were squamous cell papillomas or keratoacanthomas. . . . [Amoco interprets] these results to indicate that RHU Light Vacuum Gas Oil has the potential to initiate skin tumors."

Submission Evaluation

Based on the provided summary information, RHU Light Vacuum Gas Oil appears to be a very active tumor initiator (21/30 animals with skin tumors observed within a very short time period (17.5

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

weeks)). Although all of the tumors found were reported to be benign, one needs to consider the short duration of and the low dose of material used in this study. Amoco should be asked to ensure that EPA receives a complete copy of the final report from the company's tumor initiation study of RHU Light Vacuum Gas Oil.

Current Production and Use

Amoco reported non-confidentially by phone that the CAS Registry Number for the company's RHU Light Vacuum Gas Oil is 64741-75-9.

Appendix A of the printed 1985 Edition of EPA's initial TSCA Chemical Substance Inventory reports that CAS No. 64741-75-9 refers to hydrocracked petroleum residues and identifies this material as follows:

> "A complex combination of hydrocarbons produced as the residual fraction from distillation of the products of a hydrocracking process. It consists of hydrocarbons having carbon numbers predominantly greater than C_{20} and boiling above approximately 350°C (662°F)."

A review of the production range (includes importation volumes) statistics for CAS No. 64741-75-9, which is listed in the initial TSCA Chemical Substance Inventory, has shown that over 1 billion pounds were reported as manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

Amoco did not submit any information with regard to the current production or use(s) of RHU Light Vacuum Gas Oil nor was such information located in the secondary literature sources searched by EPA.

Comments/Recommendations

The Amoco Oil Company stated that the RHU Light Vacuum Gas Oil Material Safety Data Sheet (MSDS) and label are being revised to reflect the findings from the company's tumor initiation study.

EPA's Office of Toxic Substances has received and evaluated a number of TSCA Section 8(e) and "For Your Information" (FYI) submissions containing toxicologic and/or exposure information on coal-, shale- and petroleum-derived oil products, process streams and/or waste materials.

a) The Chemical Screening Branch will request Amoco to ensure that EPA receives a full copy of the final report (including the actual experimental protocol,

results of gross and histopathological examinations, results of any statistical analyses, etc.) from the tumor initiation study of RHU Light Vacuum Gas Oil cited in the submission.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Amoco will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Amoco is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of or the exposure to RHU Light Vacuum Gas Oil.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of RHU Light Vacuum Gas Oil.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: JAN 23 1989

SUBJECT: Status Report* 8EHQ-1288-0775 Approved: 1/27/89

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Amoco Oil Company provided the following summary information regarding the conduct and preliminary results of a chronic mouse skin application study of Amoco NT-45 Process Oil, a hydrotreated middle distillate (CAS No. 64742-46-7):

> "Two groups of 50 male mice were used in the study. One group was treated dermally twice weekly for 104 weeks with 50 microliters of undiluted test material. The second group of 50 mice served as sham controls, and were treated the same as the test-article group except that no material was applied to the skin. All mice underwent gross necropsy, and the application site skin and other organs were collected, fixed, stained, and examined microscopically.
>
> "Preliminary histopathological examination indicates that five mice in the test-article treated group had histologically confirmed tumors. Four of those mice had squamous cell carcinomas, one mouse had a squamous cell papilloma, and one of the mice with a carcinoma also had a keratoacanthoma. The mean latency period was 97.7 weeks. Tissues from the sham control group have not yet been processed histologically, so tumor information on this group is incomplete. This study indicates that the test material possessed weak tumorigenic potential. . . . .
>
> ". . . [Amoco interprets] these results to indicate that this hydrotreated distillate has the potential to induce skin tumors following lifetime exposure."

In its submission, Amoco also reported that "previous studies have shown that the test material is not a tumor initiator, but that it does possess weak tumor promoting activity."

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

It should be noted that in a previously received supplemental TSCA Section 8(e) submission (8EHQ-1087-0604 Supplement), the Amoco Corporation provided a full copy of the final report from a CD-1 mouse tumor initiation study of a number of Amoco products including Amoco NT-45 Process Oil. The "SUMMARY" section of that final report presents the following information with regard to the conduct and results of the initiation study:

> "Dermal tumorigenicity bioassays were conducted to assess the initiation potential of Amoco NT-45 Process Oil . . . Groups of 30 male [CD-1] mice were topically dosed once a day for 5 days with 50 ul of the undiluted test article. The initiated mice, along with 60 sham control mice, were rested for 2 weeks and then dosed twice weekly for 25 weeks with 50 ul (0.1 mg/ml) of phorbol-12-myristate-13-acetate (PMA) in acetone as a promoter. . . . .
>
> "No significant differences in tumor incidence were detected between [the] groups treated with Amoco NT-45 Process Oil . . . and the sham controls."

The reader's attention is directed also to the status report that was prepared by EPA in response to another previously received TSCA Section 8(e) submission (8EHQ-0280-0333). In this previous Section 8(e) submission, the Kerr-McGee Corporation reported that Kermac 600W (also CAS No. 64742-46-7) was found to be mutagenic in an Ames Salmonella typhimurium (bacteria) assay.

Submission Evaluation

An EPA evaluation of the overall significance of the reported oncogenicity findings should be possible upon EPA's receipt of full copies of the final reports from the chronic mouse skin application study and the previously conducted tumor promotion study cited in the present Amoco submission; EPA's evaluation will also include the Amoco NT-45 Process Oil tumor initiation study and Kermac 600W Ames test submitted previously to EPA.

Current Production and Use

Appendix A of the printed 1985 Edition of EPA's initial TSCA Chemical Substance Inventory reports that CAS No. 64742-46-7 refers to "hydrotreated middle distillates (petroleum)" and identifies this material as follows:

> "A complex combination of hydrocarbons obtained by treating a petroleum fraction with hydrogen in the presence of a catalyst. It consists of hydrocarbons having carbon numbers predominantly in the range of C_{11} through C_{25} and boiling in the range of approximately 205°C to 400°C (401°F to 752°F)."

A review of the production range (includes importation volumes) statistics for CAS No. 64742-46-7, which is listed in the initial TSCA Chemical Substance Inventory, has shown that over 1 billion pounds were reported as manufactured and/or imported in 1977. This production range information does not include any information claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All data reported for the initial TSCA Inventory, including the production range data, are subject to the limitations contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

In the present TSCA Section 8(e) submission, Amoco reported that Amoco NT-45 Process Oil is "sold as a highly purified mineral seal oil." It should be noted also that in a previous TSCA Section 8(e) notice (8EHQ-0280-0333), the Kerr-McGee Corporation reported that one of its customers may have used Kerr-McGee's mineral seal oil product (Kermac 600W; CAS No. 64742-46-7) in the formulation of printing inks. Kerr-McGee also stated, however, that the company no longer produced or sold Kermac 600W and had replaced the Kermac 600W with Kermac 600 (CAS No. 64741-44-2). According to Kerr-McGee, Kermac 600 is similar to Kermac 600W in composition, constituents and physical characteristics and is the petroleum feed-stock from which the Kermac 600W was produced via hydrotreating.

Comments/Recommendations

In the present Section 8(e) notice, Amoco stated that although the current Amoco NT-45 Process Oil Material Safety Data Sheet (MSDS) already contains a warning about possible tumorigenic effects, Amoco is revising that MSDS to reflect the findings from the company's new chronic mouse skin application study.

EPA's Office of Toxic Substances has received and evaluated a number of TSCA Section 8(e) and "For Your Information" (FYI) submissions containing toxicologic and/or exposure information on coal-, shale- and petroleum-derived oil products, process streams and/or waste materials.

a) The Chemical Screening Branch will ask Amoco to ensure that EPA receives complete copies of the final reports (including the actual experimental protocols, results of gross and histopathological examinations, results of any statistical analyses, etc.) from the chronic mouse skin application study and the previously conducted tumor promotion study cited in the submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Amoco will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA

or those cited in the open scientific literature) about which Amoco is aware or that Amoco has conducted, is conducting or plans to conduct that are designed to determine the toxicity of or the exposure to hydrotreated middle distillate.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of hydrotreated middle distillate.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: JAN 24 1989

SUBJECT: Status Report* 8EHQ-1288-0776 Approved: JDK 1/27/89

FROM: James F. Darr, Section Head James F. Darr
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Note

In its TSCA Section 8(e) submission, the American Telephone and Telegraph Company (AT&T) reported that the subject chemical substance is Bordon Chemical Compound 9MKU10108R, an "acrylate coating compound." AT&T also reported, however, that AT&T "is not at liberty to disclose the formulation."

Submission Description

AT&T submitted a full copy of a draft final report from a mouse Micronucleus Test (MNT) of the acrylate coating compound (test material 220). The "SUMMARY" of the provided report presents the following information with regard to the conduct and results of this study and a preliminary study:

> "In a preliminary Dose-Range-Finding Study, test material 220 was administered intraperitoneally to 6 groups of CD-1 mice at dose levels of 500, 1000, 1750, 2500, 3100 and 3700 mg/kg of body weight prior to dosing. Due to mortality at 3700 mg/kg and pharmacotoxic signs observed in the study and in discussion with the sponsor [(AT&T)], 3100 mg/kg was selected as the high dose for the MNT.
>
> "In the MNT, three groups of mice were given single doses of test material 220 by intraperitoneal injection at 3100 mg/kg and sacrificed at 24, 48 or 72 hours post dosing. Two additional groups of mice were administered 310 and 1500 mg/kg and sacrificed 24 hours later. Three groups of mice [that were] administered the vehicle control, dimethylsulfoxide/corn oil (DMSO/CO), were evaluated concurrently at each sacrifice interval. An

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

> additional group of mice was administered triethylenemelamine (TEM) at a dose of 0.5 mg/kg and sacrificed at 24 hours, serving as the positive control. Slides were [then] prepared from the bone marrow of the femurs and stained. Coded slides were scored for the number of polychromatic erythrocytes (PCE) with micronuclei in 1000 PCE/animal. The ratio of polychromatic to normochromatic erythrocytes (NCE) per 1000 erythrocytes was determined for each animal.
>
> "Statistical analyses of the data indicated a significant increase in the number of micronucleated PCEs in the 3100 mg/kg dose group (24 hour sacrifice time) versus the vehicle control group. Statistically significant depression in PCE/NCE ratios were noted at doses of 310 mg/kg and 1500 mg/kg at 24 hour sacrifice time and also [at] 3100 mg/kg at the 48 hour sacrifice time, as compared to their respective controls.
>
> "In conclusion, test material 220 is deemed positive at [the] 3100 mg/kg dose level of the 24 hour sacrifice time under the experimental conditions of this [mouse MNT] protocol."

In the cover letter to its TSCA Section 8(e) submission, AT&T presented the following information with regard to the company's interpretation of the reported genotoxicity findings:

> "The study revealed a statistically significant positive response in the [mouse] micronucleus test conducted at the highest dose level of the [acrylate] compound administered (3100 mg/kg). The conclusion reached as a result of these findings is that the compound is a weak inducer of micronucleated polychromatic erythrocytes, which in the context of the full test results is only suggestive that the compound may exhibit clastogenic activity. While statistically significant reductions in the ratio of polychromatic to normochromatic erythrocytes were observed in the 24 hour test animals exposed to the test compound at levels of 310 mg/kg and 1500 mg/kg, and in the 48 hour test animals exposed to the test material at 3100 mg/kg AT&T notes that an Ames/Salmonella plate incorporation assay for the same material was negative."

In the cover letter to its submission, AT&T also provided the following summary information regarding pharmacotoxic signs that were observed in the dose-range-finding study as well as the actual mouse micronucleus assay:

> ". . . . Animals were observed immediately and at 24, 48 and 72 hours after administration [of the acrylate coating compound] for signs of mortality and pharmacotoxic signs. [The] control group animals received an

intraperitoneal [injection] dose of DMSO/Corn Oil at a volume of 10 ml/kg body weight. [The] pharmacotoxic signs reported for the vehicle control group were that most animals exhibited writhing immediately following dosing. Twenty-four hours after dosing, several animals exhibited decreased body tone. Abnormal gait was also recorded for one male mouse at this time. At 48 and 72 hours post dosing, several male and female mice in the vehicle control group were noted to have decreased body tone. All [of] these findings are consistent with pharmacotoxic findings reported in the literature for exposure to Dimethyl Sulfoxide, DMSO. Most animals dosed with the test compound not only exhibited similar pharmacotoxic signs to those observed in the vehicle control group but also exhibited additional signs including piloerection, decreased activity and abnormal stance. A few of the animals dosed with the acrylate [coating] compound were also reported to have exhibited pharmacotoxic signs of ptosis. While these findings may be considered to be indicative of the compound presenting some neurotoxic effects, based upon the neurotoxic signs observed for the vehicle control group, it is difficult to effectively assess the true neurotoxicity of this substance."

Submission Evaluation

In this MNT study, a statistically significant increase in the micronucleated PCEs was detected at the 24-hour high dose (3100 mg/kg; 0.01<P<0.05 (one-tailed t-test)). Statistically significant depressions of the PCE/NCE ratio were found at several doses and time points indicating that a sufficient level of toxicity had been achieved in the study. Also, the positive control (TEM) produced an appropriate response in the study. The concurrent negative control (DMSO/CO) response for the 24-hour sacrifice was within historical range; the DMSO/CO responses were a bit high for the 48- and 72-hour sacrifices, although probably not enough to mask any positive response for the test article. In general, the performed MNT study shows that this acrylate coating material is an *in vivo* chromosomal mutagen.

With regard to the neurotoxicologic signs seen in the MNT study, the Toxic Effects Branch (TEB/HERD/OTS) has been requested to evaluate the study report (as well as available information on DMSO) in order to determine, if possible, whether the acrylate compound itself caused and/or potentiated some or all of the observed neurotoxic effects.

Comments/Recommendations

Immediately upon receipt, the Chemical Screening Branch sent full copies of this submission to the Test Rules Development Branch (TRDB/ECAD/OTS) and the Chemical Control Division (CCD/OTS) for inclusion in their ongoing reviews of acrylate compounds.

a) The Chemical Screening Branch will request AT&T to submit a full copy of the final report (including the actual experimental protocols, results of gross and histopathological examinations, results of statistical analyses, etc.) from the dose-range-finding study cited in the company's submission. In addition, AT&T will be asked to submit a full copy of the Ames test cited also in the company's submission.

The Chemical Screening Branch will request the Bordon Chemical Company to report the exact chemical identity (including the CAS Number, if known) and amount of each component in Bordon Chemical Compound 9MKU1Ø1Ø8R.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, both companies will be asked to describe the actions they have taken or plan to take 1) to notify workers and others about the reported information, and 2) to reduce or eliminate exposure to the subject acrylate coating compound. In addition, both companies will be asked to describe the nature and results, if available, of all studies (other than those reported already to the Agency or those cited in the open scientific literature) about which the companies are aware or that they have conducted, are conducting or plan to conduct that are designed to determine the toxicity (especially the potential neurotoxicity) of or the exposure to this material.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of this acrylate coating compound.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA, CCD/OTS/OPTS/EPA and TRDB/ECAD/OTS/OPTS/EPA; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: DEC 29 1988

SUBJECT: Status Report* 8EHQ-1288-0777 Approved: Barbara Ostrow for DEC 29 1988

FROM: James F. Darr, Section Head James F. Darr
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Amoco Chemical Company submitted the following summarized information regarding the conduct and preliminary results of a study designed to determine the rat respiratory sensitization potential of isopropylidenebis(phthalic anhydride) (IPAN):

> "One group of 10 male and 10 female Sprague-Dawley rats was exposed to IPAN at a target concentration of 50 ug/m^3 for 6 hours/day for 5 days. Two additional groups were exposed to filtered air. Following a 3-week rest period, [the] IPAN-exposed [rats] and one group of filtered air-exposed rats were challenged with the same concentration of IPAN for 6 hours. The second filtered air-exposed group served as a non-challenged control.
>
> "Serum IgG antibody levels were significantly elevated in the IPAN-treated females and combined males/females compared to the challenged and non-challenged controls. There were no other effects of treatment associated with the increased serum IgG. Lung foci, absolute lung weight, and relative lung weight were not significantly different in IPAN-treated animals compared to controls.
>
> ". . .[Amoco interprets] these results to indicate that there is evidence to support the conclusion that IPAN is a potential respiratory sensitizer at concentrations of 50 ug/m^3 for 6 hours/day for 5 days."

Submission Evaluation

An EPA review of the overall significance of the submitted toxicologic findings should be possible upon EPA's receipt of a full copy of the final report from the cited rat respiratory sensitization study.

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

Current Production and Use

The Amoco Chemical Company reported non-confidentially by phone that IPAN has the following Chemical Abstracts Service (CAS) Registry Number: 1779-17-5. A review of the non-confidential computerized version of the initial TSCA Chemical Substance Inventory has shown that CAS No. 1779-17-5 is not listed on the TSCA Inventory.

The Amoco Chemical Company did not provide any information in its submission regarding the use(s) of IPAN nor was such information located in the secondary literature sources consulted by EPA.

Comments/Recommendations

In its submission, the Amoco Chemical Company reported that the IPAN product label and Material Safety Data Sheet (MSDS) were being updated to reflect the reported toxicologic findings.

a) The Chemical Screening Branch will ask Amoco to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, results of gross and histopathological examinations, results of any statistical analyses, etc.) from the respiratory sensitization study cited in the company's submission.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Amoco will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those cited in the open scientific literature) about which Amoco is aware or that Amoco has conducted, is conducting or plans to conduct that are designed to determine the toxicity of or the exposure to IPAN.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject chemical substance.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JAN 3 1 1989

SUBJECT: Status Report* 8EHQ-1288-0778

Approved: 2/1/89

FROM: David R. Williams for
James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Eastman Kodak Company provided the final report from an oral developmental toxicity probe study of 2-ethyl-1,3-hexanediol (CAS No. 94-96-2) in rats. The submitter's cover letter presents the following information regarding the conduct and results of this study:

> "In a developmental toxicity probe [study], pregnant rats received doses of . . . [0, 500, 1000, 2000 or 4000] mg/kg by gavage on the 6th through the 15th days of gestation. At 2000 and 4000 mg/kg, mortality was observed in 1/8 and 7/8 rats, respectively. The eighth rat at the high dose level was euthanatized due to its moribund condition. No mortality was observed at the 500 or 1000 mg/kg dose levels. Clinically observable changes seen in the one animal dying at 2000 mg/kg and in animals at 4000 mg/kg included weakness, respiratory difficulty, sialorrhea, gait disturbances, nasal discharge, porphyrin tears, and unkempt haircoats. At 4000 mg/kg, hypothermia, partially closed eyes, excessive tearing, and piloerection were also seen. No clinical abnormalities were seen at the 500 or 1000 mg/kg dose levels. Mean relative liver weight was significantly increased for the 2000 mg/kg dams. Necropsy changes, seen only in dams dying or euthanatized prior to [the] scheduled study termination, included necrosis of the glandular gastric mucosa, excessive mucus in the cecum, and atrophy of the thymus and [the] adipose tissue. No necropsy lesions were seen at the 500 or 1000 mg/kg dose levels.
>
> "An increase in post-implantation losses and an increase in the incidence of malformed fetuses were seen in [the] dams treated with 2000 mg/kg of the test

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* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

> article. Malformations at the 2000 mg/kg dose level included rudimentary (filamentous) tails, missing tails, abnormal curvature of the hindlimbs, arthrogryposis, shortened trunk, and umbilical hernia. [The] malformations at the lower dose levels were restricted to the tail. One fetus at 500 mg/kg and two fetuses, each from a different litter, in the 1000 mg/kg dose group had rudimentary tails.
>
> "In summary, the test chemical produced maternal toxicity and lethality at oral doses of 2000 and 4000 mg/kg. Significant fetal toxicity and teratogenicity were evident at a maternally toxic dose (2000 mg/kg), while only one fetus in the 500 mg/kg and two fetuses in the 1000 mg/kg group had malformations."

In its TSCA Section 8(e) submission, Eastman Kodak also provided a report summarizing the conduct and final results of a number of Eastman Kodak acute toxicity studies on the subject chemical. The company's cover letter presents the following information regarding the results of these acute studies:

> "In the acute oral toxicity study, the oral LD50 values were greater than 5000 mg/kg in both male and female rats. When applied to the skin, the test article had an estimated acute lethal dose of greater than 20 ml/kg for rats and did not produce abnormal clinical signs. The test article was, at most, a slight skin irritant [in guinea pigs], and it was not a skin sensitizer [in guinea pigs]. When placed in the [rabbit] eye, the test article produced moderate irritation. Immediate irrigation of the eye following exposure to the test article was beneficial and significantly reduced the irritation."

Eastman Kodak also submitted a copy of the company's 2-ethyl-1,3-hexanediol Material Safety Data Sheet (MSDS) that had been revised to reflect the results of the reported developmental toxicity probe study. The submitted MSDS presents the following summary information taken from published 1-ethyl-1,3-hexanediol studies:

> "Skin absorption studies: Skin absorption has been demonstrated in the hairless dog . . .
>
> "Inhalation study: Rats exposed to a fog generated at 70°C with a nebulizer at a concentration estimated to be 4800 ppm for 8 hours all survived. . . . .
>
> "Feeding study: Rats fed 700 mg/kg/day in the diet for 90 days did not grow as well as the controls, but apparently suffered no organic [organ ?] injury. At 480 mg/kg/day, growth was normal and no adverse effects were noted. . . . ."

Submission Evaluation

Oral administration of 2-ethyl-1,3-hexanediol to pregnant rats during the major period of organogenesis produced both maternal toxicity and lethality at doses of 2000 and 4000 mg/kg/day. The Maternal toxicity seen was in the form of increased incidence of clinical signs, pathological findings and increased liver weight. Although the mean maternal body weight gain was less than the controls in all treated groups during the period of days 6-9 of gestation, the differences were not statistically significant. Thus, there were no significant maternal effects observed at 500 or 1000 mg/kg/day. It should be noted that Eastman Kodak's cover letter states that the results of an acute oral toxicity study indicate the LD_{50} values to be greater than 5000 mg/kg/day in both male and female rats. In the developmental toxicity probe study, on the other hand, all of the maternal animals in the 4000 mg/kg/day group either died or had to be sacrificed following several days of exposure. Therefore, the possibility exists that pregnant animals represent a uniquely sensitive population.

Oral administration of 2-ethyl-1,3-hexanediol to pregnant rats during the major period of organogenesis produced developmental toxicity at all dose levels administered, i.e., 500, 1000 and 2000 mg/kg/day; at 4000 mg/kg/day there were no live dams to evaluate. Developmental toxicity was in the form of increased incidences of external malformations and variations at all dose levels, and, at 2000 mg/kg/day, a significant increase in post-implantation loss and a significant decrease in the fetal body weight. At 2000 mg/kg/day, there was a statistically significant increase (indicated by an *) in the total and several specific incidence(s) of external malformations. These malformations included: rudimentary or filamentous tails (15 fetuses in 4 litters, 15/4*), missing tails (11/3*), small tail (1/1), curly tail (1/1), edematous or hemorrhagic tails (2/2), cyst on tail (1/1), abnormal curvature of the hindlimbs (13/4*), arthrogryposis (3/3), shortened trunk-lumbar region (5/3), umbilical hernia (4/2). There was also a statistically significant increase observed in the incidence of a variation, hematomas (9/4*). In the 1000 mg/kg/day dose group, 2 fetuses in 2 litters had rudimentary or filamentous tails and 1 fetus had a hematoma. At 500 mg/kg/day, 1 fetus had a rudimentary or filamentous tail; no external malformations or variations were observed in the control animals. While the values from the 500 and 1000 mg/kg/day groups do not represent a statistically significant increase, the fact remains that the malformations observed were of the same nature (i.e., tail malformations) as those observed at significantly increased levels at 2000 mg/kg/day. Therefore, EPA regards those malformations seen at 500 and 1000 mg/kg/day as being indicators of developmental toxicity. This is in contrast with the probe study report which states that the significance of the effects seen at the low doses is obscured by the small number of control fetuses available for examination. The number of fetuses/litters at 1000 mg/kg/day was not much larger (i.e., 38/3, 75/6, 45/4 and 66/6 for 0, 500, 1000 and 2000 mg/kg/day, respectively).

It must be kept in mind that this Eastman Kodak study is merely a probe study in which a limited number of animals were used per dose group and a limited number of developmental parameters were evaluated (i.e., visceral and skeletal examinations were not conducted). Despite the limited nature, however, the study is of sufficient design to clearly identify 2-ethyl-1,3-hexanediol as a maternal and developmental toxicant. As indicated in the probe study, a definitive developmental toxicity study would need to be conducted to further characterize the toxicity of this chemical. Further, and considering the fact that the submitted MSDS reports that 2-ethyl-1,3-hexanediol has been shown to be absorbed through the skin, it would be of interest to know if Eastman Kodak is conducting or plans to conduct a full developmental toxicity study in rats exposed to the subject chemical via the skin.

The structural similarity between 2-ethyl-1,3-hexanediol and 2-ethylhexanol (2-EH), which is metabolized to 2-ethylhexanoic acid (2-EHA) in vivo, should be noted. In addition, it should be noted 2-ethyl-1,3-hexanediol could be metabolized to a hydroxylated analogue of 2-EHA. 2-EHA has been tested by members of the chemical industry for potential developmental toxicity in rabbits and rats pursuant to a "test rule" under TSCA Section 4. While the industry-conducted TSCA Section 4 study of 2-EHA in the rat demonstrated clear signs of developmental toxicity, the specific developmental findings reported in the present Eastman Kodak TSCA Section 8(e) notice (i.e., the high incidence of malformations of the tail) do not mimic those seen in the Section 4 study of 2-EHA in rats. However, there was a significant decrease observed in the number of caudal segments in the Section 4 study of 2-EHA in rats. A possible explanation for the lack of externally observed rat tail malformations could be due to strain differences; the strain of rats used in the 2-EHA Section 4 study was Fischer 344, whereas, the rat strain used by Eastman Kodak in its study of 2-ethyl-1,3-hexanediol was CD Sprague Dawley.

Some support for this theory comes from preliminary findings from an EPA-sponsored testing program (EPA's Health Effects Research Laboratories is conducting studies on the potential developmental toxicity of a series of short-chain carboxylic acids and has been using CD Sprague Dawley rats). According to a recently released progress report, preliminary data from this EPA-sponsored testing program show a dramatic increase in the incidence of no tail or vestigial tail (nine pups, four litters) associated with 2-EHA treatment at 900 mg/kg. In addition, a published study (Ritter et al.; 1987) on the teratogenicity of di(2-ethylhexyl)phthalate (DEHP), 2-EH, 2-EHA and valproic acid in Wistar rats reported tail malformations for all of the compounds following treatment on day 12 of gestation. Also, a recent Union Carbide Corporation Section 8(e) submission (8EHQ-1088-0764 S) reported malformations of the tail or caudal region of CD Sprague Dawley rat fetuses after prenatal exposure to two chemicals which, according to the company, are metabolized to 2-EHA. With all of these studies, there has been an increased incidence of pre- or early postnatal death as well as a decrease in fetal or neonatal body weight.

It is not possible at this time to determine whether there is consistency with the results of other specific developmental tests because the Eastman Kodak study of 2-ethyl-1,3-hexanediol is a probe study, and, as such, did not include any visceral or skeletal analyses of the fetuses. The structural similarity among these agents and the similarity in test results, however, are quite interesting and raise further concern regarding the number of untested substances that are themselves short-chain carboxylic acids or may be metabolized to short-chain carboxylic acids or their analogues.

The reader's attention is directed to the second paragraph of the Comments/Recommendations section of this status report for more information about current OTS chemical assessment/testing-related activities for 2-EH and 2-EHA. The reader's attention is directed also to the "Status Report" prepared by EPA in response to the recently received TSCA Section 8(e) submission (8EHQ-1088-0764 S) in which Union Carbide reported that anal and caudal defects were seen in oral rat teratology studies of two chemicals that yield 2-ethylhexanoic acid as a metabolite.

Current Production and Use

A review of the production range (includes importation volumes) statistics for 2-ethyl-1,3-hexanediol (CAS No. 94-96-2), which is listed in the initial TSCA Chemical Substance Inventory, shows that no 1977 manufacture/importation of the chemical was reported or that all of the manufacturing and/or importation data reported were claimed as TSCA Confidential Business Information (CBI) by the person(s) reporting for the initial Inventory and cannot be disclosed (Section 14(a) of TSCA; U.S.C. 2613(a)). All of the data that have been submitted for the initial TSCA Inventory, including the production range data, are subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

The 10th Edition of the **Condensed Chemical Dictionary** reports that 2-ethyl-1,3-hexanediol has the following uses: "Insect repellent; cosmetics; vehicle and solvent in printing inks; medicine; chelating agent for boric acid."

In its Section 8(e) notice, Eastman Kodak provided the following information regarding the potential for exposure to 2-ethyl-1,3-hexanediol at Eastman Kodak:

> "Potential exposure to this material from Eastman Kodak Company activities comes from two sources. Approximately 100 kg have been manufactured in essentially closed equipment for evaluation by customers. A maximum of 12 employees have been involved during the synthesis and laboratory development work during which good laboratory practices were used. Approximately 40 kg have been sampled to one customer. In addition, the substance has been purchased and repackaged for sales

as a laboratory reagent with sales of less than 10 kg in 1988. . . .[Eastman Kodak is] not aware of any adverse human health problems associated with . . . manufacture or use [of 2-ethyl-1,3-hexanediol]."

Comments/Recommendations

In addition to modifying the 2-ethyl-1,3-hexanediol MSDS to reflect the reported developmental toxicity probe study findings, Eastman Kodak stated that the company is considering the need for further toxicologic testing of this chemical substance.

Considering that 2-ethyl-1,3-hexanediol is structurally similar to 2-ethylhexanol (2-EH; CAS No. 104-76-7), a chemical substance that metabolizes rapidly to 2-ethylhexanoic acid (2-EHA; CAS No. 149-57-5), the Chemical Screening Branch immediately provided copies of this Section 8(e) notice to the Test Rules Development Branch (TRDB/ECAD/OTS) and Risk Analysis Branch (RAB/ECAD/OTS) for inclusion in their ongoing review of available toxicologic and exposure data on 2-EH and 2-EHA. Further, the Agency has published TSCA Section 8(a) and 8(d) information gathering rules for 2-EHA and a TSCA Section 8(d) information gathering rule for 2-EH. In addition, EPA has published TSCA Section 4 "test rules" covering 2-EH and 2-EHA. Finally, EPA has recieved several TSCA Section 8(e) and "For Your Information" (FYI) notices on 2-EH, 2-EHA and chemicals that metabolize to yield those substances.

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure data, Eastman Kodak will be asked to describe the nature and results, if available, of all studies (other than those reported already to EPA or those published in the open scientific literature) about which Eastman Kodak is aware or that the company has conducted, is conducting or plans to conduct that are designed to determine the toxicity of 2-ethyl-1,3-hexanediol, especially the developmental toxicity of the chemical via dermal exposure.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of 2-ethyl-1,3-hexanediol.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OW/EPA, OSWER/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA, and TRDB and RAB/ECAD/OTS/OPTS/EPA; copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

REFERENCE

Ritter et al.; Teratology; Vol. 35, pg. 41-46; 1987

APPENDIX A

THURSDAY, MARCH 16, 1978
PART V

federal register

ENVIRONMENTAL PROTECTION AGENCY

■

TOXIC SUBSTANCES CONTROL ACT

Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk

[6560-01]

ENVIRONMENTAL PROTECTION AGENCY

[FRL 849-2]

TOXIC SUBSTANCES CONTROL ACT

Notification of Substantial Risk Under Section 8(e)

AGENCY: Environmental Protection Agency.

ACTION: Statement of interpretation and enforcement policy.

SUMMARY: This action states EPA's interpretation of, and enforcement policy concerning, section 8(e) of the Toxic Substances Control Act (TSCA) (90 Stat. 2029, 15 U.S.C. 2607). The provisions of that section went into effect on January 1, 1977.

Section 8(e) states that "any person who manufactures, processes, or distributes in commerce a chemical substance or mixture and who obtains information which reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment shall immediately inform the Administrator of such information unless such person has actual knowledge that the Administrator has been adequately informed of such information."

DATES: The policy expressed in this document is in effect as of the date of publication.

FOR FURTHER INFORMATION CONTACT:

Frank D. Kover, Assessment Division, Office of Toxic Substances (WH-557), Environmental Protection Agency, 401 M Street SW., Washington, D.C. 20460, 202-755-2110.

SUPPLEMENTARY INFORMATION: On September 9, 1977, the Agency proposed guidance (42 FR 45362) on its interpretation of and policy concerning the provisions of section 8(e). Although the proposed "guidance" was an interpretive rule and statement of policy exempt from the notice and public comment provisions of the Administrative Procedure Act (5 U.S.C. 553), the Agency solicited comments on several issues to make more informed decisions. On October 11, the comment period was extended from October 15 to October 31, 1977 (42 FR 54857). On November 4, 1977, a supplemental notice to the proposed guidance was published (42 FR 57744), deleting the November 15 date for reporting certain information obtained before 1977 and stating that a new date would be established in the final guidance.

In developing this policy statement, two meetings have been held (February 1, 1977, and October 26, 1977) with selected representatives of industry and environmental and other interested groups. Comments submitted pursuant to the February 1 meeting were addressed in the preamble to the September 9 proposal. Over 100 written comments have been submitted pursuant to the September 9 proposal from trade associations, businesses, environmental groups, labor unions, State and Federal agencies, and other interested parties. Appendix B describes significant issues raised in these comments and the Agency's response to them.

The major modifications to the September 9 proposal are summarized in points 1 through 7 below.

(1) Pursuant to some question over the definition and nature of "guidance," this document is now described more accurately as a "policy statement." It is exempt from the notice and public comment provisions of the Administrative Procedure Act, as well as provisions concerning delayed effective dates.

(2) Many commenters expressed the view that to apply these requirements to officers and employees of a business organization would result in ill-considered, premature reports and would unfairly subject employees to conflicting responsibilities as individual respondents and as corporate agents. Other commenters expressed support for the view that certain employees have a responsibility to report pertinent information, and felt that the phrase "capable of appreciating pertinent information" appropriately described those employees.

The September 9 proposal would have applied section 8(e) requirements to commercial establishments as well as to employees capable of appreciating pertinent information, but stipulated enforcement priorities intended to encourage corporate processing and centralized reporting of such information (42 FR 45363). The intent was to ensure that pertinent information obtained by employees is promptly and appropriately considered, while minimizing duplicative or ill-considered submissions.

The Agency now feels that these objectives would best be served by allowing commercial establishments—under certain conditions designed to ensure full disclosure—to assume exclusive responsibility for reporting to EPA any substantial-risk information obtained by individual officers or employees. Accordingly, this policy statement stipulates that individual officers and employees will have fully discharged their section 8(e) obligations once they have notified the designated responsible company supervisor or official of pertinent information, *provided*, that the employing company or firm has established, internally publicizes, and affirmatively implements procedures governing such notifications. These procedures, at a minimum, must: (1) Specify the information that must be reported; (2) indicate how the notifications are to be prepared and submitted; (3) note the Federal penalties for failing to report; and (4) provide a mechanism for promptly notifying officers and employees who have submitted reports of the company's disposition of those reports, including whether or not they were submitted to EPA (and if not, informing employees of their right to report to EPA, as protected by TSCA section 23). EPA believes these four criteria will ensure prompt and appropriate processing of pertinent information.

Establishment of such procedures notwithstanding, all officials responsible and having authority for the organization's execution of its section 8(e) obligations retain personal liability for ensuring that substantial-risk information is reported to EPA.

(3) The September 9 proposal stated, in Part III, that a person obtains information when he is aware that it "may suggest" substantial risk. Numerous commenters questioned the Administrator's authority to compel the reporting of information which "may suggest" substantial risk. The Administrator agrees that section 8(e) addresses information that "reasonably supports the conclusion" of substantial risk and has deleted the "may suggest" provision, but emphasizes that "reasonably supports the conclusion" of substantial risk is not identical to a conclusive demonstration of substantial risk. The former typically occurs, and must be reported, at an earlier stage. Part VI in this policy statement provides Agency interpretation of the types of information that "reasonably support" such a conclusion.

(4) Numerous commenters requested clarification of different aspects of Part V of the September 9 proposal ("Information Which Reasonably Supports a Conclusion of Substantial Risk"), particularly concerning environmental effects, and suggested different interpretations of what constitutes a "substantial risk". The Agency continues to focus in this policy statement on the effects set forth in the September 9 proposal, but clarifies that the substantiality of a risk is a function of both the seriousness of the effect and the probability of its occurrence (see Part V).

(5) Numerous commenters maintained that section 8(e) only applies prospectively to information obtained after January 1, 1977. The Agency disagrees, as explained in the preamble to the September 9 proposal. This policy statement continues to apply section 8(e) to information obtained before 1977 of which a person has

been aware since January 1, 1977. In response to requests for clarification, the statement defines what constitutes such awareness. In this manner, EPA intends to limit the need for searches of historical records and files.

(6) This policy statement now provides that any information published in scientific literature, in any language, is exempt if it is referred to in abstracts published by specified abstracting services.

(7) This policy statement describes in a new Part X how to submit claims of confidentiality.

Accordingly, the Administrator's interpretation of and policy towards section 8(e) is set forth below.

Dated: February 24, 1978.

DOUGLAS COSTLE
Administrator.

I. DEFINITIONS

The definitions set forth in TSCA section 3 apply to these requirements. In addition, the following definitions are provided for purposes of this policy statement:

The term "manufacture or process 'for commercial purposes' " means to manufacture or process: (1) For distribution in commerce, including for test marketing purposes, (2) for use as a catalyst or an intermediate, (3) for the exclusive use by the manufacturer or processor, or (4) for product research and development.

The term "person" includes any natural person, corporation, firm, company, joint-venture, partnership, sole proprietorship, association, or any other business entity, any State or political subdivision thereof, any municipality, any interstate body and any department, agency, or instrumentality of the Federal Government.

The term "substantial-risk information" means information which reasonably supports the conclusion that a chemical substance or mixture presents a substantial risk of injury to health or the environment.

II. PERSONS SUBJECT TO THE REQUIREMENT

Persons subject to section 8(e) requirements include both natural persons and business entities engaged in manufacturing, processing, or distributing in commerce a chemical substance or mixture. In the case of business entities, the president, chief executive officer, and any other officers responsible and having authority for the organization's execution of its section 8(e) obligations must ensure that the organization reports substantial-risk information to EPA. The business organization is considered to have obtained any information which any officer or employee capable of appreciating the significance of that information has obtained. It is therefore incumbent upon business organizations to establish procedures for expeditiously processing pertinent information in order to comply with the schedule set forth in Part IV.

Those officers and employees of business organizations who are capable of appreciating the significance of pertinent information are also subject to these reporting requirements. An employing organization may relieve its individual officers and employees of any responsibility for reporting substantial-risk information directly to EPA by establishing, internally publicizing, and affirmatively implementing procedures for employee submission and corporate processing of pertinent information. These procedures, at a minimum, must: (1) Specify the information that officers and employees must submit; (2) indicate how such submissions are to be prepared and the company official to whom they are to be submitted; (3) note the Federal penalties for failing to report; and (4) provide a mechanism for promptly advising officers and employees in writing of the company's disposition of the report, including whether or not the report was submitted to EPA (and if not informing employees of their right to report to EPA, as protected by TSCA section 23). An employee of any company that has established and publicized such procedures, who has internally submitted pertinent information in accordance with them, shall have discharged his section 8(e) obligation. Establishment of such procedures notwithstanding, all officials responsible and having authority for the organization's execution of its section 8(e) obligations retain personal liability for ensuring that the appropriate substantial-risk information is reported to EPA.

Business organizations that do not establish such procedures cannot relieve their individual officers and employees of the responsibility for ensuring that substantial-risk information they obtain is reported to EPA. While officers and employees of such organizations may also elect to submit substantial-risk information to their superiors for corporate processing and reporting, rather than to EPA directly, they have not discharged their individual section 8(e) obligation until EPA has received the information.

NOTE.—Irrespective of a business organization's decision to establish and publicize the procedures described above, it is responsible for becoming cognizant of any substantial-risk information obtained by its officers and employees, and for ensuring that such information is reported to EPA within 15 working days.

III. WHEN A PERSON WILL BE REGARDED AS HAVING OBTAINED INFORMATION

A person obtains substantial-risk information at the time he first comes into possession of or knows of such information.

NOTE.—This includes information of which a prudent person similarly situated could reasonably be expected to possess or have knowledge.

An establishment obtains information at the time any officer or employee capable of appreciating the significance of such information obtains it.

IV. REQUIREMENT THAT A PERSON "IMMEDIATELY INFORM" THE ADMINISTRATOR

With the exception of information on emergency incidents of environmental contamination [see Part V(c)] a person has "immediately informed" the Administrator if information is received by EPA not later than the 15th working day after the date the person obtained such information. Supplementary information generated after a section 8(e) notification should, if appropriate, be immediately reported. For emergency incidents of environmental contamination, a person shall report the incident to the Administrator by telephone as soon as he has knowledge of the incident (see Part IX for appropriate telephone contacts). The report should contain as much of the information required by Part IX as possible. A written report in accordance with Part IX (a) through (f) is to be submitted within 15 days.

Information currently in the possession of a person who is subject to reporting must be reported within 60 days of publication of this policy statement.

V. WHAT CONSTITUTES SUBSTANTIAL RISKS

A "substantial risk of injury to health or the environment" is a risk of considerable concern because of (a) the seriousness of the effect [see Subparts (a), (b), and (c) below for an illustrative list of effects of concern], and (b) the fact or probability of its occurrence. (Economic or social benefits of use, or costs of restricting use, are not to be considered in determining whether a risk is "substantial".) These two criteria are differentially weighted for different types of effects. The human health effects listed in Subpart (a) below, for example, are so serious that relatively little weight is given to exposure; the mere fact the implicated chemical is in commerce constitutes sufficient evidence of exposure. In contrast, the remaining effects listed in Subparts (b) and (c) below must involve, or be accompanied by the potential for, significant levels of exposure (because of general production levels, persistence, typical uses, common means of disposal, or other pertinent factors).

Note that: (i) The effects outlined below should not be reported if the re-

spondent has actual knowledge that the Administrator is already informed of them.

(ii) Information respecting these effects can be obtained either directly, by observation of their occurrence, or inferred from designed studies as discussed in Part VI.

The Agency considers effects for which substantial-risk information must be reported to include the following:

(a) *Human health effects*—(1) Any instance of cancer, birth defects, mutagenicity, death, or serious or prolonged incapacitation, including the loss of or inability to use a normal bodily function with a consequent relatively serious impairment of normal activities, if one (or a few) chemical(s) is strongly implicated.

(2) Any pattern of effects or evidence which reasonably supports the conclusion that the chemical substance or mixture can produce cancer, mutation, birth defects or toxic effects resulting in death, or serious or prolonged incapacitation.

(b) *Environmental effects*—(1) Widespread and previously unsuspected distribution in environmental media, as indicated in studies (excluding materials contained within appropriate disposal facilities).

(2) Pronounced bioaccumulation. Measurements and indicators of pronounced bioaccumulation heretofore unknown to the Administrator (including bioaccumulation in fish beyond 5,000 times water concentration in a 30-day exposure or having an n-octanol/water partition coefficient greater than 25,000) should be reported when coupled with potential for widespread exposure and any non-trivial adverse effect.

(3) Any non-trivial adverse effect, heretofore unknown to the Administrator, associated with a chemical known to have bioaccumulated to a pronounced degree or to be widespread in environmental media.

(4) Ecologically significant changes in species' interrelationships; that is, changes in population behavior, growth, survival, etc. that in turn affect other species' behavior, growth, or survival.

Examples include: (i) Excessive stimulation of primary producers (algae, macrophytes) in aquatic ecosystems, e.g., resulting in nutrient enrichment, or eutrophication, of aquatic ecosystems.

(ii) Interference with critical biogeochemical cycles, such as the nitrogen cycle.

(5) Facile transformation or degradation to a chemical having an unacceptable risk as defined above.

(c) *Emergency incidents of environmental contamination*—Any environmental contamination by a chemical substance or mixture to which any of the above adverse effects has been ascribed and which because of the pattern, extent, and amount of contamination (1) seriously threatens humans with cancer, birth defects, mutation, death, or serious or prolonged incapacitation, or (2) seriously threatens non-human organisms with large-scale or ecologically significant population destruction.

VI. Nature and Sources of Information Which "Reasonably Supports the Conclusion" of Substantial Risk

Information attributing any of the effects described in Part V above to a chemical substance or mixture is to be reported if it is one of the types listed below and if it is not exempt from the reporting requirement by reason of Part VII of this policy statement. A person is not to delay reporting until he obtains conclusive information that a substantial risk exists, but is to immediately report any evidence which "reasonably supports" that conclusion. Such evidence will generally not be conclusive as to the substantiality of the risk; it should, however, reliably ascribe the effect to the chemical.

Information from the following sources concerning the effects described in Part V will often "reasonably support" a conclusion of substantial risk. Consideration of corroborative information before reporting can only occur where it is indicated below.

(1) *Designed, controlled studies.* In assessing the quality of information, the respondent is to consider whether it contains reliable evidence ascribing the effect to the chemical. Not only should final results from such studies be reported, but also preliminary results from incomplete studies where appropriate. Designed, controlled studies include:

(i) In vivo experiments and tests.

(ii) In vitro experiments and tests. Consideration may be given to the existence of corroborative information, if necessary to reasonably support the conclusion that a chemical presents a substantial risk.

(iii) Epidemiological studies.

(iv) Environmental monitoring studies.

(2) *Reports concerning and studies of undesigned, uncontrolled circumstances.* It is anticipated here that reportable effects will generally occur in a pattern, where a significant common feature is exposure to the chemical. However, a single instance of cancer, birth defects, mutation, death, or serious incapacitation in a human would be reportable if one (or a few) chemical(s) was strongly implicated. In addition, it is possible that effects less serious than those described in Part V(a) may be preliminary manifestations of the more serious effects and, together with another triggering piece of information, constitute reportable information; an example would be a group of exposed workers experiencing dizziness together with preliminary experimental results demonstrating neurological dysfunctions.

Reports and studies of undesigned circumstances include:

(i) Medical and health surveys.

(ii) Clinical studies.

(iii) Reports concerning and evidence of effects in consumers, workers, or the environment.

VII. Information Which Need Not Be Reported

Information need not be reported if it:

(a) Has been published by EPA in reports;

(b) Has been submitted in writing to EPA pursuant to mandatory reporting requirements under TSCA or any other authority administered by EPA (including the Federal Insecticide, Fungicide and Rodenticide Act, the Clean Air Act, the Federal Water Pollution Control Act, the Marine Protection, Research, and Sanctuaries Act, the Safe Drinking Water Act, and the Resource Conservation and Recovery Act), provided that the information: (1) Encompasses that required by Part IX (c) through (f); and (2) is from now on submitted within the time constraints set forth in Part IV and identified as a section 8(e) notice in accordance with Part IX(b);

(c) Has been published in the scientific literature and referenced by the following abstract services: (1) Agricola, (2) Biological Abstracts, (3) Chemical Abstracts, (4) Dissertation Abstracts, (5) Index Medicus, (6) National Technical Information Service.

(d) Is corroborative of well-established adverse effects already documented in the scientific literature and referenced as described in (c) above, unless such information concerns emergency incidents of environmental contamination as described in Part V(c), or

(e) Is contained in notification of spills under section 311(b)(5) of the Federal Water Pollution Control Act.

VIII. Information First Received by a Person Prior to the Effective Date of TSCA

Any substantial risk information possessed by a person prior to January 1, 1977, of which he is aware after that date shall be reported within 60 days of publication of this policy statement. The Agency considers that a person is "aware" of:

(a) Any information reviewed after January 1, 1977, including not only written reports, memoranda and other documents examined after January 1, 1977, but also information referred to in discussions and conferences in which the person participated after January 1, 1977;

(b) Any information the contents of which a person has been alerted to by date received after January 1, 1977, including any information concerning a chemical for which the person is presently assessing health and environmental effects;

(c) Any other information of which the person has actual knowledge.

IX. Reporting Requirements

Notices shall be delivered to the Document Control Officer, Chemical Information Division, Office of Toxic Substances (WH-557), Environmental Protection Agency, 401 M Street SW., Washington, D.C. 20460. (****)

A notice should:

(a) Be sent by certified mail, or in any other way permitting verification of its receipt by the Agency,

(b) State that it is being submitted in accordance with section 8(e),

(c) Contain the job title, name, address, telephone number, and signature of the person reporting and the name and address of the manufacturing, processing, or distributing establishment with which he is associated,

(d) Identify the chemical substance or mixture (including, if known, the CAS Registry Number),

(e) Summarize the adverse effects being reported, describing the nature and the extent of the risk involved, and

(f) Contain the specific source of the information together with a summary and the source of any available supporting technical data.

For emergency incidents of environmental contamination (see Part V(c)), a person shall report the incident to the Administrator by telephone as soon as he has knowledge of the incident (see below for appropriate telephone contacts). The report should contain as much of the information required by instructions (b) through (f) above as possible. A written report, in accordance with instructions (a) through (f) above, is to be submitted within 15 days. Twenty-four hour emergency telephone numbers are:

Region I (Maine, Rhode Island, Connecticut, Vermont, Massachusetts, New Hampshire), 617-223-7265.

Region II (New York, New Jersey, Puerto Rico, Virgin Islands), 201-548-8730.

Region III (Pennsylvania, West Virginia, Virginia, Maryland, Delaware, District of Columbia), 215-597-9898.

Region IV (Kentucky, Tennessee, North Carolina, South Carolina, Georgia, Alabama, Mississippi, Florida), 404-881-4062.

Region V (Wisconsin, Illinois, Indiana, Michigan Ohio, Minnesota), 312-353-2318.

Region VI (New Mexico, Texas, Oklahoma, Arkansas, Louisiana), 214-749-3840.

Region VII (Nebraska, Iowa, Missouri, Kansas), 816-374-3778.

Region VIII (Colorado, Utah, Wyoming, Montana, North Dakota, South Dakota), 303-837-3880.

Region IX (California, Nevada, Arizona, Hawaii, Guam), 415-556-6254.

Region X (Washington, Oregon, Idaho, Alaska), 206-442-1200.

X. Confidentiality Claims

(a) Any person submitting a notice to EPA under section 8(e) of TSCA may assert a business confidentiality claim covering all or part of the information contained in the notice. Any information covered by a claim will be disclosed by EPA only to the extent, and by means of the procedures, set forth in 40 CFR Part 2 (41 FR 36902, September 1, 1976).

(b) If no claim accompanies the notice at the time it is submitted to EPA, the notice will be placed in an open file to be available to the public without further notice to the submitter.

(c) To assert a claim of confidentiality for information contained in a notice, the submitter must submit two copies of the notice.

(1) One copy must be complete. In that copy the submitter must indicate what information, if any, is claimed as confidential by marking the specified information on each page with a label such as "confidential," "proprietary," or "trade secret."

(2) If some information in the notice is claimed as confidential, the submitter must submit a second copy. The second copy must be complete except that all information claimed as confidential in the first copy must be deleted.

(3) The first copy of the notice will be disclosed by EPA only to the extent, and by means of the procedures, set forth in 40 CFR Part 2. The second copy will be placed in an open file to be available to the public.

(d) Any person submitting a notice containing information for which they are asserting a confidentiality claim should send the notice in a double envelope.

(1) The outside envelope should bear the same address outlined in section IX of this policy statement.

(2) The inside envelope should be clearly marked "To be opened only by the OTS Document Control Officer."

XI. Failure To Report Information

Section 15(3) of TSCA makes it unlawful for any person to fail or refuse to submit information required under section 8(e). Section 16 provides that a violation of section 15 renders a person liable to the United States for a civil penalty and possible criminal prosecution. Pursuant to section 17, the Government may seek judicial relief to compel submittal of section 8(e) information and to otherwise restrain any violation of section 8(e).

Appendix A.—Quick Reference Summary for Emergency Incidents of Environmental Contamination

A. WHAT SHOULD BE REPORTED AS AN EMERGENCY INCIDENT

An emergency incident of environmental contamination is "any environmental contamination by a chemical substance or mixture . . . which, because of the pattern, extent and amount of contamination, (1) Seriously threatens humans with cancer, birth defects, mutation, death, or serious or prolonged incapacitation, or (2) seriously threatens non-human organisms with large scale or ecologically significant population destruction". (See Part V(c) for complete description.)

B. WHAT NEED NOT BE REPORTED AS AN EMERGENCY INCIDENT

Information contained in notification of spills under section 311(b)(5) of the Federal Water Pollution Control Act (FWPCA). (For a complete list of exemptions to reporting, see Part VII.)

C. WHEN AND WHERE TO REPORT EMERGENCY INCIDENTS

Emergency incidents of environmental contamination are to be reported immediately by telephone to the appropriate EPA Regional 24-hour telephone emergency line listed below.

Region I (Maine, Rhode Island, Connecticut, Vermont, Massachusetts, New Hampshire), 617-223-7265.

Region II (New York, New Jersey, Puerto Rico, Virgin Islands), 201-548-8730.

Region III (Pennsylvania, West Virginia, Virginia, Maryland, Delaware, District of Columbia), 215-597-9898.

Region IV (Kentucky, Tennessee, North Carolina, South Carolina, Georgia, Alabama, Mississippi, Florida), 404-881-4062.

Region V (Wisconsin, Illinois, Indiana, Michigan, Ohio, Minnesota), 312-353-2318.

Region VI (New Mexico, Texas, Oklahoma, Arkansas, Louisiana), 214-749-3840.

Region VII (Nebraska, Iowa, Missouri, Kansas), 816-374-3778.

Region VIII (Colorado, Utah, Wyoming, Montana, North Dakota, South Dakota), 303-837-3880.

Region IX (California, Nevada, Arizona, Hawaii, Guam), 415-556-6254.

Region X (Washington, Oregon, Idaho, Alaska), 206-442-1200.

In addition, a written report, in accordance with instructions (a) through (f) of Part IX, is to be submitted within 15 days to the Document Control Officer, Chemical Information Division, Office of Toxic Substances (WH-557), 401 M Street SW., Washington, D.C. 20460.

Appendix B—Significant Comments and Responses

A. PERSONS SUBJECT TO THESE REQUIREMENTS

Comment 1: Employees cannot be held subject to these requirements, since: (a) They only have a partial role in the manufacture, processing, or distribution of chemicals, (b) in other sections of TSCA, the term "person who manufactures, processes, or distributes" chemicals clearly refers to business organizations; "persons" should be consistently defined, and (c) the application of criminal penalties mandates a strict interpretation of this word.

(****) See NOTE on last page of Appendix A

Response: The Agency considers that different sections of TSCA, having different purposes, are appropriately directed to different respondents. In the case of section 8(e), officers and employees who are capable of appreciating the significance of information have a legitimate responsibility to be alert to and report substantial-risk information. The guidance has been modified so that natural persons and business entities can fulfill their section 8(e) obligations in different ways. Most officers and employees can discharge their section 8(e) obligations by submitting pertinent information to corporate superiors, provided that the company has established the risk-evaluation procedures characterized in Part II. In the case of a business organization, its president, chief executive officer, and other officials responsible and having authority for the business organization's execution of its section 8(e) obligations must ensure that the organization reports substantial-risk information to EPA.

Comment 2: Even if employees can be held subject to these requirements, they should not be. To do so would force employees and employers into conflicting positions, inviting internal corporate dissension and over- reporting. Further, individuals often do not have the overview necessary to reach considered, well-supported decisions. Corporate reporting by designated officials will provide EPA with more reliable data.

Response: The Agency considers that employees have a legitimate role in risk reporting; it is imperative that risk information obtained by employees be appropriately considered. Officers and employees can fulfill their role in the reporting of substantial-risk information, without the disadvantages described above, by reporting information to superiors for corporate consideration, and, having done so, will have discharged their obligation to EPA. This is contingent upon the establishment by the business organization of certain procedures for risk-evaluation, thereby assuring the appropriate consideration of such reports. Those officers responsible and having authority for the organization's execution of its section 8(e) obligations must ensure that the organization reports substantial-risk information to EPA.

Comment 3: Clarify which employees are covered, and the extent of their obligation. Are employees "capable of appreciating pertinent information" by virtue of rank, or knowledge? Are rank and file employees subject to these requirements, or just supervisory and managerial personnel, company toxicologists, etc.? Is an employee absolved of further responsibility if he reports to his supervisor?

Response: The Agency considers that the phrase "capable of appreciating the significance of pertinent information" appropriately describes those officers and employees who have a responsibility to be alert to and report substantial-risk information, including not only relatively senior corporate officers but also many corporate employees. The policy statement modifies the September 9 proposal, in response to the concerns expressed in Comments 2 and 3, to permit most officers and employees to discharge their obligation by submitting information to corporate superiors, subject to the conditions described in Part II.

Comment 4: Consultants and independent labs should not be subject to these requirements.

Response: Contractors and independent labs are not responsible for reporting information they have obtained directly to EPA; rather, their client manufacturers, processors and distributors are responsible for reporting such information.

B. THE "OBTAINING" OF INFORMATION

Comment 5: The "may suggest" criterion in Part III of the proposal serves to compel further examination of information that by itself is not subject to section 8(e) requirements. The statutory language calling for "reasonable support" does not support this. Further, risk assessment often requires anywhere from months to several years of study after preliminary results "suggest" risk, far exceeding the 15-day compliance period.

Response: The Agency does not intend to compel under section 8(e) examination of information that by itself is not subject to section 8(e) requirements and has deleted the "may suggest" provision, providing its interpretation of what constitutes evidence that "reasonably supports the conclusion" of substantial risk in a new Part VI.

Comment 6: Section 8(e) obligations are incurred upon obtaining conclusory substantial-risk information.

Response: The Agency disagrees, and considers that "reasonable support" of a conclusion of substantial risk is not identical to the conclusion itself. The former typically occurs, and must be reported, at an earlier stage.

Comment 7: The statement, in Part III of the proposal that a person has obtained information if he " . . should know of the existence of such information not in his possession but which would be delivered to him on request," tends to compel an active search for substantial-risk information rather than the reporting of substantial-risk information a person "obtains." This is of particular concern to importers with limited access to information possessed by their suppliers.

Response: The Agency considers that section 8(e) applies to information which a person possesses or of which he knows. It is not intended to compel searches for information or extraordinary efforts to acquire information. The Agency further considers, however, that "known" information includes information which a prudent person similarly situated could reasonably be expected to know. Negligence or intentional avoidance of information does not absolve a person of his section 8(e) obligation. Part III has been modified to express these intentions.

Comment 8: Circumstances can exist when coming "into possession" of risk information does not correspond to an understanding of the implications of the information; "obtains" should be defined in terms of possession of information and awareness of its import.

Response: The "obtaining" of information occurs via persons who are "capable of appreciating the significance of pertinent information." There will likely be circumstances in which the evaluation of information clarifies its full import; the establishment of corporate procedures for processing risk-information prescribed in Part II will expedite this.

C. TIME ALLOWED FOR COMPLIANCE

Comment 9: Fifteen calendar days is insufficient to determine whether information which "may suggest" substantial risk should be reported; it is even insufficient to accommodate normal procedural time constraints (corporate processing, mailing, holidays, etc.).

Response: The Agency has changed the compliance period to 15 business days. It is imperative that procedures be established to expedite the reporting of substantial-risk information, not that reporting conform to existing procedures.

Comment 10: Allow from 30 to 90 days for the second phase of reporting; alternatively, do not prescribe a time limit for additional reporting.

Response: Having deleted the "may suggest" criterion, the Agency sees no need to provide a second phase to the reporting period. Supplemental information that is generated after a section 8(e) notification should, if appropriate, be immediately reported.

Comment 11: Allow from 30 to 120 days to report pre-1977 information; this period should commence: (a) upon final publication, (b) January 1, 1978, (c) following the inventory reporting period since many of the same corporate personnel will be implementing both requirements.

Response: The policy statement prescribes a 60 day reporting period, commencing immediately upon publication. Section 8(e) has been in effect since January 1, 1977; postponement in reporting substantial-risk information is not warranted.

D. EFFECTS AND INFORMATION THAT MUST BE REPORTED

Comment 12: The reporting of "any instance" of cancer, birth defects, etc., in humans is too broad and such information will be of little use; chemical workers, like the general population, develop cancers and other ailments of uncertain etiology.

Response: This policy statement clarifies that the reporting of single occurrences of human cancer or other serious effects will depend upon evidence strongly implicating one (or a few) chemical(s).

Comment 13: Dermal ailments and nausea are poorly chosen examples of precursor symptoms. Deleting these examples will avoid unduly emphasizing them when other symptoms may be more important, yet will not eliminate the obligation to report them if they are suspected precursors.

Response: The Agency agrees.

Comment 14: How are reportable data distinguished from routine tests including range tests such as LD_{50}'s?

Response: This policy statement directs the reporting of specified effects when unknown to the Administrator. Many routine tests are based on a knowledge of toxicity associated with a chemical; unknown effects occurring during such a range test may have to be reported if they are those of concern to the Agency and if the information meets the criteria set forth in Parts V and VI.

Comment 15: The most widespread "in vitro" test is the Ames test, which is subject to considerable debate. Clarify the circumstances under which positive results of in vitro tests must be reported.

Response: Part VI clarifies that the reporting of in vitro tests will depend upon the existence of corroborative information if necessary to reasonably support the conclusion of substantial risk.

Comment 16: The description of "extreme persistence" as a substantial risk is an example of the need to redefine Part V(c) ("Environmental Effects"). Persistence and bioaccumulation should be considered risks only when coupled with toxicity and significant exposure.

Response: Part V now clarifies those effects for which reporting depends upon a significant exposure potential. Persistence by itself is no longer itemized as a reportable effect but rather is considered to be a component of exposure potential; it may also underlie the measurements described in Part V(b)(1). Laboratory indicators of pronounced bioaccumulation are to be reported when coupled with potential for widespread exposure and any non-trivial adverse effect.

Comment 17: The n-octanol/water partition coefficient addresses a physico-chemical property, not biological effects, and is not alone an indicator of substantial risk; further, the values stated for the coefficient and the bioaccumulation factor in fish do not correspond.

Response: The Agency acknowledges the numerical error and has amended the values to correspond. This policy statement now directs the reporting of an experimental measurement of bioaccumulation when coupled with an adverse effect and potential for widespread exposure.

Comment 18: The requirement that information which "links" an effect to a chemical be reported is too broad and contradicts the statutory language of "reasonably supports".

Response: The Agency has provided in a new Part VI its interpretation of "reasonably supports".

Comment 19: A determination that information "reasonably supports the conclusion" of substantial risk cannot be made independently of considerations of use since the method and manner of using a chemical may influence the occurrence of an effect; in particular, the criteria should reflect a distinction between normal and abnormal uses of chemicals.

Response: The Agency considers that the appropriate components of a "substantial risk" with respect to a chemical are (a) the seriousness of the effect, and (b) total exposure potential. The method and manner of using a chemical is one of several factors determining its exposure potential. As described in Part V, the importance of exposure potential as a component of "substantial risk" depends upon the kind of effect of concern. Thus, the effects described in Part V(a) are so serious that relatively little weight is given to exposure; the effects described in Parts V (b) and (c) involve a significant exposure or exposure potential.

The Agency further considers that a definition of "normal" use for a particular chemical will often depend upon a knowledge of the risks associated with the chemical.

E. INFORMATION THAT NEED NOT BE REPORTED

Comment 20: Information published in scientific literature in languages other than English should be exempted if published in summary form by abstracting services. Can the accuracy of English language abstracts and commercial translations of foreign literature be assumed?

Response: This policy statement now provides that information published in scientific literature, whether in English or another language, is exempt from reporting if published in summary form by certain specified abstract services.

Comment 21: Information exchange systems with other Federal agencies should be immediately established so that respondents need not report to EPA information already reported to other Agencies, and vice versa. Such duplicative reports are unduly burdensome.

Response: EPA is coordinating this program with other agencies now. When this coordination is successfully completed, the policy statement will be amended to exempt from the reporting requirement information that has been submitted to other specified agencies. In the meantime, substantial-risk information must be reported directly to EPA; such a report does not discharge any reporting obligation to other agencies.

F. INFORMATION FIRST RECEIVED PRIOR TO THE EFFECTIVE DATE OF TSCA

Comment 22: The tense of the verb "obtains" reveals that section 8(e) was intended to be applied prospectively to information newly acquired after January 1, 1977. Utilize section 8(d) or other rules to acquire information obtained before then.

Response: As discussed in the preamble to the September 9 proposal, the Agency considers section 8(e) to apply to risk information possessed by or known to a person before, on, or after January 1, 1977. Concerning information first obtained before 1977, this policy statement continues to require reporting of information received if a person has been aware of it since January 1, 1977, for the reasons discussed in the September 9 preamble.

Comment 23: The term "aware" is too vague to be of any help in responding to these requirements. Since many corporate employees are potentially subject to these requirements, and given uncertainty over the extent to which they ought to be aware of pre-1977 information, this provision tends to compel the very file search it was intended to avoid. The term "aware" should be further defined, possibly in terms of actual knowledge.

Response: The Agency in Part VIII of this policy statement now defines the pre-1977 information of which a person is considered to be aware.

G. CONFIDENTIAL INFORMATION

Comment 24: EPA should delay guidance until procedures are published governing the treatment of confidential submissions.

Comment 25: EPA should treat all submissions as confidential until the information is verified.

Comment 26: EPA should automatically publish section 8(e) notices.

Response to Comments 24 through 26: EPA has included a new Part X which describes how to submit a claim of confidentiality and states that any or all of the information submitted may be claimed as confidential. Such information will be disclosed by EPA only to the extent, and by means of the procedures, set forth in 40 CFR Part 2.

H. MISCELLANEOUS

Comment 27: What is the statutory basis or need for guidance? What is its exact status under the Administrative Procedure Act?

Response: This policy statement sets forth EPA's interpretation of and policy concerning TSCA section 8(e). As an interpretive rule and statement of policy it is not subject to the comment period and delayed effective date provisions of the Administrative Procedure Act (5 U.S.C. 553). Although TSCA does not mandate a policy statement, the Agency of necessity must develop the criteria which will govern enforcement activities. Trade associations and businesses were among those who previously expressed interest in such a statement to guide their compliance.

Comment 28: Clarify whether these requirements apply to chemicals previously but no longer manufactured, processed, or distributed in commerce by a person.

Response: Information obtained before 1977 must be reported if the person has been aware of it since January 1, 1977, as prescribed by Part VIII. Concerning chemicals which a person has discontinued manufacturing, processing, or distributing since January 1, 1977, information obtained before the time of discontinuation is subject to these requirements. It is expected that the acquisition of information after that time will be minimal; however, should additional information be acquired, it may trigger the reporting described in Part VIII.

Comment 29: Clarify the meaning of "substantial risk" relative to other risks addressed by TSCA.

Response: A substantial risk is defined in Part V(a) of this policy statement as a risk of considerable concern because of (a) the seriousness of the effect, and (b) the fact or probability of its occurrence. As opposed to other risks addressed by TSCA, economic or social benefits of use, or costs of restricting use, are not to be considered in determining whether a risk is "substantial".

Comment 30: To what extent are "users" of chemicals subject to these requirements?

Response: The Agency considers that many industrial uses of chemicals actually fall within the scope of "processing" chemicals. A manufacturer, processor, or distributor who obtains substantial-risk information concerning chemicals he handles should be alert to the possibility he may have to report it.

Comment 31: Are chemicals manufactured, processed and distributed in commerce in small quantities solely for purposes of research and development subject to these requirements?

Response: In general, the Agency considers that much manufacturing, processing, and distribution in commerce of chemicals in small quantities solely for purposes of research and development is conducted for "commercial purposes". Such purposes would include the sale and distribution of such materials, as well as their use by the manufacturer or processor in activities (for example, product research and development and studies assessing the feasibility and safety of using chemicals) preceding his or a client's commercial use of such materials or others on a larger scale.

As described in Part V, the Agency considers that "substantial risks" depend in part upon an exposure potential. Thus, the occurrence of the effects described in Part V(a) presuppose exposure to the chemical and must be reported; reporting of the other effects will depend upon a potential for significant levels of exposure.

Comment 32: Are raw materials, intermediates, and inert ingredients produced or used in the manufacture of a pesticide subject to TSCA?

Response: The Administrator considers that raw materials, intermediates and inert ingredients produced or used in the manufacture of a pesticide are substances or mixtures which can be regulated under TSCA.

In order to be considered a pesticide, a substance must be intended for use as a pesticide. Raw materials, intermediates, and inert ingredients produced or used in the manufacture of a pesticide are not themselves regulated under FIFRA (unless they happen to be pesticides themselves) and, therefore, are subject to TSCA. The pesti-

cide regulations at 40 CFR 162.4 are consistent with this view.

Comment 33: Are intermediates and catalysts intended solely for use in the production of a food, food additive, drug, cosmetic, or device subject to TSCA?

Response: The Administrator considers that intermediates and catalysts intended solely for use in the production of a food, food additive, drug, cosmetic, or device are excluded from regulation under TSCA. The definitions of the FFDCA provide that chemical substances which are intended for use as a component of a food, food additive, drug, cosmetic, or device are encompassed within the meaning of such terms, respectively. The FDA considers intermediates and catalysts to be such components. Therefore, they are subject to regulation under the FFDCA. Any such substance is excluded from regulation under TSCA insofar as it is actually manufactured, processed, or distributed in commerce solely for use in the production of a food, food additive, drug, cosmetic, or device.

Comment 34: Employees should have the option to submit reports anonymously.

Response: EPA considers that any person may report information to EPA under TSCA. Those who are required to do so under section 8(e) are persons who manufacture, process, or distribute in commerce chemical substances or mixtures, including not only business entities but also such employees as described in Part II. In order to establish that such persons have discharged their obligations, and in order to encourage responsible review of the quality of information and the substantiality of risks, EPA believes that notifiers should identify themselves. Section 23 will adequately protect employees from discrimination pursuant to notifications they have made under section 8(e).

[FR Doc. 78-7064 Filed 3-15-78; 8:45 am]

NOTE

According to technical amendments published by EPA in the May 29, 1987 FEDERAL REGISTER (52 FR 20083), TSCA Section 8(e) submissions are to be addressed to the Agency as follows:

Document Processing Center (TS-790)
(Attn: Section 8(e) Coordinator)
Office of Toxic Substances
U.S. Environmental Protection Agency
401 "M" Street, S.W.
Washington, D.C. 20460

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 58-08-2 CHEMICAL NAME: CAFFEINE
SUBMISSION #: 8EHQ-0587-0672 S

CAS NUMBER: 58-08-2 CHEMICAL NAME: 1H-PURINE-2,6-DIONE, 3,7-DIHYDRO-1,3,7-TRIMETHYL-
SUBMISSION #: 8EHQ-0587-0672 S

CAS NUMBER: 67-63-0 CHEMICAL NAME: ISOPROPANOL
SUBMISSION #: 8EHQ-1088-0760 S

CAS NUMBER: 67-63-0 CHEMICAL NAME: 2-PROPANOL
SUBMISSION #: 8EHQ-1088-0760 S

CAS NUMBER: 67-64-1 CHEMICAL NAME: ACETONE
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 67-64-1 CHEMICAL NAME: 2-PROPANONE
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 67-66-3 CHEMICAL NAME: CHLOROFORM
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 67-66-3 CHEMICAL NAME: METHANE, TRICHLORO-
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 75-00-3 CHEMICAL NAME: ETHANE, CHLORO-
SUBMISSION #: 8EHQ-0188-0713

CAS NUMBER: 75-09-2 CHEMICAL NAME: METHANE, DICHLORO-
SUBMISSION #: 8EHQ-1188-0772

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 75-09-2 CHEMICAL NAME: METHYLENE CHLORIDE
SUBMISSION #: 8EHQ-1188-0772

CAS NUMBER: 75-15-0 CHEMICAL NAME: CARBON DISULFIDE
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 75-69-4 CHEMICAL NAME: METHANE, TRICHLOROFLUORO-
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 78-30-8 CHEMICAL NAME: PHOSPHORIC ACID, TRIS(2-METHYLPHENYL) ESTER
SUBMISSION #: 8EHQ-0788-0744 S

CAS NUMBER: 78-79-5 CHEMICAL NAME: 1,3-BUTADIENE, 2-METHYL-
SUBMISSION #: 8EHQ-0887-0689 *

CAS NUMBER: 78-79-5 CHEMICAL NAME: ISOPRENE
SUBMISSION #: 8EHQ-0887-0689 *

CAS NUMBER: 78-93-3 CHEMICAL NAME: 2-BUTANONE
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 78-93-3 CHEMICAL NAME: METHYLETHYLKETONE (MEK)
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 78-95-5 CHEMICAL NAME: 2-PROPANONE, 1-CHLORO-
SUBMISSION #: 8EHQ-0387-0660

CAS NUMBER: 78-97-7 CHEMICAL NAME: PROPANENITRILE, 2-HYDROXY-
SUBMISSION #: 8EHQ-0988-0754

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 87-86-5 CHEMICAL NAME: PHENOL, PENTACHLORO-
SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: 89-32-7 CHEMICAL NAME: 1H,3H-BENZO[1,2-C:4,5-C']DIFURAN-1,3,5,7-TETRONE
SUBMISSION #: 8EHQ-1287-0711

CAS NUMBER: 89-32-7 CHEMICAL NAME: PYROMELLITIC DIANHYDRIDE
SUBMISSION #: 8EHQ-1287-0711

CAS NUMBER: 91-20-3 CHEMICAL NAME: NAPHTHALENE
SUBMISSION #: 8EHQ-1287-0704

CAS NUMBER: 94-96-2 CHEMICAL NAME: 1,3-HEXANEDIOL, 2-ETHYL-
SUBMISSION #: 8EHQ-1288-0778

CAS NUMBER: 98-73-7 CHEMICAL NAME: BENZOIC ACID, P-TERT-BUTYL-
SUBMISSION #: 8EHQ-0388-0726 *

CAS NUMBER: 98-73-7 CHEMICAL NAME: BENZOIC ACID, 4-(1,1-DIMETHYLETHYL)-
SUBMISSION #: 8EHQ-0388-0726 *

CAS NUMBER: 99-42-3 CHEMICAL NAME: BENZOIC ACID, 4-HYDROXY-3-NITRO-, METHYL ESTER
SUBMISSION #: 8EHQ-0287-0657 S

CAS NUMBER: 99-66-1 CHEMICAL NAME: PENTANOIC ACID, 2-PROPYL-
SUBMISSION #: 8EHQ-0587-0672 S

CAS NUMBER: 101-54-2 CHEMICAL NAME: 1,4-BENZENEDIAMINE, N-PHENYL-
SUBMISSION #: 8EHQ-0888-0746

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 104-76-7 CHEMICAL NAME: 1-HEXANOL, 2-ETHYL-
SUBMISSION #: 8EHQ-0587-0672 S

CAS NUMBER: 106-89-8 CHEMICAL NAME: EPICHLOROHYDRIN
SUBMISSION #: 8EHQ-1287-0709 S

CAS NUMBER: 106-89-8 CHEMICAL NAME: OXIRANE, (CHLOROMETHYL)-
SUBMISSION #: 8EHQ-1287-0709 S

CAS NUMBER: 106-97-8 CHEMICAL NAME: BUTANE
SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: 107-06-2 CHEMICAL NAME: ETHANE, 1,2-DICHLORO-
SUBMISSION #: 8EHQ-0487-0662

CAS NUMBER: 107-07-3 CHEMICAL NAME: ETHANOL, 2-CHLORO-
SUBMISSION #: 8EHQ-1187-0698

CAS NUMBER: 107-16-4 CHEMICAL NAME: ACETONITRILE, HYDROXY-
SUBMISSION #: 8EHQ-0988-0754

CAS NUMBER: 107-20-0 CHEMICAL NAME: ACETALDEHYDE, CHLORO-
SUBMISSION #: 8EHQ-0387-0660

CAS NUMBER: 107-21-1 CHEMICAL NAME: 1,2-ETHANEDIOL
SUBMISSION #: 8EHQ-1088-0761

CAS NUMBER: 107-21-1 CHEMICAL NAME: ETHYLENE GLYCOL
SUBMISSION #: 8EHQ-1088-0761

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 108-05-4 CHEMICAL NAME: ACETIC ACID ETHENYL ESTER
SUBMISSION #: 8EHQ-0187-0650

CAS NUMBER: 108-05-4 CHEMICAL NAME: VINYL ACETATE
SUBMISSION #: 8EHQ-0187-0650

CAS NUMBER: 108-18-9 CHEMICAL NAME: 2-PROPANAMINE, N-(1-METHYLETHYL)-
SUBMISSION #: 8EHQ-1287-0705

CAS NUMBER: 108-20-3 CHEMICAL NAME: PROPANE, 2,2'-OXYBIS-
SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: 108-95-2 CHEMICAL NAME: PHENOL
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 109-77-3 CHEMICAL NAME: PROPANEDINITRILE
SUBMISSION #: 8EHQ-0988-0754

CAS NUMBER: 111-87-5 CHEMICAL NAME: 1-OCTANOL
SUBMISSION #: 8EHQ-1088-0762

CAS NUMBER: 112-60-7 CHEMICAL NAME: ETHANOL, 2,2'-[OXYBIS(2,1-ETHANEDIYLOXY)]BIS-
SUBMISSION #: 8EHQ-0987-0693

CAS NUMBER: 117-81-7 CHEMICAL NAME: 1,2-BENZENEDICARBOXYLIC ACID, BIS(2-ETHYLHEXYL) ESTER
SUBMISSION #: 8EHQ-0587-0672 S

CAS NUMBER: 123-86-4 CHEMICAL NAME: ACETIC ACID, BUTYL ESTER
SUBMISSION #: 8EHQ-0387-0659

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 123-91-1 CHEMICAL NAME: 1,4-DIOXANE
SUBMISSION #: 8EHQ-1088-0761

CAS NUMBER: 126-99-8 CHEMICAL NAME: 1,3-BUTADIENE, 2-CHLORO-
SUBMISSION #: 8EHQ-0887-0689 *

CAS NUMBER: 126-99-8 CHEMICAL NAME: CHLOROPRENE
SUBMISSION #: 8EHQ-0887-0689 *

CAS NUMBER: 137-40-6 CHEMICAL NAME: MYCOBAN (SODIUM SALT)
SUBMISSION #: 8EHQ-1287-0699

CAS NUMBER: 137-40-6 CHEMICAL NAME: PROPANOIC ACID, SODIUM SALT
SUBMISSION #: 8EHQ-1287-0699

CAS NUMBER: 142-22-3 CHEMICAL NAME: CR-39 MONOMER
SUBMISSION #: 8EHQ-0487-0666 S

CAS NUMBER: 142-22-3 CHEMICAL NAME: 2,5,8,10-TETRAOXATRIDEC-12-ENOIC ACID, 9-OXO-, 2-PROPENYL ESTER
SUBMISSION #: 8EHQ-0487-0666 S

CAS NUMBER: 149-57-5 CHEMICAL NAME: HEXANOIC ACID, 2-ETHYL-
SUBMISSION #: 8EHQ-0587-0672 S 8EHQ-1088-0764 S

CAS NUMBER: 151-21-3 CHEMICAL NAME: SODIUM DODECYL SULFATE (SDS)
SUBMISSION #: 8EHQ-0987-0694 *

CAS NUMBER: 151-21-3 CHEMICAL NAME: SODIUM LAURYL SULFATE (SLS)
SUBMISSION #: 8EHQ-0987-0694 *

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 151-21-3 CHEMICAL NAME: SULFURIC ACID MONODODECYL ESTER SODIUM SALT
SUBMISSION #: 8EHQ-0987-0694 *

CAS NUMBER: 552-30-7 CHEMICAL NAME: 5-ISOBENZOFURANCARBOXYLIC ACID, 1,3-DIHYDRO-1,3-DIOXO-
SUBMISSION #: 8EHQ-1287-0711

CAS NUMBER: 552-30-7 CHEMICAL NAME: TRIMELLITIC ANHYDRIDE
SUBMISSION #: 8EHQ-1287-0711

CAS NUMBER: 556-67-2 CHEMICAL NAME: CYCLOTETRASILOXANE, OCTAMETHYL-
SUBMISSION #: 8EHQ-0288-0718 *

CAS NUMBER: 565-74-2 CHEMICAL NAME: BUTANOIC ACID, 2-BROMO-3-METHYL-
SUBMISSION #: 8EHQ-0188-0714

CAS NUMBER: 593-88-4 CHEMICAL NAME: ARSINE, TRIMETHYL-
SUBMISSION #: 8EHQ-0688-0735

CAS NUMBER: 680-31-9 CHEMICAL NAME: HEXAMETHYLPHOSPHORAMIDE
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 680-31-9 CHEMICAL NAME: PHOSPHORIC TRIAMIDE, HEXAMETHYL-
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 760-67-8 CHEMICAL NAME: HEXANOYL CHLORIDE, 2-ETHYL-
SUBMISSION #: 8EHQ-0387-0656

CAS NUMBER: 768-52-5 CHEMICAL NAME: BENZENAMINE, N-(1-METHYLETHYL)-
SUBMISSION #: 8EHQ-1287-0702 8EHQ-1287-0703

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 872-50-4 CHEMICAL NAME: 2-PYRROLIDINONE, 1-METHYL-
SUBMISSION #: 8EHQ-1087-0695

CAS NUMBER: 941-69-5 CHEMICAL NAME: 1H-PYRROLE-2,5-DIONE, 1-PHENYL-
SUBMISSION #: 8EHQ-0887-0690

CAS NUMBER: 1072-98-6 CHEMICAL NAME: PYRIDINE, 2-AMINO-5-CHLORO-
SUBMISSION #: 8EHQ-0688-0736

CAS NUMBER: 1163-19-5 CHEMICAL NAME: BENZENE, 1,1'-OXYBIS[2,3,4,5,6-PENTABROMO-
SUBMISSION #: 8EHQ-0288-0720

CAS NUMBER: 1309-64-4 CHEMICAL NAME: ANTIMONY OXIDE (SB2O3)
SUBMISSION #: 8EHQ-0688-0737

CAS NUMBER: 1322-93-6 CHEMICAL NAME: NAPHTHALENESULFONIC ACID, BIS(1-METHYLETHYL)-, SODIUM SALT
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 1322-93-6 CHEMICAL NAME: SELLOGEN HR
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 1327-33-9 CHEMICAL NAME: ANTIMONY OXIDE
SUBMISSION #: 8EHQ-0288-0720

CAS NUMBER: 1330-78-5 CHEMICAL NAME: PHOSPHORIC ACID, TRIS(METHYLPHENYL) ESTER
SUBMISSION #: 8EHQ-0788-0744 S

CAS NUMBER: 1332-58-7 CHEMICAL NAME: KAOLIN
SUBMISSION #: 8EHQ-1088-0755

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 1332-58-7 CHEMICAL NAME: SPESWHITE (CLAY)
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 1336-36-3 CHEMICAL NAME: 1,1'-BIPHENYL, CHLORO DERIVS.
SUBMISSION #: 8EHQ-1188-0769 *

CAS NUMBER: 1336-36-3 CHEMICAL NAME: POLYBROMINATED BIPHENYLS (PCB)
SUBMISSION #: 8EHQ-1188-0769 *

CAS NUMBER: 1649-08-7 CHEMICAL NAME: ETHANE, 1,2-DICHLORO-1,1-DIFLUORO-
SUBMISSION #: 8EHQ-0587-0676

CAS NUMBER: 1649-08-7 CHEMICAL NAME: HCFC-132B
SUBMISSION #: 8EHQ-0587-0676

CAS NUMBER: 1746-01-6 CHEMICAL NAME: DIOXIN, 2,3,7,8-TETRACHLORODIBENZO-P-
SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: 1746-81-2 CHEMICAL NAME: ARESIN
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 1746-81-2 CHEMICAL NAME: LINURON, MONO-
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 1746-81-2 CHEMICAL NAME: UREA, N'-(4-CHLOROPHENYL)-N-METHOXY-N-METHYL-
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 1779-17-5 CHEMICAL NAME: 1,3-ISOBENZOFURANDIONE, 5,5'-(1-METHYLETHYLIDENE)BIS-
SUBMISSION #: 8EHQ-1288-0777

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 2004-03-7 CHEMICAL NAME: PURINE, 6-METHYL-

SUBMISSION #: 8EHQ-0388-0723

CAS NUMBER: 2465-27-2 CHEMICAL NAME: AURAMINE HYDROCHLORIDE

SUBMISSION #: 8EHQ-0588-0730

CAS NUMBER: 2465-27-2 CHEMICAL NAME: C. I. BASIC YELLOW 2

SUBMISSION #: 8EHQ-0588-0730

CAS NUMBER: 2465-27-2 CHEMICAL NAME: BENZENAMINE, 4,4'-CARBONIMIDOYLBIS[N,N-DIMETHYL-, MONOHYDROC HLORIDE

SUBMISSION #: 8EHQ-0588-0730

CAS NUMBER: 3033-62-3 CHEMICAL NAME: ETHANAMINE, 2,2'-OXYBIS[N,N-DIMETHYL-

SUBMISSION #: 8EHQ-0687-0683

CAS NUMBER: 3033-62-3 CHEMICAL NAME: NIAX CATALYST A-99

SUBMISSION #: 8EHQ-0687-0683

CAS NUMBER: 3064-70-8 CHEMICAL NAME: METHANE, SULFONYLBIS[TRICHLORO-

SUBMISSION #: 8EHQ-0587-0673

CAS NUMBER: 3126-63-4 CHEMICAL NAME: OXIRANE, 2,2'-[2,2-BIS[(OXIRANYLMETHOXY)METHYL]-1,3-PROPANED IYLBIS(OXYMETHYLENE)]BIS-

SUBMISSION #: 8EHQ-0787-0685

CAS NUMBER: 3236-71-3 CHEMICAL NAME: FLUORENE, 9,9-BIS(4-HYDROXYPHENYL)-

SUBMISSION #: 8EHQ-1287-0700

CAS NUMBER: 3734-67-6 CHEMICAL NAME: C. I. ACID RED 1

SUBMISSION #: 8EHQ-0788-0743

CAS NUMBER: 3734-67-6 CHEMICAL NAME: 2,7-NAPHTHALENEDISULFONIC ACID, 5-(ACETYLAMINO)-4-HYDROXY-3-(PHENYLAZO)-, DISODIUM SALT

SUBMISSION #: 8EHQ-0788-0743

CAS NUMBER: 3734-67-6 CHEMICAL NAME: RED 2G

SUBMISSION #: 8EHQ-0788-0743

CAS NUMBER: 3846-71-7 CHEMICAL NAME: PHENOL, 2-(2H-BENZOTRIAZOL-2-YL)-4,6-BIS(1,1-DIMETHYLETHYL)-

SUBMISSION #: 8EHQ-0888-0747

CAS NUMBER: 3846-71-7 CHEMICAL NAME: TINUVIN 320

SUBMISSION #: 8EHQ-0888-0747

CAS NUMBER: 3864-99-1 CHEMICAL NAME: PHENOL, 2-(5-CHLORO-2H-BENZOTRIAZOL-2-YL)-4,6-BIS(1,1-DIMETHYLETHYL)-

SUBMISSION #: 8EHQ-1088-0756

CAS NUMBER: 3864-99-1 CHEMICAL NAME: TINUVIN 327

SUBMISSION #: 8EHQ-1088-0756

CAS NUMBER: 4075-81-4 CHEMICAL NAME: MYCOBAN (CALCIUM SALT)

SUBMISSION #: 8EHQ-1287-0699

CAS NUMBER: 4075-81-4 CHEMICAL NAME: PROPANOIC ACID, CALCIUM SALT

SUBMISSION #: 8EHQ-1287-0699

CAS NUMBER: 4338-98-1 CHEMICAL NAME: 2(3H)-BENZOTHIAZOLONE, 3-METHYL-, HYDRAZONE, MONOHYDROCHLORIDE

SUBMISSION #: 8EHQ-0287-0654

CAS NUMBER: 5417-82-3 CHEMICAL NAME: PROPANEDINITRILE, (1-ETHOXYETHYLIDENE)-

SUBMISSION #: 8EHQ-0487-0663

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 6262-51-7 CHEMICAL NAME: CYCLOPROPANE, PENTACHLORO-
SUBMISSION #: 8EHQ-0587-0678

CAS NUMBER: 6294-52-6 CHEMICAL NAME: BENZOTHIAZOLE, 2-AMINO-5,6-DIMETHOXY-
SUBMISSION #: 8EHQ-0588-0732

CAS NUMBER: 7173-51-5 CHEMICAL NAME: 1-DECANAMINIUM, N-DECYL-N,N-DIMETHYL-, CHLORIDE
SUBMISSION #: 8EHQ-0188-0712 *

CAS NUMBER: 7440-38-2 CHEMICAL NAME: ARSENIC
SUBMISSION #: 8EHQ-0688-0735 8EHQ-1088-0759

CAS NUMBER: 7440-41-7 CHEMICAL NAME: BERYLLIUM
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 7440-44-0 CHEMICAL NAME: CARBON
SUBMISSION #: 8EHQ-0487-0668

CAS NUMBER: 7440-47-3 CHEMICAL NAME: CHROMIUM
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 7440-66-6 CHEMICAL NAME: ZINC
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 7631-86-9 CHEMICAL NAME: SILICA
SUBMISSION #: 8EHQ-0487-0668

CAS NUMBER: 7647-01-0 CHEMICAL NAME: HYDROCHLORIC ACID
SUBMISSION #: 8EHQ-0887-0688

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 7647-01-0 CHEMICAL NAME: MURIATIC ACID
SUBMISSION #: 8EHQ-0887-0688

CAS NUMBER: 7647-14-5 CHEMICAL NAME: SODIUM CHLORIDE, (NACL)
SUBMISSION #: 8EHQ-0887-0688

CAS NUMBER: 7647-18-9 CHEMICAL NAME: ANTIMONY CHLORIDE (SBCL5)
SUBMISSION #: 8EHQ-0688-0737

CAS NUMBER: 7664-93-9 CHEMICAL NAME: SULFURIC ACID
SUBMISSION #: 8EHQ-0887-0688

CAS NUMBER: 7757-82-6 CHEMICAL NAME: SULFURIC ACID DISODIUM SALT
SUBMISSION #: 8EHQ-0887-0688

CAS NUMBER: 7783-06-4 CHEMICAL NAME: HYDROGEN SULFIDE, (H2S)
SUBMISSION #: 8EHQ-0488-0727

CAS NUMBER: 8005-72-9 CHEMICAL NAME: 7-BENZOTHIAZOLESULFONIC ACID, 6-METHYL-2-(4-(4-(6-METHYL-7-SULFOBENZOTHIAZOL-2-YL)PHENYLAZO)PHENYL)-
SUBMISSION #: 8EHQ-0687-0677

CAS NUMBER: 8005-72-9 CHEMICAL NAME: C.I. DIRECT YELLOW 28
SUBMISSION #: 8EHQ-0687-0677

CAS NUMBER: 8005-72-9 CHEMICAL NAME: PYRAZOL YELLOW BG 250%
SUBMISSION #: 8EHQ-0687-0677

CAS NUMBER: 8005-72-9 CHEMICAL NAME: SOLAR YELLOW RG
SUBMISSION #: 8EHQ-0687-0677

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 8006-14-2 CHEMICAL NAME: NATURAL GAS
SUBMISSION #: 8EHQ-0688-0735

CAS NUMBER: 8061-51-6 CHEMICAL NAME: LIGNOSULFONIC ACID, SODIUM SALT
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 8061-51-6 CHEMICAL NAME: POLYFON H
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 9005-64-5 CHEMICAL NAME: SORBITAN, MONODODECANOATE, POLY(OXY-1,2-ETHANEDIYL) DERIVS.
SUBMISSION #: 8EHQ-0288-0718 *

CAS NUMBER: 9012-09-3 CHEMICAL NAME: CELLULOSE, TRIACETATE
SUBMISSION #: 8EHQ-1188-0772

CAS NUMBER: 9012-09-3 CHEMICAL NAME: TRIACETATE FIBERS, CELLULOSE
SUBMISSION #: 8EHQ-1188-0772

CAS NUMBER: 9016-87-9 CHEMICAL NAME: ISOCYANIC ACID, POLYMETHYLENEPOLYPHENYLENE ESTER
SUBMISSION #: 8EHQ-0788-0741

CAS NUMBER: 10025-91-9 CHEMICAL NAME: ANTIMONY CHLORIDE, (SBCL3)
SUBMISSION #: 8EHQ-0688-0737

CAS NUMBER: 10025-91-9 CHEMICAL NAME: STIBINE, TRICHLORO-
SUBMISSION #: 8EHQ-0688-0737

CAS NUMBER: 11096-82-5 CHEMICAL NAME: AROCHLOR 1260
SUBMISSION #: 8EHQ-1188-0769 *

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 13047-13-7 CHEMICAL NAME: DIMEZONE S
SUBMISSION #: 8EHQ-0287-0653

CAS NUMBER: 13047-13-7 CHEMICAL NAME: IRGAFORM 1266
SUBMISSION #: 8EHQ-0287-0653

CAS NUMBER: 13047-13-7 CHEMICAL NAME: 3-PYRAZOLIDINONE, 4-(HYDROXYMETHYL)-4-METHYL-1-PHENYL-
SUBMISSION #: 8EHQ-0287-0653

CAS NUMBER: 13463-67-7 CHEMICAL NAME: TITANIUM OXIDE (TIO2)
SUBMISSION #: 8EHQ-0487-0668

CAS NUMBER: 13893-53-3 CHEMICAL NAME: BUTANENITRILE, 2-AMINO-2,3-DIMETHYL-
SUBMISSION #: 8EHQ-0988-0754

CAS NUMBER: 14447-15-5 CHEMICAL NAME: ACETIC ACID, CYANO-, PROPYL ESTER
SUBMISSION #: 8EHQ-0688-0739

CAS NUMBER: 14448-67-0 CHEMICAL NAME: 2(3H)-BENZOTHIAZOLONE, 3-METHYL-, HYDROZONE, HYDROCHLORIDE
SUBMISSION #: 8EHQ-0287-0654

CAS NUMBER: 17796-82-6 CHEMICAL NAME: 1H-ISOINDOLE-1,3(2H)-DIONE, 2-(CYCLOHEXYLTHIO)-
SUBMISSION #: 8EHQ-0786-0681

CAS NUMBER: 17796-82-6 CHEMICAL NAME: SANTOGARD PVI
SUBMISSION #: 8EHQ-0786-0681

CAS NUMBER: 25213-39-2 CHEMICAL NAME: 2-PROPENOIC ACID, 2-METHYL-, BUTYL ESTER, POLYMER WITH ETHENYLBENZENE
SUBMISSION #: 8EHQ-0487-0668

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 25322-68-3 CHEMICAL NAME: CARBOWAX PEG-8000

SUBMISSION #: 8EHQ-0488-0728

CAS NUMBER: 25322-68-3 CHEMICAL NAME: POLY(OXY-1,2-ETHANEDIYL), .ALPHA.-HYDRO-.OMEGA.-HYDROXY-

SUBMISSION #: 8EHQ-0488-0728

CAS NUMBER: 25973-55-1 CHEMICAL NAME: PHENOL, 2-(2H-BENZOTRIAZOL-2-YL)-4,6-BIS(1,1-DIMETHYLPROPYL)

SUBMISSION #: 8EHQ-0988-0748

CAS NUMBER: 25973-55-1 CHEMICAL NAME: TINUVIN 328

SUBMISSION #: 8EHQ-0988-0748

CAS NUMBER: 26741-53-7 CHEMICAL NAME: 2,4,8,10-TETRAOXA-3,9-DIPHOSPHASPIRO[5.5]UNDECANE, 3,9-BIS[2,4-BIS(1,1-DIMETHYLETHYL)PHENOXY]-

SUBMISSION #: 8EHQ-1287-0706

CAS NUMBER: 26741-53-7 CHEMICAL NAME: ULTRANOX 624

SUBMISSION #: 8EHQ-1287-0706

CAS NUMBER: 26741-53-7 CHEMICAL NAME: ULTRANOX 626

SUBMISSION #: 8EHQ-1287-0706

CAS NUMBER: 26741-53-7 CHEMICAL NAME: ULTRANOX 626A

SUBMISSION #: 8EHQ-1287-0706

CAS NUMBER: 26741-53-7 CHEMICAL NAME: WESTON MDW-6140

SUBMISSION #: 8EHQ-1287-0706

CAS NUMBER: 26741-53-7 CHEMICAL NAME: WESTON XR-1452

SUBMISSION #: 8EHQ-1287-0706

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 26741-53-7 CHEMICAL NAME: WESTON XR-1532

SUBMISSION #: 8EHQ-1287-0706

CAS NUMBER: 27193-86-8 CHEMICAL NAME: PHENOL, DODECYL-

SUBMISSION #: 8EHQ-0687-0682

CAS NUMBER: 30965-26-5 CHEMICAL NAME: 1,4-BENZENEDICARBOXYLIC ACID, DIMETHYL ESTER, POLYMER WITH 1,4-BUTANEDIOL

SUBMISSION #: 8EHQ-0288-0720

CAS NUMBER: 36443-68-2 CHEMICAL NAME: BENZENEPROPANOIC ACID, 3-(1,1-DIMETHYLETHYL)-4-HYDROXY-5-METHYL-, 1,2-ETHANEDIYLBIS(OXY-2,1-ETHANEDIYL) ESTER

SUBMISSION #: 8EHQ-0388-0725

CAS NUMBER: 36443-68-2 CHEMICAL NAME: IRGANOX 245

SUBMISSION #: 8EHQ-0388-0725

CAS NUMBER: 43130-12-7 CHEMICAL NAME: AURAMINE, ETHYL-, NITRATE SALT

SUBMISSION #: 8EHQ-0588-0730

CAS NUMBER: 43130-12-7 CHEMICAL NAME: C. I. BASIC YELLOW 37

SUBMISSION #: 8EHQ-0588-0730

CAS NUMBER: 43130-12-7 CHEMICAL NAME: BENZENAMINE, 4,4'-CARBONIMIDOYLBIS[N,N-DIETHYL-, MONONITRATE

SUBMISSION #: 8EHQ-0588-0730

CAS NUMBER: 52495-71-3 CHEMICAL NAME: POLY(OXY-1,2-ETHANEDIYL), A-HYDRO-W-(OXIRANYLMETHOXY)-, ETHER WITH 2-ETHYL-2-(HYDROXYMETHYL)-1,3-PROPANEDIOL (3:1)

SUBMISSION #: 8EHQ-1287-0709 S

CAS NUMBER: 55283-68-6 CHEMICAL NAME: BENZENAMINE, N-ETHYL-N-(2-METHYL-2-PROPENYL)-2,6-DINITRO-4-(TRIFLUOROMETHYL)-

SUBMISSION #: 8EHQ-1088-0755

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 55283-68-6 CHEMICAL NAME: ETHALFLURALIN
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 55283-68-6 CHEMICAL NAME: SONALAN
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 55406-53-6 CHEMICAL NAME: CARBAMIC ACID, BUTYL-, 3-IODO-2-PROPYNYL ESTER
SUBMISSION #: 8EHQ-0188-0712 *

CAS NUMBER: 59607-71-5 CHEMICAL NAME: THIOCYANIC ACID, 4-METHOXY-2-NITROPHENYL ESTER
SUBMISSION #: 8EHQ-0388-0721

CAS NUMBER: 61789-36-4 CHEMICAL NAME: NAPHTHENIC ACIDS, CALCIUM SALTS
SUBMISSION #: 8EHQ-0587-0675 *

CAS NUMBER: 63231-67-4 CHEMICAL NAME: HI-SIL 233
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 63231-67-4 CHEMICAL NAME: SILICA GEL
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 63943-38-4 CHEMICAL NAME: POLY[(DIMETHYLIMINIO)-1,6-HEXANEDIYL(DIMETHYLIMINIO)METHYLENE[1,1'-BIPHENYL]-4,4'-DIYLMETHYLENE DICHLORIDE]
SUBMISSION #: 8EHQ-0487-0661 S

CAS NUMBER: 64741-52-2 CHEMICAL NAME: DISTILLATES (PETROLEUM), LIGHT NAPHTHENIC
SUBMISSION #: 8EHQ-0887-0691 S

CAS NUMBER: 64741-53-3 CHEMICAL NAME: DISTILLATES (PETROLEUM), HEAVY NAPHTHENIC
SUBMISSION #: 8EHQ-0887-0691 S

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 64741-56-6 CHEMICAL NAME: RESIDUES (PETROLEUM), VACUUM
SUBMISSION #: 8EHQ-0488-0727

CAS NUMBER: 64741-60-2 CHEMICAL NAME: DISTILLATES (PETROLEUM), INTERMEDIATE CATALYTIC CRACKED
SUBMISSION #: 8EHQ-0488-0727

CAS NUMBER: 64741-62-4 CHEMICAL NAME: CLARIFIED OILS, (PETROLEUM), CATALYTIC CRACKED
SUBMISSION #: 8EHQ-0488-0727

CAS NUMBER: 64741-75-9 CHEMICAL NAME: RESID HYDROPROCESSING UNIT (RHU) LIGHT VACUUM GAS OILS
SUBMISSION #: 8EHQ-1288-0774

CAS NUMBER: 64741-75-9 CHEMICAL NAME: RESIDUES, (PETROLEUM), HYDROCRACKED
SUBMISSION #: 8EHQ-1288-0774

CAS NUMBER: 64741-76-0 CHEMICAL NAME: DISTILLATES (PETROLEUM), HEAVY HYDROCRACKED
SUBMISSION #: 8EHQ-1288-0773

CAS NUMBER: 64741-76-0 CHEMICAL NAME: RESID HYDROPROCESSING UNIT (RHU) MIDDLE DISTILLATES
SUBMISSION #: 8EHQ-1288-0773

CAS NUMBER: 64741-88-4 CHEMICAL NAME: DISTILLATES (PETROLEUM), SOLVENT-REFINED HEAVY PARAFFINIC
SUBMISSION #: 8EHQ-0887-0691 S

CAS NUMBER: 64742-46-7 CHEMICAL NAME: AMOCO NT-45 PROCESS OIL
SUBMISSION #: 8EHQ-1288-0775

CAS NUMBER: 64742-46-7 CHEMICAL NAME: DISTILLATES (PETROLEUM), HYDROTREATED MIDDLE
SUBMISSION #: 8EHQ-1288-0775

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 64742-52-5 CHEMICAL NAME: DISTILLATES, (PETROLEUM), HYDROTREATED HEAVY NAPHTHENIC
SUBMISSION #: 8EHQ-0887-0691 S

CAS NUMBER: 64742-53-6 CHEMICAL NAME: DISTILLATES (PETROLEUM), HYDROTREATED LIGHT NAPHTHENIC
SUBMISSION #: 8EHQ-0887-0691 S

CAS NUMBER: 64742-65-0 CHEMICAL NAME: DISTILLATES (PETROLEUM), SOLVENT-DEWAXED HEAVY PARAFFINIC
SUBMISSION #: 8EHQ-0887-0691 S

CAS NUMBER: 64742-86-5 CHEMICAL NAME: GAS OILS, (PETROLEUM), HYDRODESULFURIZED HEAVY VACUUM
SUBMISSION #: 8EHQ-0887-0687 8EHQ-1287-0710

CAS NUMBER: 64742-87-6 CHEMICAL NAME: GAS OILS, (PETROLEUM), HYDRODESULFURIZED LIGHT VACUUM
SUBMISSION #: 8EHQ-1287-0710

CAS NUMBER: 64742-95-6 CHEMICAL NAME: SOLVENT NAPHTHA (PETROLEUM), LIGHT AROM.
SUBMISSION #: 8EHQ-0587-0673

CAS NUMBER: 68214-81-3 CHEMICAL NAME: CHEMICAL 400, STEP 1
SUBMISSION #: 8EHQ-0288-0719

CAS NUMBER: 68214-81-3 CHEMICAL NAME: ETHANOL, 2-[ETHYL[3-METHYL-4-(PHENYLAZO)PHENYL]AMINO]-
SUBMISSION #: 8EHQ-0288-0719

CAS NUMBER: 68334-30-5 CHEMICAL NAME: FUELS, DIESEL
SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: 68334-30-5 CHEMICAL NAME: OIL (PETROLEUM), DIESEL
SUBMISSION #: 8EHQ-0487-0671

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 68412-01-1 CHEMICAL NAME: D-GLUCITOL, REACTION PRODUCTS WITH EPICHLOROHYDRIN

SUBMISSION #: 8EHQ-0687-0679

CAS NUMBER: 68476-30-2 CHEMICAL NAME: FUEL OIL, NO. 2

SUBMISSION #: 8EHQ-1187-0697

CAS NUMBER: 68476-30-2 CHEMICAL NAME: OIL (PETROLEUM), FURNACE

SUBMISSION #: 8EHQ-1187-0697

CAS NUMBER: 68553-00-4 CHEMICAL NAME: FUEL OIL, NO. 6

SUBMISSION #: 8EHQ-0488-0727

CAS NUMBER: 87257-05-4 CHEMICAL NAME: OXIRANE, 2,2'-(3,7,7,11-TETRAMETHYL-2,5,9,12-TETRAOXATRIDECANE-1,13-DIYL)BIS-

SUBMISSION #: 8EHQ-1287-0709 S

CAS NUMBER: 94361-06-5 CHEMICAL NAME: SAN 619F

SUBMISSION #: 8EHQ-0287-0658

CAS NUMBER: 94361-06-5 CHEMICAL NAME: 1H-1,2,4-TRIAZOLE-1-ETHANOL, .ALPHA.-(4-CHLOROPHENYL)-.ALPHA.-(1-CYCLOPROPYLETHYL)-, (R*,R*)-(.+-.)-

SUBMISSION #: 8EHQ-0287-0658

CAS NUMBER: 107534-96-3 CHEMICAL NAME: TERBUCONAZOLE

SUBMISSION #: 8EHQ-0688-0738

Based on a preliminary evaluation, EPA believed that the submitted information did not warrant reporting under Section 8(e) of TSCA. In most cases, the submitter was requested to provide the basis for contending that the information offered reasonable support for the conclusion that the subject chemical substance(s) or mixture(s) presents a substantial risk of injury to health or the environment as defined in EPA's TSCA Section 8(e) policy statement (see Appendix A of this volume).

CAS NUMBER: 107-20-0 CHEMICAL NAME: ACETALDEHYDE, CHLORO-
SUBMISSION #: 8EHQ-0387-0660

CAS NUMBER: CONFIDENT CHEMICAL NAME: ACETAL, HETEROCYCLIC
SUBMISSION #: 8EHQ-1188-0770 S

CAS NUMBER: 123-86-4 CHEMICAL NAME: ACETIC ACID, BUTYL ESTER
SUBMISSION #: 8EHQ-0387-0659

CAS NUMBER: 14447-15-5 CHEMICAL NAME: ACETIC ACID, CYANO-, PROPYL ESTER
SUBMISSION #: 8EHQ-0688-0739

CAS NUMBER: 108-05-4 CHEMICAL NAME: ACETIC ACID ETHENYL ESTER
SUBMISSION #: 8EHQ-0187-0650

CAS NUMBER: UNKNOWN CHEMICAL NAME: ACETIC ACID, OXO-, METHYL ESTER OR ETHYL ESTER, HOMOPOLYMER, REACTION PRODUCTS WITH ETHOXYETHENE AND REACTION PRODUCTS W ITH METHOXYETHENE, SODIUM SALTS
SUBMISSION #: 8EHQ-0987-0692

CAS NUMBER: 67-64-1 CHEMICAL NAME: ACETONE
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 107-16-4 CHEMICAL NAME: ACETONITRILE, HYDROXY-
SUBMISSION #: 8EHQ-0988-0754

CAS NUMBER: CONFIDENT CHEMICAL NAME: ACETOPHENONE OXIME
SUBMISSION #: 8EHQ-1287-0708 S

CAS NUMBER: 3734-67-6 CHEMICAL NAME: C. I. ACID RED 1
SUBMISSION #: 8EHQ-0788-0743

CAS NUMBER: CONFIDENT CHEMICAL NAME: ACRYLIC ACID DERIVATIVES
SUBMISSION #: 8EHQ-1288-0776

CAS NUMBER: CONFIDENT CHEMICAL NAME: ALKYL HETEROCYCLIC NITROGEN COMPOUND
SUBMISSION #: 8EHQ-1088-0760 S

CAS NUMBER: CONFIDENT CHEMICAL NAME: ALKYL PHENOL, MODIFIED
SUBMISSION #: 8EHQ-0787-0686 S

CAS NUMBER: CONFIDENT CHEMICAL NAME: AMIDE, HETEROCYCLIC ARYL
SUBMISSION #: 8EHQ-0988-0750 S

CAS NUMBER: NONE CHEMICAL NAME: AMINE MIXTURE
SUBMISSION #: 8EHQ-0287-0652 S

CAS NUMBER: CONFIDENT CHEMICAL NAME: AMMONIUM CARBOXYLATE, SUBSTITUTED
SUBMISSION #: 8EHQ-0587-0674 S

CAS NUMBER: 64742-46-7 CHEMICAL NAME: AMOCO NT-45 PROCESS OIL
SUBMISSION #: 8EHQ-1288-0775

CAS NUMBER: 10025-91-9 CHEMICAL NAME: ANTIMONY CHLORIDE, (SBCL3)
SUBMISSION #: 8EHQ-0688-0737

CAS NUMBER: 7647-18-9 CHEMICAL NAME: ANTIMONY CHLORIDE (SBCL5)
SUBMISSION #: 8EHQ-0688-0737

CAS NUMBER: 1327-33-9 CHEMICAL NAME: ANTIMONY OXIDE
SUBMISSION #: 8EHQ-0288-0720

CAS NUMBER: 1309-64-4 CHEMICAL NAME: ANTIMONY OXIDE (SB2O3)
SUBMISSION #: 8EHQ-0688-0737

CAS NUMBER: NONE CHEMICAL NAME: ARCEL RESIN ANTISTAT
SUBMISSION #: 8EHQ-0287-0652 S

CAS NUMBER: 1746-81-2 CHEMICAL NAME: ARESIN
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 11096-82-5 CHEMICAL NAME: AROCHLOR 1260
SUBMISSION #: 8EHQ-1188-0769 *

CAS NUMBER: 7440-38-2 CHEMICAL NAME: ARSENIC
SUBMISSION #: 8EHQ-0688-0735 8EHQ-1088-0759

CAS NUMBER: 593-88-4 CHEMICAL NAME: ARSINE, TRIMETHYL-
SUBMISSION #: 8EHQ-0688-0735

CAS NUMBER: CONFIDENT CHEMICAL NAME: ARYL OXIME
SUBMISSION #: 8EHQ-1188-0765 S

CAS NUMBER: 43130-12-7 CHEMICAL NAME: AURAMINE, ETHYL-, NITRATE SALT
SUBMISSION #: 8EHQ-0588-0730

CAS NUMBER: 2465-27-2 CHEMICAL NAME: AURAMINE HYDROCHLORIDE
SUBMISSION #: 8EHQ-0588-0730

CAS NUMBER: 2465-27-2 CHEMICAL NAME: C. I. BASIC YELLOW 2
SUBMISSION #: 8EHQ-0588-0730

CAS NUMBER: 43130-12-7 CHEMICAL NAME: C. I. BASIC YELLOW 37
SUBMISSION #: 8EHQ-0588-0730

CAS NUMBER: 55283-68-6 CHEMICAL NAME: BENZENAMINE, N-ETHYL-N-(2-METHYL-2-PROPENYL)-2,6-DINITRO-4-(TRIFLUOROMETHYL)-
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 768-52-5 CHEMICAL NAME: BENZENAMINE, N-(1-METHYLETHYL)-
SUBMISSION #: 8EHQ-1287-0702 8EHQ-1287-0703

CAS NUMBER: 43130-12-7 CHEMICAL NAME: BENZENAMINE, 4,4'-CARBONIMIDOYLBIS[N,N-DIETHYL-, MONONITRATE
SUBMISSION #: 8EHQ-0588-0730

CAS NUMBER: 2465-27-2 CHEMICAL NAME: BENZENAMINE, 4,4'-CARBONIMIDOYLBIS[N,N-DIMETHYL-, MONOHYDROCHLORIDE
SUBMISSION #: 8EHQ-0588-0730

CAS NUMBER: 101-54-2 CHEMICAL NAME: 1,4-BENZENEDIAMINE, N-PHENYL-
SUBMISSION #: 8EHQ-0888-0746

CAS NUMBER: 117-81-7 CHEMICAL NAME: 1,2-BENZENEDICARBOXYLIC ACID, BIS(2-ETHYLHEXYL) ESTER
SUBMISSION #: 8EHQ-0587-0672 S

CAS NUMBER: UNKNOWN CHEMICAL NAME: 1,2-BENZENEDICARBOXYLIC ACID DERIV.
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 30965-26-5 CHEMICAL NAME: 1,4-BENZENEDICARBOXYLIC ACID, DIMETHYL ESTER, POLYMER WITH 1,4-BUTANEDIOL
SUBMISSION #: 8EHQ-0288-0720

CAS NUMBER: 36443-68-2 CHEMICAL NAME: BENZENEPROPANOIC ACID, 3-(1,1-DIMETHYLETHYL)-4-HYDROXY-5-METHYL-, 1,2-ETHANEDIYLBIS(OXY-2,1-ETHANEDIYL) ESTER
SUBMISSION #: 8EHQ-0388-0725

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-0288-0720
CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, BROMINATED DERIV.

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-0588-0731 S
CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, SUBSTITUTED

CAS NUMBER: 1163-19-5
SUBMISSION #: 8EHQ-0288-0720
CHEMICAL NAME: BENZENE, 1,1'-OXYBIS[2,3,4,5,6-PENTABROMO-

CAS NUMBER: 98-73-7
SUBMISSION #: 8EHQ-0388-0726
CHEMICAL NAME: BENZOIC ACID, P-TERT-BUTYL-
*

CAS NUMBER: 99-42-3
SUBMISSION #: 8EHQ-0287-0657 S
CHEMICAL NAME: BENZOIC ACID, 4-HYDROXY-3-NITRO-, METHYL ESTER

CAS NUMBER: 98-73-7
SUBMISSION #: 8EHQ-0388-0726
CHEMICAL NAME: BENZOIC ACID, 4-(1,1-DIMETHYLETHYL)-
*

CAS NUMBER: 8005-72-9
SUBMISSION #: 8EHQ-0687-0677
CHEMICAL NAME: 7-BENZOTHIAZOLESULFONIC ACID, 6-METHYL-2-(4-(4-(6-METHYL-7-SULFOBENZOTHIAZOL-2-YL)PHENYLAZO)PHENYL)-

CAS NUMBER: 6294-52-6
SUBMISSION #: 8EHQ-0588-0732
CHEMICAL NAME: BENZOTHIAZOLE, 2-AMINO-5,6-DIMETHOXY-

CAS NUMBER: 4338-98-1
SUBMISSION #: 8EHQ-0287-0654
CHEMICAL NAME: 2(3H)-BENZOTHIAZOLONE, 3-METHYL-, HYDRAZONE, MONOHYDROCHLORIDE

CAS NUMBER: 14448-67-0
SUBMISSION #: 8EHQ-0287-0654
CHEMICAL NAME: 2(3H)-BENZOTHIAZOLONE, 3-METHYL-, HYDROZONE, HYDROCHLORIDE

CAS NUMBER: 89-32-7 CHEMICAL NAME: 1H,3H-BENZO[1,2-C:4,5-C']DIFURAN-1,3,5,7-TETRONE
SUBMISSION #: 8EHQ-1287-0711

CAS NUMBER: 7440-41-7 CHEMICAL NAME: BERYLLIUM
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 1336-36-3 CHEMICAL NAME: 1,1'-BIPHENYL, CHLORO DERIVS.
SUBMISSION #: 8EHQ-1188-0769 *

CAS NUMBER: CONFIDENT CHEMICAL NAME: BORDON CHEMICAL COMPOUND 9MKU10108R
SUBMISSION #: 8EHQ-1288-0776

CAS NUMBER: CONFIDENT CHEMICAL NAME: BSC-125 SURFACTANT
SUBMISSION #: 8EHQ-0487-0665 S *

CAS NUMBER: 126-99-8 CHEMICAL NAME: 1,3-BUTADIENE, 2-CHLORO-
SUBMISSION #: 8EHQ-0887-0689 *

CAS NUMBER: 78-79-5 CHEMICAL NAME: 1,3-BUTADIENE, 2-METHYL-
SUBMISSION #: 8EHQ-0887-0689 *

CAS NUMBER: 106-97-8 CHEMICAL NAME: BUTANE
SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: 13893-53-3 CHEMICAL NAME: BUTANENITRILE, 2-AMINO-2,3-DIMETHYL-
SUBMISSION #: 8EHQ-0988-0754

CAS NUMBER: 565-74-2 CHEMICAL NAME: BUTANOIC ACID, 2-BROMO-3-METHYL-
SUBMISSION #: 8EHQ-0188-0714

CAS NUMBER: 78-93-3 CHEMICAL NAME: 2-BUTANONE
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 58-08-2 CHEMICAL NAME: CAFFEINE
SUBMISSION #: 8EHQ-0587-0672 S

CAS NUMBER: 55406-53-6 CHEMICAL NAME: CARBAMIC ACID, BUTYL-, 3-IODO-2-PROPYNYL ESTER
SUBMISSION #: 8EHQ-0188-0712 *

CAS NUMBER: CONFIDENT CHEMICAL NAME: CARBOMONOCYCLIC AMINOBUTYROLACTONE
SUBMISSION #: 8EHQ-0788-0745 S

CAS NUMBER: 7440-44-0 CHEMICAL NAME: CARBON
SUBMISSION #: 8EHQ-0487-0668

CAS NUMBER: 75-15-0 CHEMICAL NAME: CARBON DISULFIDE
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: CONFIDENT CHEMICAL NAME: CARBONOCHLORIDOTHIOIC ACID, ARYL ESTER
SUBMISSION #: 8EHQ-0487-0667 S *

CAS NUMBER: 25322-68-3 CHEMICAL NAME: CARBOWAX PEG-8000
SUBMISSION #: 8EHQ-0488-0728

CAS NUMBER: NONE CHEMICAL NAME: CATALYSTS
SUBMISSION #: 8EHQ-1287-0699

CAS NUMBER: 9012-09-3 CHEMICAL NAME: CELLULOSE, TRIACETATE
SUBMISSION #: 8EHQ-1188-0772

CAS NUMBER: 68214-81-3 CHEMICAL NAME: CHEMICAL 400, STEP 1
SUBMISSION #: 8EHQ-0288-0719

CAS NUMBER: 67-66-3 CHEMICAL NAME: CHLOROFORM
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 126-99-8 CHEMICAL NAME: CHLOROPRENE
SUBMISSION #: 8EHQ-0887-0689 *

CAS NUMBER: 7440-47-3 CHEMICAL NAME: CHROMIUM
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 64741-62-4 CHEMICAL NAME: CLARIFIED OILS, (PETROLEUM), CATALYTIC CRACKED
SUBMISSION #: 8EHQ-0488-0727

CAS NUMBER: CONFIDENT CHEMICAL NAME: CONFIDENTIAL
SUBMISSION #: 8EHQ-0187-0649 S

CAS NUMBER: NONE CHEMICAL NAME: COOLANTS, AUTOMOTIVE
SUBMISSION #: 8EHQ-1088-0761

CAS NUMBER: 142-22-3 CHEMICAL NAME: CR-39 MONOMER
SUBMISSION #: 8EHQ-0487-0666 S

CAS NUMBER: NONE CHEMICAL NAME: CUTTING FLUID
SUBMISSION #: 8EHQ-0788-0742 *

CAS NUMBER: CONFIDENT CHEMICAL NAME: CYCLOHEXENONE, SUBSTITUTED
SUBMISSION #: 8EHQ-1088-0758 S

CAS NUMBER: 6262-51-7 CHEMICAL NAME: CYCLOPROPANE, PENTACHLORO-
SUBMISSION #: 8EHQ-0587-0678

CAS NUMBER: 556-67-2 CHEMICAL NAME: CYCLOTETRASILOXANE, OCTAMETHYL-
SUBMISSION #: 8EHQ-0288-0718 *

CAS NUMBER: 7173-51-5 CHEMICAL NAME: 1-DECANAMINIUM, N-DECYL-N,N-DIMETHYL-, CHLORIDE
SUBMISSION #: 8EHQ-0188-0712 *

CAS NUMBER: NONE CHEMICAL NAME: DE-ICING FLUIDS, AIRCRAFT
SUBMISSION #: 8EHQ-1088-0761

CAS NUMBER: CONFIDENT CHEMICAL NAME: DIAMINE, ALKOXYLATED AROMATIC
SUBMISSION #: 8EHQ-0187-0649 S

CAS NUMBER: NONE CHEMICAL NAME: DIBENZOFURANS, BROMINATED
SUBMISSION #: 8EHQ-0288-0720

CAS NUMBER: 13047-13-7 CHEMICAL NAME: DIMEZONE S
SUBMISSION #: 8EHQ-0287-0653

CAS NUMBER: 123-91-1 CHEMICAL NAME: 1,4-DIOXANE
SUBMISSION #: 8EHQ-1088-0761

CAS NUMBER: NONE CHEMICAL NAME: DIOXIN, HEPTACHLORODIBENZO-P-
SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: NONE CHEMICAL NAME: DIOXIN, HEXACHLORODIBENZO-P-
SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: NONE
CHEMICAL NAME: DIOXIN, OCTACHLORODIBENZO-P-
SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: NONE
CHEMICAL NAME: DIOXIN, PENTACHLORODIBENZO-P-
SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: NONE
CHEMICAL NAME: DIOXINS, BROMINATED
SUBMISSION #: 8EHQ-0288-0720

CAS NUMBER: NONE
CHEMICAL NAME: DIOXINS, CHLORINATED
SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: NONE
CHEMICAL NAME: DIOXIN, TETRACHLORODIBENZO-P-
SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: 1746-01-6
CHEMICAL NAME: DIOXIN, 2,3,7,8-TETRACHLORODIBENZO-P-
SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: CONFIDENT
CHEMICAL NAME: DIPHENYL ETHER, SUBSTITUTED
SUBMISSION #: 8EHQ-0588-0731 S

CAS NUMBER: 8005-72-9
CHEMICAL NAME: C.I. DIRECT YELLOW 28
SUBMISSION #: 8EHQ-0687-0677

CAS NUMBER: 64741-76-0
CHEMICAL NAME: DISTILLATES (PETROLEUM), HEAVY HYDROCRACKED
SUBMISSION #: 8EHQ-1288-0773

CAS NUMBER: 64741-53-3
CHEMICAL NAME: DISTILLATES (PETROLEUM), HEAVY NAPHTHENIC
SUBMISSION #: 8EHQ-0887-0691 S

CAS NUMBER: 64742-52-5 CHEMICAL NAME: DISTILLATES, (PETROLEUM), HYDROTREATED HEAVY NAPHTHENIC
SUBMISSION #: 8EHQ-0887-0691 S

CAS NUMBER: 64742-53-6 CHEMICAL NAME: DISTILLATES (PETROLEUM), HYDROTREATED LIGHT NAPHTHENIC
SUBMISSION #: 8EHQ-0887-0691 S

CAS NUMBER: 64742-46-7 CHEMICAL NAME: DISTILLATES (PETROLEUM), HYDROTREATED MIDDLE
SUBMISSION #: 8EHQ-1288-0775

CAS NUMBER: 64741-60-2 CHEMICAL NAME: DISTILLATES (PETROLEUM), INTERMEDIATE CATALYTIC CRACKED
SUBMISSION #: 8EHQ-0488-0727

CAS NUMBER: 64741-52-2 CHEMICAL NAME: DISTILLATES (PETROLEUM), LIGHT NAPHTHENIC
SUBMISSION #: 8EHQ-0887-0691 S

CAS NUMBER: 64742-65-0 CHEMICAL NAME: DISTILLATES (PETROLEUM), SOLVENT-DEWAXED HEAVY PARAFFINIC
SUBMISSION #: 8EHQ-0887-0691 S

CAS NUMBER: 64741-88-4 CHEMICAL NAME: DISTILLATES (PETROLEUM), SOLVENT-REFINED HEAVY PARAFFINIC
SUBMISSION #: 8EHQ-0887-0691 S

CAS NUMBER: NONE CHEMICAL NAME: DOW CORNING S-5370 RTV
SUBMISSION #: 8EHQ-0787-0684 S

CAS NUMBER: 106-89-8 CHEMICAL NAME: EPICHLOROHYDRIN
SUBMISSION #: 8EHQ-1287-0709 S

CAS NUMBER: 55283-68-6 CHEMICAL NAME: ETHALFLURALIN
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 3033-62-3 CHEMICAL NAME: ETHANAMINE, 2,2'-OXYBIS[N,N-DIMETHYL-
SUBMISSION #: 8EHQ-0687-0683

CAS NUMBER: 75-00-3 CHEMICAL NAME: ETHANE, CHLORO-
SUBMISSION #: 8EHQ-0188-0713

CAS NUMBER: 107-21-1 CHEMICAL NAME: 1,2-ETHANEDIOL
SUBMISSION #: 8EHQ-1088-0761

CAS NUMBER: 107-06-2 CHEMICAL NAME: ETHANE, 1,2-DICHLORO-
SUBMISSION #: 8EHQ-0487-0662

CAS NUMBER: 1649-08-7 CHEMICAL NAME: ETHANE, 1,2-DICHLORO-1,1-DIFLUORO-
SUBMISSION #: 8EHQ-0587-0676

CAS NUMBER: NONE CHEMICAL NAME: ETHANOL (STRONG ACID PRODUCTION PROCESS)
SUBMISSION #: 8EHQ-1287-0701 *

CAS NUMBER: 107-07-3 CHEMICAL NAME: ETHANOL, 2-CHLORO-
SUBMISSION #: 8EHQ-1187-0698

CAS NUMBER: 68214-81-3 CHEMICAL NAME: ETHANOL, 2-[ETHYL[3-METHYL-4-(PHENYLAZO)PHENYL]AMINO]-
SUBMISSION #: 8EHQ-0288-0719

CAS NUMBER: 112-60-7 CHEMICAL NAME: ETHANOL, 2,2'-[OXYBIS(2,1-ETHANEDIYLOXY)]BIS-
SUBMISSION #: 8EHQ-0987-0693

CAS NUMBER: CONFIDENT CHEMICAL NAME: ETHER, ALKYL ARYL
SUBMISSION #: 8EHQ-1188-0771 S

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-0487-0664 S
CHEMICAL NAME: ETHER (CYCLIC), HALOALKYL SUBSTITUTED

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-0988-0751 S
CHEMICAL NAME: ETHER, DIARYL

CAS NUMBER: 107-21-1
SUBMISSION #: 8EHQ-1088-0761
CHEMICAL NAME: ETHYLENE GLYCOL

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-0988-0752 S
CHEMICAL NAME: FIBER, INORGANIC

CAS NUMBER: 3236-71-3
SUBMISSION #: 8EHQ-1287-0700
CHEMICAL NAME: FLUORENE, 9,9-BIS(4-HYDROXYPHENYL)-

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-0688-0738
CHEMICAL NAME: FOLICUR TECHNICAL

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-0688-0738
CHEMICAL NAME: FOLICUR 1.2 EC

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-0288-0722
CHEMICAL NAME: FREKOTE 700

CAS NUMBER: 68476-30-2
SUBMISSION #: 8EHQ-1187-0697
CHEMICAL NAME: FUEL OIL, NO. 2

CAS NUMBER: UNKNOWN
SUBMISSION #: 8EHQ-1187-0697
CHEMICAL NAME: FUEL OIL, NO. 2, SUBFRACTIONS

CAS NUMBER: 68553-00-4 CHEMICAL NAME: FUEL OIL, NO. 6
SUBMISSION #: 8EHQ-0488-0727

CAS NUMBER: 68334-30-5 CHEMICAL NAME: FUELS, DIESEL
SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: 64742-86-5 CHEMICAL NAME: GAS OILS, (PETROLEUM), HYDRODESULFURIZED HEAVY VACUUM
SUBMISSION #: 8EHQ-0887-0687 8EHQ-1287-0710

CAS NUMBER: 64742-87-6 CHEMICAL NAME: GAS OILS, (PETROLEUM), HYDRODESULFURIZED LIGHT VACUUM
SUBMISSION #: 8EHQ-1287-0710

CAS NUMBER: 68412-01-1 CHEMICAL NAME: D-GLUCITOL, REACTION PRODUCTS WITH EPICHLOROHYDRIN
SUBMISSION #: 8EHQ-0687-0679

CAS NUMBER: CONFIDENT CHEMICAL NAME: HALOALKYL HETEROCYCLE
SUBMISSION #: 8EHQ-1188-0767 S

CAS NUMBER: NONE CHEMICAL NAME: N-1386 HAN
SUBMISSION #: 8EHQ-0587-0673

CAS NUMBER: 1649-08-7 CHEMICAL NAME: HCFC-132B
SUBMISSION #: 8EHQ-0587-0676

CAS NUMBER: CONFIDENT CHEMICAL NAME: HETEROARYL ALKYL ETHER
SUBMISSION #: 8EHQ-1188-0766 S

CAS NUMBER: 680-31-9 CHEMICAL NAME: HEXAMETHYLPHOSPHORAMIDE
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 94-96-2 CHEMICAL NAME: 1,3-HEXANEDIOL, 2-ETHYL-
SUBMISSION #: 8EHQ-1288-0778

CAS NUMBER: 149-57-5 CHEMICAL NAME: HEXANOIC ACID, 2-ETHYL-
SUBMISSION #: 8EHQ-0587-0672 S 8EHQ-1088-0764 S

CAS NUMBER: 104-76-7 CHEMICAL NAME: 1-HEXANOL, 2-ETHYL-
SUBMISSION #: 8EHQ-0587-0672 S

CAS NUMBER: 760-67-8 CHEMICAL NAME: HEXANOYL CHLORIDE, 2-ETHYL-
SUBMISSION #: 8EHQ-0387-0656

CAS NUMBER: 63231-67-4 CHEMICAL NAME: HI-SIL 233
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 7647-01-0 CHEMICAL NAME: HYDROCHLORIC ACID
SUBMISSION #: 8EHQ-0887-0688

CAS NUMBER: 7783-06-4 CHEMICAL NAME: HYDROGEN SULFIDE, (H2S)
SUBMISSION #: 8EHQ-0488-0727

CAS NUMBER: UNKNOWN CHEMICAL NAME: 2-IMIDAZOLIDINONE, 1,3-DIBROMO-4,4,5,5-TETRAMETHYL-
SUBMISSION #: 8EHQ-0487-0669 *

CAS NUMBER: UNKNOWN CHEMICAL NAME: 2-IMIDAZOLIDINONE, 1,3-DICHLORO-4,4,5,5-TETRAMETHYL-
SUBMISSION #: 8EHQ-0487-0669 *

CAS NUMBER: NONE CHEMICAL NAME: IMPOSIT
SUBMISSION #: 8EHQ-0488-0728

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-0988-0753 S
CHEMICAL NAME: INDOLENINIUM SALT

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-1188-0768 S
CHEMICAL NAME: INORGANIC POTASSIUM HALIDE COMPLEX

CAS NUMBER: 13047-13-7
SUBMISSION #: 8EHQ-0287-0653
CHEMICAL NAME: IRGAFORM 1266

CAS NUMBER: 36443-68-2
SUBMISSION #: 8EHQ-0388-0725
CHEMICAL NAME: IRGANOX 245

CAS NUMBER: 552-30-7
SUBMISSION #: 8EHQ-1287-0711
CHEMICAL NAME: 5-ISOBENZOFURANCARBOXYLIC ACID, 1,3-DIHYDRO-1,3-DIOXO-

CAS NUMBER: 1779-17-5
SUBMISSION #: 8EHQ-1288-0777
CHEMICAL NAME: 1,3-ISOBENZOFURANDIONE, 5,5'-(1-METHYLETHYLIDENE)BIS-

CAS NUMBER: 9016-87-9
SUBMISSION #: 8EHQ-0788-0741
CHEMICAL NAME: ISOCYANIC ACID, POLYMETHYLENEPOLYPHENYLENE ESTER

CAS NUMBER: 17796-82-6
SUBMISSION #: 8EHQ-0786-0681
CHEMICAL NAME: 1H-ISOINDOLE-1,3(2H)-DIONE, 2-(CYCLOHEXYLTHIO)-

CAS NUMBER: 78-79-5
SUBMISSION #: 8EHQ-0887-0689 *
CHEMICAL NAME: ISOPRENE

CAS NUMBER: 67-63-0
SUBMISSION #: 8EHQ-1088-0760 S
CHEMICAL NAME: ISOPROPANOL

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-1287-0701
CHEMICAL NAME: ISOPROPANOL (STRONG ACID PRODUCTION PROCESS)
*

CAS NUMBER: 1332-58-7
SUBMISSION #: 8EHQ-1088-0755
CHEMICAL NAME: KAOLIN

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-0488-0728
CHEMICAL NAME: LEDERMIX

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-0188-0712
CHEMICAL NAME: LH-25 PRESERVATIVE
*

CAS NUMBER: 8061-51-6
SUBMISSION #: 8EHQ-1088-0755
CHEMICAL NAME: LIGNOSULFONIC ACID, SODIUM SALT

CAS NUMBER: 1746-81-2
SUBMISSION #: 8EHQ-1088-0755
CHEMICAL NAME: LINURON, MONO-

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-0688-0738
CHEMICAL NAME: LYNX 1.2

CAS NUMBER: 75-09-2
SUBMISSION #: 8EHQ-1188-0772
CHEMICAL NAME: METHANE, DICHLORO-

CAS NUMBER: 3064-70-8
SUBMISSION #: 8EHQ-0587-0673
CHEMICAL NAME: METHANE, SULFONYLBIS[TRICHLORO-

CAS NUMBER: 67-66-3
SUBMISSION #: 8EHQ-1088-0759
CHEMICAL NAME: METHANE, TRICHLORO-

CAS NUMBER: 75-69-4 CHEMICAL NAME: METHANE, TRICHLOROFLUORO-
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 75-09-2 CHEMICAL NAME: METHYLENE CHLORIDE
SUBMISSION #: 8EHQ-1188-0772

CAS NUMBER: 78-93-3 CHEMICAL NAME: METHYLETHYLKETONE (MEK)
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: NONE CHEMICAL NAME: MISC. CHEMICALS
SUBMISSION #: 8EHQ-1287-0699 8EHQ-1287-0701 * 8EHQ-0288-0722

CAS NUMBER: 7647-01-0 CHEMICAL NAME: MURIATIC ACID
SUBMISSION #: 8EHQ-0887-0688

CAS NUMBER: 4075-81-4 CHEMICAL NAME: MYCOBAN (CALCIUM SALT)
SUBMISSION #: 8EHQ-1287-0699

CAS NUMBER: 137-40-6 CHEMICAL NAME: MYCOBAN (SODIUM SALT)
SUBMISSION #: 8EHQ-1287-0699

CAS NUMBER: 91-20-3 CHEMICAL NAME: NAPHTHALENE
SUBMISSION #: 8EHQ-1287-0704

CAS NUMBER: UNKNOWN CHEMICAL NAME: NAPHTHALENE, DIIODO-
SUBMISSION #: 8EHQ-0687-0680

CAS NUMBER: 3734-67-6 CHEMICAL NAME: 2,7-NAPHTHALENEDISULFONIC ACID, 5-(ACETYLAMINO)-4-HYDROXY-3-(PHENYLAZO)-, DISODIUM SALT
SUBMISSION #: 8EHQ-0788-0743

CAS NUMBER: UNKNOWN — CHEMICAL NAME: NAPHTHALENES, DI-, TRI-, AND TETRAIODO-, MIXED
SUBMISSION #: 8EHQ-0687-0680

CAS NUMBER: 1322-93-6 — CHEMICAL NAME: NAPHTHALENESULFONIC ACID, BIS(1-METHYLETHYL)-, SODIUM SALT
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: UNKNOWN — CHEMICAL NAME: NAPHTHALENE, TETRAIODO-
SUBMISSION #: 8EHQ-0687-0680

CAS NUMBER: UNKNOWN — CHEMICAL NAME: NAPHTHALENE, TRIIODO-
SUBMISSION #: 8EHQ-0687-0680

CAS NUMBER: 61789-36-4 — CHEMICAL NAME: NAPHTHENIC ACIDS, CALCIUM SALTS
SUBMISSION #: 8EHQ-0587-0675 *

CAS NUMBER: 8006-14-2 — CHEMICAL NAME: NATURAL GAS
SUBMISSION #: 8EHQ-0688-0735

CAS NUMBER: 3033-62-3 — CHEMICAL NAME: NIAX CATALYST A-99
SUBMISSION #: 8EHQ-0687-0683

CAS NUMBER: CONFIDENT — CHEMICAL NAME: NITROBENZENE, SUBSTITUTED
SUBMISSION #: 8EHQ-0487-0670 S

CAS NUMBER: 111-87-5 — CHEMICAL NAME: 1-OCTANOL
SUBMISSION #: 8EHQ-1088-0762

CAS NUMBER: NONE — CHEMICAL NAME: OIL, JET ENGINE
SUBMISSION #: 8EHQ-0788-0744 S

CAS NUMBER: 68334-30-5 CHEMICAL NAME: OIL (PETROLEUM), DIESEL
SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: 68476-30-2 CHEMICAL NAME: OIL (PETROLEUM), FURNACE
SUBMISSION #: 8EHQ-1187-0697

CAS NUMBER: UNKNOWN CHEMICAL NAME: OIL (PETROLEUM), FURNACE, SUBFRACTIONS
SUBMISSION #: 8EHQ-1187-0697

CAS NUMBER: UNKNOWN CHEMICAL NAME: OIL (PETROLEUM), MINERAL CARRIER
SUBMISSION #: 8EHQ-0587-0675 *

CAS NUMBER: CONFIDENT CHEMICAL NAME: OLEFIN, SULFURIZED
SUBMISSION #: 8EHQ-0587-0674 S

CAS NUMBER: 106-89-8 CHEMICAL NAME: OXIRANE, (CHLOROMETHYL)-
SUBMISSION #: 8EHQ-1287-0709 S

CAS NUMBER: CONFIDENT CHEMICAL NAME: OXIRANE, METHYL-, POLYMER WITH OXIRANE, BLOCKED
SUBMISSION #: 8EHQ-0487-0665 S *

CAS NUMBER: 3126-63-4 CHEMICAL NAME: OXIRANE, 2,2'-[2,2-BIS[(OXIRANYLMETHOXY)METHYL]-1,3-PROPANEDIYLBIS(OXYMETHYLENE)]BIS-
SUBMISSION #: 8EHQ-0787-0685

CAS NUMBER: 87257-05-4 CHEMICAL NAME: OXIRANE, 2,2'-(3,7,7,11-TETRAMETHYL-2,5,9,12-TETRAOXATRIDECANE-1,13-DIYL)BIS-
SUBMISSION #: 8EHQ-1287-0709 S

CAS NUMBER: NONE CHEMICAL NAME: PALLADIUM PLATING COMPOUND
SUBMISSION #: 8EHQ-0588-0733

CAS NUMBER: NONE
CHEMICAL NAME: PD MAKEUP
SUBMISSION #: 8EHQ-0588-0733

CAS NUMBER: 99-66-1
CHEMICAL NAME: PENTANOIC ACID, 2-PROPYL-
SUBMISSION #: 8EHQ-0587-0672 S

CAS NUMBER: 108-95-2
CHEMICAL NAME: PHENOL
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: NONE
CHEMICAL NAME: PHENOL DERIVATIVES, STERICALLY HINDERED, MIXTURE
SUBMISSION #: 8EHQ-0388-0724 S

CAS NUMBER: CONFIDENT
CHEMICAL NAME: PHENOL DERIVATIVE, STERICALLY HINDERED
SUBMISSION #: 8EHQ-0388-0724 S

CAS NUMBER: 27193-86-8
CHEMICAL NAME: PHENOL, DODECYL-
SUBMISSION #: 8EHQ-0687-0682

CAS NUMBER: 87-86-5
CHEMICAL NAME: PHENOL, PENTACHLORO-
SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: 3846-71-7
CHEMICAL NAME: PHENOL, 2-(2H-BENZOTRIAZOL-2-YL)-4,6-BIS(1,1-DIMETHYLETHYL)-
SUBMISSION #: 8EHQ-0888-0747

CAS NUMBER: 25973-55-1
CHEMICAL NAME: PHENOL, 2-(2H-BENZOTRIAZOL-2-YL)-4,6-BIS(1,1-DIMETHYLPROPYL)
SUBMISSION #: 8EHQ-0988-0748

CAS NUMBER: 3864-99-1
CHEMICAL NAME: PHENOL, 2-(5-CHLORO-2H-BENZOTRIAZOL-2-YL)-4,6-BIS(1,1-DIMETH YLETHYL)-
SUBMISSION #: 8EHQ-1088-0756

CAS NUMBER: 1330-78-5 CHEMICAL NAME: PHOSPHORIC ACID, TRIS(METHYLPHENYL) ESTER
SUBMISSION #: 8EHQ-0788-0744 S

CAS NUMBER: 78-30-8 CHEMICAL NAME: PHOSPHORIC ACID, TRIS(2-METHYLPHENYL) ESTER
SUBMISSION #: 8EHQ-0788-0744 S

CAS NUMBER: 680-31-9 CHEMICAL NAME: PHOSPHORIC TRIAMIDE, HEXAMETHYL-
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: NONE CHEMICAL NAME: PHOTOCOPYING PRODUCTS/PROCESS
SUBMISSION #: 8EHQ-0487-0668

CAS NUMBER: CONFIDENT CHEMICAL NAME: PHTHALIMIDE (III), SUBSTITUTED
SUBMISSION #: 8EHQ-1088-0758 S

CAS NUMBER: CONFIDENT CHEMICAL NAME: PHTHALIMIDE (II), SUBSTITUTED
SUBMISSION #: 8EHQ-1088-0758 S

CAS NUMBER: CONFIDENT CHEMICAL NAME: PHTHALIMIDE (I), SUBSTITUTED
SUBMISSION #: 8EHQ-1088-0758 S

CAS NUMBER: 1336-36-3 CHEMICAL NAME: POLYBROMINATED BIPHENYLS (PCB)
SUBMISSION #: 8EHQ-1188-0769 *

CAS NUMBER: 63943-38-4 CHEMICAL NAME: POLY[(DIMETHYLIMINIO)-1,6-HEXANEDIYL(DIMETHYLIMINIO)METHYLENE[1,1'-BIPHENYL]-4,4'-DIYLMETHYLENE DICHLORIDE]
SUBMISSION #: 8EHQ-0487-0661 S

CAS NUMBER: CONFIDENT CHEMICAL NAME: POLYESTER, MODIFIED ALIPHATIC ALICYCLIC
SUBMISSION #: 8EHQ-0688-0734 S

CAS NUMBER: 8061-51-6 CHEMICAL NAME: POLYFON H

SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: UNKNOWN CHEMICAL NAME: POLYGLYCIDYL ETHYL, 2,2,6,6-TETRAMETHYLOL CYCLOHEXANOL

SUBMISSION #: 8EHQ-0288-0715

CAS NUMBER: 52495-71-3 CHEMICAL NAME: POLY(OXY-1,2-ETHANEDIYL), A-HYDRO-W-(OXIRANYLMETHOXY)-, ETHER WITH 2-ETHYL-2-(HYDROXYMETHYL)-1,3-PROPANEDIOL (3:1)

SUBMISSION #: 8EHQ-1287-0709 S

CAS NUMBER: 25322-68-3 CHEMICAL NAME: POLY(OXY-1,2-ETHANEDIYL), .ALPHA.-HYDRO-.OMEGA.-HYDROXY-

SUBMISSION #: 8EHQ-0488-0728

CAS NUMBER: 108-18-9 CHEMICAL NAME: 2-PROPANAMINE, N-(1-METHYLETHYL)-

SUBMISSION #: 8EHQ-1287-0705

CAS NUMBER: 109-77-3 CHEMICAL NAME: PROPANEDINITRILE

SUBMISSION #: 8EHQ-0988-0754

CAS NUMBER: 5417-82-3 CHEMICAL NAME: PROPANEDINITRILE, (1-ETHOXYETHYLIDENE)-

SUBMISSION #: 8EHQ-0487-0663

CAS NUMBER: 78-97-7 CHEMICAL NAME: PROPANENITRILE, 2-HYDROXY-

SUBMISSION #: 8EHQ-0988-0754

CAS NUMBER: 108-20-3 CHEMICAL NAME: PROPANE, 2,2'-OXYBIS-

SUBMISSION #: 8EHQ-0487-0671

CAS NUMBER: 4075-81-4 CHEMICAL NAME: PROPANOIC ACID, CALCIUM SALT

SUBMISSION #: 8EHQ-1287-0699

CAS NUMBER: 137-40-6 CHEMICAL NAME: PROPANOIC ACID, SODIUM SALT
SUBMISSION #: 8EHQ-1287-0699

CAS NUMBER: 67-63-0 CHEMICAL NAME: 2-PROPANOL
SUBMISSION #: 8EHQ-1088-0760 S

CAS NUMBER: UNKNOWN CHEMICAL NAME: 2-PROPANOL, 1-[BIS(2-HYDROXYETHYL)AMINO]-3-(4-ISONONYLPHENOXY)-
SUBMISSION #: 8EHQ-1088-0757

CAS NUMBER: 67-64-1 CHEMICAL NAME: 2-PROPANONE
SUBMISSION #: 8EHQ-1088-0759

CAS NUMBER: 78-95-5 CHEMICAL NAME: 2-PROPANONE, 1-CHLORO-
SUBMISSION #: 8EHQ-0387-0660

CAS NUMBER: CONFIDENT CHEMICAL NAME: 2-PROPENOIC ACID DERIVATIVES
SUBMISSION #: 8EHQ-1288-0776

CAS NUMBER: 25213-39-2 CHEMICAL NAME: 2-PROPENOIC ACID, 2-METHYL-, BUTYL ESTER, POLYMER WITH ETHENYLBENZENE
SUBMISSION #: 8EHQ-0487-0668

CAS NUMBER: 58-08-2 CHEMICAL NAME: 1H-PURINE-2,6-DIONE, 3,7-DIHYDRO-1,3,7-TRIMETHYL-
SUBMISSION #: 8EHQ-0587-0672 S

CAS NUMBER: 2004-03-7 CHEMICAL NAME: PURINE, 6-METHYL-
SUBMISSION #: 8EHQ-0388-0723

CAS NUMBER: 13047-13-7 CHEMICAL NAME: 3-PYRAZOLIDINONE, 4-(HYDROXYMETHYL)-4-METHYL-1-PHENYL-
SUBMISSION #: 8EHQ-0287-0653

CAS NUMBER: CONFIDENT CHEMICAL NAME: 2-PYRAZOLIN-5-ONE, 1-PHENYL-ALKYLAMINO-
SUBMISSION #: 8EHQ-0287-0655 S

CAS NUMBER: 8005-72-9 CHEMICAL NAME: PYRAZOL YELLOW BG 250%
SUBMISSION #: 8EHQ-0687-0677

CAS NUMBER: CONFIDENT CHEMICAL NAME: PYRIDINE, ALKYL
SUBMISSION #: 8EHQ-0988-0749 S

CAS NUMBER: CONFIDENT CHEMICAL NAME: PYRIDINECARBOXYLATE
SUBMISSION #: 8EHQ-1287-0707 S 8EHQ-0288-0716 S 8EHQ-0288-0717 S

CAS NUMBER: 1072-98-6 CHEMICAL NAME: PYRIDINE, 2-AMINO-5-CHLORO-
SUBMISSION #: 8EHQ-0688-0736

CAS NUMBER: 89-32-7 CHEMICAL NAME: PYROMELLITIC DIANHYDRIDE
SUBMISSION #: 8EHQ-1287-0711

CAS NUMBER: 941-69-5 CHEMICAL NAME: 1H-PYRROLE-2,5-DIONE, 1-PHENYL-
SUBMISSION #: 8EHQ-0887-0690

CAS NUMBER: 872-50-4 CHEMICAL NAME: 2-PYRROLIDINONE, 1-METHYL-
SUBMISSION #: 8EHQ-1087-0695

CAS NUMBER: 3734-67-6 CHEMICAL NAME: RED 2G
SUBMISSION #: 8EHQ-0788-0743

CAS NUMBER: 64741-75-9 CHEMICAL NAME: RESID HYDROPROCESSING UNIT (RHU) LIGHT VACUUM GAS OILS
SUBMISSION #: 8EHQ-1288-0774

CAS NUMBER: 64741-76-0 CHEMICAL NAME: RESID HYDROPROCESSING UNIT (RHU) MIDDLE DISTILLATES
SUBMISSION #: 8EHQ-1288-0773

CAS NUMBER: 64741-75-9 CHEMICAL NAME: RESIDUES, (PETROLEUM), HYDROCRACKED
SUBMISSION #: 8EHQ-1288-0774

CAS NUMBER: 64741-56-6 CHEMICAL NAME: RESIDUES (PETROLEUM), VACUUM
SUBMISSION #: 8EHQ-0488-0727

CAS NUMBER: 17796-82-6 CHEMICAL NAME: SANTOGARD PVI
SUBMISSION #: 8EHQ-0786-0681

CAS NUMBER: 94361-06-5 CHEMICAL NAME: SAN 619F
SUBMISSION #: 8EHQ-0287-0658

CAS NUMBER: NONE CHEMICAL NAME: SAPSTAIN CONTROL CHEMICAL NP-1
SUBMISSION #: 8EHQ-0188-0712 *

CAS NUMBER: NONE CHEMICAL NAME: SCOTCHWELD AF-163-2 OST
SUBMISSION #: 8EHQ-0288-0722

CAS NUMBER: 1322-93-6 CHEMICAL NAME: SELLOGEN HR
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: CONFIDENT CHEMICAL NAME: SILANE
SUBMISSION #: 8EHQ-0688-0734 S

CAS NUMBER: 7631-86-9 CHEMICAL NAME: SILICA
SUBMISSION #: 8EHQ-0487-0668

CAS NUMBER: 63231-67-4 CHEMICAL NAME: SILICA GEL
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 7647-14-5 CHEMICAL NAME: SODIUM CHLORIDE, (NACL)
SUBMISSION #: 8EHQ-0887-0688

CAS NUMBER: 151-21-3 CHEMICAL NAME: SODIUM DODECYL SULFATE (SDS)
SUBMISSION #: 8EHQ-0987-0694 *

CAS NUMBER: 151-21-3 CHEMICAL NAME: SODIUM LAURYL SULFATE (SLS)
SUBMISSION #: 8EHQ-0987-0694 *

CAS NUMBER: 8005-72-9 CHEMICAL NAME: SOLAR YELLOW RG
SUBMISSION #: 8EHQ-0687-0677

CAS NUMBER: 64742-95-6 CHEMICAL NAME: SOLVENT NAPHTHA (PETROLEUM), LIGHT AROM.
SUBMISSION #: 8EHQ-0587-0673

CAS NUMBER: 55283-68-6 CHEMICAL NAME: SONALAN
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 9005-64-5 CHEMICAL NAME: SORBITAN, MONODODECANOATE, POLY(OXY-1,2-ETHANEDIYL) DERIVS.
SUBMISSION #: 8EHQ-0288-0718 *

CAS NUMBER: 1332-58-7 CHEMICAL NAME: SPESWHITE (CLAY)
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 10025-91-9 CHEMICAL NAME: STIBINE, TRICHLORO-
SUBMISSION #: 8EHQ-0688-0737

CAS NUMBER: CONFIDENT
CHEMICAL NAME: SULFLURAMID, ETHYL
SUBMISSION #: 8EHQ-0488-0729 S

CAS NUMBER: 7664-93-9
CHEMICAL NAME: SULFURIC ACID
SUBMISSION #: 8EHQ-0887-0688

CAS NUMBER: 7757-82-6
CHEMICAL NAME: SULFURIC ACID DISODIUM SALT
SUBMISSION #: 8EHQ-0887-0688

CAS NUMBER: 151-21-3
CHEMICAL NAME: SULFURIC ACID MONODODECYL ESTER SODIUM SALT
SUBMISSION #: 8EHQ-0987-0694 *

CAS NUMBER: NONE
CHEMICAL NAME: SURFACTANTS (NON-IONIC), ALKOXYLATED
SUBMISSION #: 8EHQ-1087-0696

CAS NUMBER: 107534-96-3
CHEMICAL NAME: TERBUCONAZOLE
SUBMISSION #: 8EHQ-0688-0738

CAS NUMBER: 142-22-3
CHEMICAL NAME: 2,5,8,10-TETRAOXATRIDEC-12-ENOIC ACID, 9-OXO-, 2-PROPENYL ESTER
SUBMISSION #: 8EHQ-0487-0666 S

CAS NUMBER: 26741-53-7
CHEMICAL NAME: 2,4,8,10-TETRAOXA-3,9-DIPHOSPHASPIRO[5.5]UNDECANE, 3,9-BIS[2,4-BIS(1,1-DIMETHYLETHYL)PHENOXY]-
SUBMISSION #: 8EHQ-1287-0706

CAS NUMBER: CONFIDENT
CHEMICAL NAME: THIADIAZOLE SULFONAMIDE, ALKYLAMINOCARBONYL SUBSTITUTED
SUBMISSION #: 8EHQ-1088-0763 S

CAS NUMBER: CONFIDENT
CHEMICAL NAME: THIAZINOHYDRAZINE, SUBSTITUTED
SUBMISSION #: 8EHQ-0688-0740 S

CAS NUMBER: 59607-71-5 CHEMICAL NAME: THIOCYANIC ACID, 4-METHOXY-2-NITROPHENYL ESTER
SUBMISSION #: 8EHQ-0388-0721

CAS NUMBER: 3846-71-7 CHEMICAL NAME: TINUVIN 320
SUBMISSION #: 8EHQ-0888-0747

CAS NUMBER: 3864-99-1 CHEMICAL NAME: TINUVIN 327
SUBMISSION #: 8EHQ-1088-0756

CAS NUMBER: 25973-55-1 CHEMICAL NAME: TINUVIN 328
SUBMISSION #: 8EHQ-0988-0748

CAS NUMBER: 13463-67-7 CHEMICAL NAME: TITANIUM OXIDE (TIO2)
SUBMISSION #: 8EHQ-0487-0668

CAS NUMBER: CONFIDENT CHEMICAL NAME: TOLYLCYCLOALKENYL SUBSTITUTED ALKYL ESTER
SUBMISSION #: 8EHQ-1088-0764 S

CAS NUMBER: CONFIDENT CHEMICAL NAME: TOLYLCYCLOALKENYL SUBSTITUTED PHOSPHOROTHIOATE ESTER
SUBMISSION #: 8EHQ-1088-0764 S

CAS NUMBER: 9012-09-3 CHEMICAL NAME: TRIACETATE FIBERS, CELLULOSE
SUBMISSION #: 8EHQ-1188-0772

CAS NUMBER: 107534-96-3 CHEMICAL NAME: 1H-1,2,4-TRIAZOLE-1-ETHANOL, .ALPHA.-[2-(4-CHLOROPHENYL)ETHYL]-.ALPHA.-(1,1-DIMETHYLETHYL)-(.+-.)-
SUBMISSION #: 8EHQ-0688-0738

CAS NUMBER: 94361-06-5 CHEMICAL NAME: 1H-1,2,4-TRIAZOLE-1-ETHANOL, .ALPHA.-(4-CHLOROPHENYL)-.ALPHA.-(1-CYCLOPROPYLETHYL)-, (R*,R*)-(.+-.)-
SUBMISSION #: 8EHQ-0287-0658

CAS NUMBER: 552-30-7 CHEMICAL NAME: TRIMELLITIC ANHYDRIDE
SUBMISSION #: 8EHQ-1287-0711

CAS NUMBER: 26741-53-7 CHEMICAL NAME: ULTRANOX 624
SUBMISSION #: 8EHQ-1287-0706

CAS NUMBER: 26741-53-7 CHEMICAL NAME: ULTRANOX 626
SUBMISSION #: 8EHQ-1287-0706

CAS NUMBER: 26741-53-7 CHEMICAL NAME: ULTRANOX 626A
SUBMISSION #: 8EHQ-1287-0706

CAS NUMBER: NONE CHEMICAL NAME: UNKNOWN CHEMICAL(S)
SUBMISSION #: 8EHQ-0187-0651 *

CAS NUMBER: 1746-81-2 CHEMICAL NAME: UREA, N'-(4-CHLOROPHENYL)-N-METHOXY-N-METHYL-
SUBMISSION #: 8EHQ-1088-0755

CAS NUMBER: 108-05-4 CHEMICAL NAME: VINYL ACETATE
SUBMISSION #: 8EHQ-0187-0650

CAS NUMBER: 26741-53-7 CHEMICAL NAME: WESTON MDW-6140
SUBMISSION #: 8EHQ-1287-0706

CAS NUMBER: 26741-53-7 CHEMICAL NAME: WESTON XR-1452
SUBMISSION #: 8EHQ-1287-0706

CAS NUMBER: 26741-53-7 CHEMICAL NAME: WESTON XR-1532
SUBMISSION #: 8EHQ-1287-0706

CAS NUMBER: NONE

CHEMICAL NAME: XEROX 9000-TYPE XEROGRAPHIC TONER

SUBMISSION #: 8EHQ-0487-0668

CAS NUMBER: CONFIDENT

CHEMICAL NAME: XYLYLCYCLOALKENYL SUBSTITUTED ALKYL ESTER

SUBMISSION #: 8EHQ-1088-0764 S

* Based on a preliminary evaluation, EPA believed that the submitted information did not warrant reporting under Section 8(e) of TSCA. In most cases, the submitter was requested to provide the basis for contending that the information offered reasonable support for the conclusion that the subject chemical substance(s) or mixture(s) presents a substantial risk of injury to health or the environment as defined in EPA's TSCA Section 8(e) policy statement (see Appendix A of this volume).

APPENDIX (D): STATUS REPORTS BY INFORMATION TYPE

ACUTE TOXICITY (ANIMAL)

SUBMISSION #:	8EHQ-0287-0652 S	8EHQ-0287-0653	8EHQ-0287-0654
	8EHQ-0287-0655 S	8EHQ-0387-0656	8EHQ-0287-0657 S
	8EHQ-0387-0659	8EHQ-0387-0660	8EHQ-0487-0661 S
	8EHQ-0487-0663	8EHQ-0487-0665 S *	8EHQ-0487-0666 S
	8EHQ-0487-0667 S *	8EHQ-0487-0669 *	8EHQ-0487-0670 S
	8EHQ-0587-0673	8EHQ-0587-0678	8EHQ-0687-0680
	8EHQ-0787-0686 S	8EHQ-1087-0696	8EHQ-1287-0700
	8EHQ-1287-0706	8EHQ-1287-0707 S	8EHQ-0188-0714
	8EHQ-0388-0721	8EHQ-0388-0723	8EHQ-0588-0732
	8EHQ-0688-0739	8EHQ-0688-0740 S	8EHQ-0788-0742 *
	8EHQ-0788-0744 S	8EHQ-0988-0753 S	8EHQ-0988-0754
	8EHQ-1088-0760 S	8EHQ-1088-0762	8EHQ-1188-0768 S
	8EHQ-1288-0778		

ACUTE TOXICITY (HUMAN)

SUBMISSION #:	8EHQ-0487-0666 S	8EHQ-0487-0671	8EHQ-1287-0700
	8EHQ-0688-0736	8EHQ-1088-0755	

ALLERGENICITY (ANIMAL)

SUBMISSION #:	8EHQ-0287-0653	8EHQ-0287-0657 S	8EHQ-0487-0661 S
	8EHQ-0687-0680	8EHQ-0787-0686 S	8EHQ-0887-0690
	8EHQ-1287-0700	8EHQ-1287-0711	8EHQ-0188-0712 *
	8EHQ-0388-0721	8EHQ-0588-0733	8EHQ-0688-0739
	8EHQ-0688-0740 S	8EHQ-1188-0768 S	8EHQ-1288-0777
	8EHQ-1288-0778		

APPENDIX (D): STATUS REPORTS BY INFORMATION TYPE

ALLERGENICITY (HUMAN)

SUBMISSION #:	8EHQ-0987-0694	*	8EHQ-0488-0728		

CELL TRANSFORMATION (IN VITRO)

SUBMISSION #:	8EHQ-0687-0679				

CHEMICAL/PHYSICAL PROPERTIES

SUBMISSION #:	8EHQ-0287-0653		8EHQ-0287-0654		8EHQ-0287-0655 S
	8EHQ-0387-0656		8EHQ-0287-0657 S		8EHQ-0387-0659
	8EHQ-0487-0661 S		8EHQ-0487-0663		8EHQ-0487-0666 S
	8EHQ-0487-0667 S	*	8EHQ-0487-0668		8EHQ-0587-0673
	8EHQ-0587-0678		8EHQ-0687-0679		8EHQ-0687-0680
	8EHQ-0687-0682		8EHQ-0787-0686 S		8EHQ-0887-0691 S
	8EHQ-1287-0706		8EHQ-1287-0711		8EHQ-0288-0720
	8EHQ-0388-0721		8EHQ-0488-0727		8EHQ-0588-0732
	8EHQ-0688-0739		8EHQ-0688-0740 S		8EHQ-0788-0741
	8EHQ-1088-0755		8EHQ-1088-0757		8EHQ-1088-0762
	8EHQ-1188-0768 S		8EHQ-1288-0778		

CHRONIC TOXICITY (ANIMAL)

SUBMISSION #:	8EHQ-0187-0650		8EHQ-0487-0668		8EHQ-0587-0675 *
	8EHQ-0786-0681		8EHQ-0787-0684 S		8EHQ-0887-0687
	8EHQ-0887-0691 S		8EHQ-0987-0692		8EHQ-1187-0697
	8EHQ-1287-0704		8EHQ-1287-0708 S		8EHQ-1287-0710
	8EHQ-0188-0713		8EHQ-0388-0725		8EHQ-0588-0730
	8EHQ-0788-0741		8EHQ-0788-0745 S		8EHQ-0988-0752 S

APPENDIX (D): STATUS REPORTS BY INFORMATION TYPE

CHRONIC TOXICITY (ANIMAL)

SUBMISSION #:	8EHQ-1088-0760	S	8EHQ-1288-0773	8EHQ-1288-0774	
	8EHQ-1288-0775				

CHRONIC TOXICITY (HUMAN)

SUBMISSION #:	8EHQ-0187-0651	*	8EHQ-0887-0688	8EHQ-0987-0694	*
	8EHQ-1187-0698		8EHQ-1287-0699	8EHQ-1287-0701	*
	8EHQ-1188-0772				

CLASTOGENICITY (ANIMAL)

SUBMISSION #:	8EHQ-0887-0689	*	8EHQ-0987-0692	8EHQ-0987-0693	
	8EHQ-1088-0758	S	8EHQ-1288-0776		

CLASTOGENICITY (IN VITRO)

SUBMISSION #:	8EHQ-0687-0679		8EHQ-0787-0685	8EHQ-0787-0686	S
	8EHQ-0987-0693		8EHQ-0288-0715	8EHQ-1088-0758	S

DNA DAMAGE/REPAIR

SUBMISSION #:	8EHQ-0187-0649	S	8EHQ-0687-0679	8EHQ-0787-0685	
	8EHQ-0987-0692		8EHQ-0288-0715	8EHQ-0688-0737	

ECOTOXICITY/AQUATIC TOXICITY

SUBMISSION #:	8EHQ-0287-0653		8EHQ-0487-0666	S	8EHQ-0288-0718 *

EMERGENCY INCIDENT OF ENV. CONTAMINATION

SUBMISSION #:	8EHQ-1188-0769	*

APPENDIX (D): STATUS REPORTS BY INFORMATION TYPE

ENV. OCCURRENCE/RELEASE/FATE

SUBMISSION #:	8EHQ-0287-0653	8EHQ-0487-0662	8EHQ-0487-0671
	8EHQ-0688-0735	8EHQ-1088-0759	8EHQ-1088-0761
	8EHQ-1188-0769 *		

EPIDEMIOLOGY/CLINICAL

SUBMISSION #:	8EHQ-0187-0651 *	8EHQ-0487-0671	8EHQ-0887-0688
	8EHQ-0987-0694 *	8EHQ-1187-0698	8EHQ-1287-0699
	8EHQ-1287-0701 *	8EHQ-0288-0722	8EHQ-0688-0736
	8EHQ-1088-0755	8EHQ-1188-0772	

GROUNDWATER CONTAMINATION

SUBMISSION #:	8EHQ-0487-0662	8EHQ-1088-0759

HUMAN EXPOSURE (ACCIDENTAL)

SUBMISSION #:	8EHQ-0487-0671	8EHQ-0688-0736

HUMAN EXPOSURE (MONITORING)

SUBMISSION #:	8EHQ-0487-0662	8EHQ-0487-0671	8EHQ-0587-0672 S
	8EHQ-0687-0682	8EHQ-0288-0722	8EHQ-0688-0735
	8EHQ-0988-0752 S	8EHQ-1088-0761	

HUMAN EXPOSURE (PRODUCT CONTAMINATION)

SUBMISSION #:	8EHQ-0288-0720	8EHQ-0688-0735	8EHQ-1088-0761

IMMUNOTOXICITY (ANIMAL)

SUBMISSION #:	8EHQ-0588-0732		

METABOLISM/PHARMACOKINETICS (ANIMAL)

SUBMISSION #:	8EHQ-0487-0666 S	8EHQ-0587-0672 S	

MUTAGENICITY (IN VITRO)

SUBMISSION #:	8EHQ-0187-0649 S	8EHQ-0287-0653	8EHQ-0287-0654
	8EHQ-0687-0677	8EHQ-0687-0679	8EHQ-0787-0685
	8EHQ-0787-0686 S	8EHQ-0987-0692	8EHQ-0987-0693
	8EHQ-1287-0706	8EHQ-1287-0709 S	8EHQ-0288-0715
	8EHQ-0288-0719	8EHQ-0688-0737	8EHQ-0788-0743
	8EHQ-1088-0758 S	8EHQ-1088-0760 S	

NEUROTOXICITY (ANIMAL)

SUBMISSION #:	8EHQ-0287-0655 S	8EHQ-0587-0678	8EHQ-1287-0706
	8EHQ-0188-0714	8EHQ-0588-0733	8EHQ-0688-0739
	8EHQ-0688-0740 S	8EHQ-0788-0744 S	8EHQ-1088-0757
	8EHQ-1288-0776		

ONCOGENICITY (ANIMAL)

SUBMISSION #:	8EHQ-0187-0650	8EHQ-0587-0675	*	8EHQ-0786-0681
	8EHQ-0787-0684 S	8EHQ-0887-0687		8EHQ-0887-0691 S
	8EHQ-0987-0692	8EHQ-1187-0697		8EHQ-1287-0704
	8EHQ-1287-0708 S	8EHQ-1287-0710		8EHQ-0188-0713
	8EHQ-0388-0725	8EHQ-0588-0730		8EHQ-0788-0741

APPENDIX (D): STATUS REPORTS BY INFORMATION TYPE

ONCOGENICITY (ANIMAL)

SUBMISSION #:	8EHQ-0788-0745 S	8EHQ-1088-0760 S	8EHQ-1088-0763 S
	8EHQ-1288-0773	8EHQ-1288-0774	8EHQ-1288-0775

ONCOGENICITY (HUMAN)

SUBMISSION #:	8EHQ-0187-0651	*	8EHQ-0887-0688		8EHQ-1187-0698
	8EHQ-1287-0699		8EHQ-1287-0701	*	8EHQ-1188-0772

PRODUCT COMPOSITION/CHEMICAL IDENTITY

SUBMISSION #:	8EHQ-0187-0649 S		8EHQ-0287-0652 S		8EHQ-0287-0655 S
	8EHQ-0387-0656		8EHQ-0487-0661 S		8EHQ-0487-0664 S
	8EHQ-0487-0665 S	*	8EHQ-0487-0667 S	*	8EHQ-0487-0668
	8EHQ-0487-0669	*	8EHQ-0487-0670 S		8EHQ-0487-0671
	8EHQ-0587-0674 S		8EHQ-0687-0680		8EHQ-0787-0684 S
	8EHQ-0787-0686 S		8EHQ-1187-0697		8EHQ-1287-0707 S
	8EHQ-1287-0708 S		8EHQ-1287-0709 S		8EHQ-0188-0714
	8EHQ-0288-0716 S		8EHQ-0288-0717 S		8EHQ-0288-0720
	8EHQ-0388-0724 S		8EHQ-0388-0725		8EHQ-0488-0727
	8EHQ-0488-0728		8EHQ-0488-0729 S		8EHQ-0588-0731 S
	8EHQ-0588-0733		8EHQ-0688-0734 S		8EHQ-0688-0735
	8EHQ-0688-0740 S		8EHQ-0788-0744 S		8EHQ-0788-0745 S
	8EHQ-0988-0749 S		8EHQ-0988-0750 S		8EHQ-0988-0751 S
	8EHQ-0988-0752 S		8EHQ-0988-0753 S		8EHQ-1088-0755
	8EHQ-1088-0758 S		8EHQ-1088-0760 S		8EHQ-1088-0761
	8EHQ-1088-0763 S		8EHQ-1088-0764 S		8EHQ-1188-0765 S
	8EHQ-1188-0766 S		8EHQ-1188-0767 S		8EHQ-1188-0768 S

APPENDIX (D): STATUS REPORTS BY INFORMATION TYPE

PRODUCT COMPOSITION/CHEMICAL IDENTITY

SUBMISSION #:	8EHQ-1188-0770 S	8EHQ-1188-0771 S	8EHQ-1288-0776

PRODUCTION/USE/PROCESS

SUBMISSION #:	8EHQ-0187-0649 S	8EHQ-0287-0653	8EHQ-0287-0654
	8EHQ-0287-0655 S	8EHQ-0287-0657 S	8EHQ-0287-0658
	8EHQ-0387-0659	8EHQ-0487-0661 S	8EHQ-0487-0663
	8EHQ-0487-0664 S	8EHQ-0487-0665 S *	8EHQ-0487-0667 S *
	8EHQ-0487-0669 *	8EHQ-0487-0670 S	8EHQ-0487-0671
	8EHQ-0587-0672 S	8EHQ-0587-0673	8EHQ-0587-0674 S
	8EHQ-0587-0675 *	8EHQ-0587-0676	8EHQ-0687-0677
	8EHQ-0587-0678	8EHQ-0687-0679	8EHQ-0687-0680
	8EHQ-0687-0682	8EHQ-0687-0683	8EHQ-0787-0684 S
	8EHQ-0787-0685	8EHQ-0787-0686 S	8EHQ-0887-0687
	8EHQ-0887-0688	8EHQ-0887-0689 *	8EHQ-0887-0690
	8EHQ-0887-0691 S	8EHQ-0987-0692	8EHQ-0987-0694 *
	8EHQ-1087-0695	8EHQ-1187-0698	8EHQ-1287-0699
	8EHQ-1287-0700	8EHQ-1287-0701 *	8EHQ-1287-0704
	8EHQ-1287-0706	8EHQ-1287-0709 S	8EHQ-1287-0710
	8EHQ-0188-0714	8EHQ-0288-0715	8EHQ-0288-0716 S
	8EHQ-0288-0717 S	8EHQ-0288-0719	8EHQ-0288-0720
	8EHQ-0388-0721	8EHQ-0288-0722	8EHQ-0388-0723
	8EHQ-0388-0724 S	8EHQ-0388-0725	8EHQ-0488-0729 S
	8EHQ-0588-0730	8EHQ-0588-0731 S	8EHQ-0588-0732
	8EHQ-0588-0733	8EHQ-0688-0734 S	8EHQ-0688-0735
	8EHQ-0688-0738	8EHQ-0688-0739	8EHQ-0688-0740 S

APPENDIX (D): STATUS REPORTS BY INFORMATION TYPE

PRODUCTION/USE/PROCESS

SUBMISSION #:	8EHQ-0788-0742 *	8EHQ-0788-0744 S	8EHQ-0788-0745 S
	8EHQ-0888-0746	8EHQ-0888-0747	8EHQ-0988-0748
	8EHQ-0988-0749 S	8EHQ-0988-0750 S	8EHQ-0988-0751 S
	8EHQ-0988-0752 S	8EHQ-0988-0753 S	8EHQ-0988-0754
	8EHQ-1088-0755	8EHQ-1088-0756	8EHQ-1088-0757
	8EHQ-1088-0758 S	8EHQ-1088-0759	8EHQ-1088-0760 S
	8EHQ-1088-0763 S	8EHQ-1188-0765 S	8EHQ-1188-0766 S
	8EHQ-1188-0767 S	8EHQ-1188-0768 S	8EHQ-1188-0770 S
	8EHQ-1188-0771 S	8EHQ-1288-0775	8EHQ-1288-0776
	8EHQ-1288-0778		

REPORTING RATIONALE

SUBMISSION #:	8EHQ-0587-0672 S	8EHQ-1287-0706	8EHQ-0488-0729 S
	8EHQ-1188-0772		

REPRODUCTIVE TOXICITY/TERATO. (ANIMAL)

SUBMISSION #:	8EHQ-0287-0653	8EHQ-0287-0658	8EHQ-0487-0664 S
	8EHQ-0487-0666 S	8EHQ-0587-0672 S	8EHQ-0587-0676
	8EHQ-0687-0682	8EHQ-1087-0695	8EHQ-1287-0706
	8EHQ-0288-0716 S	8EHQ-0288-0717 S	8EHQ-0388-0721
	8EHQ-0388-0726 *	8EHQ-0488-0727	8EHQ-0488-0729 S
	8EHQ-0588-0731 S	8EHQ-0688-0738	8EHQ-0888-0746
	8EHQ-0988-0748	8EHQ-0988-0749 S	8EHQ-0988-0750 S
	8EHQ-0988-0751 S	8EHQ-1088-0758 S	8EHQ-1088-0760 S
	8EHQ-1088-0764 S	8EHQ-1188-0765 S	8EHQ-1188-0766 S

REPRODUCTIVE TOXICITY/TERATO. (ANIMAL)

SUBMISSION #: 8EHQ-1188-0767 S	8EHQ-1188-0770 S	8EHQ-1188-0771 S
8EHQ-1288-0778		

REPRODUCTIVE TOXICITY/TERATO. (HUMAN)

SUBMISSION #: 8EHQ-0288-0722

SUBACUTE TOXICITY (ANIMAL)

SUBMISSION #: 8EHQ-0287-0653	8EHQ-0487-0664 S	8EHQ-0587-0674 S
8EHQ-0687-0680	8EHQ-0687-0683	8EHQ-0787-0686 S
8EHQ-1287-0700	8EHQ-1287-0703	8EHQ-1287-0705
8EHQ-0188-0714	8EHQ-0388-0724 S	8EHQ-0488-0727
8EHQ-0688-0734 S	8EHQ-1088-0757	8EHQ-1288-0777

SUBCHRONIC TOXICITY (ANIMAL)

SUBMISSION #: 8EHQ-0487-0668	8EHQ-0587-0676	8EHQ-1287-0702
8EHQ-1287-0706	8EHQ-0488-0729 S	8EHQ-0788-0744 S
8EHQ-0888-0747	8EHQ-0988-0748	8EHQ-1088-0756
8EHQ-1088-0760 S	8EHQ-1088-0763 S	

TSCA 8(C) ALLEGATION

SUBMISSION #: 8EHQ-0887-0690	8EHQ-0987-0694 *	

* Based on a preliminary evaluation, EPA believed that the submitted information did not warrant reporting under Section 8(e) of TSCA. In most cases, the submitter was requested to provide the basis for contending that the information offered reasonable support for the conclusion that the subject chemical substance(s) or mixture(s) presents a substantial risk of injury to health or the environment as defined in EPA's TSCA Section 8(e) policy statement (see Appendix A of this volume).

8EHQ-0187-0649 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: DIAMINE, ALKOXYLATED AROMATIC

8EHQ-0187-0650 SUBMITTER: SOCIETY OF THE PLASTICS INDUSTRY, INC.

CAS NUMBER : 108-05-4 CHEMICAL NAME: ACETIC ACID ETHENYL ESTER

CAS NUMBER : 108-05-4 CHEMICAL NAME: VINYL ACETATE

8EHQ-0187-0651 * SUBMITTER: XEROX CORPORATION

CAS NUMBER : NONE CHEMICAL NAME: UNKNOWN CHEMICAL(S)

8EHQ-0287-0652 S SUBMITTER: ATLANTIC RICHFIELD COMPANY

CAS NUMBER : NONE CHEMICAL NAME: AMINE MIXTURE

CAS NUMBER : NONE CHEMICAL NAME: ARCEL RESIN ANTISTAT

8EHQ-0287-0653 SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : 13047-13-7 CHEMICAL NAME: DIMEZONE S

CAS NUMBER : 13047-13-7 CHEMICAL NAME: IRGAFORM 1266

CAS NUMBER : 13047-13-7 CHEMICAL NAME: 3-PYRAZOLIDINONE, 4-(HYDROXYMETHYL)-4-METHYL-1-PHENYL-

8EHQ-0287-0654 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : 4338-98-1 CHEMICAL NAME: 2(3H)-BENZOTHIAZOLONE, 3-METHYL-, HYDRAZONE, MONOHYDROCHLORIDE

CAS NUMBER : 14448-67-0 CHEMICAL NAME: 2(3H)-BENZOTHIAZOLONE, 3-METHYL-, HYDROZONE, HYDROCHLORIDE

8EHQ-0287-0655 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: 2-PYRAZOLIN-5-ONE, 1-PHENYL-ALKYLAMINO-

8EHQ-0387-0656 SUBMITTER: PPG INDUSTRIES, INC.

CAS NUMBER : 760-67-8 CHEMICAL NAME: HEXANOYL CHLORIDE, 2-ETHYL-

8EHQ-0287-0657 S SUBMITTER: EASTMAN KODAK COMPANY

CAS NUMBER : 99-42-3 CHEMICAL NAME: BENZOIC ACID, 4-HYDROXY-3-NITRO-, METHYL ESTER

8EHQ-0287-0658 SUBMITTER: SANDOZ CROP PROTECTION CORPORATION

CAS NUMBER : 94361-06-5 CHEMICAL NAME: SAN 619F

CAS NUMBER : 94361-06-5 CHEMICAL NAME: 1H-1,2,4-TRIAZOLE-1-ETHANOL, .ALPHA.-(4-CHLOROPHENYL)-.ALPHA .-(1-CYCLOPROPYLETHYL)-, (R*,R*)-(.+-.)-

8EHQ-0387-0659 SUBMITTER: 3M COMPANY

CAS NUMBER : 123-86-4 CHEMICAL NAME: ACETIC ACID, BUTYL ESTER

8EHQ-0387-0660 SUBMITTER: WACKER CHEMICALS (USA), INC.

CAS NUMBER : 78-95-5 CHEMICAL NAME: 2-PROPANONE, 1-CHLORO-

CAS NUMBER : 107-20-0 CHEMICAL NAME: ACETALDEHYDE, CHLORO-

8EHQ-0487-0661 S SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : 63943-38-4 CHEMICAL NAME: POLY[(DIMETHYLIMINIO)-1,6-HEXANEDIYL(DIMETHYLIMINIO)METHYLEN E[1,1'-BIPHENYL]-4,4'-DIYLMETHYLENE DICHLORIDE]

8EHQ-0487-0662 SUBMITTER: VISTA CHEMICAL COMPANY

CAS NUMBER : 107-06-2 CHEMICAL NAME: ETHANE, 1,2-DICHLORO-

8EHQ-0487-0663 SUBMITTER: EASTMAN KODAK COMPANY

CAS NUMBER : 5417-82-3 CHEMICAL NAME: PROPANEDINITRILE, (1-ETHOXYETHYLIDENE)-

8EHQ-0487-0664 S SUBMITTER: E. I. DUPONT DE NEMOURS & COMPANY, INC.

CAS NUMBER : CONFIDENT CHEMICAL NAME: ETHER (CYCLIC), HALOALKYL SUBSTITUTED

8EHQ-0487-0665 S * SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: BSC-125 SURFACTANT

CAS NUMBER : CONFIDENT CHEMICAL NAME: OXIRANE, METHYL-, POLYMER WITH OXIRANE, BLOCKED

8EHQ-0487-0666 S SUBMITTER: CONFIDENTIAL

CAS NUMBER :	142-22-3	CHEMICAL NAME:	CR-39 MONOMER
CAS NUMBER :	142-22-3	CHEMICAL NAME:	2,5,8,10-TETRAOXATRIDEC-12-ENOIC ACID, 9-OXO-, 2-PROPENYL ESTER

8EHQ-0487-0667 S * SUBMITTER: CONFIDENTIAL

CAS NUMBER :	CONFIDENT	CHEMICAL NAME:	CARBONOCHLORIDOTHIOIC ACID, ARYL ESTER

8EHQ-0487-0668 SUBMITTER: XEROX CORPORATION

CAS NUMBER :	NONE	CHEMICAL NAME:	PHOTOCOPYING PRODUCTS/PROCESS
CAS NUMBER :	NONE	CHEMICAL NAME:	XEROX 9000-TYPE XEROGRAPHIC TONER
CAS NUMBER :	7440-44-0	CHEMICAL NAME:	CARBON
CAS NUMBER :	7631-86-9	CHEMICAL NAME:	SILICA
CAS NUMBER :	13463-67-7	CHEMICAL NAME:	TITANIUM OXIDE, (TIO2)
CAS NUMBER :	25213-39-2	CHEMICAL NAME:	2-PROPENOIC ACID, 2-METHYL-, BUTYL ESTER, POLYMER WITH ETHENYLBENZENE

8EHQ-0487-0669 * SUBMITTER: PPG INDUSTRIES, INC.

CAS NUMBER :	UNKNOWN	CHEMICAL NAME:	2-IMIDAZOLIDINONE, 1,3-DIBROMO-4,4,5,5-TETRAMETHYL-
CAS NUMBER :	UNKNOWN	CHEMICAL NAME:	2-IMIDAZOLIDINONE, 1,3-DICHLORO-4,4,5,5-TETRAMETHYL-

8EHQ-0487-0670 S SUBMITTER: CONFIDENTIAL

CAS NUMBER :	CONFIDENT	CHEMICAL NAME:	NITROBENZENE, SUBSTITUTED

8EHQ-0487-0671 SUBMITTER: KOPPERS COMPANY, INC.

CAS NUMBER :	NONE	CHEMICAL NAME:	DIOXIN, HEPTACHLORODIBENZO-P-
CAS NUMBER :	NONE	CHEMICAL NAME:	DIOXIN, HEXACHLORODIBENZO-P-
CAS NUMBER :	NONE	CHEMICAL NAME:	DIOXIN, OCTACHLORODIBENZO-P-
CAS NUMBER :	NONE	CHEMICAL NAME:	DIOXIN, PENTACHLORODIBENZO-P-
CAS NUMBER :	NONE	CHEMICAL NAME:	DIOXINS, CHLORINATED

8EHQ-0487-0671 SUBMITTER: KOPPERS COMPANY, INC.

CAS NUMBER : NONE	CHEMICAL NAME: DIOXIN, TETRACHLORODIBENZO-P-
CAS NUMBER : 87-86-5	CHEMICAL NAME: PHENOL, PENTACHLORO-
CAS NUMBER : 106-97-8	CHEMICAL NAME: BUTANE
CAS NUMBER : 108-20-3	CHEMICAL NAME: PROPANE, 2,2'-OXYBIS-
CAS NUMBER : 1746-01-6	CHEMICAL NAME: DIOXIN, 2,3,7,8-TETRACHLORODIBENZO-P-
CAS NUMBER : 68334-30-5	CHEMICAL NAME: FUELS, DIESEL
CAS NUMBER : 68334-30-5	CHEMICAL NAME: OIL (PETROLEUM), DIESEL

8EHQ-0587-0672 S SUBMITTER: SHELL OIL COMPANY

CAS NUMBER : 58-08-2	CHEMICAL NAME: CAFFEINE
CAS NUMBER : 58-08-2	CHEMICAL NAME: 1H-PURINE-2,6-DIONE, 3,7-DIHYDRO-1,3,7-TRIMETHYL-
CAS NUMBER : 99-66-1	CHEMICAL NAME: PENTANOIC ACID, 2-PROPYL-
CAS NUMBER : 104-76-7	CHEMICAL NAME: 1-HEXANOL, 2-ETHYL-
CAS NUMBER : 117-81-7	CHEMICAL NAME: 1,2-BENZENEDICARBOXYLIC ACID, BIS(2-ETHYLHEXYL) ESTER
CAS NUMBER : 149-57-5	CHEMICAL NAME: HEXANOIC ACID, 2-ETHYL-

8EHQ-0587-0673 SUBMITTER: STAUFFER CHEMICAL COMPANY

CAS NUMBER : NONE	CHEMICAL NAME: N-1386 HAN
CAS NUMBER : 3064-70-8	CHEMICAL NAME: METHANE, SULFONYLBIS[TRICHLORO-
CAS NUMBER : 64742-95-6	CHEMICAL NAME: SOLVENT NAPHTHA, (PETROLEUM), LIGHT AROM.

8EHQ-0587-0674 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT	CHEMICAL NAME: AMMONIUM CARBOXYLATE, SUBSTITUTED
CAS NUMBER : CONFIDENT	CHEMICAL NAME: OLEFIN, SULFURIZED

8EHQ-0587-0675 * SUBMITTER: CHEMICAL MANUFACTURERS ASSOCIATION

CAS NUMBER : UNKNOWN	CHEMICAL NAME: OIL (PETROLEUM), MINERAL CARRIER
CAS NUMBER : 61789-36-4	CHEMICAL NAME: NAPHTHENIC ACIDS, CALCIUM SALTS

8EHQ-0587-0675 * SUBMITTER: CHEMICAL MANUFACTURERS ASSOCIATION

8EHQ-0587-0676 SUBMITTER: E. I. DUPONT DE NEMOURS & COMPANY, INC.

CAS NUMBER : 1649-08-7 CHEMICAL NAME: ETHANE, 1,2-DICHLORO-1,1-DIFLUORO-

CAS NUMBER : 1649-08-7 CHEMICAL NAME: HCFC-132B

8EHQ-0687-0677 SUBMITTER: LEVER BROTHERS COMPANY

CAS NUMBER : 8005-72-9 CHEMICAL NAME: 7-BENZOTHIAZOLESULFONIC ACID, 6-METHYL-2-(4-(4-(6-METHYL-7-SULFOBENZOTHIAZOL-2-YL)PHENYLAZO)PHENYL)-

CAS NUMBER : 8005-72-9 CHEMICAL NAME: C.I. DIRECT YELLOW 28

CAS NUMBER : 8005-72-9 CHEMICAL NAME: PYRAZOL YELLOW BG 250%

CAS NUMBER : 8005-72-9 CHEMICAL NAME: SOLAR YELLOW RG

8EHQ-0587-0678 SUBMITTER: EASTMAN KODAK COMPANY

CAS NUMBER : 6262-51-7 CHEMICAL NAME: CYCLOPROPANE, PENTACHLORO-

8EHQ-0687-0679 SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : 68412-01-1 CHEMICAL NAME: D-GLUCITOL, REACTION PRODUCTS WITH EPICHLOROHYDRIN

8EHQ-0687-0680 SUBMITTER: EASTMAN KODAK COMPANY

CAS NUMBER : UNKNOWN CHEMICAL NAME: NAPHTHALENE, DIIODO-

CAS NUMBER : UNKNOWN CHEMICAL NAME: NAPHTHALENES, DI-, TRI-, AND TETRAIODO-, MIXED

CAS NUMBER : UNKNOWN CHEMICAL NAME: NAPHTHALENE, TETRAIODO-

CAS NUMBER : UNKNOWN CHEMICAL NAME: NAPHTHALENE, TRIIODO-

8EHQ-0786-0681 SUBMITTER: MONSANTO COMPANY

CAS NUMBER : 17796-82-6 CHEMICAL NAME: 1H-ISOINDOLE-1,3(2H)-DIONE, 2-(CYCLOHEXYLTHIO)-

CAS NUMBER : 17796-82-6 CHEMICAL NAME: SANTOGARD PVI

8EHQ-0687-0682 SUBMITTER: MONSANTO COMPANY

CAS NUMBER : 27193-86-8 CHEMICAL NAME: PHENOL, DODECYL-

8EHQ-0687-0682 SUBMITTER: MONSANTO COMPANY

8EHQ-0687-0683 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : 3033-62-3 CHEMICAL NAME: ETHANAMINE, 2,2'-OXYBIS[N,N-DIMETHYL-

CAS NUMBER : 3033-62-3 CHEMICAL NAME: NIAX CATALYST A-99

8EHQ-0787-0684 S SUBMITTER: DOW CORNING CORPORATION

CAS NUMBER : NONE CHEMICAL NAME: DOW CORNING S-5370 RTV

8EHQ-0787-0685 SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : 3126-63-4 CHEMICAL NAME: OXIRANE, 2,2'-[2,2-BIS[(OXIRANYLMETHOXY)METHYL]-1,3-PROPANEDIYLBIS(OXYMETHYLENE)]BIS-

8EHQ-0787-0686 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: ALKYL PHENOL, MODIFIED

8EHQ-0887-0687 SUBMITTER: TEXACO INC.

CAS NUMBER : 64742-86-5 CHEMICAL NAME: GAS OILS, (PETROLEUM), HYDRODESULFURIZED HEAVY VACUUM

8EHQ-0887-0688 SUBMITTER: AMERICAN CYANAMID COMPANY

CAS NUMBER : 7647-01-0 CHEMICAL NAME: HYDROCHLORIC ACID

CAS NUMBER : 7647-01-0 CHEMICAL NAME: MURIATIC ACID

CAS NUMBER : 7647-14-5 CHEMICAL NAME: SODIUM CHLORIDE, (NACL)

CAS NUMBER : 7664-93-9 CHEMICAL NAME: SULFURIC ACID

CAS NUMBER : 7757-82-6 CHEMICAL NAME: SULFURIC ACID DISODIUM SALT

8EHQ-0887-0689 * SUBMITTER: NATIONAL TOXICOLOGY PROGRAM

CAS NUMBER : 78-79-5 CHEMICAL NAME: 1,3-BUTADIENE, 2-METHYL-

CAS NUMBER : 78-79-5 CHEMICAL NAME: ISOPRENE

CAS NUMBER : 126-99-8 CHEMICAL NAME: 1,3-BUTADIENE, 2-CHLORO-

CAS NUMBER : 126-99-8 CHEMICAL NAME: CHLOROPRENE

8EHQ-0887-0689 * SUBMITTER: NATIONAL TOXICOLOGY PROGRAM

8EHQ-0887-0690 SUBMITTER: ATLANTIC RICHFIELD COMPANY

CAS NUMBER : 941-69-5 CHEMICAL NAME: 1H-PYRROLE-2,5-DIONE, 1-PHENYL-

8EHQ-0887-0691 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : 64741-52-2 CHEMICAL NAME: DISTILLATES, (PETROLEUM), LIGHT NAPHTHENIC

CAS NUMBER : 64741-53-3 CHEMICAL NAME: DISTILLATES, (PETROLEUM), HEAVY NAPHTHENIC

CAS NUMBER : 64741-88-4 CHEMICAL NAME: DISTILLATES, (PETROLEUM), SOLVENT-REFINED HEAVY PARAFFINIC

CAS NUMBER : 64742-52-5 CHEMICAL NAME: DISTILLATES, (PETROLEUM), HYDROTREATED HEAVY NAPHTHENIC

CAS NUMBER : 64742-53-6 CHEMICAL NAME: DISTILLATES, (PETROLEUM), HYDROTREATED LIGHT NAPHTHENIC

CAS NUMBER : 64742-65-0 CHEMICAL NAME: DISTILLATES, (PETROLEUM), SOLVENT-DEWAXED HEAVY PARAFFINIC

8EHQ-0987-0692 SUBMITTER: MONSANTO COMPANY

CAS NUMBER : UNKNOWN CHEMICAL NAME: ACETIC ACID, OXO-, METHYL ESTER OR ETHYL ESTER, HOMOPOLYMER, REACTION PRODUCTS WITH ETHOXYETHENE AND REACTION PRODUCTS W ITH METHOXYETHENE, SODIUM SALTS

8EHQ-0987-0693 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : 112-60-7 CHEMICAL NAME: ETHANOL, 2,2'-[OXYBIS(2,1-ETHANEDIYLOXY)]BIS-

8EHQ-0987-0694 * SUBMITTER: WESTVACO CORPORATION

CAS NUMBER : 151-21-3 CHEMICAL NAME: SODIUM DODECYL SULFATE (SDS)

CAS NUMBER : 151-21-3 CHEMICAL NAME: SODIUM LAURYL SULFATE (SLS)

CAS NUMBER : 151-21-3 CHEMICAL NAME: SULFURIC ACID MONODODECYL ESTER SODIUM SALT

8EHQ-1087-0695 SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : 872-50-4 CHEMICAL NAME: 2-PYRROLIDINONE, 1-METHYL-

8EHQ-1087-0696 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : NONE CHEMICAL NAME: SURFACTANTS (NON-IONIC), ALKOXYLATED

8EHQ-1087-0696 SUBMITTER: UNION CARBIDE CORPORATION

8EHQ-1187-0697 SUBMITTER: AMOCO CORPORATION

CAS NUMBER : UNKNOWN CHEMICAL NAME: FUEL OIL, NO. 2, SUBFRACTIONS

CAS NUMBER : UNKNOWN CHEMICAL NAME: OIL (PETROLEUM), FURNACE, SUBFRACTIONS

CAS NUMBER : 68476-30-2 CHEMICAL NAME: FUEL OIL, NO. 2

CAS NUMBER : 68476-30-2 CHEMICAL NAME: OIL (PETROLEUM), FURNACE

8EHQ-1187-0698 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : 107-07-3 CHEMICAL NAME: ETHANOL, 2-CHLORO-

8EHQ-1287-0699 SUBMITTER: E. I. DUPONT DE NEMOURS & COMPANY, INC.

CAS NUMBER : NONE CHEMICAL NAME: CATALYSTS

CAS NUMBER : NONE CHEMICAL NAME: MISC. CHEMICALS

CAS NUMBER : 137-40-6 CHEMICAL NAME: MYCOBAN (SODIUM SALT)

CAS NUMBER : 137-40-6 CHEMICAL NAME: PROPANOIC ACID, SODIUM SALT

CAS NUMBER : 4075-81-4 CHEMICAL NAME: MYCOBAN (CALCIUM SALT)

CAS NUMBER : 4075-81-4 CHEMICAL NAME: PROPANOIC ACID, CALCIUM SALT

8EHQ-1287-0700 SUBMITTER: SHELL OIL COMPANY

CAS NUMBER : 3236-71-3 CHEMICAL NAME: FLUORENE, 9,9-BIS(4-HYDROXYPHENYL)-

8EHQ-1287-0701 * SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : NONE CHEMICAL NAME: ETHANOL (STRONG ACID PRODUCTION PROCESS)

CAS NUMBER : NONE CHEMICAL NAME: ISOPROPANOL (STRONG ACID PRODUCTION PROCESS)

CAS NUMBER : NONE CHEMICAL NAME: MISC. CHEMICALS

8EHQ-1287-0702 SUBMITTER: MONSANTO COMPANY

CAS NUMBER : 768-52-5 CHEMICAL NAME: BENZENAMINE, N-(1-METHYLETHYL)-

8EHQ-1287-0703 SUBMITTER: MONSANTO COMPANY

CAS NUMBER : 768-52-5 CHEMICAL NAME: BENZENAMINE, N-(1-METHYLETHYL)-

8EHQ-1287-0704 SUBMITTER: TEXACO INC.

CAS NUMBER : 91-20-3 CHEMICAL NAME: NAPHTHALENE

8EHQ-1287-0705 SUBMITTER: MONSANTO COMPANY

CAS NUMBER : 108-18-9 CHEMICAL NAME: 2-PROPANAMINE, N-(1-METHYLETHYL)-

8EHQ-1287-0706 SUBMITTER: BORG-WARNER CHEMICALS, INC.

CAS NUMBER : 26741-53-7 CHEMICAL NAME: 2,4,8,10-TETRAOXA-3,9-DIPHOSPHASPIRO[5.5]UNDECANE, 3,9-BIS[2,4-BIS(1,1-DIMETHYLETHYL)PHENOXY]-

CAS NUMBER : 26741-53-7 CHEMICAL NAME: ULTRANOX 624

CAS NUMBER : 26741-53-7 CHEMICAL NAME: ULTRANOX 626

CAS NUMBER : 26741-53-7 CHEMICAL NAME: ULTRANOX 626A

CAS NUMBER : 26741-53-7 CHEMICAL NAME: WESTON MDW-6140

CAS NUMBER : 26741-53-7 CHEMICAL NAME: WESTON XR-1452

CAS NUMBER : 26741-53-7 CHEMICAL NAME: WESTON XR-1532

8EHQ-1287-0707 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: PYRIDINECARBOXYLATE

8EHQ-1287-0708 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: ACETOPHENONE OXIME

8EHQ-1287-0709 S SUBMITTER: HENKEL CORPORATION

CAS NUMBER : 106-89-8 CHEMICAL NAME: EPICHLOROHYDRIN

CAS NUMBER : 106-89-8 CHEMICAL NAME: OXIRANE, (CHLOROMETHYL)-

CAS NUMBER : 52495-71-3 CHEMICAL NAME: POLY(OXY-1,2-ETHANEDIYL), A-HYDRO-W-(OXIRANYLMETHOXY)-, ETHER WITH 2-ETHYL-2-(HYDROXYMETHYL)-1,3-PROPANEDIOL (3:1)

CAS NUMBER : 87257-05-4 CHEMICAL NAME: OXIRANE, 2,2'-(3,7,7,11-TETRAMETHYL-2,5,9,12-TETRAOXATRIDECANE-1,13-DIYL)BIS-

8EHQ-1287-0709 S SUBMITTER: HENKEL CORPORATION

8EHQ-1287-0710 SUBMITTER: TEXACO INC.

CAS NUMBER : 64742-86-5 CHEMICAL NAME: GAS OILS, (PETROLEUM), HYDRODESULFURIZED HEAVY VACUUM

CAS NUMBER : 64742-87-6 CHEMICAL NAME: GAS OILS, (PETROLEUM), HYDRODESULFURIZED LIGHT VACUUM

8EHQ-1287-0711 SUBMITTER: AMOCO CORPORATION

CAS NUMBER : 89-32-7 CHEMICAL NAME: 1H,3H-BENZO[1,2-C:4,5-C']DIFURAN-1,3,5,7-TETRONE

CAS NUMBER : 89-32-7 CHEMICAL NAME: PYROMELLITIC DIANHYDRIDE

CAS NUMBER : 552-30-7 CHEMICAL NAME: 5-ISOBENZOFURANCARBOXYLIC ACID, 1,3-DIHYDRO-1,3-DIOXO-

CAS NUMBER : 552-30-7 CHEMICAL NAME: TRIMELLITIC ANHYDRIDE

8EHQ-0188-0712 * SUBMITTER: KOPPERS COMPANY, INC.

CAS NUMBER : NONE CHEMICAL NAME: LH-25 PRESERVATIVE

CAS NUMBER : NONE CHEMICAL NAME: SAPSTAIN CONTROL CHEMICAL NP-1

CAS NUMBER : 7173-51-5 CHEMICAL NAME: 1-DECANAMINIUM, N-DECYL-N,N-DIMETHYL-, CHLORIDE

CAS NUMBER : 55406-53-6 CHEMICAL NAME: CARBAMIC ACID, BUTYL-, 3-IODO-2-PROPYNYL ESTER

8EHQ-0188-0713 SUBMITTER: DOW CHEMICAL COMPANY

CAS NUMBER : 75-00-3 CHEMICAL NAME: ETHANE, CHLORO-

8EHQ-0188-0714 SUBMITTER: EASTMAN KODAK COMPANY

CAS NUMBER : 565-74-2 CHEMICAL NAME: BUTANOIC ACID, 2-BROMO-3-METHYL-

8EHQ-0288-0715 SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : UNKNOWN CHEMICAL NAME: POLYGLYCIDYL ETHYL, 2,2,6,6-TETRAMETHYLOL CYCLOHEXANOL

8EHQ-0288-0716 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: PYRIDINECARBOXYLATE

8EHQ-0288-0717 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: PYRIDINECARBOXYLATE

8EHQ-0288-0717 S SUBMITTER: CONFIDENTIAL

8EHQ-0288-0718 * SUBMITTER: DOW CORNING CORPORATION

CAS NUMBER : 556-67-2 CHEMICAL NAME: CYCLOTETRASILOXANE, OCTAMETHYL-

CAS NUMBER : 9005-64-5 CHEMICAL NAME: SORBITAN, MONODODECANOATE, POLY(OXY-1,2-ETHANEDIYL) DERIVS.

8EHQ-0288-0719 SUBMITTER: OLIN CORPORATION

CAS NUMBER : 68214-81-3 CHEMICAL NAME: CHEMICAL 400, STEP 1

CAS NUMBER : 68214-81-3 CHEMICAL NAME: ETHANOL, 2-[ETHYL[3-METHYL-4-(PHENYLAZO)PHENYL]AMINO]-

8EHQ-0288-0720 SUBMITTER: GENERAL ELECTRIC COMPANY

CAS NUMBER : NONE CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, BROMINATED DERIV.

CAS NUMBER : NONE CHEMICAL NAME: DIBENZOFURANS, BROMINATED

CAS NUMBER : NONE CHEMICAL NAME: DIOXINS, BROMINATED

CAS NUMBER : 1163-19-5 CHEMICAL NAME: BENZENE, 1,1'-OXYBIS[2,3,4,5,6-PENTABROMO-

CAS NUMBER : 1327-33-9 CHEMICAL NAME: ANTIMONY OXIDE

CAS NUMBER : 30965-26-5 CHEMICAL NAME: 1,4-BENZENEDICARBOXYLIC ACID, DIMETHYL ESTER, POLYMER WITH 1,4-BUTANEDIOL

8EHQ-0388-0721 SUBMITTER: EASTMAN KODAK COMPANY

CAS NUMBER : 59607-71-5 CHEMICAL NAME: THIOCYANIC ACID, 4-METHOXY-2-NITROPHENYL ESTER

8EHQ-0288-0722 SUBMITTER: BOEING COMPANY

CAS NUMBER : NONE CHEMICAL NAME: FREKOTE 700

CAS NUMBER : NONE CHEMICAL NAME: MISC. CHEMICALS

CAS NUMBER : NONE CHEMICAL NAME: SCOTCHWELD AF-163-2 OST

8EHQ-0388-0723 SUBMITTER: MONSANTO COMPANY

CAS NUMBER : 2004-03-7 CHEMICAL NAME: PURINE, 6-METHYL-

8EHQ-0388-0724 S SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : CONFIDENT CHEMICAL NAME: PHENOL DERIVATIVE, STERICALLY HINDERED

8EHQ-0388-0724 S SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : CONFIDENT	CHEMICAL NAME: PHENOL DERIVATIVE, STERICALLY HINDERED
CAS NUMBER : NONE	CHEMICAL NAME: PHENOL DERIVATIVES, STERICALLY HINDERED, MIXTURE

8EHQ-0388-0725 SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : 36443-68-2	CHEMICAL NAME: BENZENEPROPANOIC ACID, 3-(1,1-DIMETHYLETHYL)-4-HYDROXY-5-MET HYL-, 1,2-ETHANEDIYLBIS(OXY-2,1-ETHANEDIYL) ESTER
CAS NUMBER : 36443-68-2	CHEMICAL NAME: IRGANOX 245

8EHQ-0388-0726 * SUBMITTER: HOECHST CELANESE CORPORATION

CAS NUMBER : 98-73-7	CHEMICAL NAME: BENZOIC ACID, P-TERT-BUTYL-
CAS NUMBER : 98-73-7	CHEMICAL NAME: BENZOIC ACID, 4-(1,1-DIMETHYLETHYL)-

8EHQ-0488-0727 SUBMITTER: AMOCO CORPORATION

CAS NUMBER : 7783-06-4	CHEMICAL NAME: HYDROGEN SULFIDE, (H2S)
CAS NUMBER : 64741-56-6	CHEMICAL NAME: RESIDUES, (PETROLEUM), VACUUM
CAS NUMBER : 64741-60-2	CHEMICAL NAME: DISTILLATES, (PETROLEUM), INTERMEDIATE CATALYTIC CRACKED
CAS NUMBER : 64741-62-4	CHEMICAL NAME: CLARIFIED OILS, (PETROLEUM), CATALYTIC CRACKED
CAS NUMBER : 68553-00-4	CHEMICAL NAME: FUEL OIL, NO. 6

8EHQ-0488-0728 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : NONE	CHEMICAL NAME: IMPOSIT
CAS NUMBER : NONE	CHEMICAL NAME: LEDERMIX
CAS NUMBER : 25322-68-3	CHEMICAL NAME: CARBOWAX PEG-8000
CAS NUMBER : 25322-68-3	CHEMICAL NAME: POLY(OXY-1,2-ETHANEDIYL), .ALPHA.-HYDRO-.OMEGA.-HYDROXY-

8EHQ-0488-0729 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT	CHEMICAL NAME: SULFLURAMID, ETHYL

8EHQ-0588-0730 SUBMITTER: BASF CORPORATION

CAS NUMBER : 2465-27-2	CHEMICAL NAME: AURAMINE HYDROCHLORIDE

8EHQ-0588-0730 SUBMITTER: BASF CORPORATION

CAS NUMBER : 2465-27-2	CHEMICAL NAME: C. I. BASIC YELLOW 2
CAS NUMBER : 2465-27-2	CHEMICAL NAME: BENZENAMINE, 4,4'-CARBONIMIDOYLBIS[N,N-DIMETHYL-, MONOHYDROCHLORIDE
CAS NUMBER : 43130-12-7	CHEMICAL NAME: AURAMINE, ETHYL-, NITRATE SALT
CAS NUMBER : 43130-12-7	CHEMICAL NAME: C. I. BASIC YELLOW 37
CAS NUMBER : 43130-12-7	CHEMICAL NAME: BENZENAMINE, 4,4'-CARBONIMIDOYLBIS[N,N-DIETHYL-, MONONITRATE

8EHQ-0588-0731 S SUBMITTER: DOW CHEMICAL COMPANY

CAS NUMBER : CONFIDENT	CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, SUBSTITUTED
CAS NUMBER : CONFIDENT	CHEMICAL NAME: DIPHENYL ETHER, SUBSTITUTED

8EHQ-0588-0732 SUBMITTER: EASTMAN KODAK COMPANY

CAS NUMBER : 6294-52-6	CHEMICAL NAME: BENZOTHIAZOLE, 2-AMINO-5,6-DIMETHOXY-

8EHQ-0588-0733 SUBMITTER: AMERICAN TELEPHONE AND TELEGRAPH COMPANY (AT&T)

CAS NUMBER : NONE	CHEMICAL NAME: PALLADIUM PLATING COMPOUND
CAS NUMBER : NONE	CHEMICAL NAME: PD MAKEUP

8EHQ-0688-0734 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT	CHEMICAL NAME: POLYESTER, MODIFIED ALIPHATIC ALICYCLIC
CAS NUMBER : CONFIDENT	CHEMICAL NAME: SILANE

8EHQ-0688-0735 SUBMITTER: PENNZOIL COMPANY

CAS NUMBER : 593-88-4	CHEMICAL NAME: ARSINE, TRIMETHYL-
CAS NUMBER : 7440-38-2	CHEMICAL NAME: ARSENIC
CAS NUMBER : 8006-14-2	CHEMICAL NAME: NATURAL GAS

8EHQ-0688-0736 SUBMITTER: REILLY TAR & CHEMICAL CORPORATION

CAS NUMBER : 1072-98-6	CHEMICAL NAME: PYRIDINE, 2-AMINO-5-CHLORO-

8EHQ-0688-0736 SUBMITTER: REILLY TAR & CHEMICAL CORPORATION

8EHQ-0688-0737 SUBMITTER: ANITMONY OXIDE INDUSTRY ASSOCIATION

CAS NUMBER : 1309-64-4	CHEMICAL NAME: ANTIMONY OXIDE, (SB2O3)
CAS NUMBER : 7647-18-9	CHEMICAL NAME: ANTIMONY CHLORIDE, (SBCL5)
CAS NUMBER : 10025-91-9	CHEMICAL NAME: ANTIMONY CHLORIDE, (SBCL3)
CAS NUMBER : 10025-91-9	CHEMICAL NAME: STIBINE, TRICHLORO-

8EHQ-0688-0738 SUBMITTER: MOBAY CORPORATION

CAS NUMBER : NONE	CHEMICAL NAME: FOLICUR TECHNICAL
CAS NUMBER : NONE	CHEMICAL NAME: FOLICUR 1.2 EC
CAS NUMBER : NONE	CHEMICAL NAME: LYNX 1.2
CAS NUMBER : 107534-96-3	CHEMICAL NAME: TERBUCONAZOLE
CAS NUMBER : 107534-96-3	CHEMICAL NAME: 1H-1,2,4-TRIAZOLE-1-ETHANOL, .ALPHA.-[2-(4-CHLOROPHENYL)ETHYL]-.ALPHA.-(1,1-DIMETHYLETHYL)-(.+-.)-

8EHQ-0688-0739 SUBMITTER: EASTMAN KODAK COMPANY

CAS NUMBER : 14447-15-5	CHEMICAL NAME: ACETIC ACID, CYANO-, PROPYL ESTER

8EHQ-0688-0740 S SUBMITTER: EASTMAN KODAK COMPANY

CAS NUMBER : CONFIDENT	CHEMICAL NAME: THIAZINOHYDRAZINE, SUBSTITUTED

8EHQ-0788-0741 SUBMITTER: INTERNATIONAL ISOCYANATE INSTITUTE, INC.

CAS NUMBER : 9016-87-9	CHEMICAL NAME: ISOCYANIC ACID, POLYMETHYLENEPOLYPHENYLENE ESTER

8EHQ-0788-0742 * SUBMITTER: ATLANTIC RICHFIELD COMPANY

CAS NUMBER : NONE	CHEMICAL NAME: CUTTING FLUID

8EHQ-0788-0743 SUBMITTER: PROCTER & GAMBLE COMPANY

CAS NUMBER : 3734-67-6	CHEMICAL NAME: C. I. ACID RED 1
CAS NUMBER : 3734-67-6	CHEMICAL NAME: 2,7-NAPHTHALENEDISULFONIC ACID, 5-(ACETYLAMINO)-4-HYDROXY-3-(PHENYLAZO)-, DISODIUM SALT

8EHQ-0788-0743 SUBMITTER: PROCTER & GAMBLE COMPANY

CAS NUMBER : 3734-67-6 CHEMICAL NAME: RED 2G

8EHQ-0788-0744 S SUBMITTER: MOBIL RESEARCH AND DEVELOPMENT CORPORATION

CAS NUMBER : NONE CHEMICAL NAME: OIL, JET ENGINE

CAS NUMBER : 78-30-8 CHEMICAL NAME: PHOSPHORIC ACID, TRIS(2-METHYLPHENYL) ESTER

CAS NUMBER : 1330-78-5 CHEMICAL NAME: PHOSPHORIC ACID, TRIS(METHYLPHENYL) ESTER

8EHQ-0788-0745 S SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : CONFIDENT CHEMICAL NAME: CARBOMONOCYCLIC AMINOBUTYROLACTONE

8EHQ-0888-0746 SUBMITTER: MONSANTO COMPANY

CAS NUMBER : 101-54-2 CHEMICAL NAME: 1,4-BENZENEDIAMINE, N-PHENYL-

8EHQ-0888-0747 SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : 3846-71-7 CHEMICAL NAME: PHENOL, 2-(2H-BENZOTRIAZOL-2-YL)-4,6-BIS(1,1-DIMETHYLETHYL)-

CAS NUMBER : 3846-71-7 CHEMICAL NAME: TINUVIN 320

8EHQ-0988-0748 SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : 25973-55-1 CHEMICAL NAME: PHENOL, 2-(2H-BENZOTRIAZOL-2-YL)-4,6-BIS(1,1-DIMETHYLPROPYL)

CAS NUMBER : 25973-55-1 CHEMICAL NAME: TINUVIN 328

8EHQ-0988-0749 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: PYRIDINE, ALKYL

8EHQ-0988-0750 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: AMIDE, HETEROCYCLIC ARYL

8EHQ-0988-0751 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: ETHER, DIARYL

8EHQ-0988-0751 S SUBMITTER: CONFIDENTIAL

8EHQ-0988-0752 S SUBMITTER: 3M COMPANY

CAS NUMBER : CONFIDENT CHEMICAL NAME: FIBER, INORGANIC

8EHQ-0988-0753 S SUBMITTER: HOECHST CELANESE CORPORATION

CAS NUMBER : CONFIDENT CHEMICAL NAME: INDOLENINIUM SALT

8EHQ-0988-0754 SUBMITTER: AMERICAN CYANAMID COMPANY

CAS NUMBER : 78-97-7 CHEMICAL NAME: PROPANENITRILE, 2-HYDROXY-

CAS NUMBER : 107-16-4 CHEMICAL NAME: ACETONITRILE, HYDROXY-

CAS NUMBER : 109-77-3 CHEMICAL NAME: PROPANEDINITRILE

CAS NUMBER : 13893-53-3 CHEMICAL NAME: BUTANENITRILE, 2-AMINO-2,3-DIMETHYL-

8EHQ-1088-0755 SUBMITTER: ELI LILLY AND COMPANY

CAS NUMBER : 1322-93-6 CHEMICAL NAME: NAPHTHALENESULFONIC ACID, BIS(1-METHYLETHYL)-, SODIUM SALT

CAS NUMBER : 1322-93-6 CHEMICAL NAME: SELLOGEN HR

CAS NUMBER : 1332-58-7 CHEMICAL NAME: KAOLIN

CAS NUMBER : 1332-58-7 CHEMICAL NAME: SPESWHITE (CLAY)

CAS NUMBER : 1746-81-2 CHEMICAL NAME: ARESIN

CAS NUMBER : 1746-81-2 CHEMICAL NAME: LINURON, MONO-

CAS NUMBER : 1746-81-2 CHEMICAL NAME: UREA, N'-(4-CHLOROPHENYL)-N-METHOXY-N-METHYL-

CAS NUMBER : 8061-51-6 CHEMICAL NAME: LIGNOSULFONIC ACID, SODIUM SALT

CAS NUMBER : 8061 51-6 CHEMICAL NAME: POLYFON H

CAS NUMBER : 55283-68-6 CHEMICAL NAME: BENZENAMINE, N-ETHYL-N-(2-METHYL-2-PROPENYL)-2,6-DINITRO-4-(TRIFLUOROMETHYL)-

CAS NUMBER : 55283-68-6 CHEMICAL NAME: ETHALFLURALIN

CAS NUMBER : 55283-68-6 CHEMICAL NAME: SONALAN

CAS NUMBER : 63231-67-4 CHEMICAL NAME: HI-SIL 233

8EHQ-1088-0755 SUBMITTER: ELI LILLY AND COMPANY

CAS NUMBER : 63231-67-4 CHEMICAL NAME: SILICA GEL

8EHQ-1088-0756 SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : 3864-99-1 CHEMICAL NAME: PHENOL, 2-(5-CHLORO-2H-BENZOTRIAZOL-2-YL)-4,6-BIS(1,1-DIMETHYLETHYL)-

CAS NUMBER : 3864-99-1 CHEMICAL NAME: TINUVIN 327

8EHQ-1088-0757 SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : UNKNOWN CHEMICAL NAME: 2-PROPANOL, 1-[BIS(2-HYDROXYETHYL)AMINO]-3-(4-ISONONYLPHENOXY)-

8EHQ-1088-0758 S SUBMITTER: VALENT U.S.A. CORPORATION

CAS NUMBER : CONFIDENT CHEMICAL NAME: CYCLOHEXENONE, SUBSTITUTED

CAS NUMBER : CONFIDENT CHEMICAL NAME: PHTHALIMIDE (III), SUBSTITUTED

CAS NUMBER : CONFIDENT CHEMICAL NAME: PHTHALIMIDE (II), SUBSTITUTED

CAS NUMBER : CONFIDENT CHEMICAL NAME: PHTHALIMIDE (I), SUBSTITUTED

8EHQ-1088-0759 SUBMITTER: E. I. DUPONT DE NEMOURS & COMPANY, INC.

CAS NUMBER : UNKNOWN CHEMICAL NAME: 1,2-BENZENEDICARBOXYLIC ACID DERIV.

CAS NUMBER : 67-64-1 CHEMICAL NAME: ACETONE

CAS NUMBER : 67-64-1 CHEMICAL NAME: 2-PROPANONE

CAS NUMBER : 67-66-3 CHEMICAL NAME: CHLOROFORM

CAS NUMBER : 67-66-3 CHEMICAL NAME: METHANE, TRICHLORO-

CAS NUMBER : 75-15-0 CHEMICAL NAME: CARBON DISULFIDE

CAS NUMBER : 75-69-4 CHEMICAL NAME: METHANE, TRICHLOROFLUORO-

CAS NUMBER : 78-93-3 CHEMICAL NAME: 2-BUTANONE

CAS NUMBER : 78-93-3 CHEMICAL NAME: METHYLETHYLKETONE (MEK)

CAS NUMBER : 108-95-2 CHEMICAL NAME: PHENOL

CAS NUMBER : 680-31-9 CHEMICAL NAME: HEXAMETHYLPHOSPHORAMIDE

8EHQ-1088-0759 SUBMITTER: E. I. DUPONT DE NEMOURS & COMPANY, INC.

CAS NUMBER : 680-31-9	CHEMICAL NAME: PHOSPHORIC TRIAMIDE, HEXAMETHYL-
CAS NUMBER : 7440-38-2	CHEMICAL NAME: ARSENIC
CAS NUMBER : 7440-41-7	CHEMICAL NAME: BERYLLIUM
CAS NUMBER : 7440-47-3	CHEMICAL NAME: CHROMIUM
CAS NUMBER : 7440-66-6	CHEMICAL NAME: ZINC

8EHQ-1088-0760 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT	CHEMICAL NAME: ALKYL HETEROCYCLIC NITROGEN COMPOUND
CAS NUMBER : 67-63-0	CHEMICAL NAME: ISOPROPANOL
CAS NUMBER : 67-63-0	CHEMICAL NAME: 2-PROPANOL

8EHQ-1088-0761 SUBMITTER: GELMAN SCIENCES INC.

CAS NUMBER : NONE	CHEMICAL NAME: COOLANTS, AUTOMOTIVE
CAS NUMBER : NONE	CHEMICAL NAME: DE-ICING FLUIDS, AIRCRAFT
CAS NUMBER : 107-21-1	CHEMICAL NAME: 1,2-ETHANEDIOL
CAS NUMBER : 107-21-1	CHEMICAL NAME: ETHYLENE GLYCOL
CAS NUMBER : 123-91-1	CHEMICAL NAME: 1,4-DIOXANE

8EHQ-1088-0762 SUBMITTER: AMOCO CORPORATION

CAS NUMBER : 111-87-5	CHEMICAL NAME: 1-OCTANOL

8EHQ-1088-0763 S SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : CONFIDENT	CHEMICAL NAME: THIADIAZOLE SULFONAMIDE, ALKYLAMINOCARBONYL SUBSTITUTED

8EHQ-1088-0764 S SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : CONFIDENT	CHEMICAL NAME: TOLYLCYCLOALKENYL SUBSTITUTED ALKYL ESTER
CAS NUMBER : CONFIDENT	CHEMICAL NAME: TOLYLCYCLOALKENYL SUBSTITUTED PHOSPHOROTHIOATE ESTER
CAS NUMBER : CONFIDENT	CHEMICAL NAME: XYLYLCYCLOALKENYL SUBSTITUTED ALKYL ESTER

8EHQ-1088-0764 S SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : 149-57-5 CHEMICAL NAME: HEXANOIC ACID, 2-ETHYL-

8EHQ-1188-0765 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: ARYL OXIME

8EHQ-1188-0766 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: HETEROARYL ALKYL ETHER

8EHQ-1188-0767 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: HALOALKYL HETEROCYCLE

8EHQ-1188-0768 S SUBMITTER: EASTMAN KODAK COMPANY

CAS NUMBER : CONFIDENT CHEMICAL NAME: INORGANIC POTASSIUM HALIDE COMPLEX

8EHQ-1188-0769 * SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : 1336-36-3 CHEMICAL NAME: 1,1'-BIPHENYL, CHLORO DERIVS.

CAS NUMBER : 1336-36-3 CHEMICAL NAME: POLYBROMINATED BIPHENYLS (PCB)

CAS NUMBER : 11096-82-5 CHEMICAL NAME: AROCHLOR 1260

8EHQ-1188-0770 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: ACETAL, HETEROCYCLIC

8EHQ-1188-0771 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: ETHER, ALKYL ARYL

8EHQ-1188-0772 SUBMITTER: HOECHST CELANESE CORPORATION

CAS NUMBER : 75-09-2 CHEMICAL NAME: METHANE, DICHLORO-

CAS NUMBER : 75-09-2 CHEMICAL NAME: METHYLENE CHLORIDE

CAS NUMBER : 9012-09-3 CHEMICAL NAME: CELLULOSE, TRIACETATE

CAS NUMBER : 9012-09-3 CHEMICAL NAME: TRIACETATE FIBERS, CELLULOSE

8EHQ-1188-0772 SUBMITTER: HOECHST CELANESE CORPORATION

8EHQ-1288-0773 SUBMITTER: AMOCO OIL COMPANY

CAS NUMBER : 64741-76-0 CHEMICAL NAME: DISTILLATES (PETROLEUM), HEAVY HYDROCRACKED

CAS NUMBER : 64741-76-0 CHEMICAL NAME: RESID HYDROPROCESSING UNIT (RHU) MIDDLE DISTILLATES

8EHQ-1288-0774 SUBMITTER: AMOCO OIL COMPANY

CAS NUMBER : 64741-75-9 CHEMICAL NAME: RESID HYDROPROCESSING UNIT (RHU) LIGHT VACUUM GAS OILS

CAS NUMBER : 64741-75-9 CHEMICAL NAME: RESIDUES, (PETROLEUM), HYDROCRACKED

8EHQ-1288-0775 SUBMITTER: AMOCO OIL COMPANY

CAS NUMBER : 64742-46-7 CHEMICAL NAME: AMOCO NT-45 PROCESS OIL

CAS NUMBER : 64742-46-7 CHEMICAL NAME: DISTILLATES, (PETROLEUM), HYDROTREATED MIDDLE

8EHQ-1288-0776 SUBMITTER: AMERICAN TELEPHONE AND TELEGRAPH COMPANY

CAS NUMBER : CONFIDENT CHEMICAL NAME: ACRYLIC ACID DERIVATIVES

CAS NUMBER : CONFIDENT CHEMICAL NAME: BORDON CHEMICAL COMPOUND 9MKU10108R

CAS NUMBER : CONFIDENT CHEMICAL NAME: 2-PROPENOIC ACID DERIVATIVES

8EHQ-1288-0777 SUBMITTER: AMOCO CHEMICAL COMPANY

CAS NUMBER : 1779-17-5 CHEMICAL NAME: 1,3-ISOBENZOFURANDIONE, 5,5'-(1-METHYLETHYLIDENE)BIS-

8EHQ-1288-0778 SUBMITTER: EASTMAN KODAK COMPANY

CAS NUMBER : 94-96-2 CHEMICAL NAME: 1,3-HEXANEDIOL, 2-ETHYL-

* Based on a preliminary evaluation, EPA believed that the submitted information did not warrant reporting under Section 8(e) of TSCA. In most cases, the submitter was requested to provide the basis for contending that the information offered reasonable support for the conclusion that the subject chemical substance(s) or mixture(s) presents a substantial risk of injury to health or the environment as defined in EPA's TSCA Section 8(e) policy statement (see Appendix A of this volume).

50272-101

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7. Author(s) Office of Toxic Substances/OPTS U.S. Environmental Protection Agency (EPA)			8. Performing Organization Rept. No.
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15. Supplementary Notes

16. Abstract (Limit: 200 words)

This volume contains, in ascending submission number order, "status reports" (i.e., preliminary evaluations) prepared by the staff of the Office of Toxic Substances in EPA's Office of Pesticides and Toxic Substances for initial submissions received by EPA from chemical manufacturers, importers, processors and distributors from January 1, 1987 to December 31, 1988 under Section 8(e), the "substantial risk" information reporting provision of the Toxic Substances Control Act (TSCA). The status reports contained in this compendium reflect only the initial phase of the Agency's evaluation process for the submitted information.

This TSCA Section 8(e) status report volume has been published by EPA for two reasons. First, a volume of Section 8(e) status reports with appropriate indices will make the submitted information more accessible. Second, this volume may, by providing specific examples of submitted information and EPA's preliminary evaluation of that information, help those persons who are subject to Section 8(e) understand better the types of information that should be submitted to EPA under this mandatory reporting provision of TSCA.

17. Document Analysis a. Descriptors

Toxic Substances Control Act
TSCA
Section 8(e)
Substantial Risk

b. Identifiers/Open-Ended Terms

c. COSATI Field/Group

18. Availability Statement:	19. Security Class (This Report)	21. No. of Pages
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