United States
Environmental Protection
Agency

Office of Pesticides
and Toxic Substances
Washington DC 20460

March 1987
EPA 560/2-87-001

EPA

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

January 1, 1985 - December 31, 1986

NOTICE TO ADMINISTRATOR OF SUBSTANTIAL RISKS. 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 [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 560/2-87-001
MARCH 1987

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

JANUARY 1, 1985 TO DECEMBER 31, 1986

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. 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 EPA from chemical manufacturers, processors, and distributors between January 1, 1985, and December 31, 1986, 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

The Agency plans to print a limited number of copies of this volume. After the Agency'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 three previously published Section 8(e) status report volumes (PB# 80-221609, PB# 81-145732, PB# 83-187815 and PB# 87-129409) 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, Chief
Chemical Screening Branch
Existing Chemical Assessment Division (TS-778)
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 which are located at EPA Headquarters, Room G-004, Northeast Mall, 401 "M" Street S.W., Washington, D.C. Copies of Section 8(e) submissions and status reports can be obtained by writing to EPA's Freedom of Information Office at the following address:

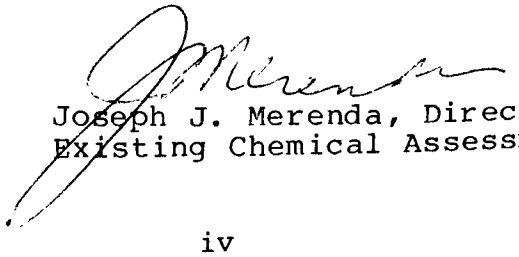
Freedom of Information Office (A-101)
U.S. Environmental Protection Agency
401 "M" Street, S.W.
Washington, D.C. 20460

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 525 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:

ALCOLAC
ALLIED-SIGNAL INC.
AMERICAN CYANAMID COMPANY
AMERICAN HOECHST CORPORATION
AMOCO CORPORATION
ATLANTIC RICHFIELD COMPANY
AZS CORPORATION
BASF WYANDOTTE CORPORATION
CELANESE CORPORATION
CHEMICAL MANUFACTURERS ASSOCIATION
CHEVRON CHEMICAL COMPANY
CIBA-GEIGY CORPORATION
DOW CORNING CORPORATION
EASTMAN KODAK COMPANY
E. I. DU PONT DE NEMOURS & COMPANY, INC.
ELI LILLY AND COMPANY
ETHYL CORPORATION
FRAGRANCE MATERIALS ASSOCIATION (U.S.)
HERCULES INCORPORATED
IBM CORPORATION
INTERNATIONAL LEAD ZINC RESEARCH ORGANIZATION INC.
INTERNATIONAL MINERALS & CHEMICAL CORPORATION
LEVER BROTHERS COMPANY (INCORPORATED)
MOBIL RESEARCH AND DEVELOPMENT CORPORATION
MONSANTO COMPANY
NALCO CHEMICAL COMPANY
NATIONAL STARCH AND CHEMICAL CORPORATION
NUODEX INC.
OLIN CORPORATION
PPG INDUSTRIES, INC.
PROCTER & GAMBLE COMPANY
ROHM AND HAAS COMPANY
R. T. VANDERBILT COMPANY, INC.
SMELTER ENVIRONMENTAL RESEARCH ASSOCIATION
SOCIETY OF THE PLASTICS INDUSTRY, INC.
SOHIO ENGINEERED MATERIALS COMPANY
SYNTEX (U.S.A.) INC.
TEXACO INC.
TOTAL PETROLEUM, INC.
UNION CARBIDE CORPORATION
U. S. DEPRARTMENT OF ENERGY
VELSICOL CHEMICAL CORPORATION

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Introduction

Section 8(e) of the Toxic Substances Control Act (TSCA; the Act) 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 [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, 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, EPA (following receipt and review of public comments) published its March 16, 1978 TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110). 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 which 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 650 initial TSCA Section 8(e) notices 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). 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 the 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., -0579-) 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 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 EPA to be unwarranted for reporting under 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.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: FEB 21 1985

SUBJECT: Status Report* 8EHQ-0185-0542 S

Approved 2/21/85

Revision Needed

FROM: David R. Williams, Section 8(e) Coordinator
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 as TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS) has requested the submitting company to substantiate this confidentiality claim.

Submission Description

The submitting company provided the following information with regard to nitrite-containing metalworking fluids:

"N-nitrosodiethanolamine (NDELA) can form in nitrite-containing metalworking fluids. R. Preussmann, et al have reported on the carcinogenic effects of NDELA (Cancer Research, 42, 5167, 1982). The degree of exposure to NDELA by users of these fluids has been believed to be minimal because NDELA is also known to decompose rapidly under use conditions (D.P. Rounbehler and J.M. Fajen, N-NITROSO COMPOUNDS IN THE FACTORY ENVIRONMENT (1983)).

"...[The submitting company has] recently discovered that for those metalworking fluids that contain nitrite and high levels of diethanolamine (DEA), the rate of NDELA formation may be significantly greater than the rate of decomposition, resulting in accumulation of NDELA. Specifically, ...[the submitting company has] found that a product which contains 10% DEA in the original concentrate can have as much as 600 ppm of NDELA in a used mix, while simple dilution of year-old samples of the same product concentrate tested at a level of 150 ppm. In contrast, Rounbehler and Fajen reported typical levels of 1-5 ppm in conventional nitrite-containing metalworking fluids."

Submission Evaluation

Information available to the Agency does not support the impression given by the submitter's statement that "...exposure to NDELA in metalworking fluids was believed to be minimal because NDELA is known to decompose rapidly under use conditions...."

*NOTE: This status report is the result of a preliminary staff evaluation of information submitted to EPA. Statements made herein are not to be regarded as expressing final Agency policy or intent with respect to this particular chemical. Any review of the status report should take into consideration the fact that it may be based on incomplete information.

In fact, the Agency's analysis of available data indicates that the concentration of NDELA does not, on average, significantly increase or decrease with time in dilute (working) metalworking baths. This does not mean, however, that in individual metalworking fluid baths, significant NDELA formation or degradation cannot occur, as evidenced by the formation of significant levels reported in this Section 8(e) submission.

The submitter, in commenting on the company's measurement of 600 ppm NDELA in a metalworking fluid sample, stated that a study "...reported typical levels of 1-5 ppm NDELA in conventional nitrite-containing metalworking fluids." Here again, the information available to EPA does not indicate that 1-5 ppm NDELA in nitrite-containing metalworking fluids is "typical." Over 100 metalworking fluid samples have been analyzed for the presence of nitrosamines by a number of investigators. The levels of NDELA reported range from non-detected to 29,900 ppm in cutting fluid concentrate. In samples of dilute metalworking fluids (working baths) known to have been nitrite-containing formulations, the nitrosamine (NDELA) levels ranged from below the detection limit to as high as 315 ppm, with an average observed NDELA concentration of approximately 88 ppm.

Immediately upon receipt of this Section 8(e) submission, the Chemical Screening Branch (CSB/ECAD/OTS) provided copies of the notice to the Risk Management Branch (RMB/ECAD/OTS), Existing Chemical Control Branch (ECCB/CCD/OTS), and Regulatory Impacts Branch (RIB/ETD/OTS) for inclusion in the ongoing OTS evaluation of the potential risks posed by exposure to nitrite-containing metalworking fluids. It should be noted that in September 1984, EPA published two "Chemical Advisories" that outline EPA's concerns about nitrosamines in metalworking fluids. Copies of these advisories may be obtained by calling toll free at 800-424-9065 or in the Washington D.C. area at 202-554-1404, or by writing to:

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

Current Production and Use

Metalworking fluids (also known 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. An estimated 5 million gallons (approximately 40 million pounds) of nitrite-containing metalworking fluid concentrate were consumed in the U.S. during 1983.

Comments/Recommendations

On the basis of the obtained results, the submitter reported that the company is taking steps to 1) "withdraw this type of product from the market" and 2) inform customers about the reported findings.

EPA's Office of Toxic Substances (OTS) has received and evaluated a number of TSCA Section 8(e) and "For Your Information" (FYI) submissions containing toxicity/exposure information on cutting fluids and/or various nitrosamines. In addition, the Chemical Screening Branch/ECAD has prepared Chemical Hazard Information Profiles (CHIPs) on cutting fluids and certain N-nitroso compounds, including nitrosodiethanolamine (NDELA).

a) The Chemical Screening Branch will request the submitting company to provide the following information with regard to the reported findings:

- the length of time the metalworking fluid bath (from which the sample reported to contain 600 ppm NDELA) had been in use;
- the NDELA concentration at the time this used metalworking bath fluid was initially analyzed; and
- if the used metalworking bath fluid sample was analyzed for NDELA over time, indicate the interval of time between each successive analysis and the NDELA concentration measured at each successive analysis.

The Chemical Screening Branch will also ask the submitting company to provide the following information with regard to the metalworking fluid concentrate that was reported by the company to contain 10% diethanolamine (DEA)

- the product name(s) of the concentrate;
- the actual chemical name, CAS Registry Number (if known), and amount of each constituent (including contaminants and impurities if detected) in the concentrate;
- the product name(s) of all products (if any) formulated via dilution of the concentrate; and
- the actual chemical name, CAS Registry Number (if known) and amount of each constituent (including contaminants and impurities if detected) in all products (if any) formulated via dilution of the concentrate.

In addition, the Chemical Screening Branch will request the submitter to describe the nature and results of all studies, assays, analyses, etc. conducted by or for the submitting company in which a nitrosamine was detected at any level in any metalworking fluid concentrate or dilution thereof.

Finally, the submitting company will be requested to provide a complete copy of the written communication(s) by which the submitter's customers have been or are being notified about the reported findings and/or the withdrawal of metalworking fluids from commerce.

b) The Chemical Screening Branch will provide copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, ORD/EPA, OAR/EPA, RMB/ECAD/OTS, ECCB/CCD/OTS and RIB/ETD/OTS. Copies of this status report will also be provided to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAR - 6 1985

SUBJECT: Status Report* 8EHQ-0185-0543

Approved 3/11/85

Revision Needed _____

FROM: David R. Williams, Section 8(e) Coordinator
Chemical Risk Identification Section/CSB

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

Submission Description

On behalf of member companies of its Vinyl Acetate Task Force, the Society of the Plastics Industry, Inc. (SPI) submitted summarized preliminary findings from a two-generation reproduction study of rats dosed orally at 0, 200, 1000, and 5000 ppm vinyl acetate (CAS No. 108-05-4) in water. In addition, SPI reported that a two-year in utero oral study and a two-year inhalation study of vinyl acetate are also underway. According to SPI,

> "The preliminary data indicate that when rats were first treated with vinyl acetate via the oral route and bred to produce off-spring for the in utero study and to start the two generation reproduction study, a decrease in overall fertility was noted in the high dose group (5000 ppm). The observed effect was a reduction in the number of litters produced, not a reduction in the number of pups per litter or in the quality of the litters. The decrease was slight and within the normal range for many labs. No such effects were seen at the 200 ppm or the 1000 ppm dose level."
>
> "In the breeding of the second generation there was again a marginal decrease in fertility in the high dose group. To further evaluate whether this result was real, an additional cross-mating study was done in which high dose treated males were mated to control females and control males were mated to treated high dose females. The object of this study was to obtain additional information on the fertility index and to assess whether there was an effect in the male or the female. The results of this study again showed a marginal decrease in the fertility index in treated males bred to control females. When control males were bred to treated females no such effect was observed. These effects were seen in the presence of decreased body weight gain ...and decreased water consumption."

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*NOTE: This status report is the result of a preliminary staff evaluation of information submitted to EPA. Statements made herein are not to be regarded as expressing final Agency policy or intent with respect to this particular chemical. Any review of the status report should take into consideration the fact that it may be based on incomplete information.

'The pattern seen in the earlier phases, plus the information generated in this cross-mating, led ...[SPI] to conclude that there is a marginal but treatment-related effect of vinyl acetate on male fertility in rats exposed via the oral route at 5000 ppm in the drinking water. Further evaluation of the significance of these results is now under review."

Submission Evaluation

Although the submitted information does indicate that vinyl acetate can produce an adverse effect on the fertility of male rats, complete copies of the final reports of the cited studies are needed in order for EPA to evaluate more completely the overall significance of the reported findings.

Immediately upon receipt of this Section 8(e) submission, the Chemical Screening Branch (CSB/ECAD/OTS) sent a copy to the Risk Management Branch (RMB/ECAD/OTS) for inclusion in the ongoing evaluation of available toxicologic/exposure information on vinyl acetate.

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 Inventory, has shown that 521 million to 2.6 billion pounds were reported as produced/imported in 1977. This production range data does not include any production/importation data claimed as TSCA Confidential Business Information (TSCA CBI) by those person(s) reporting for the TSCA Inventory, nor does it include any information that would compromise TSCA CBI. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

According to the May 7, 1984 issue of Chemical & Engineering News, an estimated 2 billion pounds of vinyl acetate were produced domestically in 1983. According to secondary literature sources, the major use of vinyl acetate is in the manufacture of polymers, such as poly(vinyl acetate), poly(vinyl alcohol), vinyl chloride co-polymer, and ethylene-vinyl acetate co-polymers.

Comments/Recommendations

In view of the fact that a number of Section 8(e) notices have been received thus far on behalf of chemical companies, the purpose of the following discussion is to reiterate EPA's policy with regard to the TSCA Section 8(e) reporting obligation of organizations/associations such as SPI, the American Petroleum Institute (API), the Chemical Manufacturers Association (CMA), the Chemical Industry Institute of Toxicology (CIIT), etc. and companies that may be members of such organizations/associations.

Section 8(e) of the Toxic Substances Control 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 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" 43 FR 11110; March 16, 1978) states that the term "person" includes "any natural person, corporation, firm, company, joint-venture, sole proprietorship, association, or any other business entity ...." Therefore, the obligation to immediately report substantial risk information would apply to an organization/association such as SPI, CMA, API, CIIT, etc. only if such organization/association engages in the manufacture, import, processing, or distribution of the chemical substance or mixture about which substantial risk information has been obtained. However, it is more likely that a Section 8(e) reporting obligation would be incurred by a member (or non-member) company that obtains the results (including preliminary results) from studies conducted or sponsored by an organization/association, if the obtained results meet the reporting criteria outlined in the TSCA Section 8(e) policy statement and pertain to a chemical substance or mixture that the company manufactures, imports, processes, or distributes in commerce.

Part III of the TSCA Section 8(e) policy statement explains that substantial risk information is obtained at that time when any officer or employee of a subject company, who is capable of appreciating the significance of the information, possesses, or knows of, such information. With the exception of information about "Emergency Incidents of Environmental Contamination," the obligation to immediately report substantial risk information is considered discharged if EPA receives the information 1) in accordance with the reporting requirements specified in Part IX of the Section 8(e) policy statement, and 2) not later than the 15th working day after the date the information was obtained. Information need not be reported, however, if the subject person has actual knowledge that the Agency has already been adequately informed about the information. Part VII of the Section 8(e) policy statement provides further guidance with regard to the types of information that need not be reported to EPA under Section 8(e) of TSCA. In addition, Section 3 of TSCA itself lists those materials (e.g., drugs, pesticides) that are not regulated by TSCA.

Finally, it should be noted that a company that obtains substantial risk information and relies on another party to

submit the information to EPA under Section 8(e) on the company's behalf, must ensure that the Agency receives the information in a timely manner and in accordance with the reporting requirements specified in Part IX of the Section 8(e) policy statement.

The cover letter of SPI's TSCA Section 8(e) submission indicated that copies of the reported findings had also been sent to OSHA, CPSC and FDA.

EPA's Office of Toxic Substances (OTS) has received and evaluated a number of TSCA Section 8(e) and "For Your Information" (FYI) submissions containing toxicologic and/or exposure data on vinyl acetate. In addition, the Chemical Screening Branch has prepared a Chemical Hazard Information Profile (CHIP) on vinyl acetate.

a) The Chemical Screening Branch will ask the members of SPI's Vinyl Acetate Task Force to ensure that EPA is apprised in a timely manner about future significant findings from all studies cited in the submission and to ensure that the Agency receives in a timely manner complete copies of the final reports (including actual experimental protocols and data) from those studies. SPI will be asked to distribute copies of this status report to the members of its Vinyl Acetate Task Force.

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 the Risk Management Branch (RMB/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: MAR - 7 1985

SUBJECT: Status Report* 8EHQ-0285-0544

Approved 3/11/85

Revision Needed

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Risk Identification Section/CSB

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

Submission Description

The CIBA-GEIGY Corporation provided summarized final results from an oral (rat) range-finding study and summarized preliminary results from an ongoing oral (rat) teratology study of commercial grade [[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]thio]-acetic acid, 2-ethylhexyl ester (CAS No. 80387-97-9). CIBA-GEIGY provided the following information with regard to the design and results of the subject studies conducted at the toxicology laboratory at CIBA-GEIGY, Ltd. in Basel, Switzerland:

> "In a preliminary range-finding study, the test material was administered in peanut oil, by gavage, to 8 pregnant rats at dose levels of 200 or 400 mg/kg/day from day 6 through 15 of gestation. A control group of 8 dams was treated similarly with the peanut oil vehicle only. No overt effects were observed in the dams or the offspring of the 200 mg/kg/day group. However, at the 400 mg/kg/day level, the resorption rate was markedly increased (86%) and only 1 of 8 females had live fetuses at sacrifice on day 21 post coitum.
>
> "Based on these results, the dose levels for the standard FDA Segment II [teratology] study were selected at 50, 150, and 300 mg/kg/day. Preliminary findings from this study indicated a high resorption rate (61%) in the 300 mg/kg/day group. Thirteen [13] of 23 dams in this group had no live offspring (i.e., showed only resorption sites) and gross external examination of the fetuses from the remaining 10 dams revealed a high incidence of malformations and/or anomalies in 6 of the litters (from 1 to 12 fetuses affected per litter). The predominant type of malformation involved the distal parts of the extremities (ectrodactyly and adactyly)."

In its submission, CIBA-GEIGY stated that "an analysis and report will be prepared by the Basel toxicology laboratory, probably to be completed by June or July of ...[1985]."

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*NOTE: This status report is the result of a preliminary staff evaluation of information submitted to EPA. Statements made herein are not to be regarded as expressing final Agency policy or intent with respect to this particular chemical. Any review of the status report should take into consideration the fact that it may be based on incomplete information.

Submission Evaluation

Although the submitted information does indicate that the subject chemical and/or its metabolite(s) can cause adverse developmental effects in rats, a more in-depth evaluation of the overall significance of the reported findings should be possible upon EPA's receipt of complete copies of the final reports (including the actual experimental protocols and data) from the range-finding and Segment II teratology studies.

It should be noted that the tested chemical can hydrolyze to a "hindered" phenol methylthioacetic acid and 2-ethylhexanol. The 2-ethylhexanol can undergo further metabolism to 2-ethylhexanoic acid, a chemical structurally similar to the known developmental toxicant, valproic acid (i.e., 2-propylpentanoic acid). The Test Rules Development Branch (TRDB/ECAD/OTS) is currently evaluating available toxicity/exposure information on 2-ethylhexanoic acid, a chemical recommended by the Interagency Testing Committee (ITC) for testing consideration under TSCA Section 4. The "hindered" phenol methylthioacetic acid portion of the tested chemical contains a butylated hydroxytoluene (BHT) moiety. Staff of the Risk Management Branch (RMB/ECAD/OTS) is in the process of evaluating the available toxicity/exposure data on BHT, a substance for which the Chemical Screening Branch (CSB/ECAD/OTS) has prepared a Chemical Hazard Information Profile (CHIP).

Current Production and Use

The tested chemical (CAS No. 80387-97-9) is listed in the non-confidential version of the TSCA Inventory and was the subject of a Premanufacture Notice (PMN) submitted to EPA under Section 5 of TSCA.

CIBA-GEIGY stated that the tested chemical, which "is a very low vapor pressure, semi-viscous, liquid, (approximately 4.5×10^{-7} mm Hg at 20°C), had [a] commercial use, or potential commercial use, as an antioxidant for elastomers, adhesives and lubricating oils." CIBA-GEIGY stated that "to date, about 2000 lbs. of this substance has been commercially distributed to one customer."

Comments/Recommendations

In its submission, the CIBA-Geigy Corporation stated that a copy of the final study report would be sent to EPA upon the company's receipt and assessment of that report. In addition, CIBA-GEIGY stated that the company is planning "to confirm the preliminary results, analyze the complete result and determine the no effect level." Finally, CIBA-GEIGY stated that in response to the submitted findings, the company will 1) "inform ...[CIBA-GEIGY] employees and all companies to whom this chemical substance was distributed, whether for commercial or research and development purposes, of these preliminary findings" and 2) "withdraw the product from the market and recall, for proper disposal by CIBA-GEIGY, any samples distributed."

(a) The Chemical Screening Branch will request the CIBA-GEIGY Corporation to submit complete copies of final reports (including the actual experimental protocols and data) from the range-finding study and the Segment II teratology study cited in the submission.

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

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAR 18 1985

SUBJECT: Status Report* 8EHQ-0285-0545 S

Approved 3/19/85

Revision Needed

FROM: David R. Williams DRW Section 8(e) Coordinator
Chemical Risk Identification Section/CSB

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

Note

The CIBA-GEIGY Corporation has claimed the actual identity and use of the subject substance to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS/OPTS/EPA) has asked CIBA-GEIGY to substantiate these claims. CIBA-GEIGY did report non-confidentially, however, that the subject chemical is a "halophenoxy halophenyl substituted heteromonocyclic heteromonocycle" which has the internal product code: CGA-149071.

Submission Description

CIBA-GEIGY provided the following summarized preliminary findings from a 52-week dietary feeding study of CGA-149071 in dogs:

> "Ophthalmoscopic examinations (using focal illumination and indirect opthalmoscopy) on dogs on test day 86 (week 13 examinations), revealed bilateral (unilateral in one dog), equatorial, anterior cortical and posterior cortical lenticular aberrations affecting all dogs in the high dose group (6000 ppm) (10/10 male, 10/10 female). Opthalmoscopically, the lenticular changes were characterized as vacuoles, water clefts, spoke-like opacities, and splitting and separation of the lens suture lines with resultant "Y" shaped fissures. All other ocular structures appeared clinically unaffected at this time. No changes from normal were seen in the eyes of other dogs on this experiment and there appeared to be no visual deficit at this time."

CIBA-GEIGY also provided further information by phone concerning this study. According to the company, beagles are being exposed to the test chemical at doses of 0, 30, 1000, or 6000 ppm in the feed. The company also stated that although the dogs in the 6000 ppm dose groups showed a slight (15%) weight loss and were slightly anemic, no serious adverse effects (other than the serious adverse eye effects found only the 6000 ppm groups) have been observed thus far in any of the exposed animals.

*NOTE: This status report is the result of a preliminary staff evaluation of information submitted to EPA. Statements made herein are not to be regarded as expressing final Agency policy or intent with respect to this particular chemical. Any review of the status report should take into consideration the fact that it may be based on incomplete information.

In its submission, CIBA-GEIGY reported that in response to the preliminary findings, the company will:

" 1. Photograph the eyes of all dogs at this time.

2. Perform monthly examinations of the eyes of the dogs.

3. Remove the eyes during the scheduled 13-week necropsy and during subsequent necropsies.

4. During histological processing of the eyes, remove the lens of the left eye and process it separately while processing the second eye routinely.

5. Allow some dogs to undergo a period of compound withdrawal, in which reversibility of the lenticular changes might be seen in whole or in part."

Submission Evaluation

Although the submitted information indicates that CG-149071 can cause lenticular aberrations, a more thorough evaluation of the 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 and data) from the 52-week dietary feeding study in dogs. It should be noted that although systemic intoxication leading to lenticular aberrations is not common, such adverse effects have been reported in the published scientific literature to occur in laboratory animals and humans following exposure to a number of substances.

CIBA-GEIGY stated in the submission that the observed lenticular aberrations in the high dose groups did not appear to cause any visual impairment. CIBA-GIEGY did not report, however, how the dogs' visual integrity was tested/measured or if the sensitivity of such measurements/tests was sufficient to detect subtle but serious visual impairment over time. The proposed experimental protocol changes and followup procedures appear to be appropriate to determine whether the observed adverse effects are reversible. Finally, it should be noted that CIBA-GEIGY's proposed hazard communications pertain mainly to the avoidance of dermal and ocular exposure and do not address the potential for inhalation and/or oral exposure to the tested chemical. It may be, however, that the physical/chemical properties of the substance preclude such types of exposure.

Current Production and Use

The CIBA-GEIGY Corporation stated in its submission that the tested chemical "is a research and development material which is being evaluated for pesticidal purposes" and that the pesticidal evaluations "have been conducted only under the supervision of technically qualified personnel."

Comments/Recommendations

In its submission, the CIBA-GEIGY Corporation reported that the company plans to provide the following notice to all personnel who work with CGA-149071:

> "Ocular changes in the dog have been noted after 13 weeks of dietary exposure to high levels of CGA-149071. These changes are areas of swelling in the lens. Gloves, goggles and protective equipment should be used to prevent exposure to CGA-149071 until further information is available about this effect."

In addition, CIBA-GEIGY reported that the CGA-149071 container labels will bear the following information:

> "Eye changes in the dog have been noted in animal testing with this compound. Wear gloves and goggles when handling this compound."

The following discussion describes the relationship of the Toxic Substances Control Act (TSCA) and the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) to chemicals, pesticides, and research and development (R&D) chemicals including those intended as pesticides. Specifically, this discussion is intended to be of assistance in determining whether to submit appropriate information under TSCA §8(e) or FIFRA §6(a)(2).

EPA set forth its policy on the jurisdictional relationship of TSCA to FIFRA in the TSCA Inventory reporting regulations (43 FR 64585, December 23, 1977, Appendix A, Comments 37, 38 and 39). That jurisdictional policy is still in effect and the responses to comments discussed in 43 FR 64585 are also generally applicable to this dicussion.

Under TSCA, EPA can regulate certain activities involving "chemical substances" and "mixtures." If a substance is manufactured, processed, or distributed in commerce solely for use as a pesticide, however, §3 of TSCA excludes such substance from TSCA regulation. If a substance has multiple uses, only some of which are pesticidal, the remaining uses fall within the jurisdiction of TSCA, with certain exceptions (e.g., drugs).

In keeping with the policy expressed in the TSCA Inventory regulations, EPA generally considers a substance to be a pesticide within the meaning of FIFRA when that substance is the subject of (1) a submission made to EPA as part of the experimental use permit (EUP) process under FIFRA or (2) an application for registration submitted to EPA under FIFRA. Prior to this stage, however, the Agency treats the substance

as a "chemical substance" under the jurisdiction of TSCA. Therefore, any "substantial risk" information on an R&D substance that may arise prior to the EUP or registration stage (even though such information might be submitted later under FIFRA in an application for registration or experimental use permit) must be reported under TSCA §8(e). EPA's response to Comment 31 in Appendix B of the Agency's TSCA §8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978)) provides additional guidance with regard to the TSCA §8(e) applicability and reportability of information on R&D chemicals.

FIFRA §6(a)(2) requires registrants to submit information regarding unreasonable adverse effects of their pesticides on the environment. In view of the fact that the FIFRA §6(a)(2) requirement exists for as long as a pesticide is registered under FIFRA, any such information must be reported under FIFRA §6(a)(2) when the information becomes available to the registrant. Registrants are not required to report this same information under TSCA §8(e). (See Part VII of EPA's TSCA §8(e) policy statement.) If the substance is no longer a registered pesticide but has uses that fall under the jurisdiction of TSCA, then reporting would be required under §8(e) for "substantial risk" information obtained on the chemical.

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a) The Chemical Screening Branch (CSB/ECAD/OTS) will request the CIBA-GEIGY Corporation to ensure that EPA is apprised in a timely manner about the nature of additional significant results obtained from the ongoing dietary feeding study of CGA-149071. CIBA-GEIGY will also be requested to ensure that EPA receives a complete copy of the final report (including actual experimental protocol and data) from the subject study. In addition, CIBA-GEIGY will be asked to describe the nature and available results of all other studies that have been or are being conducted by or for the company to determine the toxicity of or the exposure to CGA-149071.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of CGA-149071.

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 also be provided to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

8EHQ-0285-0546
Page 1 of 6

DATE: APR 11 1985

Approved: 4/15/85

SUBJECT: Status Report* 8EHQ-0285-0546

FROM: David R. Williams, DRW Section 8(e) Coordinator
Chemical Risk Identification Section/CSB

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

Submission Description

On behalf of its member companies, the International Lead Zinc Research Organization (ILZRO), Inc. submitted a copy of a pre-publication draft report entitled "Mortality in Employees of Lead Battery Plants and Lead Production Plants, 1947-1980." According to ILZRO, the subject study is an update of the results of previously published analyses of mortality data for the same worker population. 1,2,3/ ILZRO provided the following information concerning the results of this new analysis:

"The report looks at two study groups occupationally exposed to lead: 4,519 lead battery plant workers and 2,300 lead smelter workers during the period 1947-1980. The limited lead exposure data available for the two groups show that the study population was exposed to lead in amounts far above current levels. The study results are, in general, consistent with previously published reports. However, certain statistical results may represent new information. In particular, there was a statistically significant excess of deaths from stomach cancer in battery workers. The excess in number of deaths from stomach cancers in lead smelter workers was not significantly greater than for the general population. The report notes that 85% of the stomach cancer deaths in battery workers and 89.9% of the total deaths of battery workers occurred in men residing in Pennsylvania which suggests that factors related to geographical residence or ethnicity may be important. The report also notes that 'it is extremely doubtful [that] lead is a carcinogen per se, the possibility remains that high local concentrations could have a co-carcinogenic effect, particularly operative in those whose dietary or alcohol intake patterns are predisposed to higher-than-average gastric cancer rates.' The report does not provide any basis for assessing

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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 extent of risk, if any, associated with lead exposure because there is no feasible way to establish the actual exposure of the study population during their working lifetime. Such information is needed to relate epidemiologic findings to risk estimates for chronic lead exposure...."

Submission Evaluation

The submitted report presents mortality analyses of 2,339 deaths for men who had worked one year or more between 1946 and 1970 in lead battery plants or in lead production facilities (smelters). Previous biological monitoring of a number of these workers indicated high level exposures to lead. For both groups (battery and lead production workers), there was increased mortality from all causes, from all neoplasms (specifically, cancers of the stomach, liver and lung), from chronic nephritis, and from other hypertensive disease (i.e., hypertensive conditions due to kidney damage and not heart disease). More importantly, however, this study showed a statistically significant trend between all-cause mortality and cumulative lead exposure. This trend is qualitative support for a possible dose response relationship.

The performed study was of historical prospective design and was composed of 6,819 males from 10 battery plants (4,519 workers) and 6 lead production plants (2,300 workers). In view of the fact that the racial composition of these workers was not known, the investigator used the mortality rates of U.S. white males to derive the expected number of deaths. The investigator noted that blood and urine monitoring from 1947-1972 indicated that some of the workers had been heavily exposed to lead. For those workers who had had their blood lead levels measured 3 or more times, 22% of the battery workers (278 of 1387) and 27% of the lead production workers (89 of 330) had blood lead means over 70 micrograms/deciliter. The current OSHA standard for blood lead is 60 micrograms/deciliter. In addition, the investigator noted that the cohort was fairly stable with the majority of workers staying in the same job category.

The investigator studied these workers previously and published several papers concerning those studies. In a follow-up study through 1970 (1,356 deaths), a significant excess of deaths from chronic renal disease and a nonsignificant excess of malignant neoplastic deaths were observed for both battery workers and lead production workers. In another follow-up study through 1975 (1,947 deaths), the investigator observed an excess of neoplastic deaths only for smelter workers; this excess was explained mainly by an excess of respiratory cancer deaths. The investigator also noted that the excess mortality from chronic renal disease found in the earlier follow-up analysis was not observed in the second follow-up analysis.

The present analysis (i.e., the subject of this 8(e) submission) extends the follow-up period through 1980, by which time 2,339 deaths had occurred. The investigator examined mortality in both

groups for (a) the entire 1947-1980 period, (b) the number of years employed, (c) moving calendar periods, and (d) year of hire (before or after January 1, 1946). In addition, a proportionate mortality analysis of the deaths was performed to examine the influence of race. The analysis for all deaths between 1947-1980 showed significant excesses in mortality for both groups from all causes ($p<0.01$). For battery workers, the excess mortality was found to be due to significant increases in total neoplastic mortality (specifically, gastrointestinal tract neoplasms (not statistically significant), and stomach, lung, and liver neoplasms), other hypertensive disease, chronic nephritis, and ill-defined cause mortality. For smelter workers, the excess mortality was found to be due to malignant neoplasms (nonsignificant), hypertensive heart disease (nonsignificant), other hypertensive heart disease ($p<0.01$), chronic nephritis (nonsignificant), and external causes of death (e.g., suicides) ($p<0.01$). The most notable findings from the investigator's analyses are 1) a dose relationship between all-cause mortality and the time since date of hire, and 2) a dose relationship between all-cause mortality and cumulative lead exposure (in years). Tables I and II below present these findings.

Table I. Deaths Per 1,000 Person-Years

	Years since hire date				
	1-9	10-19	20-29	30+	Trend
Battery Workers	2.4	6.6	16.5	41.9	Statistically significant
Lead Prod. Workers	3.5	8.7	18.9	41.7	Statistically significant

Table II. Deaths Per 1,000 Person-Years

	Cumulative lead exposure (yrs); 20 yr latency			
	1-9	10-19	20+	Trend
Battery Workers	18.1	26.2	34.3	Statistically significant
Lead Prod. Workers	18.0	29.1	30.1	Statistically significant

It should be noted that the investigator's analyses do not include enough information to examine trends in chronic renal disease mortality; the observed number of deaths were reported for this end-point while the expected number of deaths were not. Second, even though the investigator claims that the blood and urine lead level data give no indication of exposures before 1960, these data probably could have been used in the analyses.

In conclusion, occupational lead exposure has a direct impact on overall mortality, and the longer one is exposed, the greater the impact. The submitted study supports previous evidence that lead is a nephrotoxin and the observed excesses in hypertensive heart disease mortality has been reported in other studies. More important are the significant excesses in neoplastic mortality, an observation not easily found in the literature on lead-exposed populations. Certainly ethnicity, diet, and personal habits (e.g., smoking) are factors in cancer etiology, but the role of lead cannot be diminished in light of the fact that excesses for site-specific neoplasms (i.e., gastric cancers) were observed in both groups of workers.

Immediately upon receipt of this Section 8(e) submission, the Chemical Screening Branch provided copies to OW/EPA, OSWER/EPA, OAR/EPA and ORD/EPA for use in any ongoing assessments of lead toxicity and/or exposure.

Current Production and Use

A review of the production range (includes importation volumes) statistics for lead (CAS No. 7439-92-1), which is listed in the initial TSCA Inventory, has shown that between 1.7 billion and 6.4 billion pounds were reported as produced and/or imported in 1977. This production range information does not include any production/importation data claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the TSCA Inventory, nor does it include any information that would compromise TSCA CBI. The information submitted for the TSCA Inventory, including the production range information, is subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

Lead is a heavy, blue-gray, soft metal that can be easily melted, formed, rolled, cast, etc. The wide variety of lead uses include the manufacture of pipes, coatings, and tanks; lead storage batteries; metal alloys; pigments; organic/inorganic lead compounds (e.g., tetraethyl lead which is used as a motor fuel additive); and radiation shield materials. It should be noted that new EPA standards will reduce the amount of lead in gasoline by 90% as of January 1, 1986. According to EPA estimates, these new standards will (by 1992) reduce by approximately 1 million the number of persons with elevated blood lead levels.

Comments/Recommendations

In view of the fact that a number of Section 8(e) notices have been received thus far on behalf of chemical companies, the purpose of the following discussion is to reiterate EPA's policy with regard to the TSCA Section 8(e) reporting obligation of organizations/associations such as ILZRO, the American Petroleum Institute (API), the Chemical Manufacturers Association (CMA), the Chemical Industry Institute of Toxicology (CIIT), etc. and companies that may be members of such organizations/associations.

Section 8(e) of the Toxic Substances Control 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."

The Agency's TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978) states that the term "person" includes "any natural person, corporation, firm, company, joint-venture, sole proprietorship, association, or any other business entity ...." Therefore, the obligation to immediately report substantial risk information would apply to an organization/association only if that organization/association engages in the manufacture, import, processing, or distribution of the chemical substance or mixture about which substantial risk information has been obtained. However, it is more likely that an 8(e) reporting obligation would be incurred by a member or non-member company that obtains the results (including preliminary results) from studies conducted or sponsored by an organization/association, if the obtained results meet the reporting criteria outlined in the Section 8(e) policy statement and pertain to a chemical substance or mixture that the company manufactures, imports, processes, or distributes in commerce.

Part III of the TSCA Section 8(e) policy statement explains that substantial risk information is obtained at that time when any officer or employee of a subject company, who is capable of appreciating the significance of the information, possesses, or knows of, such information. With the exception of information on "Emergency Incidents of Environmental Contamination," the obligation to immediately report substantial risk information is considered discharged if EPA receives the information 1) in accordance with the reporting requirements specified in Part IX of the Section 8(e) policy statement, and 2) not later than the 15th working day after the date the information was obtained. Information need not be reported, however, if the subject person has actual knowledge that EPA has already been adequately informed about the information. Part VII of the Section 8(e) policy statement provides further guidance with regard to the types of information that need not be reported to the Agency under TSCA Section 8(e). In addition, Section 3 of TSCA itself lists those substances (e.g., drugs, pesticides) that are not regulated by TSCA.

Finally, it should be noted that a company that relies on some other party to submit information under Section 8(e) on the company's behalf, must ensure that EPA receives the information in a timely manner and in accordance with the requirements in Part IX of EPA's TSCA Section 8(e) policy statement.

a) The Chemical Screening Branch will request ILZRO, Inc. to submit, when available, a complete copy of the final report for the epidemiologic study "Mortality in Employees of Lead Battery Plants and Lead Production Plants, 1947-1980."

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

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

REFERENCES

1/ Cooper, W. et al. "Mortality of Lead Workers"; J. Occ. Med.; 17; 100-107 (1985)

2/ Cooper, W. et al. "Mortality Study of Lead Workers"; Archiv Za Higijenu Rad i Toksikologiju (Zagred); 26; 209-229; (1976)

3/ Cooper, W. et al. "Mortality in Workers in Lead Production Facilities and Lead Battery Plants During the Period 1971-1975." (This report was submitted to the International Lead Zinc Research Organization on January 31, 1978).

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: APR 10 1985

SUBJECT: Status Report* 8EHQ-0385-0547

Approved 4/11/85

Revision Needed _____

FROM: David R. Williams DRW, Section 8(e) Coordinator
Chemical Risk Identification Section/CSB

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

Submission Description

The Monsanto Company provided summarized preliminary results from an ongoing toxicity/reproduction study of rats exposed via inhalation to O,O-dimethylphosphorodithioate (CAS No. 756-80-9) at doses of 4.6, 26, or 161 mg/M^3 for 6 hours/day, 5 days/week for 11 weeks prior to mating. According to Monsanto, the preliminary data suggest that at the two highest dose levels, O,O-dimethylphosphorodithioate had a "deleterious effect" on the reproductive capacity of male rats. In an addendum to the company's initial Section 8(e) submission, Monsanto provided the following additional information concerning the ongoing study:

> "There were two sequential matings of treated males with untreated females, and of treated females with untreated males. The endpoints were the number of impregnations and conceptions. The measured mean exposure levels for this study were 0, 4.6, 26 and 172 mg/M^3. There appeared to be no adverse effect on the fertility of male rats exposed at the low dosage level. At the mid dosage level no effect was noted at the first mating, while a slight reduction in fertility was noted at the second mating. Male rat fertility was markedly reduced at the high dosage level in both matings. There were fewer offspring in the high exposure level females, but this effect is judged to be secondary to maternal toxicity, as evidenced by various clinical signs and body weight reductions of up to 28%. Since the males are still on test, only gross observations have been made on them. A previously known effect, corneal lesions, was noted at all exposure levels. This is consistent with the known corrosiveness of the material."

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 (including the actual experimental protocol(s) and data) from the ongoing inhalation toxicity/reproduction study.

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*NOTE: This status report is the result of a preliminary staff evaluation of information submitted to EPA. Statements made herein are not to be regarded as expressing final Agency policy or intent with respect to this particular chemical. Any review of the status report should take into consideration the fact that it may be based on incomplete information.

Current Production and Use

A review of the production range (includes importation volumes) statistics for O,O-dimethylphosphorodithioate (CAS No. 756-80-9), which is listed in the TSCA Inventory, has shown that between 11.1 million and 61 million pounds were reported as produced and/or imported in 1977. This production range information does not include any chemical production/importation data that were claimed as TSCA Confidential Business Information (CBI) by those persons who reported for the TSCA Inventory, nor does it include any information that would compromise TSCA CBI. The data submitted for the TSCA Inventory, including the production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

Monsanto reported that it uses O,O-dimethylphosphorodithioate as an intermediate in the manufacture of methyl parathion. According to secondary literature sources, O,O-dimethylphosphorodithioate is used to make O,O-dimethylphosphorochloridothioate, an intermediate in the production of methyl parathion as well as a number of other pesticides. Monsanto reported that the company's use of O,O-dimethylphosphorodithioate "does not result in any exposures outside the workplace." In addition, Monsanto reported that because the company's "workplace exposures are maintained well below those used in the rat study, workplace exposure to ...[O,O-dimethylphosphorodithioate] does not present a hazard to ...[Monsanto] employees." In the addendum, Monsanto stated that its internal workplace exposure limit for O,O-dimethylphosphorodithioate is 0.4 mg/M^3.

Comments/Recommendations

As stated previously, O,O-dimethylphosphorodithioate is used to manufacture O,O-dimethylphosphorochloridothioate, a chemical that has been reported (8EHQ-0381-0387 et seq.) to cause dominant lethal effects when administered orally to male rats before mating. The Chemical Screening Branch (CSB/ECAD/OTS/OPTS) has prepared Chemical Hazard Information Profiles (CHIPs) on O,O-dimethylphosphorochloridothioate and O,O-diethylphosphorochloridothioate; available toxicologic and exposure data on these esters are being assessed by the Risk Analysis Branch (RAB/ECAD/OTS/OPTS). In addition, it should be noted that O,O-dimethylphosphorodithioate bears some degree of structural analogy to the dialkylphosphorodithioate moieties of the zinc dialkyldithiophosphates (ZDDPs). EPA has received a number of TSCA Section 8(e) and "For Your Information" (FYI) submissions, and TSCA Section 5 Premanufacture Notifications (PMNs) on ZDDPs.

a) The Chemical Screening Branch (CSB/ECAD/OTS/OPTS) will request the Monsanto Company to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol(s) and data) from the ongoing toxicity/reproduction study of O,O-dimethylphosphorodithioate.

In view of EPA's general interest in corporate actions that are taken on a voluntary basis in response to toxicologic/exposure information, the Chemical Screening Branch will ask Monsanto to describe the actions the company has taken to notify its own workers about the results of the ongoing toxicity/reproduction study. In addition, Monsanto will be asked to describe the nature and available results of all other studies that Monsanto has conducted, is conducting, or plans to conduct to determine the toxicity of O,O-dimethylphosphorodithioate.

b) The Chemical Screening Branch will review the reported findings in order to determine the need for further OTS assessment of O,O-dimethylphosphorodithioate.

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, CCD/OTS, and RAB/ECAD/OTS. 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: MAY 13 1985

8EHQ-0485-0548
Page 1 of 3

SUBJECT: Status Report* 8EHQ-0485-0548

Approved: 5/14/85

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 chemical identity and proposed use of the subject chemical to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS/OPTS) will request the company to substantiate these confidentiality claims. The submitter described the subject chemical non-confidentially as a "triazole" currently at the research and development (R&D) stage.

Submission Description

The submitting company provided summarized preliminary results of a teratology study of the subject chemical administered orally at doses of 0, 62.5, 125, 250, or 500 mg/kg to pregnant rats. According to the submitter, the study results obtained thus far "indicate dose and treatment-related increases in external malformations among the fetuses from dams treated at 250 or 500 mg/kg, but not at 62.5 or 125 mg/kg." The submitter reported that internal soft tissue and skeletal findings are not yet available. The submitter also reported that "a completed rabbit teratology study conducted at lower dose levels was negative."

The submitting company also provided a sanitized version of a revised Material Safety Data Sheet (MSDS) which reflects the preliminary results of the rat teratology study as well as the final results of the rabbit teratology study. According to the MSDS, the rabbit teratology study involved oral administration of the chemical at doses of 0, 3, 10, or 30 mg/kg. In addition, the MSDS states that the oral LD50's for the chemical were found to be 639 mg/kg and 474 mg/kg in male and female rats, respectively. The MSDS states also that the subject chemical was found to be only slightly irritating to rabbit eyes and non-irritating to rabbit skin. Finally, the MSDS notes that inhalation toxicity studies have not as yet been conducted with the subject chemical.

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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

The submitted information does indicate that the tested chemical can cause dose-related adverse developmental effects in rats. A more complete evaluation of the overall significance of these findings should be possible upon EPA's receipt of full copies of the final reports (including the actual experimental protocol(s) and data) from the rat and rabbit teratology studies cited in the submission.

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

As previously stated, the subject chemical is in the research and development (R&D) stage; the planned use of the chemical has been claimed as TSCA CBI.

Comments/Recommendations

a) The Chemical Screening Branch (CSB/ECAD/OTS/OPTS) will ask the submitter to ensure that immediately upon completion, EPA receives a full copy of the final report (including the actual experimental protocol(s) and data) from the rat teratology study, the preliminary results of which were cited in the submission. In addition, the submitter will be requested to submit a complete copy of the final report (including the actual experimental protocol(s) and data) from the rabbit teratology study cited in the submission.

   In view of the Agency's general interest in company actions that are taken on a voluntary basis in response to chemical toxicity/exposure data, the Chemical Screening Branch will request the submitting company to describe the nature and available results of all studies (other than those cited in the provided MSDS) that the company has conducted, is conducting, or plans to conduct to determine the toxicity of and/or the exposure to the subject chemical substance. The submitting company will be requested also to describe the actions that the company has taken (in addition to revising and distributing the MSDS) to 1) notify workers and others about the reported rat teratology findings, and 2) reduce and/or eliminate 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.

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

NOTE

In a letter dated July 3, 1985 (8EHQ-0785-0548 Followup), the Chevron Chemical Company withdrew all confidentiality claims for the initial 8(e) submission. According to Chevron, the subject chemical is (E)-1-(2,4-dichlorophenyl)-4,4-dimethyl-2-(1,2,4-triazol-1-yl)-penten-3-ol (CAS No. 76714-88-0), an R&D fungicide for which Chevron plans to apply for an experimental use permit (EUP) and registration under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

Copies of this updated status report will be transmitted to all Offices/Agencies listed in (c) of the Comments/Recommendations section found on page 2 of the status report.

Frank D. Kover 7/18/85

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAY 14 1985

SUBJECT: Status Report* 8EHQ-0485-0549 S

Approved: 5/14/85

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 Starch and Chemical Corporation provided the final reports from acute (4-hour) and sub-acute (14-day) rat inhalation studies of a high molecular weight (>6,000,000) sodium carbonate stabilized sulfonated polystyrene, sodium salt (CAS No. 9080-79-9). The submitting company reported that the results of these studies suggest a possible risk of lung function impairment following inhalation of respirable dry polymer particles.

According to the provided acute study final report, Sprague-Dawley rats (25/sex) were exposed via inhalation to a polymer dust aerosol containing actual average concentrations of 1.2, 2.2, 3.0, or 4.6 mg/l for 4 hours followed by a 14-day observation period. The LC50s were found to be 2.6 mg/l and 3.5 mg/l for male and female rats, respectively. The combined-sex LC50 was calculated to be 3.0 mg/l.

The following information concerning the conduct and results of the 14-day sub-acute inhalation study was presented in the abstract of the submitted final report:

> "Five male and five female Sprague-Dawley rats were exposed to a dust aerosol containing either 0.14, 0.34 or 1.07 mg/l (mean average actual concentration by gravimetric determination) of . . . [the polymer] for six hours daily, five days per week (Monday-Friday), for two consecutive weeks. An additional group of five animals per sex was designated to serve as the control group.
>
> "The animals were observed periodically during each exposure as well as daily for external signs of toxicity and mortality. Body weight was recorded periodically and food consumption was determined weekly for all surviving animals. After the last

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exposure (tenth), the surviving animals of each test group were randomized to determine which animals would be assigned to the 14-day post-exposure recovery period (satellite groups). The animals which were selected (satellite groups) were observed for signs of recovery and mortality. Selected hematological, clinical chemistry and urine analysis determinations were made after ten exposures on the animals not assigned to the satellite groups. The same hematological and clinical chemistry parameters were also determined on all animals surviving the 14-day post-exposure recovery period. The animals designated for clinical laboratory studies after ten exposures were sacrificed on study day 15. The animals of the satellite groups were sacrificed on study day 26. All animals were subjected to a complete gross necropsy. The absolute and relative weights of adrenal glands, brain, kidneys, liver, lungs (including trachea) and gonads were determined for each animal. Detailed histopathological evaluations were performed on all animals in the control and high exposure groups and on any animal that expired on test.

"Under the conditions of this study, the test article . . . via inhalation by "nose-only" exposure demonstrated compound-related lesions consisting of an accumulation of septal cells in the alveoli, perivascular edema and vascular congestion of the lungs in both sexes."

Submission Evaluation

The submitted acute inhalation study established a median lethal concentration (LC50) for rats of both sexes at 3 mg/liter for a four-hour exposure. Particle sizing indicated that a substantial portion (perhaps 20%) could reach the alveoli. The findings were generally unremarkable, except that the study demonstrated that an acute exposure to a high (e.g., median-lethal) concentration of this polymer was associated with bronchiolar obstruction in rats. If similar effects occurred in humans, it would raise concern for chronic obstructive pulmonary disease (COPD).

The second study was a 14-day dust aerosol inhalation study in male and female rats exposed (nose-only) to 0.14, 0.34, or 1.2 mg/l. Approximately 30% of the particles were of a size that would be expected to reach the alveoli. There appeared to be a real, exposure-related, dose-related toxic effect. Several animal deaths were attributed to pulmonary edema. Microscopic examination of the lungs showed vascular congestion, perivascular edema, and cellular debris (i.e., "septal cells . . . [that] most likely are a mixture of alveolar macrophages and type-II pneumocytes") in the alveolar spaces in the lungs of the exposed rats. The alveolar cellular accumulation was not reversible in the 14-day recovery period. This apparent killing of pulmonary alveolar macrophages is reminiscent of findings as presented in several previous submissions received by the Agency under Sections 5 and 8(e) of TSCA.

Killing of alveolar macrophages could impair local or general host defense mechanisms and lung clearance, which could in turn have adverse health consequences in situations involving chronic exposure. Killing type-II pneumocytes could impair the production of pulmonary surfactant, which could in turn lead to lung collapse in the affected area. The findings of "fluffy" lungs upon acute exposure (with bronchiolar obstruction) does not preclude the development of foci of collapsed alveoli in areas where there was inadequate surfactant, and either effect (obstruction or alveolar collapse) would impair gaseous exchange in the lung.

The 14-day inhalation study is instructive on two points. First it shows the importance of actually measuring the concentration and/or particle sizes of the test material within the exposure chamber; the nominal (estimated) concentrations in the 14-day study were far off the mark. Second, the results of the study show that a substance with a molecular weight of several million can elicit toxic effects.

Current Production

National Starch and Chemical claimed its production volume for the polymer to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS/OPTS/EPA) will request the submitting company to substantiate this claim.

A review of the production range (includes importation volumes) statistics for CAS No. 9080-79-9, which is listed in the TSCA Inventory, has shown that between 20 thousand and 201 thousand pounds of this chemical were reported as produced/imported in 1977. This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise TSCA CBI. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

According to the submitter, the subject polymer is used as a "fluid loss control additive [in liquid form] in oil field applications." The submitter also reported that because the company believes that "the greatest potential for human exposure lies in the manufacture of the subject polymer," company employees are required "to wear protective clothing and utilize toxic dust respirators during the manufacture and packaging operations."

Comments/Recommendations

The National Starch and Chemical Corporation submitted the following information with regard to the company's additional risk-reduction activities for the subject polymer:

"The submitting company has an active program to eliminate or minimize the dust hazard due to this polymer. Changes in the manufacturing process are being studied which will result in less dust produced during the manufacturing and packaging process. Additional changes to the manufacturing process are being considered to increase the particle size dimension thereby reducing respirable particles. Consideration is also being given to changing the physical form of the end product from a powder to a liquid. The submitting company has taken measures to amend the product technical bulletin and MSDS [Material Safety Data Sheet] to reflect a potential health hazard due to inhalation of respirable particles. Customers will receive the amended product information accompanied by an explanatory covering letter, recommending appropriate dust protection measures."

a) In view of EPA's general interest in company actions that are taken on a voluntary basis in response to chemical toxicity or exposure data, the Chemical Screening Branch (CSB/ECAD/OTS) will request the National Starch and Chemical Corporation to describe the nature and available results of all other studies that the company has conducted, is conducting, or plans to conduct to define the toxicity of and/or the exposure to the subject polymer. National Starch and Chemical will be asked also to provide complete copies of the updated product bulletin and MSDS for the tested polymer as well as a copy of the customer notification letter.

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

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAY 16 1985

SUBJECT: Status Report* 8EHQ-0485-0550

Approved: 5/17/85

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. DuPont de Nemours & Company, Inc. submitted summarized preliminary results from a two-year study of rats exposed via inhalation to respirable fibrils of poly p-phenylene terepthalamide (PPD-T) aramid fibers. According to DuPont,

> "Exposure of test animals to respirable PPD-T aramid fibrils in a two year inhalation study resulted in a low incidence of lung tumors but only at the two highest levels of exposure - 100 and 400 fibrils/cc of air. The lower [PPD-T aramid fibril] level is greater than 500 to 1000 times that which typically occurs in the workplace and both levels are attainable only under artificially generated conditions in the laboratory. The tumors observed are of a type not found in humans. Exposures of animals at lower levels, but still many times greater than those which typically occur under actual use conditions with PPD-T aramid, are free of toxicologically significant effects."

DuPont also provided the following information with regard to the conduct and results of the performed study:

> "Exposure atmospheres for this study had to be artificially generated since airborne concentrations of respirable PPD-T fibrils at the levels selected for testing cannot normally be obtained even by suspending commercially available PPD-T pulp in air. [Pulp is a finely ground form of PPD-T fiber which because of its physical nature contains more fibrils than other forms of the fiber.] Initial attempts with conventional dust-generating techniques failed to produce sufficient concentrations of respirable particles to conduct the test because

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respirable PPD-T fibrils are readily agglomerated by physical entanglement and electrostatic attraction. To overcome this natural bonding of fibrils in pulp, a high-pressure, air impinging device was developed for the specific purpose of separating the ultrafine fibrils from the pulp matrix and keeping them suspended in air.

"In this study, 100 male and 100 female Sprague-Dawley rats were exposed to respirable PPD-T fibrils at atmospheric concentrations of 0, 2.5, 25, 100 or 400 fibrils/cc, six hours a day, five days a week. Exposures at 0, 2.5, 25, and 100 fibrils/cc were for 104 weeks. However, because of early mortality due to obliterative bronchiolitis (i.e., the lower airways of the test animals were blocked by the reaction to the massive dose of fibrils which reagglomerated in the lungs), rats were exposed to 400 fibrils/cc for only 52 weeks and were held for an additional 52 weeks prior to sacrifice.

"All rats were sacrificed at the end of the 104-week exposure period. Histopathological examination of the lungs of these rats showed no increased incidence of lung tumors at exposure concentrations below 100 fibrils/cc. Those rats exposed to 100 fibrils/cc and 400 fibrils/cc revealed an incidence of tumors identified as cystic keratinizing squamous cell carcinomas (6 of 56 females and 1 of 36 males at 400 fibrils/cc; 4 of 69 females and 0 of 68 males at 100 fibrils/cc). Most tumors were noninvasive, none metastasized to regional lymph nodes or other vital organs and they were not life shortening. Slight fibrosis was also observed in the lungs of rats exposed to 100 or 400 fibrils/cc. This slight fibrogenic response was equivocal at 25 fibrils/cc, and was not observed at 2.5 fibrils/cc.

"Among [those] rats sacrificed at interim times of three, six and twelve months, no tumors were observed at any of the exposure concentrations. A lung tumor (also a cystic keratinizing squamous cell carcinoma) was observed in a female rat exposed to 400 fibrils/cc and sacrificed at 18 months.

"In those rats found to have lung tumors, all other major organs and tissues have been examined, and have been found to be free of tumors or other compound related abnormalities.

"Based on . . . [DuPont's] review of these test results and other data, . . . [DuPont believes] that current industrial practices are sufficient to preclude exposures to humans that would result in any adverse health effects. This is especially true because of 1) the extreme difficulty in creating conditions in which high levels of fibrils are suspended in air, and 2) the fact that . . . [Dupont knows] of no case from any cause in which tumors of the type observed in the test rats have occurred in man (the tumors observed in this study are identical to some observed in rats exposed to high levels of several other particulates)."

In addition to reporting the preliminary results of the 2-year inhalation study, DuPont provided the following information with regard to the results of other toxicologic studies of PPD-T:

> "PPD-T polymer has very low acute oral toxicity (approximate lethal dose is greater than 7500 mg/kg). Both human and animal dermal tests have indicated no potential for skin sensitization and minimal skin irritation. Previous published pulmonary toxicity studies [Lee et al., Pulmonary Response to Inhaled Kevlar® Aramid Synthetic Fibers Toxicology and Applied Pharmacology; 71: 242-253; 1983] have shown that a two week exposure of rats to extremely high concentrations (approximately 1000 fibrils/cc) of respirable size particles can produce pulmonary fibrosis that is detectable one month after cessation of exposure."

Submission Evaluation

Evidence that has been accumulating since about 1970 increasingly lends credence to the view that the carcinogenicity of asbestos fibers is due mainly to their submicroscopic, needle-like shape, rather than to their chemical composition, physical/chemical properties, or impurities. It appears that asbestos fibers exhibit maximal carcinogenic activity when they have diameters less than 1.5 um and lengths greater than 8 um. In addition, it appears that tumorigenicity is enhanced by decreases in fiber diameter and increases in fiber length.

Accordingly, mesotheliomas have been induced experimentally with non-asbestos substances that occur naturally as fibers or that are processed to critical fiber dimensions. Such substances include: the fibrous magnesium hydroxide minerals (i.e., brucite and nemalith), various types of fibrous glass, and different types of fibrous aluminum oxide. Non-fibrous samples of these same materials have not been shown to date to exhibit oncogenic activity in laboratory animals. Most of the experiments that involve asbestos and asbestiform fibers have been conducted with rodents exposed by intraperitoneal injection, a route of exposure that appears to be much more sensitive than other exposure routes (including inhalation) to detect the maximal carcinogenicity of fibrous materials. Also, there is an increasing realization that the carcinogenic potential of asbestos in humans is not limited to induction of lung carcinomas and pleural mesothelioma, the typical asbestos cancer. It has been shown that exposure to asbestos can lead also to mesothelioma of the peritoneum and to carcinoma of the larynx, esophagus, and stomach.

The potential risk(s) posed by human exposure to PPD-T aramid fibers (the subject of the present submission) should be considered against the above background information. In DuPont's two-year rat inhalation study, PPD-T aramid fibers were found to produce tumors only at the 100 and 400 fibrils/cc dose levels. It is not known if these fibers have ever been tested via intraperitoneal injection in rodents.

Current Production and Use

Aramid fibers and a number of other substances (e.g., polytetrafluoroethylene (Teflon®), polyethylene, polypropylene, polyester, ductile iron pipe) may be used as partial, total or potential substitutes for asbestos. In support of the Agency's asbestos risk assessment activities, the Chemical Screening Branch (CSB/ECAD/OTS/OPTS) has prepared an asbestos substitute "health hazard profile" report on aramid fibers as well as the other substances mentioned above. The following use information for aramid fibers is presented in the summary of that report (IAG No. DW-89930405-10-0, Work Assignment 3, Task 1; SAIC/JRB Project No. 2-813-07-419-00; November 2, 1984):

> "Aramid fibers, characterized by high tensile strength, medium to low elongation, moderately high to ultra high modules, and chemical and flame resistance, lend themselves to a variety of applications as asbestos substitutes, including gaskets, brake linings, friction materials, pump packing, and electrical paper and tape."

In its TSCA Section 8(e) notice, DuPont provided the following information concerning exposure to PPD-T aramid fibers:

> "The exposure concentrations (400 fibrils/cc and 100 fibrils/cc of respirable dust) that produced tumors [in the 2-year inhalation study] are well above those that can be generated in the workplace. This opinion is supported by monitoring data using procedures prescribed by NIOSH . . . . [DuPont] has measured airborne levels of respirable fibrils in . . . [DuPont's] manufacturing operations and in some customers' plants. As examples, in . . . [DuPont's] fiber manufacturing operations, the fibril concentration is below the 0.1 fibril/cc detection limit. In a customer operation in which PPD-T aramid fiber pulp was used in combination with mineral fibers, the monitoring data indicate a typical PPD-T fibril concentration at or below the detection limit of 0.1 fibril/cc. . . . [DuPont has] also monitored the grinding operations in which PPD-T pulp is made and . . . [found that] typical fibril levels were 0.2 fibrils/cc. DuPont has adopted a workplace exposure limit of 5 fibrils/cc (8 hr. time weighted average [TWA]) for its operations and is suggesting this limit to its consumers."

Comments/Recommendations

In addition to adopting and recommending a 5 fibril/cc 8-hour TWA, DuPont reported that the company is transmitting the preliminary results of the 2-year study and DuPont's assessment of the meaning of the results to DuPont employees, customers, competitors, NIOSH, OSHA, and NCI. DuPont also stated that, upon completion, a copy of the final report of the 2-year inhalation study of PPD-T aramid fibers in rats would be submitted to EPA.

It should be noted that EPA recently received a TSCA Section 8(e) submission (8EHQ-0485-0553) reporting that ". . . intraperitoneal injection of 25 mg (total dose) of 1.8 um (mean diameter) refractory ceramic fibers in Osborne-Mendel rats has resulted thus far in an 86% incidence (19 of 22 rats) of abdominal tumors of peritoneal or omental origin." According to this submission, 18 of the tumors were malignant mesotheliomas and 1 was a "relatively well differentiated fibrosarcoma."

a) The Chemical Screening Branch will request DuPont to submit immediately to EPA a full copy of the actual experimental protocol from DuPonts's chronic (2-year) PPD-T aramid fiber inhalation study in rats. In addition, DuPont will be requested to ensure that 1) EPA is apprised immediately about all further significant findings from DuPont's 2-year PPD-T aramid fiber inhalation study, and 2) the Agency receives in a timely manner complete copies of all future interim reports as well as any draft final reports concerning the study. DuPont will be asked also to ensure that the Agency receives immediately upon completion a full copy of the final report (including all data and experimental protocol amendments) from DuPont's 2-year inhalation study of PPD-T aramid fibers.

   Finally, and 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, DuPont will be asked to describe the nature and available results of all studies (other than those studies that have been published or already submitted to EPA) about which DuPont is aware or that DuPont has conducted, is conducting, or plans to conduct to determine 1) the toxicity of aramid fibers/aramid fiber residues, or 2) the nature (e.g., physical characteristics) and amount of aramid fiber/aramid fiber residues generated during manufacture, processing, or use of aramid fibers (e.g., in friction materials, durable panels).

b) The Chemical Screening Branch will transmit a copy of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, ORD/EPA, OAR/EPA, CCD/OTS, HERD/OTS, RAB/ECAD/OTS, and to the Asbestos Action Program/OPTS. A copy of this status report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAY 14 1985

SUBJECT: Status Report* 8EHQ-0485-0551 Approved: 5/14/85

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 International Minerals & Chemical Corporation submitted a pre-publication copy of a National Institute for Occupational Safety and Health (NIOSH) "Health Hazard Evaluation" (HHE Report No. HETA 82-257). This NIOSH report provides the details and conclusions of a NIOSH investigation of occupational exposure to zeranol (CAS No. 26538-44-3), an ingredient in one of a number of human and veterinary drugs formulated, compressed, or packaged at a Manufacturing Chemists, Inc. plant in Indianapolis, Indiana. The following summary was presented in the submitted report:

"In May 1982, the National Institute for Occupational Safety and Health (NIOSH) was requested to evaluate occupational exposure to an animal growth-promoter, zeranol. One female worker had developed breast symptoms and weight gain, and her male child had been found to have gynecomastia [i.e., "excessive development of the male mammary glands"]. Information from other workers from the same plant revealed three children of current workers and one child of another ex-worker with gynecomastia. In one case, this was thought by the personal physician to be due to a possible exogenous cause.

"Environmental sampling on May 15-17, 1984 found that personal (breathing zone) exposures to zeranol (the active ingredient in Ralgro®) ranged from between 4.1 ug/m^3 to 1554 ug/m^3. The highest exposures were found in the production area (median of 6 personal air samples, 547 ug/m^3. Median concentrations of airborne zeranol in the packaging area and laboratory were 46 ug/m^3 and 6.6 ug/m^3, respectively. Median concentrations of zeranol in dermal (gauze-patch) samples from the workers' palms were 90 mg/sample in the production department, 1.3 mg/sample in the packaging area, and 0.3 mg/sample in the laboratory.

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Surface wipe samples for zeranol showed contamination levels ranging fron nondetectable (ND) to 14 mg. Measurements made in the lunch room showed levels of contamination ranging from ND to 4 mg. A wipe sample taken in the interior of a ceiling supply-air duct in the production area revealed 5.1 mg of zeranol. A sample of work clothing routinely laundered at home was contaminated with 16 mg of zeranol. At present there are no criteria or standards for occupational exposure to zeranol. However, investigators have proposed occupational exposure levels for estrogens . . . and making comparable assumptions one could propose a zeranol exposure limit ranging from 0.05-0.3 mg/m^3.

"Questionnaire interviews of the current workers and a comparison group of non-exposed volunteers showed more reporting of breast symptoms in the exposed group, though the difference was not statistically significant. There was no indication of a difference in weight change between the two groups over different periods of time. Clinical examination of male participants in both groups showed no evidence of distinct subareolar masses. One exposed worker had a serum estradiol level outside the laboratory normal range. Levels of serum prolactin [(SP)], [follicle-stimulating hormone] (FSH), and [luteinizing hormone] (LH) were normal in all exposed workers. Laboratory analysis of the blood by high performance liquid chromatography (HPLC) for zeranol, its precursor, and its main metabolites detected none of these compounds. (The limit of detection was 12.2 ng/ml for zeranol, 27.1 ng/ml for zearalenone [the precursor], 18.8 ng/ml for zearalanone [a metabolite] and 11.5 ng/ml for taleranol [a metabolite].) Serum HDL-C [high density lipoprotein cholesterol] levels, covariance adjusted for age and sex, were higher in exposed workers than in the comparison group (p=0.0539, t test).

"On the basis of the data obtained during this investigation, NIOSH has established that workers at this [Manufacturing Chemists, Inc.] plant have considerable exposure to zeranol via both airborne and skin contact routes, and this exposure poses a potential health hazard to the workers. Additionally, there is a risk of contamination of the home environment and resulting serious medical problems in exposed children. Due to the potency of zeranol, the potential health effects, and the lack of detailed information regarding human exposures, employee exposure to zeranol should be reduced to the lowest feasible level at this facility. Recommendations are included in . . . this report to reduce potential hazards and to provide a better work environment for the employees covered by this determination. Specifically, these recommendations are intended to help reduce direct skin contact with zeranol powder, to reduce exposure to zeranol dust, and to minimize the possibility of the agent being brought home on the workclothes or shoes to contaminate the home environment."

The following conclusions were presented in the body of the submitted NIOSH "Health Hazard Evaluation" report:

> "This study documented substantial exposures (both airborne and dermatologic) to zeranol, and contamination of the lunch room, ventilation ducts, and an item of worker's clothing. Exposed workers reported more breast symptoms than a non-exposed comparison group. Anecdotal and other information indicated a number of male children of different ages with transient breast symptoms. No definite cases of gynecomastia were observed among the current male workers, and no zeranol was detected in blood samples obtained. These negative physical and laboratory findings, however, do not negate the potential health hazard documented by the environmental findings, the symptoms among workers, and the reports of breast symptoms in workers' children."

In the cover letter to its submission, the International Minerals & Chemical Corporation stated that "certain NIOSH conclusions . . . are not supported by the data in the report." Although no information was provided to substantiate this contention, the submitting company did report that its "data show that is improbable that zeranol is reponsible for any of the inferred effects on humans." The company did not describe the nature of these data.

Submission Evaluation

An initial evaluation of only the information presented in the submitted NIOSH report suggests that exposure to zeranol (as opposed to the other substances reportedly handled at the plant) would be most likely responsible for the observed adverse health effects. The NIOSH findings also suggest that children may be more sensitive than adults to exposure to zeranol.

Immediately upon receipt of this TSCA Section 8(e) submission, the Chemical Screening Branch (CSB/ECAD/OTS/OPTS) sent a copy to the Office of Science Coordination/Food and Drug Administration.

Current Production and Use

A review of the production range (includes importation volumes) statistics for zeranol (CAS No. 26538-44-3), which is listed in the TSCA Inventory, has shown that no 1977 production/importation was reported or that all of the production range data reported were claimed as TSCA Confidential Business Information (TSCA CBI) by the manufacturer(s) and/or importer(s) and cannot be disclosed (Section 14(a) of the TSCA, U.S.C. 2613(a)). All of the data submitted for the TSCA Inventory, including the production range information, are subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

According to the NIOSH report, zeranol (a non-steroidal anabolic agent with some degree of estrogenic activity) is obtained by catalytic dehydrogenation of zearalenone, an estrogenic mycotoxin produced by a number of species of Fusarium, especially Fusarium graminearum, a fungus found on corn and barley in storage and in the field. The NIOSH report states that in 1969, the U.S. Food and Drug Administration (FDA) approved the use of Ralgro® (which contains zeranol as the active ingredient) for growth promotion and feed efficiency in sheep and cattle; use is prohibited in dairy or breeding animals. The NIOSH report also states that because of zeranol's estrogenic activity, the chemical is sold in some European countries as the pharmaceutical Frideron® used to treat human menopausal symptoms; zeranol has not been approved by FDA for human use in the United States.

Comments/Recommendations

It is EPA's initial position that the provided information did not warrant reporting to EPA under Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (PL 94-469). The following discussion presents the basis for EPA's position:

> Section 8(e) of the Toxic Substances Control Act [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."
>
> It should be noted, however, that TSCA Section 3 excludes from TSCA jurisdiction "any food, food additive, drug, cosmetic, or device (as such terms are defined in Section 201 of the Federal Food, Drug, and Cosmetic Act) when manufactured, processed, or distributed in commerce for use as a food, food additive, drug cosmetic, or device." According to the information currently available to EPA, zeranol is and has been produced and distributed solely for use(s) under the jurisdiction of the Federal Food, Drug, and Cosmetic Act.

Therefore, the information contained in 8EHQ-0485-0551 did not need to be reported to EPA under Section 8(e) of TSCA unless the submitting company is or has engaged in the manufacture, importation, processing, or distribution of zeranol for use(s) covered by TSCA.

a) The Chemical Screening Branch will ask the International Minerals & Chemical Corporation to provide the company's rational as to why zeranol and the information concerning zeranol would fall under the jurisdiction of TSCA. The International Minerals & Chemical Corporation will be asked also if the company is or has ever engaged in zeranol manufacture, importation, processing, or distribution for any use(s) other than use(s) covered by the Federal Food, Drug, and Cosmetic Act.

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

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAY 31 1985

Approved: 6/3/85

SUBJECT: Status Report* 8EHQ-0485-0552 and
8EHQ-0585-0552 Supplement

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 Olin Corporation reported that it was notified recently by the Sandoz Chemicals Corporation (formerly Sodyeco, Inc.) that "several [. . . Sandoz] employees experienced high blood pressure, rapid pulse, headaches and flushing during and after the manufacture of a 1,900 pound batch of DNPE [2,4-dinitrophenoxyethanol; CAS No. 2831-60-9]." Olin reported that it had been informed by Sandoz "that these symptoms, although not permanent in nature, did not clear-up immediately but lasted several [(3-5)] days." In addition, Olin reported that Sandoz informed Olin that Sandoz workers have also "handled dinitrochlorobenzene, an ingredient in the manufacture of DNPE, for several years without any serious problems, although skin rashes have been reported."

In a supplemental submission (8EHQ-0585-0552 Supplement), the Sandoz Chemicals Corporation reported that the affected workers worked in the DNPE drying operation and had been wearing protective overalls and particulate filter-equipped air-stream helmets during the DNPE drying operation.

Olin stated that Sandoz manufactures and supplies DNPE to Olin for use "in the manufacture of Olin products for the United States Government." According to Olin, both DNPE and dinitrochlorobenzene are manufactured at Sandoz plants in Charlotte, North Carolina. In addition, Olin stated that Sandoz "purchases caustic soda and ethylene glycol, the [other] major ingredients for DNPE."

Olin stated that its previous DNPE supplier (the Hummel Chemical Company) had advised Olin that Hummel "had not encountered any health problems (other than skin rashes) during the approximately 15 years . . . [Hummel] manufactured DNPE" for Olin. Olin also stated that Olin is not aware of any health problems associated with Olin's use of DNPE.

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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.

Finally, Olin stated that "numerous raw materials, intermediates and products are involved in the manufacture of DNPE and, on the basis of current toxicology known by Olin, it is difficult to determine which chemical or compound may be the causative agent of the above-described symptoms."

Submission Evaluation

It should be noted that there is an apparent discrepancy with regard to the number and job functions of the affected workers. In the supplemental 8(e) submission, Sandoz reported that 3 of its workers involved in the DNPE drying operation were affected. In the initial submission, however, Olin reported that 4 Sandoz employees were affected (3 workers in the DNPE drying operation and 1 worker in production of DNPE wet cake). Despite this discrepancy, the adverse health effects that were observed in the Sandoz workers appear to be chemical exposure related in that the effects occurred during the DNPE drying operation (and possibly during DNPE wet cake production) and subsided within one week after removal of the affected workers from the DNPE operation(s).

With the exception of the sustained high systemic blood pressure, the reported adverse effects are consistent with effects observed following human exposure to simple nitroaromatic compounds (e.g., dinitrophenol, dinitrocresol). It is possible that DNPE, a process contaminant, a residual starting material, and/or a metabolite(s) of one or more of these chemical substances was/were responsible for the observed adverse effects. In addition, it should be noted that 1) the adverse effects may have been exacerbated by the high ambient temperatures expected to be found in drying operations, and 2) the adverse health effects occurred even though the workers wore protective equipment/clothing.

Current Production and Use

A review of the production range (includes importation volumes) statistics for 2,4-dinitrophenoxyethanol (CAS No. 2831-60-9), which is listed in the TSCA Inventory, has shown that between 10 thousand and 100 thousand pounds of this chemical were reported as produced/imported in 1977. This production range information does not include any production/importation data claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the Inventory, nor does it include any data that would compromise TSCA CBI. All of the data submitted for the TSCA Inventory, including the production range data, are subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

As stated previously, Olin reported that it uses DNPE in the manufacture of products for the U.S. Government. Olin did not disclose the nature of these products. No information regarding the use(s) of DNPE was found in the secondary literature sources consulted.

Comments/Recommendations

Olin reported that communications are continuing with Sandoz on this incident. Olin stated also that its "investigation will continue and possibly include, as further findings warrant, review of existing data and information and development of additional industrial hygiene data, medical evaluation of current employees, design and implementation of appropriate toxicologic studies and inquiry regarding other similar work populations." Sandoz reported that DNPE manufacture has been halted until Sandoz is "confident that no further exposure of the chemical will produce the [reported] symptomology . . . ." In addition, Sandoz reported that its Preclinical Safety Assessment Laboratory has been reviewing the incident and is now conducting additional studies. Finally, Sandoz reported that when DNPE production is resumed, the chemical will be shipped in "wet cake" form to Olin for drying and use.

a) The Chemical Screening Branch (CSB/ECAD/OTS/OPTS) will request the Olin Corporation and the Sandoz Chemicals Corporation to describe the nature and available results of any investigation(s)/test(s) that the companies have conducted, are conducting, or plan to conduct to determine the cause(s) of the observed adverse human health effects. In addition, both companies will be requested to ensure that EPA is informed in a timely manner about all future significant findings from such efforts.

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 send a copy of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OW/EPA, OSWER/EPA, ORD/EPA, and OAR/EPA. Copies of this report will be sent also the TSCA Assistance (TAO/OTS/OPTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAY 21 1985

SUBJECT: Status Report* 8EHQ-0485-0553

Approved: 5/23/85

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 Sohio Engineered Materials Company (formerly known as the Carborundum Company) provided summarized preliminary results from ongoing intraperitoneal injection, intratracheal instillation, and inhalation studies of man-made refractory ceramic fibers in rats and hamsters. According to the submitting company, these studies are being conducted under the auspices of the Thermal Insulation Manufacturers Association (TIMA), a trade association whose membership includes manufacturers and users of man-made refractory fibers. The submitter provided the following information concerning the conduct and results of these ongoing studies:

"[The]Sohio Engineered Materials Company has learned from the investigator that experiments involving intraperitoneal injection of 25 mg (total dose) of 1.8 uM (mean diameter) refractory ceramic fibers in Osborne-Mendel rats has resulted thus far in an 86% incidence (19 of 22 rats) of abdominal tumors of peritoneal or omental origin. The investigator has reported that eighteen (18) of the tumors are mesotheliomas and one (1) a relatively well differentiated fibrosarcoma. The investigator further reported that the mesotheliomas appeared to be generally anaplastic and very malignant histologically and that four (4) of them involve the thoracic cavity through either direct invasion of the diaphragm or vascular metastasis. In conversations with the investigator, he has indicated that the tumors are pleomorphic, larger than expected and, in some cases, myxomatous. In all cases, the tumors resulted in the animals' death (180-808 days post exposure). Similarly, UICC Crocidolite exposed (25 mg intraperitoneally) concurrent positive control Osborne-Mendel rats have shown an 80% (20 of 25) incidence of abdominal mesothelioma. In addition, the median lifespan of the refractory fiber treated rats (495 days) was reduced as compared to the positive controls (600 days)."

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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 Carborundum Company] previously reported [on a "For Your Information" (FYI) basis (FYI-OTS-0184-0288)] the occurrence of a single malignant mesothelioma in a Syrian hamster which died in the ninth month of a 2-year refractory fiber (1.8 uM mean diameter) inhalation study. Histopathologic examination has been completed on an additional 50 hamsters surviving the 2-year exposure period. No additional primary lung tumors have been found in the group. Similar inhalation studies in Osborne-Mendel rats have also been conducted. While histopathologic examination is not yet complete, no primary lung tumors have occurred in the 35 rats examined to date. In both studies, the animals were exposed (nose only) to chamber concentrations of 14 mg/M^3 (200 fibers/cc) of the refractory fiber material beginning at 100 days of age, 6 hours a day, 5 days per week for 24 months.

"An additional part of the overall TIMA research program on these fibers includes intraperitoneal hamster (25 mg single dose), as well as the intratracheal rat and intratracheal hamster instillation (5 x 2 mg) studies. These investigations are ongoing and no meaningful results are yet available . . . ."

In a supplemental FYI submission (FYI-OTS-0484-0288 Supplement), the Carborundum Company provided the following summarized information concerning the conduct, preliminary results, and initial interpretations of the intraperitoneal injection studies of refractory ceramic fibers in hamsters and rats.

". . . [I]ntraperitoneal injection of 25 mg (total dose) of 1.8 uM (mean diameter) refractory [ceramic] fibers into Syrian hamsters has resulted in acute hemorrhagic peritonitis. Death, as a result of splenic and peritoneal hemorrhage, occurred typically within 12 days of administration and gave rise to approximately 50% mortality. [The] antemortem observations included lethargy, anorexia, "hunched" posture and, in some animals, diarrhea. In addition, immediately preceding death, animals were observed to have pale mucous membranes and an apparent accumulation of fluid in the abdominal cavity, identified as blood upon necropsy.

". . . [The] rats (Osborne-Mendel) injected with refractory ceramic fibers did not exhibit the acute hemorrhagic response and neither rats nor hamsters similarly injected with either crocidolite or glass fibers exhibited hemorrhagic peritonitis. Currently, the causation of acute hemorrhagic peritonitis in Syrian hamsters following intraperitoneal injection of refractory ceramic fibers is without explanation. Moreover, the significance of this finding to humans cannot currently be appreciated."

In its initial TSCA section 8(e) notice, the Sohio Engineered Materials Company also submitted the following background information concerning the oncogenicity of a number of fibrous and non-fibrous materials:

". . . [A]bdominal mesotheliomas have been observed in rats after intraperitoneal injection of a wide variety of organic and inorganic fibrous and non-fibrous substances such as fibrous glass, rock wool, refractory ceramic fibers, mineral wool, attapulgite, asbestos, brucite and erionite. Furthermore, this abnormally sensitive injection technique is a non-physiological method of exposure, bypassing both normal pulmonary protective and clearance mechanisms. Moreover, the current research program is incomplete. Therefore, it is not possible to fully appreciate the significance of the current findings."

Finally, the Sohio Engineered Materials Company reported that "a recent review of . . . [employee] x-rays and other medical records indicates no occupationally-related health effects."

Submission Evaluation

The evidence that has been accumulating since about 1970 lends increasing credence to the view that the carcinogenicity of asbestos fibers is due mainly to their submicroscopic, needle-like shape, rather than to their chemical composition, physical/chemical properties, or impurities. It appears that asbestos fibers exhibit maximal carcinogenic activity when they have diameters less than 1.5 um and lengths greater than 8 um. In addition, it appears that oncogenicity is enhanced by decreases in fiber diameter and increases in fiber length.

Accordingly, mesotheliomas have been induced experimentally with non-asbestos substances that occur naturally as fibers or that are processed to critical fiber dimensions. Such substances include: the fibrous magnesium hydroxide minerals (i.e., brucite and nemalith), various types of fibrous glass, and different types of fibrous alumimum oxide. Non-fibrous samples of these same materials have not been shown to date to exhibit oncogenic activity in laboratory animals. Most of the experiments that involve absestos and asbestiform fibers have been conducted with rodents exposed by intraperitoneal injection, a route of exposure that appears to be much more sensitive than other exposure routes (including inhalation) to detect maximal carcinogenic activity of fibrous materials. Also, there is an increasing realization that the carcinogenic potential of asbestos in humans is not limited to induction of lung carcinomas and pleural mesothelioma, the typical asbestos cancer. It has been shown that exposure to asbestos can lead also to mesothelioma of the peritoneum and to carcinoma of the larynx, esophagus, and stomach.

The potential risks posed by human exposure to refractory ceramic fibers (the subject of the present submission) should be considered against the above background information. Although the tested refractory ceramic fiber diameter of 1.8 um is slightly above the apparently critical (in terms of maximal carcinogenic response) asbestos fiber diameter of 1.5 um, the intraperitoneal

injection of 25 mg ceramic fibers to rats caused an 86% incidence of maligant tumors of peritoneal or omental origin. Of the 19 malignant tumors, 18 were found to be mesotheliomas and 1 was found to be a well differentiated fibrosarcoma. These reported findings of the intraperitoneal injection study in rats lend credence to the possibility that the single mesothelioma observed during the refractory ceramic fiber inhalation study in hamsters was actually treatment-related and not a spontaneous occurrence.

Current Production and Use

In an addendum to its initial Section 8(e) notice, the Sohio Engineered Materials Company reported that the "refractory ceramic fiber used in the animal studies has a chemical composition of alumina and silica - - nominally a 50/50 mix." According to the submitter, these fibers are used typically in high temperature operations in which the temperatures can range from 1500° to 3000° Fahrenheit.

Comments/Recommendations

Sohio Engineered Materials Company stated that it is notifying its customers and employees about the reported findings. The submitting company also reported that it "maintains workplace exposures to less than 2 fibers/cc and, as a precautionary measure, conducts annual medical examinations, including chest x-rays, of potentially exposed employees." Finally, the submitter stated that EPA would receive copies of the final reports of the ongoing animal studies cited in the submission.

It should be noted that in a recent TSCA Section 8(e) notice (8EHQ-0485-0550), E. I. DuPont de Nemours & Company, Inc. provided summarized preliminary results from a study of rats that were exposed via inhalation to respirable fibrils of poly p-phenylene terephthalamide (PPD-T) aramid fibers at atmospheric concentrations of 0, 2.5, 25, 100, or 400 fibrils/cc air for 6 hours/day, 5 days/week for 2 years. According to the submitted information, rats exposed to the highest two doses only were found to have developed lung tumors characterized histopathologically as cystic keratinizing squamous cell carcinomas.

It should be noted also that in support of the Agency's asbestos assessment/regulatory activities, the Office of Toxic Substances (OTS) has been evaluating available toxicologic and exposure data on a wide variety of natural and man-made substances that are actual or potential asbestos substitutes in various applications. As part of this ongoing OTS evaluation, the Chemical Screening Branch (CSB/ECAD/OTS) has prepared health hazard profiles on a number of asbestos substitutes and has forwarded these documents to the Chemical Control Division (CCD/OTS).

a) The Chemical Screening Branch will request the Sohio Engineered Materials Company to provide immediately (if available) full copies of the actual experimental protocols from all of the Thermal Insulation Manufacturers Association (TIMA)-sponsored studies that were cited in the company's Section 8(e) submission. In addition, the Sohio Engineered Materials Company will be requested to ensure that 1) the Agency is apprised immediately about all further significant results obtained from the cited studies, 2) the Agency receives, in a timely manner, complete copies of all future interim reports and the draft final reports concerning the cited studies, and 3) the Agency receives, immediately upon completion, full copies of the final reports (including all data and any protocol amendments) concerning the cited studies.

   In view of the Agency's general interest in corporate actions that are taken on a voluntary basis in response to chemical toxicity/exposure information, the Chemical Screening Branch will ask the Sohio Engineered Materials Company to describe the nature and available results of all studies (other than those already published in the open scientific literature or already submitted to or brought to the attention of the Agency) about which the company is aware or that the company has conducted, is conducting, or plans to conduct to determine 1) the toxicity of refractory ceramic fibers, and 2) the nature (e.g., physical characteristics) and amount of refractory ceramic fibers generated during manufacturing, processing, and use.

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

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAY 28 1985

SUBJECT: Status Report* 8EHQ-0585-0554 S Approved: 5/28/85

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 claimed its identity and the identity of an end-product to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS) has asked the submitter to substantiate these confidentiality claims.

Submission Description

The submitter reported that diethyl sulfate (DES; CAS No. 64-67-5) was detected by gas chromatography in p-ethoxyethylbenzoate (CAS No. 23676-09-7), a chemical that the submitting company purchases and uses in the manufacture of an end-product (identity claimed to be TSCA CBI). The submitting company provided the following information with regard to this new-found exposure to diethyl sulfate:

> "The levels of DES in . . . [p-ethoxyethylbenzoate] were checked in lots and samples in . . . [the submitting company's] inventory. Fourteen lots were analyzed, twelve from . . . [the] regular supplier and one each from potential alternate suppliers. The results ranged from 80 ppm wt. to 1600 ppm wt.
>
> "The process chemical [(p-ethoxyethylbenzoate)] is received at . . . [the submitter's] plant in drums from which vessels are filled as needed. Once charged to the vessel, there is little opportunity for the DES to escape. The operator enters the building containing the vessel about 3 times per shift. The level of DES in that building is unknown; monitoring data have not yet been obtained. It is apparent, however, from 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.

saturated vapor pressure (0.19 mm Hg at 20°C) that the [DES] concentration cannot exceed 0.25 to 0.3 ppm wt. and is probably less than this by at least an order of magnitude. [The] handling instructions require the use of rubber gloves and rubber boots. Supplied-air respirators are available in the handling areas in case leaks or spills occur."

"The final product of this [manufacturing] process has been analyzed (2 samples thus far) and no DES has been detectable. The detectable limit of the method used was 50 ppb."

Submission Evaluation

Diethyl sulfate is moderately toxic via ingestion, is highly irritating to the eyes (and other mucous membranes), and is moderately irritating to the skin. The chemical has been found to be mutagenic in a variety of *in vitro* and *in vivo* tests. The results of studies in laboratory animals indicate that diethyl sulfate can cause cancer by injection (rats) and via repeated skin application (mice). The findings of an epidemiologic study of workers involved in the manufacture of ethyl alcohol (diethyl sulfate was shown to be formed during the reaction sequence in a process used formerly to make ethyl alcohol) are suggestive of a risk of cancer from exposure to diethyl sulfate.

Immediately upon receipt of this TSCA Section 8(e) notice, the Chemical Screening Branch (CSB/ECAD/OTS) provided a copy to the Risk Analysis Branch (RAB/ECAD/OTS). The Risk Analysis Branch has been evaluating available toxicologic and exposure data on diethyl and dimethyl sulfate in order to determine the need for, and scope of, formal or other EPA response to reduce potential risks posed by exposure to these chemicals.

Current Production and Use

A review of the non-confidential version of the TSCA Chemical Substances Inventory shows that p-ethoxyethylbenzoate (CAS No. 23676-09-7) is not listed. As stated previously, the submitting company purchases and uses p-ethoxyethylbenzoate in the manufacture of an end-product, the identity of which was claimed by the submitter to be TSCA CBI. No information concerning the use(s) of p-ethoxyethylbenzoate was located in the secondary literature sources consulted.

Comments/Recommendations

In an effort to reduce worker exposure to DES, the submitter reported that industrial hygiene practices (other than those mentioned previously) are being evaluated. In addition, the submitter reported that "monitoring techniques and procedures are being developed to determine the air concentrations of DES

in . . . [the submitter's] manufacturing unit." Finally, the submitting company stated that its "current supplier has been requested to reduce the level of DES in the process chemical p-ethoxyethylbenzoate; . . . [the supplier] believes that he can provide the product at less than 50 ppm wt. immediately."

EPA's Office of Toxic Substances has received other Section 8(e) and "For Your Information" (FYI) submissions containing toxicologic and/or exposure data on diethyl and dimethyl sulfate. It should be noted also that OTS has received a number of Section 8(e) submissions that have reported new-found exposure to toxic chemical substances.

a) The Chemical Screening Branch will request the submitting company to describe the nature and available results of all studies/tests that the company has conducted, is conducting, and plans to conduct to determine the levels of DES in the workplace, in process chemicals, and/or in end-products.

b) 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 the Risk Analysis Branch (RAB/ECAD/OTS). Copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUN 20 1985

SUBJECT: Status Report* 8EHQ-0585-0555 Approved: 6/24/85

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 Ethyl Corporation provided an abbreviated final report from an oral rat teratology study of SAYTEX®111 (brominated diphenyl-oxide with bromination ranging mainly from 6 to 9 bromines per molecule). Although SAYTEX®111 is technically a mixture, the submitting company stated that this product is commonly known as "octabromodiphenyl oxide." The submitter reported that diphenyl-oxide molecules with 6, 7, 8, or 9 bromines per molecule have the following CAS Numbers:

CAS Number	Bromines/Diphenyloxide Molecule
36483-60-0	6 Bromines
68928-80-3	7 Bromines
32536-52-0	8 Bromines
63936-56-1	9 Bromines

The following information concerning the conduct and results of the subject teratology study of SAYTEX®111 in rats was presented in the "Summary and Conclusion" section of the submitted report:

"Pregnant Crl:COBS®CD®(SD)BR female rats were given corn oil suspensions of SAYTEX®111 via gavage at dosages of 0(Vehicle), 2.5, 10.0 or 25.0 mg/kg/day (days 6-15 of gestation). The dams were sacrificed on day 20 of gestation, and the fetuses were examined using "state-of-the-art" developmental toxicity meth-odology. The study was performed in compliance with the EPA guidelines and regulations . . . ."

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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 data generated in this study, SAYTEX®111 is more toxic to the conceptus than to the dam. The embryo/fetal no-effect level is 2.5 mg/kg/day. The maternal no-effect level is greater than 25.0 mg/kg/day (the 25.0 mg/kg/day dosage of the test substance resulted in significant ($P \leq 0.01$) effects on maternal body weight gain only after cessation of dosage, an observation inseparable from the significantly increased ($P \leq 0.01$) resorption incidence and significantly decreased ($P \leq 0.01$) fetal body weights observed for litters of these dams, as compared with control values). In a pilot dosage-range study . . ., dosages of 100 mg/kg/day and above inhibited maternal body weight gain, and dosages of 500 mg/kg/day and above were lethal to dams.

"As compared with control values, administration of 10.0 and 25.0 mg/kg/day dosages of SAYTEX®111 to the dams resulted in dosage-dependent effects on the conceptuses including reduced average fetal body weights (10.0 and 25.0 mg/kg/day dosage group litters), increased embryo/fetal death (resorption), fetal malformation and delayed skeletal ossification (25.0 mg/kg/day dosage group). These effects were statistically significant ($P \leq 0.01$) only for the high dosage group, as compared with control."

Submission Evaluation

Developmental toxicity is defined as the induction of adverse effects on developing organisms. The manifestations of developmental toxicity include: 1) death, 2) structural malformations, 3) altered growth, or 4) functional deficit. With regard to the submitted teratology study, the administration of SAYTEX®111 during gestation resulted in the induction of all three of the manifestations measured via a standard developmental toxicity or teratogenicity study (i.e., 1, 2, and 3 above). The 25 mg/kg/day dose level caused a statistically significant increase in the occurrence of 1) death (i.e., resorptions and dead fetuses), 2) structural malformations (e.g., enlarged hearts, malformed hindlimbs, rib anomalies), and 3) altered growth (i.e., delayed ossification and decreased fetal body weight). The administration of 10 and 2.5 mg/kg/day resulted in decreased fetal body weight (not statisically significant) and an increase in resorptions (statistically significant), respectively. Although the investigators concluded that the no-observable-effect level (NOEL) for the test material was 2.5 mg/kg/day, it is not possible for EPA to determine a NOEL without reviewing all of the raw data from the study. While it is not possible for EPA to determine the NOEL at this time, it is quite clear that embryos/fetuses are markedly more sensitive than adult animals to the toxic effects of the test material.

It should be noted that the test material falls under the general class of diphenyl oxides (also known as diphenyl ethers). This class contains numerous other compounds that are developmentally toxic; the most potent of which is nitrofen (the NOEL is less

than 0.3 mg/kg/day following dermal exposure). It should be noted also that decabromodiphenyl oxide was shown to be developmentally toxic in a teratology study conducted by Dow Chemical, U.S.A. (Norris et al., 1975). In this Dow study, decabromodiphenyl oxide was administered orally to rats on days 6-15 of gestation at dose levels of 10, 100 or 1000 mg/kg/day. There was no evidence of maternal toxicity at any level of exposure. At 1000 mg/kg there was an increased incidence in the number of litters with fetuses exhibiting edema and delayed ossification of the skull. The authors determined that the NOEL for decabromodiphenyl oxide was 100 mg/kg/day and stated that the significant increase of resorptions observed at 10 and 100 but not at 1000 mg/kg were due to chance.

Current Production and Use

A review of the production range (including importation volumes) statistics for the subject CAS Numbers, which are listed in the initial TSCA Inventory, has shown that no 1977 manufacture or importation was reported or that all of the production range data reported were claimed as TSCA Confidential Business Information (TSCA CBI) by the manufacturer(s) and/or importer(s) and cannot be disclosed (Section 14(a) of TSCA; U.S.C. 2613(a)). The data submitted for the TSCA Inventory, including the production range information, are subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

According to an Ethyl Corporation advertisement found in the 1985 OPD Chemical Buyers Directory, SAYTEX®111 is a flame retardant used principally in "ABS [acrylonitrile/butadiene/styrene], nylon and other thermoplastics." In its 8(e) notice, Ethyl stated that exposure of the general public to SAYTEX®111 is prevented by the plastic matrix. With regard to worker exposure, Ethyl provided the following information:

> ". . . [Ethyl controls the] exposure to [SAYTEX®111] in the workplace to <0.05 mg/M^3 by engineering controls, use of respirators and industrial hygiene practice. . . . [Ethyl's] calculations show that exposure to 0.05 mg/M^3 gives more than a 100-fold safety factor over the no-effect level in rats."

Comments/Recommendations

In its submission, the Ethyl Corporation stated that the company has notified its customers and other suppliers about the reported teratologic findings.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will request the Ethyl Corporation to submit a full copy of the final report (including the actual data and any statistical analyses of the data) from the oral teratology study of SAYTEX®111 in rats. In addition, Ethyl will be requested

to provide a complete copy of the pilot teratology study that was cited in the submitted abbreviated report as "Appendix B" but was not appended to the submitted report. Ethyl will be asked also to report (if known) the exact chemical identity and actual amount of each constituent (including impurities) in SAYTEX®111.

In light of the Agency's general interest in company actions that are taken on a voluntary basis in response to chemical toxicity or exposure information, the Ethyl Corporation will be asked if the company has notified or plans to notify its own workers about the submitted teratologic findings and, if so, to describe the nature of such notification(s). In addition, the Ethyl Corporation will be requested to describe the nature and available results of all other studies (other than those published in the scientific literature or already submitted formally to EPA) about which Ethyl is aware or that Ethyl has conducted, is conducting, or plans to conduct, that are designed to determine 1) the toxicity of SAYTEX®111 or its constituents, or 2) the exposure to SAYTEX®111 or its constituents during manufacture, processing, and use.

b) The Chemical Screening Branch will ask Dow to provide a complete copy of the final report (including the actual experimental protocol, data, statistical analyses, etc.) from the Dow rat teratology study of decabromodiphenyl oxide that was cited in the 1975 Norris et al. paper.

c) The Chemical Screening Branch will review the submitted information in order to determine the need for further OTS assessment of brominated diphenyloxide.

d) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, 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.

Reference

Norris, JM; Kociba, RJ; Schwetz, BA; Rose, JQ; Humiston, CG; Jewett, GL; Gehring, PJ; and Mailhes, JB; "Toxicology of Octabromobiphenyl and Decabromodiphenyl Oxide" Environmental Health Perspectives Vol. 11: 153-161; 1975.

DATE: JUN 28 1985

SUBJECT: Status Report* 8EHQ-0585-0556 S Approved: JS 7/2/85

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 Rohm and Haas Company claimed the exact chemical identities of the components of the subject products to be TSCA Confidential Business Information (CBI). The Information Management Division will ask the company to substantiate this claim. Rohm and Haas did report non-confidentially, however, that the subject products were "primarily mixtures of complex methacrylate monomers."

Submission Description

The Rohm and Haas Company submitted the following information concerning the conduct and results of a 2-week repeated skin application study of two products (Monomer QM-867 (or Monomer PCM-200) and Monomer QM-928 (or Monomer PCM-400)) in rabbits:

"In a repeated skin application study, either of two lots of the test substances QM-867 (Lots WJR-2272-1 and WJR-2272-2) or QM-928 (Lots WJR-2272-3 and WJR-2272-4) was applied to the unoccluded, shaved backs of four groups of ten (5 male, 5 female) New Zealand white rabbits. Materials were delivered at a constant volume of 1 ml test substance/kg body weight. Water was applied to ten (5 male, 5 female) sham-exposed (control) rabbits at a similar volume. The test substances (or water) were administered once daily for ten total exposures over a two-week period; dosing occurred on weekdays only, with recovery over the weekend; skin irritation, clinical signs, and feed consumption were assessed daily, body weight was measured twice weekly, and hematology and clinical chemistry parameters were measured at the beginning and end of the study. All rabbits were necropsied and organs examined grossly. Selected organs were weighed. Tissue samples of the liver, kidneys, brain, sciatic nerve, two sections of the spinal cord (cervical and thoracolumbar) and selected lesions were processed for microscopic examination.

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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.

"Based on mean skin irritation scores, severe skin irritation was observed in both sexes of all treatment groups following five days of dosing. In all treatment groups, one or more animals exhibited at least three of the following clinical signs: ataxia, uncoordinated movement of the hind limbs, hyperreflexia, extensor rigidity, prostration, and reduced body weight gain. Histopathology findings correlated with clinical signs. In every instance, rabbits exhibiting clinical neurotoxicity showed axonal swelling (i.e., axonal degeneration) within the thoracolumbar section of the spinal cord. In addition, one rabbit which did not exhibit in-life signs, did show axonal swelling in the spinal cord.

"Two rabbits (1 male and 1 female) treated with QM-867 and 2 males treated with QM-928 were killed prior to the scheduled termination of the study. These animals had extensor muscle rigidity of the limbs and were unable to access feed or water.

"There were no toxicologically significant changes in any of the hematologic or clinical chemistry parameters examined, nor in any other tissues examined histopathologically. Except for a slight decrease in the absolute (but not relative) weight of ovaries in females of Group 4, there were no statistically significant differences in terminal organ weights of the liver, kidney, adrenals, brain, gonads, or thyroid/parathyroids."

In its submission, Rohm and Haas also provided copies of Monomer QM-867 and Monomer QM-928 Material Safety Data Sheets revised by the company to reflect the reported neurotoxicologic findings in rabbits. With regard to other toxic effects, the product safety sheets state that Monomer QM-867 is moderately irritating to eyes and slightly irritating to skin, and Monomer QM-928 is moderately irritating to both skin and eyes. In addition, the safety sheets report that the rabbit dermal and rat oral LD50s for both products exceed 5 grams/kg. Finally, the product safety sheet for Monomer QM-928 indicates that this product caused "allergic contact dermatitis in guinea pigs (13 out of 19 guinea pigs responded positively)."

Submission Evaluation

Although the final reports of the performed studies are not yet available for review by EPA, the investigators did reportedly observe adverse neurological effects in rabbits exposed dermally to either of 2 mixtures of complex methacrylate monomers. The submitted information indicates that 15% (3 of 20) of the rabbits exposed once per day for up to 10 days to approximately 1 g/kg of the mixtures showed some signs of motor dysfunction, primarily ataxia and extensor rigidity. Although the time to onset of the neurotoxic signs was not reported, a total of 4 rabbits (2 exposed to Monomer QM-867 and 2 exposed to Monomer QM-928) were killed in a moribund state because of severe extensor rigidity and consequent inability to eat. It should be noted that the dermal application of both mixtures caused severe dermal

irritation after 5 days, thereby assuring absorption of the tested products. In all rabbits that displayed clinical signs (and 1 rabbit that did not display such signs), histopathologic changes involving axonal swelling were observed in sections of the thoracolumbar area of the spinal cord. No other significant toxic effects were reportedly observed in hematology, clinical chemistry, or histopathology (except for a decrease in absolute ovary weights in one of the test groups).

In summary, 1 to 10 dermally applied doses of approximately 1 g/kg of either of the two complex methacrylate monomer mixtures appear to have caused potentially permanent motor system dysfunction and associated pathology in rabbits. It should be noted that dermal exposure to methyl methacrylate has been associated with varying degrees of loss of distal sensory function in humans. In addition, motor system dysfunction and associated pathology have been observed in animals exposed to methacrylamide and hydroxyethyl acrylate.

Finally, it should be noted that the both the New and Existing Chemicals Programs in EPA's Office of Toxic Substances (OTS) have been evaluating toxicologic and exposure information on a number of mono- and multi-functional acrylates.

Current Production and Use

In view of the fact that the Rohm and Haas Company has claimed the exact chemical identities of the components of the two products to be TSCA CBI, no TSCA Inventory production information for these chemicals will appear in this report. According to the submission, "the major use of Monomer QM-867 and Monomer QM-928 is in polymer concrete products for concrete and spall repair or re-surfacing." The submitter did not provide any information concerning the other use(s) of the tested products.

Comments/Recommendations

In addition to revising the Material Safety Data Sheets for Monomer QM-867 and Monomer QM-928, the Rohm and Haas Company stated that it has informed its employees about the reported neurotoxicologic findings in rabbits. In its submission, the Rohm and Haas Company submitted a copy of a draft notification letter to its licensees, licensee candidates, and consultants. In this notification letter, Rohm and Haas stated that 1) the company has scheduled additional toxicologic studies of Monomer QM-867, Monomer QM-928, and another product (Monomer PCM-1100), in an attempt to determine the cause(s) of the observed neurotoxicologic effects, 2) the company believes that its products can be modified "to eliminate possible central nervous system (CNS) effects without sacrificing technical efficacy," and 3) the company is recalling existing inventories of Monomer QM-867, Monomer QM-928 and Monomer PCM-1100 except in certain critical use situations determined by Rohm and Haas to be under tight industrial hygiene control measures to avoid skin contact.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will request the Rohm and Haas Company to ensure that EPA receives a full copy of the final report (including the actual experimental protocol and data) from the 2-week rabbit dermal application study of Monomer QM-867 and Monomer QM-928 that was cited in the submission. In addition, the Rohm and Haas Company will be asked to ensure that the Agency is apprised in a timely manner about the results of all studies that the company is conducting or plans to conduct to determine the cause(s) of the neurotoxicologic effects observed in rabbits following repeated dermal application of Monomer QM-867 and Monomer QM-928. Finally, Rohm and Haas will be asked to provide a complete copy of the final report (including the actual experimental protocol and data) from each study for which results were presented in summarized form in the "Toxicity Information" sections of the submitted Monomer QM-867 and Monomer QM-928 Material Safety Data Sheets.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject products and/or their components.

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUL 3 1985

SUBJECT: Status Report* 8EHQ-0585-0557 Approved: JF 7/3/85

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

On behalf of one of its wholly-owned subsidiaries (the Amoco Oil Company), the Amoco Corporation (formerly the Standard Oil Company (Indiana)) submitted a pre-publication report concerning the conduct and "results of a retrospective cohort mortality study of over 10,000 oil refinery workers employed at ten oil refineries owned and operated by [the] Amoco Oil Company." In its submission, Amoco stated the study "revealed statistically significant elevations in mortality in three disease categories; namely, skin cancers, benign neoplasms, and digestive system cancers." Amoco noted that although "evaluations of these disease categories have been reported previously for refinery populations," this investigation has brought to light additional information that Amoco believes to be new. With regard to this new information, Amoco stated that "the data indicate an association between workplace exposure and skin cancer, specifically in jobs where employee exposure to petroleum materials has been evaluated as routine rather than occasional or none." The following information concerning the results of the retrospective cohort mortality study of Amoco oil refinery workers was presented in the report abstract:

> "This retrospective cohort mortality study of 10,763 [Amoco] oil refinery workers employed between 1970 and 1980 showed that overall mortality for the cohort compared favorably with that of the U.S. population. The Standardized Mortality Ratio (SMR) for all causes of death was 73 for white males and 68 for black males. For most of the white male subgroups analyzed, SMRs for all cancers combined were higher than those for all causes of death but were lower than would be expected in the U.S. population."
>
> "The study showed statistically significant elevations for three disease categories: skin cancers, benign neoplasms, and digestive system cancers. Significantly elevated skin cancer

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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.

SMRs were found for all white males hired in 1945 or later and those with less than 15 years latency. When the white male population was stratified by job type (Administrative, Maintenance, Operations, and Unknown), a statistically significantly elevated SMR of 378 was seen for Maintenance employees. When white males were stratified by categories for exposure to refinery processes, exposure to light aromatic hydrocarbons, and exposure to heavy oils using the groups none, occasional, routine, and unknown, [the] skin cancer SMRs were statistically significantly elevated for the highest (routine) exposure categories. For all three exposure categorizations, a dose-response effect was demonstrated, where increasing exposure was associated with increased mortality. Dose-response relationships observed among SMRs were confirmed by comparison of directly standardized mortality rates for the exposure groups. A total of 11 skin cancer deaths were observed; 10 of these were melanomas. SMRs for benign neoplasms were statistically significantly elevated for white males employed in Maintenance positions (with an SMR of 374) and for those with routine exposure to heavy oils (with an SMR of 357).

"Statistically significantly elevated SMRs for digestive system cancers were seen in several white male subgroups. An elevated SMR of 137 for all digestive cancers combined was seen in employees of the Whiting [Indiana] refinery; the stomach cancer SMR [at the Whiting, Indiana refinery] was also statistically significantly elevated at 207. For the 10-refinery population, an SMR of 139 for all digestive system cancers was observed for those with routine exposure to light aromatic hydrocarbons. The SMRs for all digestive system cancers and stomach cancer were significantly elevated in white males hired before 1940."

"The elevated SMRs for benign neoplasms and digestive system cancers did not seem to be related to job type or refinery exposure. On the other hand, the observed elevations in skin cancer SMRs, along with the dose-response relationship, support the possibility that contact with petroleum or one of its constituents is associated with skin cancer and melanoma in particular."

In order to prevent a possible misinterpretation of the results of the submitted retrospective mortality study and to give a clear understanding of how the exposure categories were determined, the Amoco Corporation also submitted a highlighted report describing the selection process for determining the exposure categories. With regard to this exposure category selection process, Amoco reported that the process "was based upon generalized qualitative evaluations of job categories and not upon the [quantitive] exposure history of individual employees." In other words, Amoco "did not measure the frequency and level of exposure received by each individual employee in the study in order to assign them to the exposure categories."

Submission Evaluation

The submitted cohort study examined the mortality experience of all full-time regular employees who worked at 10 Amoco Oil Company refineries for six months or more, at least one day of which was between January 1, 1970, and December 31, 1980. The year 1970 defined the earliest availability of nearly complete computerized records, and the cutoff date for followup was December 31, 1982. The submitted information indicates that further study is anticipated, extending the eligibility definition as the computerized data base is enlarged to include all those employed between 1940 and 1980.

Although the bulk of the cohort (10,763) was white male (9,187), standardized mortality ratios (SMRs) were also computed for black males (884) and white females (583). The Texas City (Texas) and Whiting (Indiana) refineries contributed better than half of the study population, leaving many causes of death unrepresented in the remaining eight refineries. Furthermore, this reduces the ability to detect patterns in elevations across individual refineries. The cohort generally showed deficits (i.e., SMRs less than 100), some statistically significant, in a variety of mortality causes, both compared to the U.S. general population and state-specific mortality rates; such deficits are more likely to be indicative of the "healthy worker" phenomenon. Nevertheless, significantly elevated SMRs were seen overall for skin cancer, digestive system cancers, and benign neoplasms. These elevations were largely attributable to the Whiting refinery. Other high risk characterizations include 1) those white males who were ever hourly workers, 2) white male maintenance workers, 3) white males with less than 15 years exposure prior to diagnosis (3 skin cancer deaths observed as compared to 0.6 expected (SMR=524); the total white male group had 11 skin cancer deaths), and 4) routine exposure in any of the three materials categorizations (refinery products, light aromatic hydrocarbons, and heavy oils). The investigators noted that individuals exposed routinely in one of the three exposure categories tended to have been exposed routinely in the others.

The investigators have very nicely compared their findings with most other completed studies in the petroleum and refinery field. With regard to a concern for kidney cancer, while the total number of white male kidney cancer deaths is adequate to detect elevations, the subgroups had small numbers. Interestingly, half of the white male kidney cancer deaths occurred in salaried workers. Brain and CNS cancers do appear to be elevated at a few smaller refineries and in salaried workers but, again, these small, unstable numbers together show an overall relative risk not significantly different from one. This observation is indicative of the difficulties that can be encountered even with such a large study. Although one table (i.e., Table 64) shows a quite reasonable ability to detect 2-3 fold relative risks in a variety of causes of death, these are sex- and race-specific relative risks adjusted only for age and not for other possible confounding factors. It

should be noted that the investigators did comment on the limited availability of smoking information. It should be noted also that dietary and skin complexion information could have been extremely useful. In addition, a combining of the three exposure categories (i.e., none/none/none, occasional/occasional/occasional, routine/routine/routine) might have shown an interpretable dose-response gradient. Finally, and most importantly, however, the power calculations are based on the assumption that a specific number of predetermined analyses will be carried out. When hundreds of SMRs are computed, as they have been in the submitted study, the actual level (α) overall is no longer that nominal level for which the calculations have been carried out. Therefore, interpretation of the study's detection capabilities becomes extremely difficult.

Comments/Recommendations

In the cover letter to its submission, Amoco reported that "in light of the study results, particularly those regarding skin cancer, Amoco will review past operational changes which have reduced skin contact with petroleum materials and determine what further steps are feasible [to reduce exposure], including increased emphasis on employee personal and industrial hygiene."

It should be noted that EPA's Office of Toxic Substances (OTS) has received and evaluated a number of TSCA Section 8(e) and "For Your Information" (FYI) submissions containing toxicologic and/or exposure information on a wide variety of petroleum refinery streams. In addition, the Chemical Screening Branch (CSB/ECAD/OTS) has prepared a Chemical Hazard Information Profile (CHIP) on 2 naphtha petroleum solvents. Both the Risk Analysis Branch (RAB/ECAD/OTS) and Test Rules Development Branch (TRDB/ECAD/OTS) are evaluating available toxicologic and exposure data on a number of petroleum refinery process streams and/or components of such streams.

(a) The Chemical Screening Branch will request the Amoco Corporation to ensure that the Agency is apprised about significant findings from all further refinery worker epidemiology studies/statistical analyses performed by the company.

In view of the Agency's general interest in corporate actions that are taken on a voluntary basis in response to chemical toxicity/exposure data, the Amoco Corporation will be asked if it has notified Amoco workers or other petroleum refiners about the reported findings, and, if so, to describe the nature of such notifications.

(b) The Chemical Screening Branch will review the reported information in order to determine the need for separate OTS assessment of the reported findings and/or referral of the findings to an ongoing assessment.

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

DATE: JUN 19 1985

SUBJECT: Status Report* 8EHQ-0685-0558 S Approved: JM 6/24/85

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 (TSCA CBI). The Information Management Division (IMD/OTS) has requested the submitting company to substantiate these confidentiality claims.

Submission Description

The submitting company provided the following information with regard to the conduct and final results of a battery of in vitro genotoxicity studies of a chemical identified by the submitter generically as a "substituted oximidoalkane":

> "The tests conducted were Ames Salmonella Mutagenesis, Mouse Lymphoma Forward Mutation, in vitro Sister Chromatid Exchange and the Balb-c 3T3 Cell Transformation assays. No activity was detected in the Ames Salmonella assay. Dose dependent increases in mutant frequency were induced with and without activation in the Mouse Lymphoma Forward Mutation assay. No increase in activity was observed in the in vitro Sister Chromatid Exchange assay in the presence of activation, although activity was observed without activation. A significant increase in the frequency of transformed foci was observed at the highest concentration in the Balb-c 3T3 Cell Transformation assay. The results suggest a potential for genetic activity but no judgment as to potency can be made."

In its submission, the company provided copies of the final reports of the Ames, Mouse Lymphoma, and Cell Transformation assays. The submitting company stated that the results of the Sister Chromatid Exchange assay were obtained verbally from the testing laboratory and when the company receives the final report of this assay a copy of the report would be sent to EPA.

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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

The substituted oximidoalkane was tested for genotoxic activity in a battery of short-term tests which included the Salmonella typhimurium (bacteria)/mammalian microsomal assay (Ames assay), the specific locus gene mutation assay in cultured mouse lymphoma L5178Y cells, the in vitro Sister Chromatid Exchange (SCE) assay in Chinese hamster ovary (CHO) cells, and the in vitro Balb-c 3T3 mouse cell transformation assay.

Although the substituted oximidoalkane was found to be negative in the Ames assay, the chemical did induce mutation at the TK locus in cultured mouse lymphoma L5178Y cells when tested both with and without exogenous metabolic activation. Based on these results, the tested chemical is considered to be a mammalian cell gene mutagen. The negative results from the Ames assay do not affect this conclusion nor lessen concern for the genotoxicity of this chemical substance.

The subject chemical was tested also for its ability to induce cell transformation in cultured Balb-c 3T3 mouse cells. In this assay, the chemical induced a dose-related increase in the number of morphologically transformed foci in treated versus control cultures. Although this increase was found to be statistically significant only at the highest dose level, the biological significance of this finding is enhanced by the dose-related nature of the observed response. Based on these results, the substituted oximidoalkane is considered to be a weak transforming agent in Balb-c 3T3 mouse cells in culture.

Finally, it was reported also that the substituted oximidoalkane induced SCE formation in cultured CHO cells. Although no data were presented to verify this statement, there is no apparent reason to doubt its validity and, in the absence of evidence to the contrary, the subject chemical should be considered positive in this assay.

In view of 1) the known correlation between genotoxicity and oncogenicity, and 2) the correlation between cell transforming activity and oncogenicity, the substituted oximidoalkane should be considered to be a potential oncogen in vivo.

Current Production and Use

Although the submitting company reported that this substituted oximidoalkane is still in research and development (R&D), the company did not provide any information with regard to the actual or potential use(s) of the chemical. The company did report, however, that "the number of people potentially exposed [to the chemical] is very small" and that "exposure is being controlled through prudent laboratory practices."

Comments and Recommendations

Although a positive *in vitro* genotoxicty test result, when considered alone, may not be sufficient to offer reasonable support for a conclusion of substantial risk, EPA believes that such results are of value in assessing the possible risks posed by chemicals to health and/or the environment. In addition, the Agency believes that a positive genotoxicity test result in combination with additional information (e.g., knowledge of potential exposure to or high production of the chemical substance or mixture) would suggest, in many cases, the need to conduct other studies designed to better define the toxicity of and/or the exposure to the chemical substance or mixture. The results of such additional studies should be considered also for possible submission to EPA under Section 8(e) of TSCA.

(a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the submitting company to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol and data) from the Sister Chromatid Exchange assay cited in the submission.

In light of the Agency's general interest in corporate actions that are taken on a voluntary basis in response to chemical toxicity/exposure information, the Chemical Screening Branch will ask the submitting company to describe the actions it has taken or plans to take to 1) warn workers and others, and 2) reduce or eliminate exposure to the substituted oximidoalkane. In addition, the submitting company will be asked to describe the nature and available results of all other studies that the company has conducted, is conducting, or plans to conduct to define the toxicity of and/or the exposure to the substituted oximidoalkane.

(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, FDA, CPSC, NTP, OW/EPA, OSWER/EPA, OAR/EPA, and ORD/EPA. Copies of this status report will be sent also to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUL 10 1985

SUBJECT: Status Report* 8EHQ-0685-0559 S

Approved: 7/10/85

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/OPTS) will request the submitting company to substantiate this claim.

Submission Description

The submitting company provided the following summary information with regard to the results of both new and previously conducted acute inhalation toxicity studies of tris(dimethylamino)silane (CAS No. 15112-89-7) in rats:

". . .[The submitting company] originally conducted preliminary investigations on the acute toxicity and primary irritancy of tris(dimethylamino)silane, which included a study on the effects of a single exposure of rats to an atmosphere substantially saturated with vapor from tris(dimethylamino)silane. This was achieved by introducing samples of the test material into the exposure chambers and allowing the atmosphere to equilibrate overnight. Rats, in groups of 6, were then introduced into the highly concentrated vapor. Of one group exposed for 17 minutes, all died. However, following an 8.5 minute exposure, there were no mortalities among another group of rats during a 14-day post-exposure observation period. These data allowed the calculation of an Lt50 value of 12 minutes for exposure to an atmosphere saturated with vapor from tris(dimethylamino)silane. Signs of toxicity included those of severe irritancy.

"In view of the above initial finding, . . . [the company] considered it appropriate to define the potential hazard from the vapor by conducting a further acute inhalation study to define the LC50. This was achieved by exposing rats, in 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.

of 6, for 4 hours to the following nominal concentrations of tris(dimethylamino)silane: 2010, 1010 and 534 ppm. The atmospheres were generated by a metering procedure, which involved feeding the liquid at a constant rate down the inner side of a spirally corrugated surface of a minimally heated Pyrex tube, through which air was passed in a countercurrent fashion and thence into the exposure chamber. The rate of feed of the liquid determined the atmospheric concentration of vapor. For this [acute] study, the atmospheric concentrations of tris(dimethylamino)silane were not analytically measured. A 4-hour exposure to 2010 or 1010 ppm resulted in the deaths of all animals, with preceding signs of severe irritancy to the eyes and respiratory tract. At 534 ppm, there were only mild transient signs of eye irritation, but no mortalities occurred during a 14-day post-exposure observation period. These data allowed the calculation of a 4-hour LC50 of 734 ppm (95% confidence limits of 603-893 ppm) for tris(dimethylamino)silane under the conditions of the investigation.

"The above studies were interpreted as indicating that vapor from tris(dimethylamino)silane is of moderate toxicity by acute exposure to high concentrations in the atmosphere. It was considered that the irritant and toxic effects of tris(dimethylamino)silane were due to dimethylamine which would be produced in the moist chamber atmospheres. Indeed, applying a stoichiometric relationship of 3 parts of dimethylamine arising from one part of tris(dimethylamino)silane and 2 parts of water, then an equivalent LC50 in terms of hydrolysis products would be 2202 ppm, which is close to published values on the acute LC50 for dimethylamine vapor. On the basis of the above findings, a warning of potential inhalation hazards was communicated to . . . [the submitting company's] employees working with tris(dimethylamino)silane, and steps were taken to assure good mechanical ventilation of workspaces where the chemical is handled. Respiratory protective equipment was made available in circumstances where it could be anticipated that high concentrations of vapor may be encountered.

"Recently, . . . [the company] decided to investigate further the toxicology of tris(dimethylamino)silane. In order to confirm the previous findings on the acute inhalation toxicity [of the] vapor from the material, a further study was conducted which involved the analytical measurement of tris(dimethylamino)silane and dimethylamine in the chamber atmosphere. In preliminary studies, again using a countercurrent stream of air, it was found that highly variable concentrations of tris(dimethylamino)silane were detected in the atmosphere. In view of this, and because of precipitation problems [encountered] in the glass evaporators, it was decided to develop a method to allow the maximum possibility for evaporation of tris(dimethylamino)silane as the disperse vapor molecule. This was achieved by metering the material into the vaporization tube against a countercurrent stream of nitrogen, with the resultant tris(dimethylamino)silane vapor being carried by dry nitrogen into the

chamber air intake duct. This resulted in significantly more stable analytical data. Using this nitrogen stream generation technique, groups of 10 male and 10 female rats were exposed to the following analytically verified concentrations of tris(dimethylamino)silane vapor: 395, 127, 62 and 23 ppm. The analytically measured dimethylamine concentrations were, respectively, 112, 31, 10 and 26 ppm. All rats died at concentrations of tris(dimethylamino)silane vapor of 62 ppm and above. No animals died during or in a 14-day post-exposure observation period following exposure to 23 ppm. Deaths occurred during the first 24 hours after exposure to 395 and 127 ppm, but were delayed between 2 and 14 days after 62 ppm. The concentration-mortality data allowed calculation of a 4-hour LC50, for male and female rats, to be established at 38 ppm (95% confidence limits of 34-43 ppm) . . . .

"This 4-hour LC50 of 38 ppm for tris(dimethylamino)silane vapor, based on analysis of chamber atmospheres, is very significantly lower than that previously estimated at 734 ppm by a nominal metering procedure. The comparatively low concentrations of analytically measured dimethylamine vapor, with respect to its known toxicity, suggest that the mortalities were primarily the result of exposure to tris(dimethylamino)silane vapor in the atmosphere. The findings indicate that tris(dimethylamino)silane vapor is significantly more acutely toxic than its major hydrolysis product, dimethylamine. In view of the nitrogen generation technique employed in the investigations, the quantitative relevance of these findings to the occupational environment is uncertain, since any tris(dimethylamino)silane vapor released into the workplace is likely to be hydrolyzed by water in the atmosphere to dimethylamine. However, the relative rate of this conversion will depend on both the rate of emission of tris(dimethylamino)silane and the relative humidity of the workplace atmosphere."

Submission Evaluation

It is important to note that tris(dimethylamino)silane contains two distinct functional groups (i.e., dimethylamine and silane). Inhalation exposure to either dimethylamine or silane can result in serious adverse respiratory system effects. Dimethylamine, which can be compared to ammonia, has been shown to be a severe respiratory tract irritant; exposure to silanes via inhalation has been associated with respiratory hemorrhaging. In order to evaluate the significance of the reported findings, the submitter should be asked to provide a complete copy of the final report (including the actual experimental protocol and histopathologic data) from each acute toxicity study cited in the submission.

Current Production and Use

A review of the production range (includes importation volumes) statistics for tris(dimethylamino)silane (CAS No. 15112-89-7), which is listed in the initial TSCA Inventory, has shown that

between 0 and 1000 pounds of this chemical were reported as produced/imported in 1977. This production range information does not include any production/importation data that were claimed as TSCA Confidential Business Information (TSCA CBI) by those person(s) reporting for the TSCA Inventory, nor does it include any information that would compromise TSCA CBI. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

The submitting company reported that its only involvement with tris(dimethylamino)silane is in the company's research and development (R&D) laboratories where potential exposure to the chemical is "extremely limited." No information concerning the actual or potential use(s) of tris(dimethylamino)silane was provided by the submitting company or located in the secondary literature sources consulted.

Comments/Recommendations

The submitting company stated that as soon as the final report of the recent acute inhalation toxicity study is completed a copy would be sent to EPA. The submitting company also stated that its employees, a company thought by the submitter to be involved in the manufacture, processing, or distribution of tris(dimethylamino)silane, and an academic research laboratory known to be working with the chemical were being notified about the reported acute toxicity findings.

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/exposure information on organosilanes. The Chemical Screening Branch (CSB/ECAD/OTS) has prepared a Chemical Hazard Information Profile (CHIP) on 3,4-epoxycyclohexylethyltrimethoxysilane and is now considering the preparation of CHIPs on other organosilanes. The Risk Analysis Branch (RAB/ECAD/OTS) is currently evaluating toxicologic and exposure data on 3,4-epoxycyclohexylethyltrimethoxysilane. The New Chemicals Program in OTS has also been evaluating available toxicologic and exposure data on organosilanes.

a) The Chemical Screening Branch will request the submitter to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol and available histopathologic data) from the company's recently conducted acute rat inhalation toxicity study of tris(dimethylamino)-silane. In addition, the submitter will be asked to provide complete copies of the final reports (including the actual experimental protocols and histopathologic data) from all other acute inhalation studies cited in the submission.

   In view of the Agency's general interest in company actions that are taken on a voluntary basis in response to chemical toxicity or exposure information, the submitter will be

asked to describe the nature and available results of all other studies that the company has conducted, is conducting, or plans to conduct to determine the toxicity of and/or the exposure to tris(dimethylamino)silane.

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

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

DATE: JUL 23 1985

SUBJECT: Status Report* 8EHQ-0785-0560 Approved: 7/24/85

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 Nalco Chemical Company provided preliminary results from an ongoing combined 2-generation Reproduction/Dominant Lethal study of acrylamide monomer (CAS No. 79-06-1) in rats. According to the submission, this ongoing study is being co-sponsored by Dow Chemical U.S.A., the Standard Oil Company (Ohio), and the Nalco Chemical Company who are all members of the Acrylamide Producers Association, "a special projects group of [the] Synthetic Organic Chemical Manufacturers Association (SOCMA)." In the cover letter to its submission, Nalco provided the following summary information concerning the conduct and available preliminary results of the subject study:

> ". . . Acrylamide monomer is being administered in the drinking water at 0, 0.5, 2.0 and 5.0 mg/kg/day to Fischer 344 rats. Male and female rats were treated for 10 weeks prior to breeding. Females continued to receive chemical during gestation and lactation of their F_1 litters. Males upon completion of their assigned F_0 parental responsibilities were re-mated with naive (non-exposed) females for the Dominant Lethal Assay. These preliminary draft results through weaning of F_1 animals and the Dominant Lethal portion of the study indicate that 5.0 mg/kg/day but not 2.0 or 0.5 mg/kg/day acrylamide monomer produced in Fischer 344 rats the following reproductive effects:
>
> 1. Dominant Lethal Portion
>
> A. Although the number of eggs ovulated per dam was equal among all dose groups, there was a significant reduction in total implants per litter. Therefore pre-implantation loss was significantly increased.

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B. There was also an increase in non-viable implants per litter, i.e., resorptions. Therefore, post-implantation loss was also increased.

2. Reproduction Portion (1st Generation)

Although males given acrylamide [monomer] appeared to be able to successfully mate with females (no effect on mating index), the litter size and the number of litters was reduced compared to controls.

Additionally, parental animals in the 5.0 mg/kg/day group and to a lesser extent those in the 2.0 mg/kg/day group, as expected, displayed evidence of acrylamide intoxication. Animals in these groups had decreased body weights (lower body weight gains) compared to controls. Previous investigations with acrylamide [monomer] have shown that doses below 5 mg/kg/day produce peripheral neuropathy."

Submission Evaluation

Immediately upon receipt of this TSCA Section 8(e) notice, the Chemical Screening Branch (CSB/ECAD/OTS) forwarded copies to the Risk Analysis Branch (RAB/ECAD/OTS) and Test Rules Development Branch (TRDB/ECAD/OTS) for inclusion in their ongoing evaluations of available toxicologic and exposure data on acrylamide.

Current Production and Use

A review of the production range (includes importation volumes) statistics for acrylamide (CAS No. 79-06-1), which is listed in the initial TSCA Inventory, has shown that between 10 million and 51 million pounds were reported as produced and/or imported in 1977. This production range information does not include any production or importation data that were claimed confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise TSCA Confidential Business Information. The data submitted for the TSCA Inventory, including production range data, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

The major applications of acrylamide include the chemical's use as a cross-linking agent, in certain adhesive formulations, in paper and textile sizes, as a soil conditioning agent, as a flocculant, and in sewage and waste treatment.

Comments/Recommendations

In addition to sending copies of its TSCA Section 8(e) notice to Dow Chemical U.S.A., the Standard Oil Company (Ohio), and SOCMA, Nalco stated that any additional significant findings from the ongoing study would be forwarded to EPA.

In April 1978, acrylamide was designated by the Interagency Testing Committee (ITC) for health and environmental effects testing under Section 4 of TSCA. In addition, final TSCA Section 8(a) and 8(d) chemical information reporting rules for acrylamide have been issued by the Agency. EPA has also received several TSCA Section 8(e) and "For Your Information" (FYI) submissions containing toxicologic and/or exposure data on acrylamide.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the Nalco Chemical Company to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, data, statistical analyses (if performed), etc.) from the ongoing 2-generation Reproduction/Dominant Lethal study of acrylamide monomer cited in the submission.

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: AUG 16 1985

Approved: 8/19/85

SUBJECT: Status Report* 8EHQ-0785-0561 S

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 BASF Wyandotte Corporation claimed its sales and importation volumes of the subject chemical to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division will ask BASF Wyandotte to substantiate these confidentiality claims.

Submission Description

BASF Wyandotte submitted the results of several in vitro and in vivo toxicity studies of 1-ethenyl-2-pyrrolidinone (CAS No. 88-12-0). These studies were conducted by the parent company, BASF Aktiengesellschaft (BASF AG) in Ludwigshafen, West Germany. The following summary with regard to the conduct and results of the studies was provided by BASF in the submission's cover letter:

"In 1980, BASF AG initiated a toxicology program on 1-ethenyl-2-pyrrolidinone. At first a three-month inhalation study was conducted in [Sprague-Dawley] rats at 0, 5, 15, 45, and 120 ppm with 10 animals/sex/group. [Exposure to ethenyl-2-pyrrolidinone was carried out for 6 hrs. each working day for the duration of the three month study]. 120 ppm was lethal for the rats [16/20 animals died]. The liver and the olfactory mucosa of the nasal cavity were the target organs. The severity of these changes was concentration-dependent with minimal changes at 15 ppm in the liver and 5 ppm in the nasal mucosa. A subsequent study established a no-effect level of 1 ppm.

"Because of the observation of liver toxicity in the first study, in March 1983 BASF AG initiated a preliminary study to investigate the rat liver's recovery from this toxicity. In this study, female [Sprague-Dawley] rats were exposed to 45 ppm for three months and sacrificed at 7 weeks (during treatment), 3 months (end of treatment), 12 and 24 months. The draft interim reports show that there was evidence of hepatic toxicity

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at 7 weeks which was more marked at three months. At the interim kill at 12 months, there was marked recovery of liver architecture and recovery from toxicity. Of the 15 animals, each designated for kill at 24 months, 6 of the treated group and 4 from the controls survived this period. There appeared to be no difference in mortality between control and treated. Of the animals killed at the termination, 2 possible carcinomas were observed, and 2 other animals in the treated group had nodular lesions originally reported as "neoplastic nodules". In the control group one animal showed a nodular lesion similar to the neoplastic nodules in the treated group. None of the animals in the treated group dying or killed prior to termination showed evidence of carcinoma or neoplastic nodules.

"Additional toxicity testing conducted by BASF AG includes a three-month inhalation test in [Syrian] hamsters as well as 3-week and 3-month drinking water studies in [Wistar] rats and a 3-month gavage study in rats. These studies confirmed the hepatotoxicity of 1-ethenyl-2-pyrrolidinone to the rat; however, the compound is not toxic to the hamster at the concentration tested."

BASF Wyandotte also reported that 1-ethenyl-2-pyrrolidinone was found to be negative in the following in vitro test systems: an Ames Salmonella typhimurium (bacteria) mutagenicity assay (with and without exogenous metabolic activation), a mouse lymphoma cell forward mutation assay (with and without exogenous metabolic activation), a Balb/3T3 mouse cell transformation assay, and an unscheduled DNA synthesis (UDS) assay in rat hepatocytes.

Submission Evaluation

The performed subchronic inhalation toxicity study of 1-ethenyl-2-pyrrolidinone in Sprague-Dawley rats (conducted at 1, 5, 15, 45 and 120 ppm and terminated at 3 months) showed in the 15 and 45 ppm groups an increase in liver weights and in the 120 ppm group clear signs of toxicity (e.g., severe liver damage, necrosis of the nasal mucosa, and hemorrhagic diathesis). The subchronic toxicity study in Wistar rats exposed to the chemical at 5, 12, 30 and 75 ppm in the drinking water and terminated at 13 weeks showed in the 30 and 75 ppm groups kidney hypertrophy in males only. Surprisingly, this particular finding did not appear to have a light microscopically-detectable morphological basis. In females there was no evidence of kidney hypertrophy although occasional foci of calcification were observed. In the experiment in which male and female Wistar rats were exposed to 1-ethenyl-2-pyrrolidinone via the drinking water for 3 or 4 weeks followed by gavage for 13 weeks, dose-dependent liver hypertrophy was found. This coexisted with focal parenchymal changes as well as "foci of cellular alterations."

Three to four months seems to represent the threshold beyond which chronic toxic effects begin to appear in rats. Thus, female Sprague-Dawley rats exposed to 1-ethenyl-2-pyrrolidinone via inhalation at 45 ppm for 3 months, followed by a 9 to 21 month observation period, showed degenerative liver parenchymal changes and focal metaplasia resembling cirrhosis, proliferation and cloudy vacuolar swelling of hepatocytes, and glycogen accumulation in the proliferating cells. In addition, there were clear hepatocellular carcinomas in 2 animals and "neoplastic nodules" in the livers of 2 additional animals. Moreover, there were occasional "foci of cellular alterations." These foci had cells with enlarged nuclei, some of which were "vesicular." Cells in the foci also showed glycogen accumulation.

There appears to be a marked difference in the susceptibility of rats and hamsters to the toxic effects of 1-ethenyl-2-pyrrolidinone. Male and female hamsters that underwent essentially the same dosing schedule (a 3 month period of inhalation at 45 ppm followed by a 15 month observation period) showed no pathological changes. It is somewhat surprising that hamsters were chosen as the second species as opposed to mice. Hamsters are well-known to be relatively resistant to the carcinogenic action of a number of chemical agents, as compared to rats and mice. Therefore, the absence of pathological changes in hamsters exposed to 1-ethenyl-2-pyrrolidinone is not entirely surprising nor unexpected.

1-Ethenyl-2-pyrrolidinone was reported to be non-genotoxic in 4 short-term in vitro tests (an Ames test using 4 bacterial test strains, a mouse cell transformation assay, a mouse lymphoma cell forward mutation assay and an unscheduled DNA synthesis assay in rat hepatocytes). It should be noted that the GAF Corporation submitted (8EHQ-0682-0448 S et seq.) the results of several in vitro genotoxicity studies of a structurally-related chemical. In its Section 8(e) filing, GAF reported that 1-(2-hydroxyethyl)-2-pyrrolidinone produced a positive mutagenic response in the Ames test, a suggestive mutagenic response in a Chinese Hamster Ovary (CHO)/HGPRT gene mutation assay, and negative responses in CHO/Sister Chromatid Exchange (SCE), CHO/chromosomal aberration, and Balb/3T3 mouse cell transformation assays.

On the basis of the data contained in the present submission, 1-ethenyl-2-pyrrolidinone is hepatotoxic and appears to be a weak hepatic carcinogen in rats. It should be noted also that in order to clearly establish that 1-ethenyl-2-pyrrolidinone is not genotoxic, it would be quite useful to test the chemical's ability to covalently bind to DNA in vivo. In addition, it would be very important to determine whether 1-ethenyl-2-pyrrolidinone has the ability to produce teratogenic or other adverse developmental effects.

Current Production and Use

A review of the production range (includes importation volumes) statistics for 1-ethenyl-2-pyrrolidinone (CAS No. 88-12-0), which is listed in the initial TSCA Inventory, has shown that between 0 and 1 thousand pounds of this chemical were reported as produced/imported in 1977. This production range information does not include any production/importation 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 information that was submitted 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).

In its submission, BASF Wyandotte reported that 1-ethenyl-2-pyrrolidinone is manufactured by BASF AG in West Germany and is imported to the U.S. by BASF Wyandotte. BASF Wyandotte reported also that the subject chemical "is used as a raw material for the manufacture of a variety of chemical products." According to information contained in secondary literature sources, 1-ethenyl-2-pyrrolidinone is used as a reactive diluent in ultraviolet and electron beam curable polymer systems; as an intermediate in the production of modified phenolic resins used as plasticizers, dyestuff intermediates, and textile assistants; and as the starting monomer for polyvinylpyrrolidone which has numerous applications (e.g., pharmaceuticals, cosmetics, detergents, adhesives, beer and wine clarification).

Comment/Recommendations

BASF Wyandotte stated that additional studies (e.g., in vivo DNA binding, metabolism, teratogenicity, and chronic exposure) are being considered in order to define better the potential toxicity of 1-ethenyl-2-pyrrolidinone. In addition, BASF Wyandotte stated that the company is notifying its customers about the reported findings. Finally, BASF Wyandotte stated that all final reports would be sent to EPA.

a) The Chemical Screening Branch (CSB/ECAD/OTS/OPTS) will ask the submitting company to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, data, statistical analyses (if performed), etc.) from each study (including the in vitro studies) cited in the company's submission.

   In view of EPA's general interest in company actions that are taken on a voluntary basis in response to chemical toxicity and/or exposure information, BASF Wyandotte will be asked to describe the actions the company has taken to notify its own workers about the reported findings. BASF Wyandotte will be

asked also to describe the nature and available results of all studies (other than those already published in the open scientific literature or already reported to EPA) that have been conducted by or known to the company that determine the exposure to 1-ethenyl-2-pyrrolidinone during its manufacture, processing, and/or end-use.

b) The Chemical Screening Branch will review the provided information in order to determine the need for further OTS assessment of 1-ethenyl-2-pyrrolidinone.

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: AUG 2 3 1985

UBJECT: Status Report* 8EHQ-0785-0562 S

Approved: 8/27/85

Terry O'Bryan for

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 actual identity and tradename of the subject chemical to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS) will request the submitting company to substantiate these confidentiality claims. The submitter did provide the following non-confidential generic name for the subject chemical: "dichlorophenyl-alkoxyalkyl-oxoheteromonocycle."

Submission Description

The submitting company provided preliminary and, in somes cases, final results from a number of in vivo toxicologic studies on dichlorophenyl-alkoxyalkyl-oxoheteromonocycle. According to the submitted information, the chronic toxicity and possible carcinogenic properties of the chemical were/are being examined in male and female rats in the following 3-part study that was started in September, 1983:

1) a 12-month study of 5 groups of 10 male and 10 female rats exposed to the chemical at levels of 0, 500, 750, 2250 or 4500 ppm in the food;

2) an 18-month study of 5 groups of 10 male and 10 female rats exposed to the chemical at levels of 0, 500, 750, 2250 or 4500 ppm in the food; and

3) a life-span study of 4 groups of 50 male and 50 female rats exposed to the chemical at levels of 0, 500, 750 or 2250 ppm in the food.

A submitted pathology report contained the following information concerning results of the 12-month segment of the chronic feeding study which ended in September, 1984:

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"Microscopic examination revealed treatment-related changes in the testis, the kidneys and the pituitary. The testis lesions were characterized by (1) a dose-related increase in incidence and severity of diffuse interstitial cell proliferation in all treatment groups, including the low-dose group (the differences with the controls were statistically significant in the 750, 2250 and 4500 ppm group ($p < 0.01$ for each group)) and (2) the presence of nodular interstitial cell proliferation in all treatment groups (statistically significant ($p < 0.05$) in the top-dose group only), while this finding was completely absent in the controls.

"The testicular lesions observed in the low-dose group are also considered to be treatment-related because the incidence of diffuse interstitial cell proliferation showed a dose-related increase in all treatment groups, including the low-dose group, and since, moreover, nodular interstitial cell proliferation (which is an unusual finding for 12 months old rats of the strain used), occurred also in all treatment groups including the low-dose group.

"Tumours observed were a metastasizing adenocarcinoma of the mammary gland and a fibromatous polyp of the uterus. Since both tumours occurred in control females their occurrence is not related to treatment. The other abnormalities observed are common findings in the strain of rats used. They were about equally distributed among control and test groups, or occurred only in one or two animals. Therefore they were not ascribed to the feeding of the test substance.

"The kidney changes consisted of an increase in incidence and severity of dilatation of the pars recta of the proximal renal tubules. This increase occurred in the 2250 and 4500 ppm groups in both sexes, and in the the 750 ppm groups only in females. Moreover, in females the normally occurring renal mineralisation was absent in most of the test animals, including those of the low-dose group. Since distinct signs of degeneration or necrosis were absent the toxicological significance of these renal changes is not clear.

"In the pituitary there was a dose-related increase in the severity of cellular hypertrophy of pars distalis cells in males only. Focal or diffusely distributed hypertrophic cells were present in male rats of all groups, including the controls. In controls and low-dose animals this phenomenon occurred in about similar incidences and only to a very slight degree, while in the higher dose groups (from 750 ppm and on) the cellular hypertrophy became increasingly accentuated. Distinct evidence of degeneration was absent."

The following information was presented in the submission with regard to the histopathologic findings from the 18-month segment of the chronic oral feeding study in rats:

". . .[There is] a dose-related trend in the incidence and severity of diffuse interstitial cell proliferation and nodular interstitial cell proliferation in the testes. In addition, there is now a dose-related trend in the incidence of Leydig-cell tumors in the testes."

The submitting company also provided the following information concerning the conduct and interim (week 0 to 13) results of a 1-year oral feeding study in dogs:

"In the present study four groups of beagle dogs, each consisting of four males and four females, are treated with the test substance at the dietary concentrations of 0 (control), 400, 800, or 2400 ppm. The study was started on September 20, 1984.

"One male dog in the top-dose group showed a bad health condition from week 9 and onwards. The animal showed severe anorexia and became very emaciated. Sometimes a green discharge from the anus was observed. In week 9 also signs of pain were noticed. This dog was killed in week 9. One male dog in the mid-dose group also showed signs of emaciation from week 8 onwards. Otherwise, no treatment-related changes were observed with respect to behaviour and condition.

"The male dog of the high-dose group which had to be killed in week 9 because of a very bad health condition showed the following gross findings: enlarged and green lymph nodes, markedly involuted thymus, cholelithiasis [(gall stones)], haemorrhagic nodule (diam. 1 cm) on the left hind leg, [and] several petechiae [(small bruises)] on this leg.

"Upon microscopic examination several histopathological lesions were observed. Perivasculitis was found of vessels, mainly arteries, in the mediastrum, pelvic and scrotal region, and of some coronary vessels. Several thrombi of amorpheus, eosinophilic material with polymorphonuclear inflammatory cells were found intravascularly. The liver showed slight congestion and slight accumulation of brown pigment. All lymph nodes examined were inflamed. . . . One testis showed coagulation necrosis. Aspermatogenesis was found in the contralateral testis. The thymus was atrophic and marked cell depletion was found in the T-cell dependent areas of the peripheral lymphoid tissues."

The submitter also provided a report that contained the following information from a rabbit embryotoxicity/teratogenicity study:

"Suspensions of [the subject chemical] in 1% aqueous gum tragacanth were administered [from days 6-19] to pregnant New Zealand White rabbits by intra-oesophagic intubation at dose levels of 0, 5, 10, 30 and 100 mg/kg body weight/day."

"The administration of [the test substance] did not induce any abnormalities in behaviour. Haematury was observed in a considerable number of rabbits of the 10, 30 and 100 mg/kg dose groups. In the 5 mg/kg dose group, only one rabbit revealed occult blood in the urine on day 27 of pregnancy only.

"[The] maternal performance was comparable in all groups; the fertility indices ranged from 80.9 in the 30 mg/kg dose group to 100 in the 100 mg/kg dose group. During the study one or two rabbits in each group had an abortion; total litter resorption occurred in one or two rabbits of each group except the highest dose group. Gestation indices ranged from 81.3 to 95.0 and were all within the normal range.

"[Maternal] body weight and food intake were not affected by [the test substance]. Autopsy findings, organ weights and litter data did not reveal any embryotoxic or foetotoxic effect of [the test chemical].

"Upon foetal examination, no compound related visceral malformations, anomalies or variants were observed. Microscopic examination of foetal skeletons revealed skull bone, rib and vertebral malformations in foetuses of the high-dose group that were not observed in any of the other groups. Further, the number of foetuses with supernumerary ribs was significantly increased in the high-dose group as compared to the controls.

"It was concluded that under the conditions of the present embryotoxicity/teratogenicity study: a. the no-toxic-effect level of [the test substance] for pregnant rabbits is less than 5 mg/kg body weight/day; b. 100 mg/kg body weight/day [of the test substance] is embryotoxic/teratogenic; c. the no-embryotoxic/teratogenic-effect level of [the test substance] is 30 mg/kg body weight/day."

The submitting company also provided results of a two-generation reproduction study conducted in male and female rats. In its submission, the company reported that:

"Groups of male and female rats were administered 0, 500, 750, or 2250 ppm [of the test substance] in their diets. The study is a two generation study with two litters per generation and the in-life portion has ended. [The test chemical] appears to have affected the mating and fertility indices in the second generation. . . . The histopathology findings from . . . [this] reproductive study corroborate and extend the findings from the chronic oral toxicity and carcinogenicity study [in rats]."

Finally, the submitter provided the following information with regard to the conduct and results of a 21-day sub-acute dermal toxicity study in rabbits:

"Three groups of male and female rabbits were treated dermally [with the test substance) for three weeks, five days a week . . . [with] daily doses of [0,] 10, 30 or 100 mg/kg bodyweight.

"Significant treatment-related effects were observed in males only. They consisted of decreased growth, food intake and food efficiency, [reduced spermatogenesis,] and histopathological changes in the testes with 30 and 100 mg/kg/day and of decreased testes weights with 100 mg/kg/day.

"It was concluded that 10 mg/kg/day is a no-adverse-effect dose of [the test substance] for male albino rabbits. . . . The highest test dose of 100 mg/kg/day did not cause any significant adverse effects in female albino rabbits. Therefore, it was concluded that under the conditions of the study [the test chemical] is considerably more toxic for male than for female albino rabbits."

Submission Evaluation

The submitted information relating to the chronic oral (feeding) study in rats indicates that exposure to the subject chemical has resulted thus far in a dose-dependent increase in the number of rats with Leydig-cell tumors (0 in the controls, 1 at 500 ppm, 3 at 750 ppm, 4 at 2250 ppm, and 12 at 4500 ppm). Concurrently, there was a marked dose-related increase in nodular interstitial cell proliferation in the testes and an increased severity of diffuse interstitial cell proliferation in the testes. Based on a review of the submitted interim data, the submitting company's stated concern that the subject chemical may pose an oncogenic risk is clearly correct.

In addition, it is clear from the submitted data that exposure to the subject chemical can result in serious adverse effects in the male reproductive system (e.g., a dose-related incidence of rats with Leydig-cell tumors, a dose-related increase in interstitial cell proliferation in testes, reduced spermatogenesis, interference with reproductive performance such as mating and fertility). In addition, exposure to the test substance appears also to result in developmental toxicity at doses below those that cause the forms of maternal toxicity usually observed in teratologic studies (e.g., decreased maternal body weight and food consumption; increased liver weight). It should be noted, however, that the hematuria reportedly observed in the dams in the teratology study needs to be examined in further detail in order to determine the impact of this effect, if any, on the developing fetuses.

In order for EPA to determine the overall significance of the reported toxic effects of this chemical, a complete copy of the final report from each of the cited studies is needed.

Current Production and Use

In view of the fact that the submitting company has claimed the exact chemical identity of the test substance to be TSCA CBI, no information concerning the chemical's TSCA Inventory status or production/importation volumes will appear in this status report.

In its submission, the company stated non-confidentially that the dichlorophenyl-alkoxyalkyl-oxoheteromonocycle is a pesticide with worldwide distribution that was undergoing field testing in the United States.

Comments and Recommendations

In its submission, the submitting company reported that all U.S. field testing with the subject chemical has been halted. The submitter also reported that "all Cooperators have been notified by letter that further field testing [with the chemical] is being curtailed." Finally, the submitting company reported that it plans no further development of the compound.

The Chemical Screening Branch (CSB/ECAD/OTS/OPTS) has notified the Office of Pesticide Programs (OPP/OPTS) about the reported information. OPP is now reviewing the information to determine the applicability of, and the need for action under, the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

a) The Chemical Screening Branch (CSB/ECAD/OTS) will request the submitting company to provide to EPA a complete copy of the final report (including the actual experimental protocols, data, statistical analyses (if performed), etc.) from each toxicologic study cited in the company's TSCA Section 8(e) filing on the subject chemical.

   In view of the Agency's general interest in corporate actions that are taken on a voluntary basis in response to chemical toxicity and/or exposure information, the submitting company will be requested to describe those actions the company has taken to notify its workers and others about the reported toxicologic 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.

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: SEP 5 1985

SUBJECT: Status Report* 8EHQ-0785-0563 Approved: 9/06/85

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 Dow Corning Corporation submitted the following information concerning the conduct and results (received verbally by the company from the performing laboratory) of a 5-day rat inhalation study of tetramethoxysilane (CAS No. 681-84-5):

"Treatment: 10 male & 10 female Sprague Dawley rats per dose level were exposed for 5 days, 6 hours per day to silicic acid tetramethyl ester [tetramethoxysilane] at chamber vapor concentrations of 5, 12, and 20 ppm. [The] chamber temperature and relative humidity were maintained within acceptable limits during treatment.

"Clinical Observations: No mortality was observed in any of the treated groups. No adverse effects of the eye were observed.

"Gross Pathology: Seventeen of the 20 rats in the high dose (20 ppm) group exhibited moderate lung hemorrhage with no other adverse effects found. Fifteen of 20 rats in the 12 ppm dose group exhibited mild lung hemorrhage with no other adverse effects found. No effects were found in 20 of 20 rats in the low (5 ppm) dose group."

[The submitter reported that this 5-day rat inhalation study was conducted in order "to establish dose levels for a 28-day inhalation study."]

The Dow Corning Corporation submitted the following background information concerning the known toxicity of the tested chemical and the company's rationale for submitting the 5-day inhalation study results to EPA 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.

". . .[Tetramethoxysilane] has been . . . in commerce for many years and has been regarded as hazardous and a severe eye irritant that should be handled with appropriate care. Information available to . . . [Dow Corning] indicates [that the] known health effects are due to vapor exposure and have identified the eye as the most sensitive target site. Human health effects considered in the current TLV [*] standards estimated air concentrations of 200 to 300 ppm were required for 15 minutes to produce corneal damage and that exposure to 1,000 ppm were required to produce injury requiring hospitalization. It has been reported that lung function tests were always normal if corneal damage was absent. This observation was based on a designed acute vapor study in guinea pigs."

[*] In its Section 8(e) submission, Dow Corning reported that the "current industrial hygiene standards, as established by the American Conference of Governmental Industrial Hygienists, for . . . [tetramethoxysilane] are represented by the following:"

Threshold Limit Value (TLV) for an 8-hour Time Weighted Average (8-hour TWA) = 1 ppm (approximately 6 mg/cubic meter of air)

Threshold Limit Value (TLV) for a Short Term Exposure Limit (STEL) = 5 ppm (approximately 30 mg/cubic meter of air)

According to Dow Corning, the company's use of tetramethoxysilane "is carried out with strict environmental controls appropriate to the TLV limit of 1 ppm by persons having a high degree of technical training." In addition, it was reported that "there have been no adverse health effects experienced at Dow Corning."

Submission Evaluation

Although the observed lung hemorrhages are consistent with the adverse effects seen in the lungs of animals exposed via inhalation to vapors of tetraethoxysilane or trimethoxysilane, it is quite noteworthy that the observed lung hemorrhages did not occur in conjunction with adverse eye effects. Based on the submitted findings, it appears that the lack of the ocular effects does not preclude the possiblity that toxic effects could occur elsewhere in the body.

In order for EPA to evaluate better the overall significance of these findings, Dow Corning should be asked to submit a complete copy of the final report (including the actual experimental protocol, data, statistical analyses (if performed), etc.) from the company's 5-day and 28-day tetramethoxysilane inhalation studies in rats.

Current Production and Use

A review of the production range (includes importation volumes) statistics for tetramethoxysilane (CAS No. 681-84-5), which is listed in the initial TSCA Inventory, has shown that from 0 to 1000 pounds were reported as produced/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 information that would compromise TSCA CBI. The data submitted for the TSCA Inventory, including the production range data, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

In its submission, Dow Corning reported that tetramethoxysilane "is an industrial chemical that is used as an intermediate or in chemical processing." According to secondary literature sources, tetramethoxysilane applications include the chemical's use in glass-frosting and in manufacture of specialty glass for fiber optics and solar materials.

Comments/Recommendations

In its submission, Dow Corning stated that the company is in the process of notifying other organosilicon chemical manufacturers about the reported toxicologic findings. Dow Corning stated also that, when available, a copy of the final report from the 5-day rat inhalation study would be sent to EPA.

It should be noted that EPA's Office of Toxic Substances (OTS) has received a number of Section 8(e) and "For Your Information" (FYI) submissions containing toxicity and/or exposure information on organosilanes. In particular, it should be noted that EPA has received a Section 8(e) submission (8EHQ-0680-0347 et seq.) on trimethoxysilane, a structural analog to tetramethoxysilane. The Chemical Screening Branch (CSB/ECAD/OTS) has prepared a Chemical Hazard Information Profile (CHIP) on 3,4-epoxycyclohexylethyltrimethoxysilane and is now considering the preparation of CHIPs on other organosilanes. The Risk Analysis Branch (RAB/ECAD/OTS) is currently evaluating available toxicity and exposure data on 3,4-epoxycyclohexylethyltrimethoxysilane. The New Chemicals Program in OTS has also been evaluating available toxicity and exposure data on organosilanes.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will request the Dow Corning Corporation to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol(s), data, statistical analyses (if performed), etc.) from the 5-day inhalation study and the 28-day inhalation study (when completed).

In view of the Agency's general interest in corporate actions that are taken on a voluntary basis in response to chemical toxicity or exposure information, the Dow Corning Corporation will be asked to describe the actions the company has taken to notify its own workers about the reported toxicologic findings for tetramethoxysilane.

b) The Chemical Screening Branch will review the submitted data in order to determine the need for further OTS assessment of tetramethoxysilane.

c) The Chemical Screening Branch will transmit copies of this status report to OSHA, NIOSH, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, ORD/EPA, and OAR/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 6 1985

SUBJECT: Status Report* 8EHQ-0885-0564 S Approved: 9/9/85

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, a product trade name, and the names of two other companies to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS) will request the submitter to substantiate all of these confidentiality claims.

Submission Description

The submitting company provided the following information concerning the company's detection of three nitrosamines (N-nitrosodiethanolamine, N-nitrosodimethylamine, and N-nitroso-morpholine) in coolants from automobiles manufactured by two companies whose identities were claimed to be TSCA CBI:

". . .[The submitting company] has obtained analytical data which indicate that nitrosamines are formed in automobile coolants containing triethanolamine even without nitrite added to the coolant. These samples were obtained from automobiles at dealerships in the U.S. The automobiles that were sampled did not contain . . .[the submitter's coolant] product.

"Although the presence of nitrosamines in automotive coolants has been reported in the literature, it has been reported that coolants containing triethanolamine can contain nitrosamines when nitrites are not added to the coolant. . . .[T]he levels found in these samples were low, less than 5 ppm. . . . The level of nitrosamines in the samples would be expected to be much higher if the automobiles had been "topped up" with a nitrite containing coolant. A great deal of coolant sold in the aftermarket contains nitrite and nitrite is widely used in supplemental inhibitors."

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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 formation of nitrosamines when primary, secondary, or tertiary amines react with nitrogen oxides and/or nitrites is well known. The International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence of animal carcinogenicity for serveral N-nitroso compounds including N-nitrosodiethanolamine, N-nitrosodimethylamine, and N-nitrosomorpholine. N-Nitrosodiethanolamine, for example, has been reported to be carcinogenic to animals following oral administration and subcutaneous injection and N-nitrosodimethylamine has been shown to be carcinogenic in several animal species.

"Use of nitrites and/or amines, primarily triethanolamine, in automobile coolants has been reported in Sweden. There an attempt was made to standardize automotive coolants because it was recognized that nitrosamines could be formed when automobiles containing a triethanolamine-based fluid were "topped up" with a nitrite-type of fluid. . . . Triethanolamine was voluntarily removed from coolants in Sweden.

"This matter was also acknowledged in France; but no industry standard has been established. The presence of nitrosamines in several leading French brands of antifreeze was reported in the literature. . . . [With regard to a provided copy of a French article, the submitting company noted that] the authors recommended that the use of sodium nitrite be abandoned as an anticorrosion additive.

". . . [The submitting company's] analytical data indicate that the conclusion of the French authors does not completely address the issue. The data indicate that nitrosamines are formed in triethanolamine based automobile coolants even when no nitrite was added to the coolant. Analysis of 17 samples of automotive coolant obtained from . . . [two manufacturers'] vehicles at dealerships in the U.S. indicated low levels of nitrosamines, primarily N-nitrosodiethanolamine. . . .

". . .[The submitter's] analysis indicates that . . .[the two car manufacturers'] use triethanolamine type coolants in many of their vehicles. It is speculated that exhaust gasses leaking into the coolant past the head gasket are the source of the nitrosating agent. It is well known that combustion gasses in automobile engines contain nitrogen oxides.

"Although . . .[the submitting company] does not believe that the presence of these low levels of nitrosamines in the automobile coolants constitutes a substantial risk to health or the environment, [the submitting company is providing] this information to advise EPA of a potential problem. There could be some [nitrosamine] exposure to mechanics at radiator repair shops, import car dealerships, and to the "do it yourselfer" coming into contact with nitrosamines formed in these coolants when "topped up"."

Submission Evaluation

EPA's concern about human exposure to nitrosamines is well known and is based mainly on a large number of animal studies in which nitrosamine exposure by a variety of routes resulted in cancer.

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 nitrosamines. In addition, the Chemical Screening Branch has prepared Chemical Hazard Information Profiles (CHIPs) on several nitrosamines.

Immediately upon receipt of this Section 8(e) submission, the Chemical Screening Branch (CSB/ECAD/OTS) provided copies of the notice to the Risk Analysis Branch (RAB/EACD/OTS) and Existing Chemical Control Branch (ECCB/CCD/OTS) for inclusion in the on-going OTS evaluation of available toxicologic and exposure data on nitrosamines. It should be noted that in September 1984, EPA published two "Chemical Advisories" that outline EPA's concerns about nitrosamines in metalworking fluids. Copies of these advisories may be obtained by calling toll free at 800-424-9065 or in the Washington, D.C. area at (202)-554-1404, or by writing to:

Ed Klein, Director
TSCA Assistance Office (TS-799)
Office of Toxic Substances (OTS)
Environmental Protection Agency
401 "M" Street, S.W.
Washington, D.C. 20460

Comments/Recommendations

In its Section 8(e) notice, the submitting company stated that it was notifying the two automobile manufacturers whose cars had been found to contain nitrosamines in their coolants.

a) 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, RAB/ECAD/OTS and ECCB/CCD/OTS. Copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: SEP 20 1985

SUBJECT: Status Report* 8EHQ-0885-0565 S

Approved: 9/23/85

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 identities of several chemical substances and products to be TSCA Confidential Business Information (TSCA CBI). The staff of the Information Management Division (IMD/OTS) will ask the submitting company to substantiate these confidentiality claims.

Submission Description

The submitting company provided the following information with regard to the results of acute animal studies designed to determine the level of "immersion-type dermatitis" associated with chemical substances or mixtures:

> "The reaction product of 1 mole of succinic anhydride [(CAS No. 108-30-5)] and 1 mole of Jeffamine D-2000 [an amine terminated polypropylene glycol; CAS No. 9046-10-0)] in combination with other undetermined chemicals, has been found to cause eye damage in guinea pigs following immersion to aqueous solutions. This is, to the best of . . . [the submitting company's] knowledge, a new chemical which is not listed on the TSCA Inventory.
>
> "The eye damage was observed during preliminary testing to create a new product. This laboratory testing involved a de minimus amount of product. As a part of the evaluation process, the mixture was tested on guinea pigs for skin irritation potential. At the conclusion of the test, all the test animals were found to be blind."
>
> "Subsequent tests established that the presence of the subject chemical is necessary to create the observed response; however, it alone, in the absence of 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.

other mixture components [(i.e., alkanolamines, a biocide package, an alkoxyamine, and mixed carboxylic acids)] did not cause eye damage. In none of these cases was skin irritation observed, suggesting that some other mechanism than corrosivity was involved.

"Again, these results seem to indicate that the combination of the subject chemical with at least one other component is the cause of the observed effects. There has not been time to determine which of the other chemicals present might be responsible for the observed effect. . . . ."

The submitter also provided a copy of a standard protocol used in the dermal exposure studies using guinea pigs. The following is an excerpt from the submitted protocol:

"All animals are ear-tagged with consecutive numbers. Each animal is placed in a stainless steel retainer and then put in a 600 ml graduated heavy-walled beaker containing the test material (approximately 275 ml). The beakers are placed in the immersion tank which is a constant temperature (40°C) water bath.

"The animals are placed in these retainers for four and one-half hours on three consecutive days. The test solutions are changed after 2.25 hours on each test day. At the end of the four and one-half hours, the animals are removed, washed, dried with a towel, and returned to their cages.

"Three days after the last day of the test, the [guinea] pigs' abdomens are shaved with the animal clippers and given ratings, depending on the condition of the skin of the abdomen. The ratings are from one to ten, and the higher the rating, the better the condition of the abdominal skin."

Submission Evaluation

Although the submitted information indicates that dermal exposure to the "new" chemical in combination with one or more other substances can cause blindness, a complete copy of the final report (including the actual experimental protocol(s), data, results of histopathologic examinations, statistical analyses, etc.) from each of the performed studies is needed in order for the Agency to determine the overall significance of the reported toxicologic findings.

Current Production and Use

A review of the non-confidential version of the initial TSCA Inventory shows that the reaction product of 1 mole of succinic anhydride and 1 mole of Jeffamine D-2000 is not listed.

The submitting company claimed the proposed use of the product containing the new chemical to be TSCA CBI. The Information Management Division (IMD/OTS) will also ask the submitter to substantiate this confidentiality claim.

Comments/Recommendations

In its TSCA Section 8(e) notice, the submitting company stated that based on the observed toxicologic effects, the company has "eliminated plans to pursue the use of the new chemcal."

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the submitting company to provide to EPA complete copies of the final reports (including the actual experimental protocols, data, the results of gross and histopathologic examinations, statistical analyses, etc.) from all company studies designed to determine the toxicologic properties of the "new chemical" alone or in combination with other chemicals/products.

   In view of EPA's general interest in company actions taken on a voluntary basis in response to chemical toxicity/exposure information, the submitter will be requested to describe the actions that the company has taken to notify its employees about the reported findings.

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

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, ORD/EPA, and OAR/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 9 1985

SUBJECT: Status Report* 8EHQ-0985-0566 Approved: 9/9/85

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 submitted a written followup report concerning an "emergency incident of environmental contamination" (EIEC) that occurred at the Union Carbide South Charleston (West Virginia) plant on August 13, 1985. According to Union Carbide, the incident involved the accidental release of UCON Lubricant LB-250 (a polyalkylene glycol; CAS No. 9003-13-8), sulfuric acid (CAS No. 7664-93-9), isopropyl alcohol (CAS No. 67-63-0), and various reaction products of these substances. In its letter, Union Carbide presented the following information with regard to the events surrounding this incident:

> "On August 13, product refining was being conducted at the South Charleston plant where the polyalkylene glycol is manufactured. The polyalkylene glycol is "purified" by an ion exchange process. Sulfuric acid accidentally entered the vessel containing the ion exchange resin and the polyalkylene glycol in isopropyl alcohol. At about 8:00 P.M. on August 13, [the] conditions had reached a point where [the] release of material from the reaction of the sulfuric acid with the polyalkylene glycol and isopropyl alcohol occurred. At approximately 8:30 P.M., operators activated the water deluge system to help knock down the vapors. The reaction continued until about 9:00 P.M. when the safety valve on the ion exchange bed system reseated.
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> "During the release, approximately 3500 lbs. of chemicals were released to the atmosphere. In addition, about 400 lbs. of liquid chemicals were released which went into the Kanawha River. Approximately 1220 lbs. of additional liquid chemicals entered the process sewer. The liquid

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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.

chemicals were diluted with thousands of gallons of water from the deluge system. To the extent that [a] chemical analysis (gas chromatography) of residual material in the reactor system is indicative of what was released, the materials which entered the atmosphere were principally: propylene [(CAS No. 115-07-1)] from dehydration of isopropyl alcohol, possibly other olefins, propionaldehyde [(CAS No. 123-38-6)] from acid-catalyzed degradation of the polyalkylene glycol, and a trace amount . . . of sulfuric acid. The liquid chemicals [that were] released to the Kanawha River and the process sewer were primarily the polyalkylene glycol and . . . [isopropyl alcohol]. [The Union Carbide Corporation reported in its submission that the "analytical information of residual material may be only partially relevant to a full understanding of the chemicals released."]

"Nine employees at the plant during the incident later reported to the plant dispensary. Of these [nine], seven complained of irritation to the eyes, nose, throat and/or skin. The other two employees had no complaints but reported exposure to the release. A tenth employee who was at home in an adjoining town reported to the dispensary the next day with a complaint of irritation to the eyes, nose, throat and skin. The irritation was judged to be non-serious, and the complaining employees were treated and released. Another six residents of the area went to area hospitals or urgent care centers shortly after the incident with similar complaints of irritation, and were also treated and released. The nature of the material released is such that no chronic effects in persons exposed and no long-term environmental damage are expected as a result of the incident. . . .[Union Carbide has] had no reports of ecological damage in the Kanawha River or adjacent areas."

Comments/Recommendations

In its submission, Union Carbide stated that it is preparing a full internal report on the incident and that the report will be submitted to the Occupational Safety and Health Administration (OSHA). In addition, Union Carbide stated that this incident was not reported immediately by phone to the National Response Center under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) "because the information available at the time of the incident, and that available . . .[at the time of the Union Carbide's written TSCA Section 8(e) submission], does not indicate the release of a reportable amount [(i.e., a reportable quantity or RQ)] of a chemical substance subject to the reporting requirements of CERCLA." It should be noted, however, that Union Carbide did notify the EPA Region III Office by phone within 24 hours of the incident in accordance with the "emergency incident of environmental contamination" (EIEC) reporting procedures that

are outlined in Parts IV and IX 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). Finally, Union Carbide reported that the company will keep EPA apprised of additional findings concerning the incident.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will request the Union Carbide Corporation to provide to EPA a full copy of the company's internal report concerning this incident.

b) The Chemical Screening Branch will transmit copies of this status report to OSHA, NIOSH, ORD/EPA, OAR/EPA, OSWER/EPA, OW/EPA, and to EPA's Region III Office. In addition, copies of this report will be provided to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

DATE: SEP 26 1985

SUBJECT: Status Report* 8EHQ-0985-0567 Approved: 9/27/85

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

E. I. DuPont de Nemours & Company, Inc. provided the following summarized information concerning the conduct and results of a recently performed chronic inhalation study of 1,4-dichloro-2-butene (1,4-DCB) in rats:

> ". . .[Male] rats were exposed to 1,4-DCB vapor for approximately six hours per day, five days per week at concentrations of 0 ppm, 0.1 ppm, 0.3 ppm or 1.0 ppm. Rats were exposed for 19 months and surviving rats were held without exposure for an additional five months. Compound-related nasal tumors were observed in all groups exposed to 1,4-DCB. Statistically significant increases in the incidence of nasal tumors were observed in all exposure groups for benign tumors and in the 1.0 ppm group for malignant tumors. When the incidences of benign and malignant tumors were combined, statistically significant increases were observed in the 0.3 ppm and 1.0 ppm groups. No other compound-related tumors were observed. . . . ."

In its submission, DuPont also provided the following background information concerning the company's recently conducted chronic 1,4-DCB vapor inhalation study:

> "This study was conducted as a result of the findings from a previous [chronic inhalation] study on 1,4-DCB conducted by DuPont . . . which indicated that there were statistically significant increases in the incidences of nasal tumors in [male and female rats exposed to 0.5 ppm or 5.0/2.5 ppm. ["Rats in the high concentration groups were exposed to 5.0 ppm for 30 weeks followed by 2.5 ppm for 23 weeks at which time exposures were terminated and the animals held for an additional

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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.

> 52 weeks."] Following the preliminary findings of the initial inhalation study which were reported to the [Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH), the National Cancer Institute (NCI), and the EPA] Administrator by letter dated October 7, 1977, communications were made to . . .[DuPont] employees and to other producers of 1,4-DCB. . . .[DuPont] also undertook a program to assure that workplace exposure [to 1,4-DCB] would not exceed 0.05 ppm eight-hour and twelve-hour time-weighted average."

Finally, DuPont reported that it had conducted an epidemiologic study "that followed approximately 600 workers from 1956 through 1983 for cancer incidence, and 1957 through 1980 for mortality, and did not indicate that employees are at an increased risk of developing cancer."

Submission Evaluation

The summarized information provided by DuPont concerning the two chronic rat inhalation studies indicates that 1,4-dichloro-2-butene caused 1) a dose-dependent increase in the incidence of rats with nasal tumors (benign plus malignant); 2) a statistically significant incidence of benign nasal tumors at all dose levels tested with the exception of the 5.0/2.5 ppm dose level; and 3) statistically significant increases (increasing with dose) in the incidence of malignant nasal tumors at the 0.3, 0.5, 1.0 and 5.0/2.5 ppm dose levels. In addition, it should be noted that in the earlier 1,4-DCB inhalation study, a statistically significant incidence of malignant nasal tumors had already been observed by the 11th month in rats at the 5.0/2.5 ppm 1,4-DCB dose level.

In studies conducted by Van Duuren *et al.* (Cancer Research; 35; 2553-2557; 1975), in which 1,4-DCB was tested in mice via skin application, subcutaneous injection or intraperitoneal injection, low incidences of local sarcomas were observed in the injection studies only. In reviewing the results of these mouse studies, the International Agency for Research on Cancer (IARC Monograph No. 15; August 1977) concluded that Van Duuren's data (the only oncogenicity-related data available to IARC at that time) were insufficient to allow an evaluation of the carcinogenic activity of 1,4-DCB. In light of DuPont's rat data, however, the results of Van Duuren's mouse studies cannot be discounted and, in fact, could be quite meaningful for assessing the potential oncogenic risk to humans posed by exposure to 1,4-DCB. Finally, it should be noted that 1,4-DCB has been found to be mutagenic in a number of *in vitro* and *in vivo* short-term tests, the results of which are reported in the open scientific literature.

Current Production and Use

According to secondary literature source information, commercial 1,4-dichloro-2-butene (CAS No. 764-41-0) contains from 95-98% trans- (i.e., E-) isomer (CAS No. 110-57-6) and from 2-5% cis- (i.e., Z-) isomer (CAS No. 1476-11-5). DuPont did not provide any information concerning the purity of the tested 1,4-dichloro-2-butene or the company's current production volume(s) or use(s) of the chemical(s).

The following table presents aggregated 1977 non-confidential TSCA Inventory production/importation range information for the subject chemicals: (Note: This production/importation range information does not include any data claimed as TSCA Confidential Business Information (TSCA CBI) by those person(s) reporting for the TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the data submitted for the TSCA Inventory, including the production/importation range data, are subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710)).

Chemical Name	CAS Number	Prod./Import. Range (pounds)
1,4-DCB	764-41-0	10,010,000 to 50,101,000
1,4-DCB (cis-)	1476-11-5	100,000,000 to 500,001,000
1,4-DCB (trans-)	110-57-6	100,000,000 to 500,000,000

According to secondary literature sources, the major use of 1,4-dichloro-2-butene is as an intermediate in the manufacture of chloroprene and hexamethylenediamine.

Comments/Recommendations

In its Section 8(e) submission, DuPont stated that in addition to advising DuPont workers, other 1,4-DCB manufacturers, NIOSH, OSHA and NCI about the reported toxicologic findings, DuPont's current workplace exposure limit for 1,4-DCB is being reconsidered. In addition, DuPont stated that a final report of the recent chronic 1,4-DCB inhalation study is now in preparation and when completed would be provided to EPA.

1,4-Dichloro-2-butene was included in a chlorinated alkenes "Hazard Information Review" document (IR-213; October 31, 1980) prepared under contract for the Interagency Testing Committee (ITC). It should be noted that this 1980 review fails to mention the preliminary oncogenicity findings from DuPont's first chronic 1,4-DCB rat inhalation study which were submitted to EPA, NIOSH, NCI, and OSHA by DuPont in October 1977 and published by DuPont later in 1977 (Clary, JJ; Environmental Health Perspectives; 21; 269-274; December 1977). The published preliminary oncogenicity findings from first DuPont chronic 1,4-DCB inhalation study have been cited, however, in a recent (1983) "Health and Environmental

Effects Profile" (HEEP, Number 176) prepared by EPA's Office of Research and Development (ORD) for EPA's Office of Solid Waste and Emergency Response (OSWER). Finally, Volume II of the EPA Chemical Activities Status Report (EPACASR; EPA 560/TIIS-84-001b; February 1984) shows that trans-1,4-DCB is currently regulated under the Resource Conservation and Recovery Act (RCRA) and the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA; "Superfund").

a) The Chemical Screening Branch (CSB/ECAD/OTS) will request DuPont to ensure that EPA receives a complete copy of the final report (including the actual experimental protocol, test sample purity information, results of gross and histopathologic examinations, statistical analyses, etc.) from the company's recently completed chronic inhalation study of 1,4-DCB in rats. In addition, DuPont will be requested to submit full copies of the final reports from the epidemiologic study and previous chronic 1,4-DCB rat inhalation study cited in the company's submission.

b) The Chemical Screening Branch will review the reported data in order to determine the need for further OTS assessment of 1,4-dichloro-2-butene.

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

DATE: OCT 24 1985

SUBJECT: Status Report* 8EHQ-0985-0568 S Approved: 10/25/85

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 submitting company to substantiate this confidentiality claim.

Submission Description

The submitting company provided the final report from an acute (4-hour) vapor inhalation study of an "experimental mixture" in rats. According to the submitter, the test mixture contained 50% 1,1-diethoxy-2-trimethylsilyl-1-sila-2-azacyclopentane (DETMCP; CAS No. 21297-72-3), 15% 1,1-diethoxy-2-trimethylsilyl-1-sila-2-azacyclopentane dimer (DETMCP dimer), 13% trimethylethoxysilane (TMES; CAS No. 1825-62-3; hydrolysis product of DETMCP) and 22% unidentified chemical(s). The Summary section of the submitted report contained the following information concerning the conduct and results of the performed study:

> "Five groups of 10 male and 10 female rats were exposed by nose-only inhalation for a single period of 4 hours to room air (Group 1) or to [1.78, 3.26, 8.05, or 12.98 mg/L of total] vapors of . . .[the test mixture] (Groups 2 to 5). Vapor concentrations of the major (relatively nonvolatile) component of the liquid, DETMCP, ranged from 72 ppm (0.73 mg/L) to 214 ppm (2.16 mg/L) for the various test groups. Vapor concentrations of a smaller proportion (relatively volatile) component, TMES, ranged from 218 ppm (1.05 mg/L) to 2244 ppm (10.82 mg/L). . ." [". . .[Both vapor components (DETMCP and TMES)] were monitored by gas chromatography during exposure. Most probably because of differential rates of vaporization, the ratio of these two components varied greatly with increasing concentration of the total vapor. At the low

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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.

dosage (1.78 mg/L), the ratio of DETMCP to TMES vapor was 1 to 3; at the high dosage (12.98 mg/L), the ratio was 1 to 10."] Animals were observed for 14 days after treatment and then necropsied. Lungs, liver and kidney were examined histopathologically.

"The median lethal concentration (LC50) of . . .[the test mixture] expressed in terms of total vapors was 3.7 mg/L and 4.8 mg/L for males and females, respectively, and 4.6 mg/L for combined sexes.

"Mortality in the various test groups increased with dose level except for high-dose females (214 ppm DETMCP) where mortality was 10% lower than in the group treated with 171 ppm DETMCP. This is not unusual, given the normal intersubject variability in response. Treatment-related clinical signs included respiratory rales, nasal or oral discharge, labored respiration and ataxia. The incidence, severity, and duration of these findings generally increased with dose level.

"Marked body weight loss was observed in the treated animals, and the magnitude and duration of weight loss increased with dose.

"Treatment-related gross and histopathological findings were observed in the respiratory tract of animals dying during the study and animals sacrificed after 14 days. These included tissue discoloration, fluid accumulation, intra-alveolar hemorrhage and edema in early decedents, and the incidence of these findings increased with dose level. Interstitial pneumonia accompanied by epithelial proliferation was frequently observed in late decedents and animals which survived. Lung weight was statistically increased at dose levels of 114 ppm and higher. Death was due to intra-alveolar hemorrhage associated with perivascular edema."

It should be noted that the summarized results of several acute animal toxicity studies of DETMCP were provided to the Agency on a "For Your Information" (FYI) basis (FYI-OTS-1184-0365 S). In that FYI submission, the submitting company (company name claimed as TSCA CBI) reported that additional studies would be conducted to determine 1) the LC50 of DETMCP, and 2) if any volatilization occurred during curing processes.

Submission Evaluation:

The adverse lung effects that were observed in the subject acute inhalation toxicity study are very similar to those seen in acute inhalation toxicity studies of trimethoxysilane vapors (Section 8(e) submission number 8EHQ-0680-0347 et seq.) in which the lungs of rats failed to collapse. In the present study, mottled, uncollapsed, and firm lungs were observed in all animals of both

sexes at all doses except the low dose and control groups. In addition, respiratory rales were observed in most of the animals (15/20) at the lowest dose and in all other animals at all other doses. It should be noted also that those rats surviving the 214 ppm exposure exhibited severe ataxia which disappeared on the day following exposure but eventually reappeared as moderate ataxia lasting for the duration of the study. Finally, the lungs of all treated animals were found to be hemorrhagic. This finding is consistent with those from other studies of organosilanes.

Current Production and Use

A review of the production range (includes importation volumes) statistics for trimethylethoxysilane (CAS No. 1825-62-3), which is listed on the non-confidential computerized version of the TSCA Chemical Substance Inventory, indicates that from 0 to 1000 pounds of this chemical were reported as produced and/or imported in 1977. (This information does not include any production or importation 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 submitted for the initial TSCA Inventory, including the production/importation range data, are subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710)).

According to the Information Management Division (IMD/OTS), DETMCP has been added to the non-confidential TSCA Chemical Substance Inventory.

In FYI-OTS-1184-0365 S, the submitting company reported that a mixture containing low levels of DETMCP was created for developmental purposes only. In the Section 8(e) notice, the submitter stated that the company is no longer producing the tested mixture or DETMCP.

Comments/Recommendations

EPA's Office of Toxic Substances (OTS) has received a number of TSCA Section 8(e) and "For Your Information" (FYI) submissions containing toxicologic and/or exposure information on several organosilanes. The Chemical Screening Branch (CSB/ECAD/OTS) has prepared a Chemical Hazard Information Profile (CHIP) on 3,4-epoxycyclohexylethyltrimethoxysilane and is now in the process of preparing a CHIP on organosilanes as a class. The Risk Analysis Branch (RAB/ECAD/OTS) has been evaluating available toxicologic and exposure data on 3,4-epoxycyclohexylethyltrimethoxysilane. The OTS New Chemicals Program has also been evaluating available toxicologic and exposure data on a number of organosilanes.

a) The Chemical Screening Branch will request the submitting company to provide complete copies of the final reports (including the actual experimental protocols, results of gross/histopathologic examinations, statistical analyses,

etc.) from all studies (including the volatilization study) cited in FYI-OTS-1184-0365 S. In view of EPA's general interest in company actions taken on a voluntary basis in response to chemical toxicity/exposure data, the submitter will be aksed to describe the actions the company has taken to inform workers/others about the toxicologic findings.

b) The Chemical Screening Branch will ensure that the data in this Section 8(e) submission and FYI-OTS-1184-0365 S are considered for inclusion in the CHIP on organosilanes.

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

DATE: NOV - 8 1985

SUBJECT: Status Report* 8EHQ-1085-0569 Approved: 11/14/85

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 Celanese Corporation provided standard operating procedures (SOPs) and summarized results of acute in vivo oral, dermal, and eye toxicity tests of n-octylamine (CAS No. 111-86-4). According to the submitted information, all rats (6 rats per group) died within 6 days, 1 day, and 1 day after a single oral administration of 100% n-octylamine at doses of 50, 500, or 5000 mg/kg bodyweight, respectively. The performing laboratory's report stated that no gross signs of toxicity (in terms of extreme abnormalities) were observed during the oral study. In the dermal toxicity study, 4 rabbits per group received 100% n-octylamine at doses of 200, 2000, or 3000 mg/kg bodyweight applied as a single dose to the shaved unabraded skin of the back. All rabbits in the 2000 and 3000 mg/kg dose groups died within 3 and 2 days, respectively, following exposure; hypoactivity and/or prostration were reported to have preceded death. Although no animals in the 200 mg/kg dose group died during a 7-day post-exposure observation period, necrosis was reportedly observed at the site of skin application. With regard to the eye irritation study, 0.1 ml of 100% n-octylamine placed directly into the lower conjunctival sac of one eye of each of 4 rabbits was found to be corrosive and produced severe corneal and conjunctival damage by the second day of the study.

Submission Evaluation

Many alkylamines are known to be irritating to eyes and skin, and n-octylamine demonstrated such activity in the performed studies. With regard to lethality, the provided information indicates that the dermal LD50 for n-octylamine in rabbits is between 200 and 2000 mg/kg and the oral LD50 for n-octylamine in rats is lower than 50 mg/kg. It should be noted that a chemical with an oral rat LD50 value between 5 and 50 mg/kg is regarded generally as being extremely toxic. It is important to note also that 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.

NIOSH 1981-1982 Registry of Toxic Effects of Chemical Substances (RTECS) reports that the intraperitoneal LD50 for n-octylamine in mice is 100 mg/kg. In order for EPA to evaluate better the significance of the reported toxicologic findings, Celanese should be requested to submit complete copies of the actual experimental protocols and all data from the performed studies.

Current Production and Use

A review of the production range (includes importation volumes) statistics for n-octylamine (CAS No. 111-86-4), which is listed in the initial TSCA Inventory, has shown that between 0 to 2000 pounds of this chemical were reported as produced and/or imported in 1977. This production range information does not include any production/importation 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 submitted for the TSCA Inventory, including the production range information, is subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

In the cover letter to its TSCA Section 8(e) submission, Celanese reported that n-octylamine is used primarily "as an intermediate in the manufacture of pesticides and pharmaceuticals." No information concerning the current production/importation volumes or other uses of n-octylamine was found in the secondary literature sources consulted.

Comments/Recommendations

According to the submitted SOPs, data derived from the performed studies "may serve as a basis for classification and labelling of the test material or for use in completing Material Safety Data Sheets (MSDS)."

a) The Chemical Screening Branch (CSB/ECAD/OTS) will request the Celanese Corporation to submit a complete copy of the actual experimental protocol, data, results of gross/histopathologic examinations, etc. from each acute in vivo study cited in the company's submission.

   In view of EPA's general interest in company actions that are taken on a voluntary basis in response to chemical toxicity and/or exposure information, the Chemical Screening Branch will ask Celanese to describe the actions that the company has taken to notify Celanese workers and others about the reported toxicologic findings on n-octylamine. In addition, Celanese will be asked to describe the nature and available results of all other studies that Celanese has conducted, is conducting, or plans to conduct to determine the toxicity of and/or the exposure to n-octylamine.

b) The Chemical Screening Branch will review the submitted data in order to determine the need for further OTS assessment of n-octylamine.

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: NOV 15 1985

SUBJECT: Status Report* 8EHQ-1085-0570 Approved: 11/18/85

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 Velsicol Chemical Corporation submitted draft "unaudited" results of an oral teratology study of chlordene (CAS No. 3734-48-3) in rats. The company provided the following information with regard to the conduct and results of this study:

> "In a teratology study where rats were exposed [orally via gavage] to chlordene at 0, 30, 300 or 600 mg/kg/day, a greater total number of malformations was observed in fetuses from the 600 mg/kg/day feeding level. This number of malformations was not statistically significant if the statistical unit for comparison is the litter, not the fetus. However, there was statistically significant maternal toxicity at this feeding level. This maternal toxicity was observed as weight loss and death. Neither maternal toxicity nor compound related effects were observed at the next highest [chlordene] exposure level (300 mg/kg/day)."

In addition, Velsicol provided the following summary information with regard to the conduct and results of a pilot range-finding teratology study of chlordene:

> "In a preliminary oral range-finding teratology study in rats with chlordene, overt maternal toxicity defined the limits of exposure to chlordene by female rats during the major period of organogenesis to dosages of less than 1000 mg/kg/day. A decreased maternal weight gain was observed over the entire treatment period (gestation days 6 - 16) at 500 mg/kg/day or more. Based on the results of this [preliminary range-finding teratology] study, dosage levels of 0, 30, 300 and 600 mg/kg/day were selected for the definitive teratology 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.

Submission Evaluation

Although the observed adverse developmental effects were not found to be statistically significant when the litter was used as the statistical unit, the findings were statistically significant on a fetal basis. In addition, the apparent increase in malformations together with the apparent increase in litters with two or more resorptions and the apparent increase in preimplantation losses suggests that the embryo/fetus may have been affected at the highest dose level. It must be noted, however, that 1) there was reduced maternal weight gain at the high dose level, and 2) the one maternal death that occurred in the high dose group after presumedly only three doses was most likely treatment related. It should be noted also that some of the animals in the control and treated groups had white foci on the lungs and many animals suffered hair loss from various parts of the body. Whether these findings were due to disease and what effect if any they may have had on the developmental effects observed at the high dose is not known. Although it appears that the "no-observed-effect-level" (NOEL) for chlordene when tested in pregnant rats is 300 mg/kg, it is clear that chlordene at doses of approximately 600 mg/kg and above is toxic to pregnant rats and possibly to the conceptus. It would be of interest to know if Velsicol is planning to conduct a teratology study of chlordene in another species.

Current Production and Use

A review of the production range (includes importation volumes) statistics for chlordene (CAS No. 3734-48-3), which is listed in the initial TSCA Chemical Substance Inventory, shows that no 1977 production/importation was reported or that all of the production range data provided 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 data submitted for the TSCA Inventory, including the production range data, are subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 410).

No information concerning the use(s) or current production volume of chlordene was located in the secondary literature sources consulted. In its Section 8(e) submission, Velsicol reported that worker exposure to chlordene is expected to be mimimal because chlordene is a "site limited intermediate" that is "produced in sealed reactors, pumped through a closed system into a second sealed reactor where it is converted to other chemicals."

Comments/Recommendations

Velsicol reported that as soon as the company receives the final report of the performed teratologic study of chlordene from the testing laboratory, a copy of that report will be sent to EPA.

It should be noted that EPA received previously TSCA Section 8(e) submissions concerning chlordene exposure.

a) The Chemical Screening Branch will ask the Velsicol Chemical Corporation to ensure that the Agency receives full copies of the final reports (including the actual experimental protocols, data, results of gross/histopathologic examinations, statistical analyses, etc.) from the company's preliminary range-finding and "definitive" teratology studies cited in the submission.

In view of EPA's general interest in company actions that are taken on a voluntary basis in response to chemical toxicity or exposure information, the Chemical Screening Branch will ask Velsicol to describe the nature and available results of all other studies (except those published in the open literature or those already submitted formally to the Agency) that Velsicol has conducted, is conducting, or plans to conduct to determine the toxicity of and/or the exposure to chlordene.

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

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 and OPP/OPTS/EPA. Copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: DEC 10 1985

SUBJECT: Status Report* 8EHQ-1085-0571 S Approved: 12/10/85

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. DuPont de Nemours & Company, Inc. has claimed the identity of the tested chemical substance to be TSCA Confidential Business Information (TSCA CBI). The company did state non-confidentially that the chemical was an "aromatic diamine" and that the chemical was the subject of a Premanufacture Notice (PMN 85-335) submitted to EPA under Section 5 of TSCA.

Submission Description

E. I. DuPont de Nemours & Company, Inc. (DuPont) provided the following summary information concerning the conduct and results of a recently performed sub-acute inhalation toxicity study as well as previously conducted toxicity studies of the aromatic diamine:

> "Prior to animal testing, the substance was mechanically pulverized to produce respirable particles. During the study, rats were exposed to the aromatic diamine for six hours per day, five days per week for two weeks to mean atmospheric concentrations of 0, 5.1, 23 or 98 mg/m^3. The dusts generated for the animal exposures were highly respirable (mass median aerodynamic diameters ranged from 2.2-2.9 um).
>
> "Clinical signs after exposure and after a fourteen-day post exposure recovery period were unremarkable at all levels of exposure. However, [the] histopathological examination has shown compound-related effects on the eyes, liver, spleen and adrenal glands. In the eyes, bilateral chronic choroiditis and retinal disorganization (retinopathy) were observed at all levels of exposure.

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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 earlier testing as reported with the PMN [(PMN 85-335)], it was determined that the aromatic diamine was mutagenic to Salmonella bacterial strains TA-98 and TA-100. Additional testing [conducted] with a purified sample, however, has shown that the aromatic diamine is not mutagenic in the same bacterial strains. Irritation tests showed that the chemical is not a skin irritant but is a moderate eye irritant."

It should be noted that copies of the final reports of the above referenced "earlier" toxicologic studies were submitted to EPA in conjunction with PMN 85-335.

Submission Evaluation

The submitted summarized information indicates that the tested aromatic diamine is neurotoxic, producing inflammation of the choroid layer of the eye and pathologic changes in the retina. Although these adverse effects were seen in all animals at all doses administered, the effects were delayed at the lowest dose (5/5 animals had developed choroiditis and retinopathy by the end of the two week recovery period). It is important to note also that neither a "no-observable-effect-level" (NOEL) nor a minimally toxic dose level for the aromatic diamine was found in the performed study.

The adverse eye effects reportedly observed in DuPont's study are consistent with the adverse eye effects found in animals exposed to certain aromatic diamines. In fact, a number of aromatic diamines have been used to produce the laboratory animal model for retinitis pigmentosa, a principle cause of human blindness. It should be noted that while cats and monkeys have been found to be typically susceptible to the retinopathic effects caused by these chemicals, rats are generally refractory to such effects. Also, exposure to certain aromatic diamines has been reported to result in visual disturbances in humans.

Current Production and Use

In its Section 8(e) notice, DuPont reported that a "specially ground material was required to obtain a sample with sufficient particles of a respirable range to enable the [sub-acute inhalation toxicity] test to be conducted in a meaningful manner." DuPont stated also that "it is highly unlikely that a substantial level of respirable [aromatic diamine] dust would be encountered in the manufacture and use of this material." According to the non-CBI version of PMN 85-335, the aromatic diamine is a "light cream color powder" and is "used entirely for the manufacture of monomer precursor at a DuPont site." The non-CBI version of PMN 85-335 also presented the following information with regard to the aromatic diamine manufacturing process:

"The . . . [aromatic diamine is produced at] semi-works facilities that are used for a number of similar chemicals. Exhaust ducts and shields are provided [in order] to minimize potential operator exposure. Personal protective clothing, hard hats, and safety glasses are required at all times in the operating areas. Full face shields, aprons, and gloves are also required while handling liquid chemicals or the [aromatic diamine] product. Other special handling precautions are used in full accordance with each raw material safety data sheet. The reaction is carried out in a glass lined vessel under a hydrogen atmosphere. Rupture discs and exhaust vents protect the operator and equipment from accidental over-pressure. All water soluble wastes from the operation are diluted to low concentration and sent to the site waste treatment area. Solids and catalysts are recovered or incinerated. The product is dried to remove excess fluid and packaged in plastic bags inside fiber drums. Rubber gloves, apron, air mask, and face shield are required to minimize operator exposure."

According to the Information Management Division (IMD/OTS), EPA has not as yet received a "Notice of Commencement of Manufacture" (NOC) for the aromatic diamine.

Comments/Recommendations

In its Section 8(e) submission, DuPont reported that the company plans to notify DuPont "employees, suppliers, and those customers or users, as appropriate, that are doing research or development using materials containing the aromatic diamine." In addition, DuPont reported that the company plans to conduct an industrial hygiene monitoring study.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask DuPont to provide to the Agency a complete copy of the final report (including the actual experimental protocol, data, results of statistical analyses, results of gross and histopathological examinations, etc.) from the two-week inhalation study of the aromatic diamine in rats. In addition, DuPont will be asked to submit, when available, a complete copy of the results of the planned industrial hygiene monitoring study cited in the submission.

   In view of EPA's general interest in company actions that are taken on a voluntary basis in response to chemical toxicity or exposure information, the Chemical Screening Branch will ask DuPont to describe the nature and available results of all studies (other than those already submitted to EPA) about which the company is aware or that the company has conducted, is conducting, or plans to conduct to determine the toxicity (e.g., neurotoxicity, teratogenicity, carcinogenicity) of or the exposure to the aromatic diamine.

b) As was the case with DuPont's intial Section 8(e) submission on the aromatic diamine, the Chemical Screening Branch will immediately forward all of the reported information to the Existing Chemical Control Branch (ECCB/CCD/OTS).

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: OCT 30 1985

Approved: Merenda 11/1/85

SUBJECT: Status Report* 8EHQ-0585-0572 and 8EHQ-0985-0572 Followup

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

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

Submission Description

In a "For Your Information" (FYI) submission (FYI-OTS-0585-0408), the Union Carbide Corporation reported that it had been notified informally about the findings from another company's inhalation teratology study of 2-methoxy-1-propyl acetate in pregnant rabbits. In its initial FYI submission, Union Carbide provided the following information concerning the results of this, as well as other, teratologic studies of 2-methoxy-1-propyl acetate:

> ". . . [A] strong teratogenic effect was observed when pregnant rabbits were exposed [by inhalation] to 545 ppm of 2-methoxy-1-propyl acetate and . . . no effects were observed at exposures of 145 ppm and 36 ppm. There was no evidence of maternal toxic effects at any of these exposure levels. A dermal teratology study was also conducted on the acetate on rabbits at dosage levels of 1000 and 2000 mg/kg body weight with no indications of adverse effects on the mothers or on the developing offspring. In addition, a rat inhalation teratology study was conducted with evidence of maternal toxicity and embryofetal toxicity at an air concentration of 2710 ppm, but no evidence of adverse effects was noted at two lower concentrations, 545 and 110 ppm."

In its FYI submission, Union Carbide stated that the company had "received confirmation of . . . [the reported] information via telephone conversations with the firm which conducted the [rabbit inhalation teratology] study, BASF [(BASF Aktiengesellschaft)], Ludwigshafen, West Germany." Union Carbide stated also that a copy of the study report was requested but may not be received "until the results have been published in the open literature."

Union Carbide also provided the following additional information with regard to 2-methoxy-1-propyl acetate:

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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-[M]ethoxy-1-propyl acetate is the minor component of the two isomers present in [the] propylene glycol monomethyl ether acetate currently marketed in the United States by Union Carbide and others, and commonly referred to as PM Acetate (CAS No. 108-65-6). Commercial PM Acetate in . . . [the U.S.] contains approximately 3 to 5 percent of the 2-methoxy-1-propyl [acetate] isomer, the principal isomer being 1-methoxy-2-propyl acetate. Although PM Acetate has not, to the best of . . . [Union Carbide's] knowledge, been subjected to inhalation teratology studies, the parent glycol ether has been tested and found to be free of teratogenic effect." (See reference on the last page of this status report.)

"A considerable amount of data exist to indicate that the acetate is readily hydrolyzed in the body to produce the parent glycol ether and that consequently the toxicological effects of the two - - [the] glycol ether and its ester - - are considered comparable. Thus, [the] available data support the view that PM Acetate is likewise free of teratogenic effect."

Finally, Union Carbide provided the following information with regard to the company's views concerning the TSCA Section 8(e)-applicability of findings contained in this FYI submission:

"To determine whether the new data from the BASF study might provide a reasonable basis to infer a substantial risk of injury of health, in contradiction to the best information hitherto available, all details of the study and the findings will have to be analyzed. If the conclusion presented in the preliminary communication is supported by the basic data which are not yet available to us, we believe the information is reportable under Sec. 8(e) of the Toxic Substances Control Act. Union Carbide does not consider it appropriate to make a conclusion of substantial risk at this time."

Following a review of the summary information presented in Union Carbide's initial FYI submission, EPA informed Union Carbide in writing (EPA letter dated August 12, 1985) that EPA believed that the BASF inhalation teratology study findings (about which Union Carbide had been notified informally and which were subsequently confirmed by Union Carbide via phone with BASF in West Germany) constituted "substantial risk" information and, as such, should have been reported formally by Union Carbide to EPA under Section 8(e) of the Toxic Substances Control Act (TSCA). In that August 12, 1985 letter, the Union Carbide Corporation was requested to provide additional information concerning the company's rationale as to why the subject teratology findings were not submitted to EPA under TSCA Section 8(e).

In a letter dated September 13, 1985 (FYI-OTS-0985-0408 Followup Response), Union Carbide responded to EPA's questions/statements concerning the TSCA Section 8(e)-applicability of the findings from BASF's inhalation teratology study of 2-methoxy-1-propyl acetate in rabbits. In this followup response, Union Carbide reiterated its original position with regard to the TSCA Section 8(e)-applicability of the subject teratologic findings. In addition, Union Carbide reported that the company first learned about the BASF rabbit inhalation teratology study findings via a telex message from BP Chemicals (London, England). In order to obtain additional information about the BASF findings, Union Carbide stated that the company then placed a phone call to BASF in West Germany. In its followup reponse, Union Carbide provided a 4-page summary prepared from "rough notes" taken during Union Carbide phone conversations with BASF and other foreign and U.S. chemical companies. The following excerpt is from that submitted summary and relates specifically to a phone conversation between the Union Carbide Corporation's Assistant Director of Corporate Applied Toxicology and a BASF toxicologist in West Germany:

> ". . .[BASF's toxicologist] said that BASF had conducted both a dermal and an inhalation teratology study in rabbits of . . .[2-methoxy-1-propyl acetate]. The dermal study was conducted at dosage levels of 1000 and 2000 mg/kg body weight/day. No effects were seen in dams or fetuses. The inhalation study was conducted at exposure concentrations of 36, 145 and 545 ppm. At the highest exposure level all fetuses had malformations in the absence of maternal toxicity. Both visceral and skeletal malformations were seen including cardiovascular defects and malformations of the extremities. No teratogenic effects were seen at the lower two exposure concentrations. . . .[BASF's toxicologist said] that BASF had conducted a rat inhalation teratology study of . . .[2-methoxy-1-propyl acetate] at exposure concentrations of 110, 545 and 2710 ppm. Split vertebra were seen at the highest exposure level, but not at the lower exposure levels. Maternal toxicity evidenced as irritation was observed at the 545 ppm air concentration. . . .[BASF's toxicologist said also] that BASF had conducted a 28-day subacute inhalation study in rats with . . .[2-methoxy-1-propyl acetate] at the same exposure concentrations (110, 545 and 2710 ppm) and signs of irritation were again observed; however there were no effects on bone marrow or blood."

Submission Evaluation

Although no definitive teratogenic effects have been observed in 1) teratology studies of 2-methoxy-1-propyl acetate in rats (via inhalation) and rabbits (via dermal application), or 2) inhalation teratology studies of propylene glycol monomethyl ether (containing approximately 98.7% 1-methoxy-2-propanol and 1.3% 2-methoxy-1-propanol) in rats and rabbits, the overall significance

of the results of a study reportedly demonstrating for the first time that 2-methoxy-1-propyl acetate is a strong teratogen via inhalation in rabbits cannot be minimized even in the absence of the details of and actual data from that study. It is important to note also that the observed malformations/defects 1) appear to be consistent with those seen in teratology studies of ethylene glycol ethers and their derivatives, and 2) occurred in the absence of toxic effects in the exposed dams.

In activities under Sections 4, 5, 6, and 8 of TSCA, EPA's Office of Toxic Substances (OTS) has received and has been evaluating toxicologic and exposure data on a number of glycol ethers and glycol ether derivatives. It has been well publicized that EPA has been developing regulations designed to control exposure to and/or require the testing of ethylene glycol ethers and their derivatives. For example, EPA has published an Advanced Notice of Proposed Rulemaking (ANPR 49 FR 2921; January 24, 1984) in which EPA announced its intention to develop regulations under TSCA to reduce the exposure to 2-methoxyethanol (ethylene glycol monomethyl ether), 2-ethoxyethanol (ethylene glycol monoethyl ether), and their acetates. In addition, several glycol ethers have been recommended by the Interagency Testing Committee (ITC) for testing under Section 4 of TSCA.

Current Production and Use

Neither 2-methoxy-1-propyl acetate nor 1-methoxy-2-propyl acetate are listed in the current non-confidential computerized version of the 1977 TSCA Chemical Substance Inventory. According to the 1984 edition of the American Chemical Society's CHEMCYCLOPEDIA, propylene glycol monomethyl ether acetate has a high degree of solvency and slow rate of evaporation and is used in water-based paints (as a coalescing agent), lacquers, and resin coating applications (e.g., cellulose nitrate, ethyl cellulose, acrylics, polystyrene). In general, the propylene glycol ethers and their derivatives have been or are being developed by a number of companies to replace ethylene glycol ethers and ethylene glycol ether derivatives in certain applications.

In its followup submission, Union Carbide stated that the company believes that the airborne concentrations of 2-methoxy-1-propyl acetate are "well below 5 parts per million" at the Union Carbide facility where PM Acetate is manufactured.

Comments/Recommendations

In its FYI submissions, Union Carbide stated that the company was notifying customers, employees, and other U.S. companies known by Union Carbide to manufacture, import, or market propylene glycol monomethyl ether acetate. In addition, Union Carbide stated that the Agency would be apprised of any additional information as soon as such information becomes available to the company.

Based on a review of the information presented by Union Carbide in the initial and followup FYI submissions, it is EPA's position that the findings from BASF's rabbit inhalation teratology study of 2-methoxy-1-propyl acetate, about which Union Carbide was notified initially on an informal basis and which were subsequently confirmed by Union Carbide via telephone conversations with BASF in West Germany, should have been reported to EPA under Section 8(e), the "substantial risk" information reporting provision of TSCA. The basis for EPA's position is as follows:

> 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 [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 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 . . . (b) the fact or probability of its occurrence. With regard to the seriousness of the effect, Part V explains further that that the Agency considers the 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, mutagenicity, birth defects . . . ." The information concerning these effects can be obtained directly or inferred from designed studies (e.g., in vivo studies as described in Part VI of the 8(e) policy statement). In addition, Part VI explains that "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." Part VI explains further that "not only should final results from such studies be reported, but also preliminary results from incomplete studies where appropriate."
>
> With regard to the "fact or probability of its [i.e., the serious effects'] occurrence" criterion, Part V of the policy document states that certain types of health effects (e.g., birth defects, cancer) are so serious that relatively little weight should be given to a chemical's exposure in determining whether a risk is substantial; the mere fact that an implicated chemical is in commerce would constitute sufficient evidence of exposure.

> With regard to the requirement that EPA's Administrator be informed immediately about substantial risk information, Part IV of the TSCA Section 8(e) 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 TSCA Section 8(e) policy statement] not later than the 15th working day after the date . . .[a subject] person obtained such information." Part III of the 8(e) policy statement explains that EPA considers that a company has "obtained" substantial risk information at the time that any corporate officer or employee who is capable of appreciating the significance of the information obtains (i.e., possesses or knows of) such information.
>
> Part VII of the Section 8(e) policy statement explains that EPA considers the information about which the EPA Administrator has been adequately informed (i.e., that information that need not be reported to EPA under TSCA Section 8(e)) to be that information that has been, for example, published in the open scientific literature and abstracted by certain abstract services or submitted to EPA in accordance with some other mandatory information reporting requirement under TSCA or some other authority administered by EPA.

In view of the preceding discussion and EPA's evaluation of the information presented in FYI-OTS-0585-0408 and FYI-OTS-0985-0408 Followup Response, EPA believes that Union Carbide obtained (by way of a confirming phone conversation) information that inhaled 2-methoxy-1-propyl acetate caused birth defects in a rabbit teratology study that was conducted by BASF Aktiengesellschaft in West Germany. In addition, EPA believes that this information, when combined with the knowledge that 2-methoxy-1-propyl acetate comprises 3-5% of a product in U.S. commerce, provides reasonable support for a conclusion that 2-methoxy-1-propyl acetate presents a substantial risk of injury to human health as defined in EPA's March 16, 1978 TSCA Section 8(e) policy statement. It is EPA's position, therefore, that the subject birth defects information should have been submitted to the Agency in accordance with the reporting procedures outlined in Part IX of the March 16, 1978 TSCA Section 8(e) policy statement.

EPA believes that its position in this matter is consistent fully with the guidance contained in 1) the March 16, 1978 Section 8(e) policy statement and 2) "status reports" prepared and made public by EPA's Office of Toxic Substances in response to initial TSCA Section 8(e) submissions (e.g., status report 8EHQ-1283-0503). In addition, it should be noted that since the enactment of TSCA on January 1, 1977, many members of the chemical industry have formally submitted "substantial risk" information obtained under circumstances similar to those encountered by Union Carbide.

Further, the Union Carbide Corporation filed a TSCA Section 8(e) submission (8EHQ-0378-0105) in which the company stated that its notice was "based largely on oral communications from several sources. . . ."

With regard to the timeliness of reporting, Union Carbide did notify EPA in writing within 15 working days of Union Carbide's confirmatory phone conversation with BASF in West Germany. In terms of completeness, however, it was only upon EPA's receipt of Union Carbide's September 13, 1985 followup response letter that the Agency learned that the "strong teratogenic effect" reported by Union Carbide in the initial FYI submission involved defects of the cardiovascular system and malformations of the extremities. The 4-page telephone summary contained in Union Carbide's September 13, 1985 followup letter shows that the company had obtained this more explicit information with regard to the actual nature of observed teratogenic effects prior to the initial FYI submission which was dated May 16, 1985.

a) The Existing Chemical Assessment Division (ECAD/OTS/OPTS) will inform the Union Carbide Corporation about the Agency's determination with regard to the Section 8(e)-reportability of the subject information. In light of this determination, the Chemical Screening Branch (CSB/ECAD/OTS) has delivered FYI-OTS-0585-0408 and FYI-OTS-0985-0408 Followup Response to the OTS Document Control Officer for handling/public filing under Section 8(e) of TSCA.

   In light of the fact that BASF Aktiengesellschaft reportedly refused to provide to Union Carbide any further information concerning the BASF teratology studies until such time that the results are published in the open scientific literature, the Chemical Screening Branch is attempting to obtain from BASF Aktiengesellschaft full copies of the final reports from their teratology studies of 2-methoxy-1-propyl acetate in rats and rabbits. It should be noted that any person who manufactures, imports, processes, or distributes 2-methoxy-1-propyl acetate alone or as a component in any mixture in commerce in the U.S. and who obtains these reports (or any other pertinent information from these studies) should be aware of his/her obligation to submit such information to EPA immediately unless that person has actual knowledge that EPA has already been adequately informed about the information. As explained in Part IV of the Section 8(e) policy statement, supplemental information generated/obtained after an initial 8(e) notice is filed must be transmitted to EPA immediately.

b) The Chemical Screening Branch will continue to review the submitted information to determine the need for separate OTS assessment and/or formal referral of the information to the ongoing OTS assessments of glycol ethers and glycol ether derivatives.

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

Reference

Hanley, T.R.; Calhoun, L.L.; Yano, B.L.; and Rao, K.S. (1984) "Teratologic Evaluation of Inhaled Propylene Glycol Monomethyl Ether in Rats and Rabbits" Fundamental and Applied Toxicology; Vol.4:784-794.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: DEC 3 1985

SUBJECT: Status Report* 8EHQ-1185-0573 Approved: 12/04/85

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

Nuodex Inc. reported that it was notified in writing by a foreign supplier (Chemische Fabriek Servo B.V., Delden, Holland) that a recently conducted acute skin application study of butyraldoxime (CAS No. 110-69-0) in rabbits showed an LD50 value of between 100 and 200 mg/kg. In its Section 8(e) notice, Nuodex stated that it was attempting to obtain a full copy of the final report of this study from the foreign supplier.

Submission Evaluation

According to the NIOSH Registry of the Toxic Effects of Chemical Substances (RTECS), butyraldoxime has been shown to have an LD50 of 200 mg/kg when injected intraperitoneally (ip) in mice. In some acute toxicity classification systems, this ip LD50 value indicates that the chemical is "very" toxic. Based on the newly reported rabbit dermal LD50 value of between 100-200 mg/kg, however, butyraldoxime could now be classified as "extremely" toxic. With regard to the adverse human health effects caused by overexposure to butyraldoxime, the following information was located in a Material Safety Data Sheet (MSDS) contained in a publicly available Material Safety Data Sheet collection (Material Safety Data Sheets Service published by Information Handling Services of Englewood, Colorado):

> "If the [human] contact [with butyraldoxime] is of short duration, the product will cause slight skin and eye irritation only. If the contact is of longer duration (e.g., 24 hours), a moderate irritation will occur. . . .[Butyraldoxime] may interfere with oxidation of alcohol in the body resulting in the formation of increased amounts of acetaldehyde, blotchy red marks, red eyes, tiredness, [and] visible veins."

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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 butyraldoxime (CAS No. 110-69-0), which is listed in the initial TSCA Chemical Substance Inventory, has shown that between 210 thousand and 2.1 million pounds were reported as produced and/or imported in 1977. This production range information does not contain any production/importation 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 submitted for the initial TSCA Inventory, including production range data, are subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

In its TSCA Section 8(e) submission, Nuodex Inc. reported that it imports butyraldoxime (as EXKIN® 1) from Chemische Fabriek Servo B.V. and then sells the chemical (as EXKIN® No. 1 Anti-Skinning Agent) to the paint/coatings industry for use in solvent-based coatings. According to secondary literature sources, anti-skinning agents are mixed into paints and other coatings (e.g., varnishes) to prevent oxidized film formation on exposed surfaces in containers. Nuodex reported (by phone) that butyraldoxime usually comprises less than 0.5% of final paint/coating formulations. No information on current production/importation volumes or other use(s) of butyraldoxime was located in the secondary literature sources consulted.

Comments/Recommendations

According to the submission, Nuodex Inc. and Chemische Fabriek Servo B.V. have updated their butyraldoxime Material Safety Data Sheets to include the reported toxicologic information.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask Nuodex Inc. to ensure that EPA receives a complete copy of the final report from the subject acute dermal toxicity study as soon as that report is obtained by the company. Nuodex will be asked also to provide a full copy of the company's updated EXKIN® No. 1 Anti-Skinning Agent MSDS as well as the foreign supplier's updated EXKIN® 1 MSDS.

   In view of EPA's general interest in company actions that are taken on a voluntary basis in response to chemical toxicity or exposure information, Nuodex will be asked to describe the nature and available results of all studies that Nuodex has conducted, is conducting, or plans to conduct to determine the toxicity of or the exposure to butyraldoxime. Nuodex will be asked also to describe the nature of any further actions the company has taken to notify workers and others about the reported toxicologic findings on butyraldoxime.

b) The Chemical Screening Branch will review the submitted data in order to determine the need for further OTS assessment of butyraldoxime.

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

DATE: DEC 13 1985

SUBJECT: Status Report* 8EHQ-1185-0574 Approved: 12/16/85

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 Atlantic Richfield Company provided a full copy of an interim (13 week) report from a subchronic (39 week) inhalation study of silicon carbide (CAS No. 409-21-2) fibers in rats. According to Atlantic Richfield, the objectives of the study are "to determine (1) whether silicon carbide fibers when inhaled can cause lung fibrosis; (2) the fibrogenic potency of silicon carbide fibers relative to asbestos; and (3) what airborne concentrations of silicon carbide fibers would not cause observable lung fibrosis." Atlantic Richfield stated that the company hoped that the data obtained from this study would help to provide "a scientific basis for establishing an internal workplace exposure level [for silicon carbide fibers]." The submitter's cover letter contained the following information with regard to the conduct and interim findings from the performed study:

> "The study design included five groups, each consisting of 50 male and 50 female rats. The negative control group was given filtered air; the positive control group, crocidolite asbestos (1.5 um in length x 0.2 um in diameter) at a concentration of 0.94 mg/m^3 (equivalent to 1298 fibers/cm^3). The three groups exposed to silicon carbide fibers (4.5 um in length x 0.5 um in diameter) received throughout the exposure period mean mass concentrations of 3.93, 10.7, and 60.5 mg/m^3 respectively. These concentrations correspond to 630, 1746, and 7276 fibers/cm^3. Exposures were for six hours per day, 5 days per week for 13 weeks. Half the number of animals were sacrificed at the end of the 13 weeks; the remainder were scheduled for sacrifice after a six-month (26 week) recovery 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.

"Histopathologic examination of the rats' lungs from the interim sacrifice showed mild chronic focal inflammation, as expected, with only minimal pulmonary fibrosis in the silicon carbide [fiber]-exposed rats. However, unexpected pleural changes also were detected. These included focal and generally minimal to mild visceral pleural fibrosis usually associated with subpleural inflammatory lesions. The incidence of these changes was 4, 2, and 12% in the low, mid and high [silicon carbide fiber] dose groups respectively.

"Additionally, visceral and parietal pleural hyperplasia was found in 6, 0, and 10% of the respective groups exposed to the silicon carbide fibers. Most significantly, this pleural hyperplastic effect was found in the parietal pleura of two male rats in the low dose group. While the hyperplasia observed can be regarded as minimal, a silicon carbide fiber was present in both foci in the parietal pleura, indicating that the fibers had penetrated from the lungs into the chest cavity.

"Approximately 10% of the total number of animals exposed to [the] silicon carbide fibers had some pleural changes. However, only a few animals exhibited both pleural fibrosis and hyperplasia which may be a reflection of the sampling technique [used in the study]. No changes of significance were observed in the lungs or pleura of the negative control animals."

In reporting these interim findings to EPA, Atlantic Richfield stated that "no special attempt was made to characterize the degree of pleural involvement, thereby limiting the ability to assess the true extent of this effect." Atlantic Richfield also stated that the "interpretation of the results is further limited by the lack of significant fibrotic and inflammatory activity in the asbestos control group, a result possibly due to the small fiber length of the material used in the study." Finally, the Atlantic Richfield Company stated that it plans to "review the results of the final sacrifice in an attempt to determine whether the unexpected pleural fibrosis continues to be seen or if there will be a significant regression of the preliminary findings."

Submission Evaluation

Immediately upon receipt of Atlantic Richfield's Section 8(e) submission, copies were provided to the Risk Analysis Branch (RAB/ECAD/OTS/OPTS), the Regulatory Program Development Branch (RPDB/CCD/OTS/OPTS) and the Asbestos Action Program/OPTS for inclusion in the ongoing assessment of the potential risks posed by exposure to natural and man-made fibrous materials.

Current Production and Use

A review of the production range (includes importation volumes) statistics for silicon carbide (all forms; CAS No. 409-21-2), which is listed in the initial TSCA Chemical Substance Inventory, has shown that between 82.6 and 276.2 million pounds of this chemical substance were reported as produced 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 intial 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 TSCA Chemical Substance Inventory Reporting Regulations (40 CFR 710).

According to secondary literature sources, silicon carbide is used as an abrasive in grinding, cutting, and polishing operations for metals, glass, and stone (e.g., granite). Other uses reportedly include the manufacture of porcelain, shoe soles and heat refractory materials (e.g., furnace bricks and linings). In its fibrous form, silicon carbide is reportedly used as a heat-resistant high-strength agent in certain composite materials.

Atlantic Richfield provided the following information concerning the potential for worker exposure to silicon carbide fibers:

> "At the present time, the potential for worker exposure at Atlantic Richfield facilities is minimal . . . [because silicon carbide fibers are] used in a closed system. Further, the current . . . [Material Safety Data Sheet (MSDS)] instructions for handling [silicon carbide fibers] indicate that the substance should be regarded in the same hazard class as asbestos and that personal protective equipment should be provided where necessary."

Comments/Recommendations

The Atlantic Richfield Company stated that copies of the final interim report and the final study report would be sent to the Agency as soon as those reports are received by the company.

a) As was the case with the Atlantic Richfield Company's initial Section 8(e) submission, the Chemical Screening Branch (CSB/ECAD/OTS) will forward all of the reported information to the Risk Analysis Branch (RAB/ECAD/OTS), the Regulatory Program Development Branch (RPDB/CCD/OTS) and the Asbestos Action Program (AAP/OPTS) for inclusion in the ongoing assessment of the potential risks posed by exposure to natural and man-made fibrous materials.

In view of the Agency's general interest in corporate actions that are taken on a voluntary basis in response to chemical toxicity or exposure information, Atlantic Richfield will be requested to describe the nature and available results of all studies (other than those already reported formally 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 and/or the exposure to silicon carbide in any form.

b) 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, RAB/ECAD/OTS, RPDB/CCD/OTS, and the Asbestos Action Program/OPTS. Copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: DEC 20 1985

SUBJECT: Status Report* 8EHQ-1185-0575 Approved: 12/20/85

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 Eastman Kodak Company provided the following summarized information with regard to the conduct and results of an acute oral LD50 study of 2-((4-amino-3-methylphenyl)ethylamino)ethanol sulfate (CAS No. 25646-77-9):

> "Groups of 5 male and 5 female rats per dose level were given 25, 50, 100, 200 or 400 mg/kg of the test compound in a single gavage dose as part of an oral LD50 test. The acute oral LD50 was [determined to be] 35 mg/kg in females and 81 mg/kg in males. A number of animals were subjected to gross and histopathological examination. The most consistently and severely affected organ was the kidney. Lesions in several organs were considered either directly or indirectly related to exposure to the test compound. Such organs included the kidneys, lungs, thymus, liver, heart, spleen, stomach, duodenum, and testes. The [toxic] effects observed were related both to dose and to the length of the survival period following dosing. All animals examined showed lesions indicative of renal toxicity. Changes in the lung, thymus, heart and spleen were thought to be secondary to renal failure."

Eastman Kodak stated that the subject chemical is known to be a skin/eye irritant as well as a skin sensitizer. Eastman Kodak stated also that with the exception of irritation/sensitization, the company is "not aware of any adverse health problems associated with the manufacture or use of this chemical or solutions containing this chemical." Finally, Eastman Kodak stated that it does not believe that the current handling procedures need to be changed because those procedures "are designed to prevent skin and eye irritation and skin sensitization and are sufficient to protect against the reported 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

Although the submitted summarized information indicates that the the tested chemical 1) borders on being classified as "extremely toxic" on the basis of the reported rat oral LD50 values; and 2) is toxic to the kidney as well as other organs, a full copy of the final report from the performed study is needed in order for the Agency to determine the overall significance of the reported findings.

Current Production and Use

A review of the production range (includes importation range) statistics for 2-((4-amino-3-methyphenyl)ethylamino)ethanol sulfate (CAS No. 25646-77-9), which is listed in the initial TSCA Chemical Substance Inventory, has shown that between 100 thousand and 1 million pounds of this chemical were reported as produced 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/importation data, are subject to the limitations contained in the initial TSCA Chemical Substance Inventory Reporting Regulations (40 CFR 710).

Eastman Kodak stated that the subject chemical "has been used in the photographic industry for many years." No information on the use(s) or current production/importation volumes of the chemical was located in the secondary literature sources consulted by EPA.

Finally, Eastman Kodak provided the following information with regard to the potential for exposure to the subject chemical:

> "Potential employee exposure is minimized during [the] manufacture and isolation of the damp and dry product by the use of local exhaust, gloves, safety glasses, and coveralls. In addition, employees wear air purifying respirators or use local exhaust when working with the dry product. Currently, . . .[Eastman Kodak recommends that its] customers use protective gloves and safety glasses and use good general room ventilation or local exhaust when handling this chemical."

Comments/Recommendations

In its Section 8(e) submission, the Eastman Kodak Company noted that a copy of the rat oral LD50 study final report and copies of the current product label and Material Safety Data Sheet (MSDS) would be provided to EPA.

a) The Chemical Screening Branch (CSB/ECAD/OTS/OPTS) will request the Eastman Kodak Company 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 rat oral LD50 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 information, the Chemical Screening Branch will ask Eastman Kodak to describe the actions the company has taken or plans to take to notify workers and others about the reported toxicologic findings. In addition, Eastman Kodak will be asked to describe the nature and available results of all studies (other than 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 toxicity of and/or the exposure to the subject chemical.

b) The Chemical Screening Branch will review the reported data to determine the need for further OTS assessment of 2-((4-amino-3-methylphenyl)ethylamino)ethanol sulfate.

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: DEC 30 1985

SUBJECT: Status Report* 8EHQ-1185-0576 Approved: 12/31/85

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 Mobil Research and Development Corporation reported that "as part of its ongoing program of evaluating petroleum products, streams and components, . . .[the company] has investigated the nature and basis of the dermal toxicity of a sample of fluid catalytically cracked clarified oil" (CAS No. 64741-62-4; also designated as clarified slurry oil (CSO)). Mobil noted that CSO is known to be "a potent dermal carcinogen and to cause systemic toxicity and early mortality when absorbed through the skin of laboratory animals." Specifically, Mobil provided the following information concerning the company's ongoing research activity:

> ". . .[Mobil's] research demonstrated lethal effects and generalized systemic toxicity in rats after repeated dermal application of CSO [at dose levels of 0, 8, 30, 125, 500 or 2000 mg/kg/day] in a 90-day subchronic study. Dose rates of 8 mg/kg/day or greater produced a variety of pathologic changes. The degree of liver damage and of other organ/system effects was dependent upon dose and exposure time. Chemical analysis revealed that the tested sample of CSO contained up to 22% carbazoles, a class of chemicals known to include carcinogenic and hepatotoxic congeners. Using in vivo and in vitro [skin absorption] techniques . . ., [the Mobil Research and Development Corporation has] found the carbazole derivatives to be the major dermal penetrants in CSO.
>
> "In particular, . . .[Mobil reported] the convergence of several lines of evidence: (1) the [scientific] literature shows that CSO is a dermal carcinogen and contains substantial quantities of polynuclear aromatic hydrocarbons; (2) [Mobil has] shown that, at low doses in a subchronic study, a sample of CSO is markedly toxic 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.

> the internal systems of rats by the dermal route; (3) [Mobil has] found that the sample of CSO contained up to 22% carbazoles; (4) [Mobil has] demonstrated that carbazoles are readily bioavailable in animals by the dermal route; and (5) the literature reports that some members of the carbazole class are strong hepato-carcinogens and are hepatotoxic in rodents. This evidence suggests that the lethal and toxic effects observed with CSO may be due, in whole or in part, to absorption of carbazoles."

In its submission, the Mobil Research and Development Corporation also provided 1) a short literature review and bibliography of studies conducted with catalytically cracked clarified oil; and 2) a table containing the range of chemical/physical properties for 15 samples of catalytically cracked clarified oil from U.S. oil refineries.

Submission Evaluation

Immediately upon receipt of this TSCA Section 8(e) submission, the Chemical Screening Branch (CSB/ECAD/OTS) provided a copy of the submission to the Risk Analysis Branch (RAB/ECAD/OTS) for inclusion in their ongoing assessment of available toxicologic and exposure data on catalytically cracked clarified oil.

Current Production and Use

A review of the production range (includes importation volumes) statistics for catalytically cracked clarified oil (CSO; CAS No. 64741-62-4), which is listed in EPA's TSCA Chemical Substance Inventory, has shown that over 1 billion pounds of this material were reported as produced 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 TSCA Inventory, nor does it include any data that would compromise TSCA CBI. All of the data submitted for the initial TSCA Inventory, including the production and importation range data, are subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

Appendix A of Volume I of the printed non-confidential TSCA Inventory contains the following definition for catalytically cracked clarified oil:

> "A complex combination of hydrocarbons produced as the residual fraction from distillation of the products from a catalytic cracking process. It consists of hydrocarbons having carbon numbers predominantly greater than C20 and boiling above approximately 350°C (662°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) notice, the Mobil Research and Development Corporation provided the following information with regard to the uses of and the potential for exposure to catalytically cracked clarified oil:

> ". . .[Catalytically cracked clarified oil (CSO)] is used as feed stock for the production of carbon blacks, petroleum coke and petroleum pitch; and sometimes it is included as a component of heavy fuels, including Bunker C and No. 6 Fuel Oil. Most of these materials are manufactured in sealed units, shipped in bulk and handled in closed systems, usually at temperatures of 130 to 200°F. Because of these conditions, the potential for human contact with CSO and products containing it is minimal; impervious protective equipment is recommended where that potential exists."

Comments/Recommendations

The Mobil Research and Development Corporation stated that its existing Material Safety Data Bulletin and product label (which already have a warning to avoid all personal contact with catalytically cracked clarified oil) have been revised to "emphasize the need to avoid all personal contact by using impervious protective equipment." The submitter stated also that Mobil's employees and customers as well as other interested parties have been notified about the reported findings.

It should be noted that EPA's Office of Toxic Substances (OTS) has received and reviewed a number of TSCA Section 8(e) and "For Your Information" (FYI) submissions containing toxicologic and/or exposure information on catalytically cracked clarified oil.

a) The Chemical Screening Branch will ask the Mobil Reseach and Development Corporation to submit complete copies of the final reports from the 90-day rat dermal application study, the *in vitro* and *in vivo* skin absorption studies, and the Mobil refinery worker epidemiologic studies that were cited in the submission.

b) As was the case with Mobil's initial 8(e) submission, the Chemical Screening Branch will immediately forward all reported information to the Risk Analysis Branch for inclusion in their ongoing assessment of catalytically cracked clarified oil.

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 RAB/ECAD/OTS. In addition, copies will be provided to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JAN 23 1986

SUBJECT: Status Report* 8EHQ-1285-0577 Approved: 1/24/86

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 U.S. Department of Energy (DOE) submitted full copies of the final reports from several in vivo studies designed to assess the possible mutagenic and reproductive/developmental toxicities of the following chemicals or mixtures of those chemicals:

EMP-I ERR®-4205: bis(2,2-epoxycyclopentyl)ether (BECPE; CAS No. 2386-90-5)

EMP-II 1,3-diaminobenzene (MPDA; CAS No. 108-45-2)

EMP-III Araldite® 6010 (the diglycidyl ether of bisphenol A; DGEBA; CAS No. 25068-38-6)

EMP-IV ZZL®-0820: a curing mixture containing 56.7 wt.% EMP-II, 30.3 wt% EMP-VI and 13.0 wt.% EMP-III

EMP-V ERL®-2258: a resin mixture containing 50.0 wt.% EMP-I and 50 wt.% EMP-III

EMP VI 4,4'-methylenedianiline (4,4'-MDA; CAS No. 101-77-9)

According to the submitted reports, EMP-II, EMP-IV and EMP-V were not considered to be teratogenic following oral administration to pregnant rats at dose levels sufficient to produce maternal toxicity. However, EMP-V was considered to be embryotoxic in the rat at doses sufficient to cause mild maternal toxicity. Further,

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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.

EMP-IV and EMP-V were both reported to be potentially teratogenic following oral administration to pregnant rabbits at dose levels sufficient to produce maternal toxicity. With regard to adverse effects on the male rat reproductive system, orally administered EMP-V (but not EMP-IV) was reported to produce a dose-dependent reduction in sperm production as well as a strong, dose-dependent dominant lethal effect. In a dominant lethal study in which male rats were exposed to EMP-I via inhalation, a slight but statistically significant dominant lethal effect was found but was considered to be too weak to account for the strong dose-related mutagenic effect observed in the rat oral dominant lethal study of EMP-V (a 50:50 mixture of EMP-I and EMP-III). The following discussion provides greater detail with regard to the conduct and results of the performed studies.

In a preliminary teratology study, EMP-II, EMP-IV and EMP-V were administered orally in 2% carboxymethyl cellulose to groups of 9 pregnant Sprague-Dawley rats at the following doses: 45 mg/kg (EMP-II); 50 or 100 mg/kg (EMP-IV); 600 or 1200 mg/kg (EMP-V). Although no significant teratogenic effects were reportedly observed, all tested materials at all treatment levels were found to have caused varying degrees of maternal toxicity as evidenced by maternal body weight loss. In addition, both dose levels of EMP-V were found to have caused embryotoxic effects manifested by a significant reduction in fetal body weight in both sexes of offspring. In a more "definitive" oral teratologic study using more pregnant rats per dose group (i.e., 30 rats/group), EMP-II (35 mg/kg), EMP-IV (40 and 80 mg/kg), and EMP-V (500 and 1000 mg/kg) were again found not to be teratogenic but were found to produce maternal toxicity. As in the "preliminary" study, EMP-V was shown to produce embryotoxic effects as manifested by significantly delayed ossification of the sternabrae at 500 mg/kg and reduced fetal body weight in both sexes of offspring at 1000 mg/kg. The submitted final report presented the following conclusions with regard to these oral teratology studies in rats:

> ". . . EMP-IV and EMP-V and EMP II were not teratogenic in Sprague-Dawley rats at [oral] dose levels sufficient to cause maternal toxicity. EMP-V was determined to be embryotoxic in the rat, identified by a significantly delayed ossification of the sternebrae at the 500 mg/kg level and a reduced fetal body weight in both sexes at dose levels of 600 mg/kg and above. These dose levels of EMP-V were also mildly maternally toxic."

In teratology studies in New Zealand white rabbits, EMP-IV and EMP-V were administered orally in 2% carboxymethyl cellulose to groups of approximately 25 pregnant rabbits at dose levels of 25 and 50 mg/kg (EMP-IV) and 101, 165, and 270 mg/kg (EMP-V). The following information concerning the results of these teratology studies was contained in the Summary section of the submitted final report:

"Maternal toxicity was demonstrated in at least the high-dose level for . . .[both EMP-IV and EMP-V]. One and four of the 25 and 26 rabbits at the low- and high-dose levels of EMP-IV, respectively, died. No deaths occurred at the low-dose level of EMP-V. One and five of the 25 rabbits at the mid- and high-dose levels of EMP-V, respectively, died. Common observations at necropsy in rabbits in both groups included diarrhea, loss of appetite, and hemorrhagic lungs; rabbits receiving EMP-IV also had nasal exudate and bloody urine. A decreased weight gain during treatment was also observed for rabbits at the high-dose level of EMP-V.

"Four rabbits treated with the high-dose level of EMP-IV had resorbed litters, and one other pregnancy resulted in a spontaneous abortion, causing a significantly reduced average live litter size when those pregnancies were included. Since resorbed and aborted litters are often a result of maternal toxicity, rather than a teratogenic or direct embryotoxic effect, the average live litter size was also evaluated excluding these pregnancies. The average live litter size excluding resorbed and aborted litters was not significantly affected by treatment with EMP-IV or EMP-V. The average percentage of dead or resorbed embryos per implant (excluding totally resorbed and aborted litters) and the average live fetus weights were not significantly affected by treatment with . . . [EMP-IV or EMP-V]. These results indicate that EMP-IV and EMP-V are not embryotoxic in the rabbit at dose levels [capable of] producing slight maternal toxicity.

"The incidence of any one individual malformation was not significantly increased with either of the test agents; however, the total percentage of fetuses with any malformation (including rib, limb, spinal, and skull anomalies) was significantly increased at the low-dose level of EMP-IV and the mid-dose level of EMP-V. Only five viable litters were produced at the high-dose level of EMP-IV (35 fetuses). One of these fetuses had a major congenital anomaly; however, the incidence of malformed fetuses was not significant at the high-dose level of EMP-V.

"The results of these studies indicate that EMP-IV and EMP-V are potentially teratogenic to New Zealand White rabbits at dose levels sufficient to cause maternal toxicity. The spontaneous malformation rate in the concurrent vehicle control group was very low (1 of 161 fetuses were malformed) and the increased incidence of malformed fetuses in the treated groups was not far above a normal spontaneous rate for this strain of rabbit. Therefore, these compounds are not positively being identified as teratogens in this species."

Further with regard to the teratologic studies in rabbits, the Conclusion section of the submitted final report contains the following information:

> ". . .[Although EMP-IV and EMP-V] are not positively being identified as teratogens in New Zealand White rabbits, . . .[these materials] must be considered to be potentially teratogenic at dose levels sufficient to cause maternal toxicity in this species. Previous work with . . .[EMP-IV and EMP-V] determined that EMP-V was embryotoxic in the rat at mildy maternally toxic dose levels, but neither. . . [mixture] was found to be teratogenic in this species. In regards to human health, . . . [both EMP-IV and EMP-V] must be considered to be a potential risk to the developing embryo at maternal exposure levels approaching that which would also cause maternal toxicity. Although these studies did not provide data at low dose levels, since the teratogenic response of . . . [EMP-IV and EMP-V] was equivocal at the very high dose levels tested, it is unlikely that a developmental hazard exists at a very low level of exposure to EMP-IV or EMP-V. At exposure levels producing a comparable degree of maternal toxicity, since EMP-V was also found to be embryotoxic in the rat, it would be considered to be more of a developmental hazard than EMP-IV."

In a study designed to assess possible in vivo mutagenic (i.e., dominant lethal) effects and possible adverse effects on spermatogenesis caused by either EMP-IV or EMP-V, these mixtures were administered orally in 1% carboxymethyl cellulose to groups of approximately 25 male Sprague-Dawley rats at dose levels of 20, 40 or 80 mg/kg/day (EMP-IV) and 250, 500, or 1000 mg/kg/day (EMP-V) for 13 consecutive weeks. In the dominant lethal portion of the study, male rats were bred to two female rats each after an initial 10-week treatment period and continued to receive daily doses during the 2-week mating period and for one week following the mating period. The investigators noted that the daily treatment beyond 10-weeks was to allow the separate evaluation of the possible adverse effects on sperm production following a total exposure of 13 weeks. The following information concerning the dominant lethality portion of this subchronic study was presented in the Summary section of the submitted final report:

> "Evaluation of the females during mid-gestation revealed that treatment of the males with EMP-IV did not result in dominant lethal effects or [in] effects on fertility. However, treatment with EMP-V resulted in a strong dominant lethal effect with a clear dose response. In addition to the positive mutagenicity of EMP-V, a reduction in the fertility of male rats was evident. Although EMP-V was positive for mutagenicity in male germ cells, it would be extremely unusual for a mutagen to affect

> testicular tissue exclusively. Therefore, EMP-V is likely to be a general mutagen, in which case many tissues of either sex could be at risk following exposure of this mixture."

With regard to the results of the spermatogenesis portion of the performed sub-chronic study, the following information was presented in the Summary section of the final report:

> "EMP-IV had no effect on sperm production except for a small reduction in the percentage of motile cells recovered from the cauda epididymis in rats treated with 40 and 80 mg/kg/day. Treatment of rats with EMP-V resulted in significantly decreased sperm production, epididymal sperm numbers, and percentage of motile cells in rats exposed to 1000 mg/kg/day. These results clearly indicate that EMP-V is deleterious to spermatogenesis in Sprague-Dawley rats under the conditions used in this study."

In another dominant lethality study, EMP-I was administered via inhalation to groups of approximately 25 male Sprague-Dawley rats at dose levels ranging from 0.05 to 0.3 mg/l for 6 hours/day, 5 days/week for 10 weeks. Following the last exposure, 20 males from each group were selected for mating at a 2 female/1 male ratio. The Results and Discussion section of the final report contained the following information concerning the findings from this study as well as the relationship of these findings to those of the oral dominant lethal study of EMP-IV and EMP-V described previously:

> ". . .[A]lthough EMP-I exhibited some mutagenic activity in this study, the activity observed was much less than would be expected if it had been the primary cause of the mutagenesis resulting from treatment with the EMP-V mixture. From the effects of this study, . . . [the investigators] conclude that EMP-I may have weak mutagenic effects on the germ cells of male Sprague-Dawley rats. It is difficult to compare the equivalency of [the] dose levels received from inhalation and oral routes of exposure. However, if the two routes of exposure can be considered to deliver similar doses to the testes, the data from this study would indicate that EMP-I was not the sole or major contributor to the mutagenesis seen following oral exposure to the EMP-V mixture."

Submission Evaluation

Immediately upon receipt of this Section 8(e) submission, the Chemical Screening Branch (CSB/ECAD/OTS) provided copies of the submitted reports to the Risk Analysis Branch (RAB/ECAD/OTS) and the Test Rules Development Branch (TRDB/ECAD/OTS) for inclusion in their ongoing evaluations of the available toxicologic or

exposure information on epoxides and 4,4'-methylenedianiline (RAB/ECAD/OTS), phenylene diamines (TRDB/ECAD/OTS), and glycidol and its derivatives (RAB/ECAD/OTS and TRDB/ECAD/OTS).

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 volumes were reported as manufactured and/or imported in 1977. (Note: The following 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 TSCA Inventory Reporting Regulations (40 CFR 710).)

Chemical	CAS Number	Production/Importation Range
BECPE	2386-90-5	0*
MPDA	108-45-2	110,000 to 1,100,000 lbs.
DGEBA	25068-38-6	126,983,000 to 669,836,000 lbs.
4,4'-MDA	101-77-9	10,030,000 to 50,301,000 lbs.

* This "0" indicates that no production/importation was reported for 1977 or that all of the production range data that were reported were claimed as TSCA CBI by the manufacturer(s) or importer(s) and cannot be disclosed (Section 14(a) of TSCA, U.S.C. 2613(a)).

Although DOE's submission did not contain any information with regard to DOE's use(s) of the subject chemicals or mixtures, it is clear from the provided reports that the subject materials are used in an epoxy resin hardening/curing process of some type.

Comments/Recommendations

According to DOE, additional studies on the subject chemicals and mixtures are planned and/or underway. DOE has stated that copies of the final reports from these additional studies would be sent to EPA upon completion of those reports. In addition, DOE has stated that workers involved with the subject chemicals/mixtures have been notified about the reported toxicologic findings.

EPA's Office of Toxic Substances (OTS) has received and reviewed a number of TSCA Section 8(e) and/or "For Your Information" (FYI) submissions containing toxicologic or exposure data on several of the chemical substances mentioned in DOE's Section 8(e) notice.

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 Section 8(e), "any person who manufactures, [imports,] processes, or distributes in [US] 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 Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978) 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 DOE is a "person" within the TSCA 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 DOE unless DOE is or has engaged commercially in the manufacture, import, processing, or distribution of the chemical substance(s) or mixture(s) about which the substantial risk information was obtained.

a) The Chemical Screening Branch will request DOE to ensure that EPA receives complete copies of the final reports (including the actual experimental protocols, results of gross/histopathologic examinations, etc.) from all of the studies reportedly underway or planned to determine the reproductive/developmental toxicities of the subject chemicals or mixtures.

b) As was the case with DOE's initial Section 8(e) notice, the Chemical Screening Branch will provide full copies of all further DOE reports on the subject chemicals or mixtures to RAB/ECAD and/or TRDB/ECAD staff.

c) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OAR/EPA, ORD/EPA, OW/EPA, OPP/OPTS/EPA, OCM/OPTS/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: JAN 9 1986

SUBJECT: Status Report* 8EHQ-1285-0578 Approved: 1/15/86

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

Syntex (U.S.A.) Inc. submitted the following summary information with regard to the conduct and results of several acute in vivo toxicity studies of acetyl ferrocene (CAS No. 1271-55-2):

"Oral toxicity studies were initially conducted on groups of two male and two female rats at doses of 50, 150, and 500 mg/kg. All of the animals died within thirteen days after dosing, with most deaths occurring on the second and third days. Toxic signs included inactivity, kyphosis, rough coat, unthriftiness, salivation and ptosis. Female animals appeared to be more sensitive than males. These preliminary data suggested that the oral LD50 for acetyl ferrocene in rats was less than 50 mg/kg.

"To further confirm and define the oral toxicity of acetyl ferrocene, the oral toxicity testing was repeated on two groups of five male and five female rats. One group was administered one dose at 50 mg/kg, and the second group was given 5 mg/kg. All females in both groups died within four days. All of the male rats given low doses survived, but only one male rat survived at the high dose. A sexual difference in sensitivity was again observed. The oral LD50 of acetyl ferrocene for female rats appears to be less than 5 mg/kg, while the comparable LD50 for males seems to be between 5 mg/kg and 50 mg/kg.

"Eye irritation tests were then performed on three female rabbits. Doses of 30 mg/kg (100 mg/rabbit) were administered to each rabbit in the conjunctival sac of the eye. All of the rabbits died on the second or third days following dosing.

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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.

> "Acute dermal toxicity tests were then conducted on groups comprising two male and two female rats, at doses of 50, 500 and 2000 mg/kg. Three animals from the high dose group, and one animal from the medium dose group died on the second and third days, respectively, following dosing. The dermal LD50 in rats appears to be between 50 and 500 mg/kg."

In addition, Syntex stated that no adverse human health effects have been reported to the company during the 15 years that acetyl ferrocene has been used at one Syntex facility. Finally, Syntex stated that in view of the absence of reported adverse effects in Syntex workers, the submitted data suggest "that there may be important differences in sensitivity between humans and animals."

Submission Evaluation

Based on the submitted summarized information, acetyl ferrocene would be classified as "extremely" toxic. In order for EPA to evaluate the overall significance of the reported findings, however, Syntex should be asked to submit complete copies of the final reports from all of the cited studies. It should be noted that the NIOSH Registry of Toxic Effects of Chemical Substances (RTECS) cites the results of a study demonstrating that acetyl ferrocene has an LD50 value of 75 mg/kg in mice following intravenous injection. It should be noted also that the submitter's argument concerning the species specificity of the toxic action of acetyl ferrocene is weakened by observations of acute lethality at low doses in several species (rats, rabbits, and mice) and via several routes of exposure (oral, dermal, and ocular administration as well as intravenous injection). The lack of reported adverse health effects in Syntex workers could be explained just as well by the possibility that the company's industrial hygiene program has been sufficient to date in minimizing or eliminating exposure to the subject chemical. In the absence of data to lend support to Syntex's argument concerning species specificity, the submitted information suggests that human exposure to even small amounts of acetyl ferrocene could prove to be toxic if not fatal.

Current Production and Use

A review of the production range (includes importation volumes) statistics for acetyl ferrocene (CAS No. 1271-55-2), which is listed in the initial TSCA Chemical Substance Inventory, shows that between 1,000 and 11,000 pounds were reported as produced 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 that was reported for the initial TSCA Inventory, including the production range information, is subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

In its Section 8(e) notice, Syntex stated that acetyl ferrocene is an intermediate used in the manufacture of one of the company's ultimate products. (Syntex did not disclose the identity of this product.) Syntex stated also that there is no current or contemplated contact between acetyl ferrocene and the general public. No information concerning the use(s) or current production/importation volumes of acetyl ferrocene was found in the secondary literature sources consulted.

Comments/Recommendations

Syntex stated that based on the submitted toxicologic findings, the company has 1) reviewed and modified current personal protective equipment requirements for acetyl ferrocene; and 2) updated and distributed a revised acetyl ferrocene Material Safety Data Sheet (MSDS) to "pertinent" Syntex employees. Syntex stated also that the company is considering "performing additional testing to further interpret the toxic potential of this chemical."

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask Syntex to provide to EPA 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 each toxicologic study cited in the company's submission.

   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, Syntex will be asked to describe the nature and available results of all other studies that the company has conducted, is conducting, or plans to conduct to determine the toxicity of and/or the exposure to acetyl ferrocene.

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

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. 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: JAN 15 1986

SUBJECT: Status Report* 8EHQ-1285-0579 S Approved: 1/15/86

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 submitting company to substantiate this confidentiality claim.

Submission Description

The submitting company provided final results from an in vitro mutagenicity study and several acute in vivo toxicologic studies of p-vinyl phenol (CAS No. 2628-17-3). According to the submitted information, p-vinyl phenol at doses of 200, 2000, or 4800 mg/kg caused the death (within 1 to 2 days) of all rabbits (4 rabbits per dose group) to which the chemical was administered dermally as a solid moistened with saline solution. In addition, the submitting company stated that edema and dermal corrosion were observed during this acute rabbit dermal study. The submitter stated also that p-vinyl phenol was found to be highly corrosive to the eyes of rabbits following instillation of 100 mg of the chemical and that 1 of 4 rabbits exposed to the chemical died (cause of death unknown) on the seventh day of the study. With regard to oral toxicity, the company reported that p-vinyl phenol was found to have an oral LD50 greater than 500 mg/kg in rats. Finally, the submitter reported that p-vinyl phenol was non-mutagenic when tested with or without exogenous metabolic activation in an Ames Salmonella typhimurium (bacteria) assay.

Submission Evaluation

Although p-vinyl phenol appears to be only slightly or moderately toxic upon oral administration, based on the data from the acute rabbit skin application study, the chemical can be categorized as "extremely" toxic. Further, the results of the rabbit dermal application and eye instillation studies demonstrate that p-vinyl

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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.

phenol is both highly irritating and corrosive. In addition, it should be noted that the results of the eye instillation study suggest that p-vinyl phenol may have produced systemic toxicity resulting in the one death observed on the seventh day of that study.

In order for the Agency to evaluate the overall significance of the reported findings, the submitter should be requested to provide complete copies of the final reports (including the actual experimental protocols, data, results of gross/histopathologic examinations, results of statistical analyses, etc.) from all of the studies (including the reportedly negative in vitro mutagenicity study) that were cited in the company's submission.

Current Production and Use

p-Vinyl phenol is not listed in the non-confidential computerized version of the initial (1977) TSCA Chemical Substance Inventory. Although the submitting company did not provide any information concerning the actual/planned use(s) of p-vinyl phenol, the submitting company did state that "p-vinyl phenol is currently an experimental material . . .[that] has been made and handled solely for purposes of R&D in small quantities." The submitting company stated also that potential human or environmental exposure to p-vinyl phenol "is limited by the fact that the material is a solid." No information concerning the use(s) of p-vinyl phenol was located in the secondary literature sources consulted.

Comments/Recommendations

In its Section 8(e) notice, the submitting company stated that "all employees who may come in contact with . . .[p-vinyl phenol] have been informed of the hazardous nature of this material and have been instructed on the protective measures to be taken while working with this material."

a) The Chemical Screening Branch (CSB/ECAD/OTS/OPTS) will request the submitter to provide to EPA complete copies of the final reports (including the actual experimental protocol, data, results of gross and histopathological examinations, results of any statistical analyses, etc.) from all of the studies (including the reportedly negative in vitro mutagenicity assay) that were cited in the company's Section 8(e) submission.

   In view of the Agency's general interest in corporate actions that are taken on a voluntary basis in response to chemical toxicity or exposure information, the submitting company will be requested to describe the nature and available results of all other studies that the company has conducted, is conducting, or plans to conduct to determine the toxicity of or the exposure to p-vinyl phenol.

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

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. Copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: DEC 30 1985

SUBJECT: Status Report* 8EHQ-1285-0580 Approved: 12/31/85

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 International Business Machines Corporation (IBM) provided summarized final results from a battery of in vitro genotoxicity assays of 1-methylamino-4-(p-tolylamino)anthraquinone (Sudan Blue GA; Color Index (C.I.) Solvent Blue 11; C.I. No. 61525; CAS No. 128-85-8). According to IBM, the tested chemical had been found to be weakly mutagenic with and without metabolic activation both in the Ames Salmonella typhimurium (bacteria) Assay and the Mouse Lymphoma Cell Forward Mutation Assay. In addition, IBM reported that the chemical had been found to cause chromosomal aberrations only in the presence of metabolic activation in cultured Chinese Hamster Ovary (CHO) cells. With regard to in vivo toxicity, IBM reported that although an oral LD50 study had not been conducted, the subject chemical was mildly irritating to the skin of guinea pigs but was not a skin sensitizer.

Submission Evaluation

Although the submitted summarized information does indicate that the subject chemical possesses some degree of genotoxic activity, a full copy of the final report from each study (including the in vivo guinea pig studies) cited in the 8(e) submission are needed in order for the Agency to evaluate the overall significance of the reported findings.

Current Production and Use

A review of the production range (includes importation volumes) statistics for Sudan Blue GA (CAS No. 128-85-8), which is listed in the initial TSCA Chemical Substance Inventory, has shown that from 0 and 1,000 pounds were reported as produced and/or imported

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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 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/importation range information, is subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

In its TSCA Section 8(e) submission, IBM provided the following information concerning the company's use of and the potential for exposure to Sudan Blue GA:

> "IBM uses Sudan Blue GA exclusively in the manufacturing of metallo-ceramic chips. ["Exposure is controlled in a vented hood during the weighing of the dye stuff for incorporation into the paste coating in which [the dye] is used."] After application and processing, the chips are heated to 825 degrees Celsius [(825°C)] and the dye stuff and paste are destroyed."

No information concerning other uses or the current production volume of Sudan Blue GA was located in the secondary literature sources consulted.

Comments/Recommendations

Although a positive in vitro genotoxicity test result, when considered alone, may not be sufficient to offer reasonable support for a conclusion of substantial risk, EPA does believe that such results are of value in assessing the possible risks posed by chemicals to health or the environment. The Agency believes also that positive genotoxicity test results in combination with other information (e.g., knowledge of potential exposure to and/or high production of the tested chemical or mixture) would suggest, in many cases, the need to conduct further studies designed to define better the toxicologic properties of and/or the exposure to the subject chemical or mixture. The results of such additional studies should be considered also for possible submission to EPA under Section 8(e) of TSCA.

a) The Chemical Screening Branch (CSB/ECAD/OTS/OPTS) will request IBM to submit a full copy of the final report (including the actual experimental protocol, data, the results of gross/histopathological examinations, the results of statistical analyses, etc.) from each 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 chemical toxicity and/or exposure information, IBM will be asked to describe the actions the company has taken to notify its workers and others about the submitted findings. IBM

will be asked also to describe the nature and available results of all other studies that IBM has conducted, is conducting, or plans to conduct to define the toxicity of and/or the exposure to Sudan Blue GA.

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

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. Copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: JAN 23 1986

SUBJECT: Status Report* 8EHQ-1285-0581 Approved: 1/24/86

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 American Cyanamid Company provided the summarized results of an acute rat oral study of Calcozine® Red BG Liquid, a 45% solution of Color Index (C.I.) Basic Red 12 (CAS No. 6320-14-5) in acetic acid. According to the submitted information, the tested product (i.e., dye and solvent) was found to have an oral LD50 of approximately 41 mg/kg in the performed study. In view of the fact that 1) the oral LD50 for acetic acid is approximately 3310 mg/kg in rats, and 2) the subject product is a 45% solution, the submitter calculated the oral LD50 for undiluted C.I. Basic Red 12 to be approximately 18 mg/kg for rats. In addition, the submitting company noted that, due mainly to acetic acid content, Calcozine® Red BG Liquid can cause "irreversible eye injury and causes moderate skin irritation."

Submission Evaluation

Based on the submitted information, Calcozine® Red BG Liquid and C.I. Basic Red 12 dye could be classified as being "extremely" toxic. In order for EPA to evaluate the overall significance of the reported findings, however, American Cyanamid should be asked to provide a complete copy of the final report from the company's acute rat oral toxicity study of Calcozine® Red BG Liquid.

Current Production and Use

A review of the production range (includes importation volumes) statistics for C.I. Basic Red 12 (CAS No. 6320-14-5), 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/importation data reported were claimed as

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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.

TSCA Confidential Business Information (TSCA CBI) by the manufacturer(s) and/or importer(s) 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 TSCA Inventory Reporting Regulations (40 CFR 710).

According to the submitter, "Basic Red 12 is a coal tar dye of the methine class." According to secondary literature sources, Basic Red 12, has a "bluish-pink" fluorescent hue and may be used for both natural and synthetic fibers (e.g., silk, cotton, and nylon), leather, paper, carbon paper, and pigments.

Comments/Recommendations

In its Section 8(e) submission, American Cyanamid stated that the company has notified its customers about the reported toxicologic findings and updated the Calcozine® Red BG Liquid Material Safety Data Sheet (MSDS).

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the American Cyanamid Company to submit a complete copy of the final report (including the actual experimental protocol, results of gross/histopathologic examinations, statistical analyses, etc.) from the company's acute rat oral toxicity study of Calcozine® Red BG Liquid.

   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, American Cyanamid will be asked to describe both the nature and available results obtained from all other studies that the company has conducted, is conducting, or is planning to conduct to determine the toxicity of and/or exposure to Basic Red 12 alone or in combination with other chemicals.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of C.I. Basic Red 12.

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: JAN 30 1986

SUBJECT: Status Report* 8EHQ-0186-0582 S

Approved: 1/30/86

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 CIBA-GEIGY Corporation has claimed the exact identity of the subject chemical to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS) has requested the company to substantiate this confidentiality claim. In an addendum dated January 23, 1986, CIBA-GEIGY provided the following generic names for the subject chemical: "chlorophenoxy chlorophenyl alkyl substituted heteromonocyclic heteromonocycle" or "haloaryl biheteromonocycle."

Submission Description

The CIBA-GEIGY Corporation provided the following information with regard to the conduct and preliminary results of a 13-week dietary feeding study of the subject chemical in dogs:

> "Ophthalmoscopic examinations (using focal illumination and indirect opthalmoscopy) on dogs on test day 71 (week 10 examinations), revealed bilateral equatorial, anterior cortical and posterior cortical lenticular aberrations affecting all dogs in the high level group (6000 ppm, (3/3 male, 3/3 female)) and 1 female from the 3000 ppm level. Ophthalmoscopically, the lenticular changes were characterized as vacuoles, water clefts, spoke-like opacities, and splitting and separation of the lens suture lines with resultant "Y" shaped fissures. All [of the] other ocular structures appeared clinically unaffected at this time. No changes from normal were seen in the eyes of other dogs administered 3000 ppm or in [those] dogs treated with 1000 or 100 ppm of the test material and there appeared to be no visual deficit at this time."

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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, CIBA-GEIGY stated that in response to the reported preliminary findings, the company will:

"1. Photograph the eyes of all dogs at this time.

2. Perform bi-monthly examinations of the eyes of the dogs.

3. Remove the eyes at the scheduled 13-week necropsy.

4. During histological processing of the eyes, remove the lens of the left eye and process it separately while processing the second eye routinely."

Submission Evaluation

Although the submitted information does indicate that the tested chemical can cause dose-related lenticular aberrations, a more thorough evaluation of the 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(s), results of gross/histopathological examinations, results of any statistical analyses, etc.) from the company's dietary feeding study in dogs. In its submission, CIBA-GEIGY stated also that "there appeared to be no visual deficit . . . [in the exposed dogs]." CIBA-GEIGY did not report, however, how the exposed dogs' visual integrity was tested or if the sensitivity of such tests was sensitive enough to detect subtle but serious visual disturbances.

It should be noted that although systemic intoxication leading to lenticular aberrations is not common, such adverse effects have been reported in the published scientific literature to occur in laboratory animals and humans following exposure to a number of substances. Finally, it should be noted that the preliminary findings reported in the present submission are very similar to those submitted on a previous occasion by CIBA-GEIGY pursuant to Section 8(e) of TSCA. In 8EHQ-0285-0545 S, CIBA-GEIGY submitted the preliminary results of a dietary (dog) feeding study of CGA-149071, an R&D chemical being evaluated for pesticidal purposes and identified generically by CIBA-GEIGY as a "halophenoxy halophenyl substituted heteromonocyclic heteromonocycle."

Current Production and Use

In the present TSCA Section 8(e) submission, CIBA-GEIGY stated that the subject haloaryl biheteromonocycle "is a research and development material which is being evaluated for pesticidal purposes" and that the pesticidal evaluations "have been conducted only under the supervision of technically qualified personnel."

Comments/Recommendations

The CIBA-GEIGY Corporation reported that in addition to providing a full copy of the final report from the cited study to EPA, the company plans to provide the following notice to all personnel who work with the subject chemical:

> "Ocular changes in the dog have been noted after 10 weeks of dietary exposure to high levels of [the subject chemical]. These changes are areas of swelling in the lens. Gloves, goggles and protective equipment should be used to prevent exposure to [the chemical] until further information is available about this effect."

In addition, CIBA-GEIGY reported that the labels on containers of the subject chemical will bear the following information:

> "Eye changes in the dog have been noted in animal testing with this compound. Wear gloves and goggles when handling this compound."

It should be noted that these proposed CIBA-GEIGY communications pertain mainly to the avoidance of dermal and ocular exposure and do not address the potential for inhalation or oral exposure to the tested chemical.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask CIBA-GEIGY to ensure that EPA receives a complete copy of the final report (including actual experimental protocol(s), results of gross/histopathologic examinations, results of statistical analyses, etc.) from the dietary feeding study which is the subject of the company's present submission.

   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, CIBA-GEIGY will be requested to describe the nature and available results of all other studies that the company 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 the subject chemical.

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 also be provided to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JAN - 7 1986

SUBJECT: Status Report* 8EHQ-0685-0583 S
8EHQ-1085-0583 S FLWP

Approved: 1/3/86

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

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

NOTE

Although the CIBA-GEIGY Corporation claimed the exact chemical identity of the subject chemical as TSCA Confidential Business Information (TSCA CBI), the company did provide the following non-confidential code number for the chemical: CGA-143686. The CIBA-GEIGY Corporation has been requested to substantiate this confidentiality claim.

Submission Description

On a "For Your Information" (FYI) basis (FYI-OTS-0685-0420 S), the CIBA-GEIGY Corporation provided the following information concerning the conduct and interim results of a two-year dietary oncogenicity and chronic toxicity study of CGA-143686 in mice:

> "The dose levels [of CGA-143686] for the two-year dietary oncogenicity and chronic toxicity study are [0,] 10, 100, 1000 and 2000 ppm. The results of microscopic examination of the liver masses and nodules of animals dying on study or sacrificed *in extremis* up to month 22 indicate a statistically significant increase in liver tumors [(hepatocellular adenomas and carcinomas)] in male mice at the 2000 ppm dose level."
>
> ". . .[The] historical incidence data for mouse liver tumors of this type in the male for the . . .[testing] facility is purported to be about 8%."

In its initial FYI notice, CIBA-GEIGY also provided the following information with regard to the conduct and available results of a chronic feeding study of CGA-143686 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 addition to . . .[the 2-year oncogenicity and chronic toxicity] mouse study, CGA-143686 is being fed to rats in a two-year combined chronic toxicity/oncogenicity study. This study is also in the in-life phase. No oncogenic response has been noted in this study."

Finally, CIBA-GEIGY stated that it believed that the results of the chronic mouse feeding study did not warrant filing a Section 8(e) submission because the results were interim in nature.

Following a review of the summarized information presented in CIBA-GEIGY's initial FYI submission, EPA informed CIBA-GEIGY in writing (EPA letter dated September 19, 1985) that EPA believed that the company's interim CGA-143686 oncogenicity results constituted "substantial risk" information and, as such, should have been submitted formally to the Agency pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Cotrol Act (TSCA). The basis for the Agency's initial position with regard to the TSCA Section 8(e)-applicability of the subject findings was as follows:

> "The CIBA-GEIGY Corporation's stated position that Section 8(e) of TSCA does not pertain to interim results of toxicity studies is incorrect. Part VI of EPA's March 16, 1978 TSCA Section 8(e) policy document ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110) states that "a person is not to delay reporting until he obtains [(i.e, possesses or knows of)] conclusive information that a substantial risk exists, but is to immediately report any evidence which reasonably supports that conclusion." Part VI of the 8(e) policy document states further that "not only should [the] final results from . . . studies be reported, but also preliminary results from incomplete studies where appropriate."

In EPA's September 19, 1985 letter, CIBA-GEIGY was requested to provide additional information concerning the company's rationale as to why the subject findings were not submitted to the Agency under Section 8(e) of TSCA.

In a letter dated October 22, 1985 (FYI-OTS-1085-0420 S Followup Response), CIBA-GEIGY responded to EPA's questions and statements with regard to the TSCA Section 8(e)-applicability of the interim findings from the company's two-year dietary feeding and chronic toxicity study of CGA-143686 in mice. In its followup response, CIBA-GEIGY stated that although the company agreed with EPA that interim results of such studies could be subject to TSCA Section 8(e) reporting, one of the major reasons the company did not report the observed mouse liver tumors to EPA under Section 8(e) was that CIBA-GIEGY considered the findings to be only "limited" evidence of carcinogenicity when viewed in the context of EPA's November 23, 1984, proposed "Guidelines for Carcinogenic Risk Assessment."

In addition, CIBA-GIEGY pointed out that the tested substance was a research and development (R&D) chemical for which pesticide field testing had been halted due to lack of efficacy and all ongoing toxicologic studies of the chemical had been terminated. According to CIBA-GEIGY, the reports from the two-year dietary toxicity/oncogenicity studies of CGA-143686 in mice and rats are expected to be completed in the first and third quarters of 1986, respectively. (In additional correspondence, CIBA-GEIGY stated that a copy of the final report from an Ames test conducted with an analog of CGA-143686 would be sent to EPA when that report is received from CIBA-GEIGY Limited in Basle, Switzerland.)

Finally, CIBA-GEIGY provided the following summarized information concerning the purpose and results of other toxicologic studies that the company had conducted with CGA-143686:

> "28/90 Day Mouse Study. No observable effect level = <100 ppm. Maximum tolerated dose = ~ 1000 ppm. This study was the range-finding study used to establish dose levels in the two-year dietary oncogenicity and chronic toxicity study in mice.
>
> 28/90 Day Rat Study. No observable effect level = 100 ppm. Maximum tolerated dose = ~ 1000 ppm. This study was the range-finding study used to establish dose levels in the two-year dietary oncogenicity and chronic toxicity study in rats.
>
> 28 Day Dog Range-Finding Study. No observable effect level = <1000 ppm. Maximum tolerated dose = <5000 ppm. This study was to establish dose levels for a one-year dog study. However, the one-year dog study was cancelled when the product was dropped from further development."

Submission Evaluation

The preliminary data from CIBA-GEIGY's two-year dietary study of CGA-143686 in mice show that the heptocellular carcinoma and the hepatocellular adenoma plus hepatocellular carcinoma incidences were statistically significant in male mice at the 2000 ppm dose level when compared to concurrent controls. There is no reasonable scientific justification or merit in invoking historical control data in this case in view of the fact that the most reliable control data are those obtained under rigorously identical laboratory conditions as those for exposed animals. (In the present study, the concurrent control mice showed much less than the 8% incidence of liver tumors reportedly observed in historical control mice.) Although statistical significance was not established at 2000 ppm for hepatocellular adenomas in male or female mice or for hepatocellular carcinomas or hepatocellular carcinomas plus adenomas in female mice, the latter two tumor incidences were elevated sufficiently when compared to concurrent controls to indicate that the tumorigenic response in the female mice was

treatment related. Finally, it is most important to note that "limited" evidence of carcinogenicity (as that term is used in the Agency's proposed carcinogenicity "weight of the evidence" classification system) should not be interpreted to mean that the evidence can be dismissed or that the evidence is not reasonable in terms of its ability to support a conclusion that the chemical can cause cancer.

Current Production and Use

In view of the fact that CIBA-GEIGY asserted a confidentiality claim for the exact chemical identity of CGA-143686, no information concerning the chemical's TSCA Inventory status will appear in this report. In its initial FYI submission, CIBA-GEIGY stated that CGA-143686 was "a research and development (R&D) chemical currently being evaluated solely for pesticidal purposes" and that the pesticidal evaluations had been "conducted under the supervision of technically qualified personnel, knowledgeable in handling potentially hazardous chemicals." In its followup response letter, CIBA-GEIGY reported that CGA-143686 was, but is no longer, being evaluated by the company as an herbicide.

Comments and Recommendations

In the initial FYI notice, CIBA-GEIGY stated that all personnel involved with CGA-143686 would receive the following information:

> "Preliminary results . . . [obtained from] a two-year oncogenicity and chronic toxicity study in mice indicate there may be an increased incidence of liver tumors in male mice at the highest feeding level. Confirmation of this effect cannot be made until the study is complete and all animals examined. Until . . . [CIBA-GEIGY's] evaluation is complete, CGA-143686 should be handled in such a manner as to prevent ingestion, inhalation, or skin absorption."

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Following a review of FYI-OTS-0685-0420 S and FYI-OTS-1085-0420 S Followup Response, EPA's position is unchanged with regard to the TSCA Section 8(e)-applicability/reportability of the interim oncogenicity findings from CIBA-GEIGY's two-year dietary study of CGA-143686 in mice. The basis for EPA's decision is as follows:

> Under TSCA, the Agency can regulate certain activities involving "chemical substances" and "mixtures." If a substance is manufactured, processed, or distributed in commerce solely for use as a pesticide, however, Section 3 of TSCA excludes such substance from TSCA regulation. (See Section 3 of TSCA for other exempt substances.)

In keeping with the policy expressed by EPA in the TSCA Chemical Substance Inventory reporting regulations (43 FR 64585, December 23, 1977, Appendix A, Comment 37, 38 and 39), EPA considers a substance to be a "pesticide" within the meaning of the Federal Insecticide, Fungicide an Rodenticide Act (FIFRA) once that substance is the subject of (1) a submission made to EPA as part of the experimental use permit (EUP) process under FIFRA or (2) an application for registration submitted to EPA under FIFRA. Prior to the EUP or registration stage, however, EPA treats the substance as a "chemical substance" under the jurisdiction of TSCA.

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 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." In addition, Part VI explains that "not only should final results from such studies be reported, but also preliminary results from incomplete studies where appropriate."

With regard to the "fact or probability of its [i.e., the serious effect's] occurrence" criterion, Part V of the 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 the chemical's exposure in determining whether a risk

is substantial. Further, EPA's response to a question concerning R&D chemicals (EPA response to Comment 31 in Appendix B of the TSCA Section 8(e) policy statement) explains that the occurrence of serious effects such as those described in Part V(a) of the policy statement (e.g., cancer, birth defects) presuppose exposure to the tested chemical and must be reported under Section 8(e). Therefore, if a subject person obtains "substantial risk" information concerning an R&D chemical prior to the application for an experimental use permit (EUP) as a pesticide or registration as a pesticide under FIFRA (even though such information might be submitted at a later date to EPA under FIFRA), the "substantial risk" information must be reported under Section 8(e).

Finally, it is important to note that previously unknown evidence (preliminary or otherwise) of chemical-induced carcinogenicity observed in an animal study, regardless of how that evidence could be classified ultimately under various cancer risk assessment systems/guidelines, should be considered for immediate submission to EPA under Section 8(e) of TSCA. It should be noted also that the mere fact that cancer-related findings from an animal study could be classified as "limited" evidence of carcinogenicity (as that category is defined in EPA's proposed cancer risk assessment guidelines) does not preclude those findings in any way from reasonably supporting a conclusion that the tested chemical can cause cancer.

In view of the preceding discussion and EPA's review of the information contained in CIBA-GEIGY's initial and followup FYI submissions, EPA believes that the interim oncogenicity findings from the 2-year dietary study of CGA-143686 in mice do reasonably support a conclusion that this TSCA-covered substance can cause cancer. It is EPA's decision, therefore, that the subject cancer findings should have been reported formally to the Agency under Section 8(e) of TSCA.

a The Existing Chemical Assessment Division (ECAD/OTS) will notify CIBA-GEIGY about EPA's decision with regard to the TSCA Section 8(e)-applicability/reportability of the company's interim oncogenicity findings in mice. The Chemical Screening Branch (CSB/ECAD/OTS) will forward FYI-OTS-0685-0420 S/FYI-OTS-1085-0420 S Followup Response to the OTS Document Control Office (DCO) for appropriate handling and public 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 CGA-143686.

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, OCM/OPTS/EPA, and the Office of Pesticide Programs (OPP/OPTS). In addition, copies of this report will be provided to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: FEB 20 1986

SUBJECT: Status Report* 8EHQ-0186-0584

Approved: 2/21/86

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 Chevron Chemical Company provided the following summarized information with regard to the conduct and results of an acute oral LD50 study of RE-45550 (5-[(2-ethylthio)propyl]-2-(1-oxopropyl)-1,3-cyclohexanedione; CAS No. 99422-01-2) in rats:

> "This study was conducted to determine the acute oral toxicity of RE-45550. A previous preliminary acute oral toxicity study of RE-45550 . . . found clinical motor activity effects but no concomitant histopathological lesions in the nervous system through four days after dosing. In this recent [acute oral] study, the animals were held for 21 days after dosing to determine whether any neuropathological changes would develop over an extended study period. Five rats of each sex were dosed intragastrically with . . . [0, 50, 100, 150, 220, or] 330 mg/kg of RE-45550.
>
> "In animals that received 220 or 330 mg/kg, RE-45550 induced motor effects which included slight to severe hindlimb and/or forelimb ataxia, splayed hindlimbs, loss of pain reflex in paws, inability to grasp and/or loss of righting reflex. Other signs of toxicity in these two groups included lacrimation, nasal and ocular discharges, and pupillary miosis or mydriasis. With the exception of one male in the 220 mg/kg dose group, all animals in these two groups died or were sacrificed in moribund condition. In [the] females dosed with 150 mg/kg, signs of toxicity included slow pupil response and mydriasis. No motor or nervous system effects were observed in animals receiving 50, 100 or 150 (males) mg/kg of RE-45550. There was no mortality in these dose groups. The estimated LD50 value for both males and females is approximately 170 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.

> "Histopathologically, degeneration of the spinal nerves with hemorrhage of the spinal nerves, brain, and/or spinal cord occurred in a dose-related manner in females at 150 mg/kg and higher and in males at 220 or 330 mg/kg. . . . These lesions are considered irreversible and apparently take several days to develop after treatment. The no-effect level was 150 mg/kg for males and 100 mg/kg for females, which agreed with the in-life observations. . . . Compound-related congestion, hemorrhage acute cystitis or necrosis was present in the urinary bladder of most animals of both sexes in the 220 mg/kg group and in several animals at the 330 mg/kg group.
>
> "In summary, RE-45550 produced clinical signs of toxicity which correlated with microscopic pathological lesions."

According to the submitted information, RE-45550 has not as yet been tested for acute dermal, eye or inhalation toxicity but has been found to be non-mutagenic when tested either in the presence or absence of exogenous metabolic activation in two strains of Salmonella typhimurium (bacteria) in an in vitro Ames assay.

In its TSCA Section 8(e) notice, Chevron reported that RE-45550 is structurally similar to RE-36015 (5-[(2-ethylthio)propyl]-3-hydroxy-2-(2-oxobutyl)-2-cyclohexene-1-one; CAS No. 79419-43-5). It should be noted that in a previous TSCA Section 8(e) notice (8EHQ-1283-0501 et seq.), Chevron reported that RE-36015 caused severe and persistent paralysis in rats following acute oral exposure to non-lethal doses of the chemical.

Submission Evaluation

Based on the submitted summarized information, RE-45550 would be classified as being "very toxic" by the oral route of exposure. In addition to the observed lethality at 220 and 330 mg/kg, the provided information reveals a number of clinical effects on the motor system and widespread degeneration in the nervous system. The upper doses were accompanied by such signs as limb ataxia; loss of the grasping, pain, and righting reflexes; and pupillary dilatation and/or slowed pupillary response. Although the onset and duration of the observed neurotoxicologic signs was not reported, these signs were found to correlate with the hemorrhage and degeneration of both peripheral and central neurons in the spinal cord and brain stem observed in male and female rats at 220 and 330 mg/kg and in a few females at 150 mg/kg. Finally, the submitted summarized information indicates that exposure to RE-45550 could result in renal dysfunction and possibly failure as a consequence of the adverse effects observed histologically in the urinary tract.

Current/Production and Use

In the cover letter to its Section 8(e) notice, Chevron reported that RE-45550 "is the fifth intermediate in a series of seven in the production of a chemical, which if developed successfully, would be registered and sold as a pesticide." The company did not report whether RE-45550 would be an isolated or non-isolated intermediate in the final pesticide production process. A review of the computerized version of the non-confidential TSCA Chemical Substance Inventory shows that CAS No. 99422-01-2 is not listed.

Comments/Recommendations

In its Section 8(e) notice, Chevron submitted an interim version of the company's RE-45550 Material Safety Data Sheet (MSDS). It should be noted that the interim MSDS (which states that RE-45550 has an oral rat LD50 value of 222 mg/kg, whereas the Section 8(e) submission states that the oral rat LD50 is 170 mg/kg), does not appear to address the full extent or overall severity of some of the reported toxicologic findings.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the Chevron Chemical Company to provide complete copies of the final reports (including the actual experimental protocols, results of gross/histopathological examinations, results of any statistical analyses, etc.) from the two acute in vivo oral toxicity studies and the in vitro mutagenicity 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 information, Chevron will be asked to describe the nature and available results of all other studies that the company has conducted, is conducting, or plans to conduct to determine the toxicity of and/or the exposure to RE-45550.

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 status report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: FEB 25 1986

SUBJECT: Status Report* 8EHQ-0186-0585 S Approved: JFD for JDZ 2/25/86

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 CIBA-GEIGY Corporation submitted final results from a 28-day oral gavage study of Tinuvin® 144 (CAS No. 63843-89-0)** in rats. In the cover letter to its submission, CIBA-GEIGY presented the following information with regard to the conduct and results of the performed study, which, according to the company, shows a potential immunosuppressive activity for Tinuvin® 144:

> "Rats received daily gavage doses of 0, 60, 100, 300, 600 and 1000 mg/kg for 28 days. The corresponding mortality rates for these respective groups were as follows: 0, 0, 30, 70, 80 and 100%. Where observations could be made, all [of the] dose levels produced alterations in white blood cell parameters and thymus weight as well as lesions in the spleen, abdominal lymph nodes, and liver. The lesions were described as abscesses which occurred in 5 of 10 animals at 100 mg/kg and in 2 of 10 animals at 60 mg/kg. In addition to these lesions, there was a significant dose-related decrease in thymus weight and thymic tissue atrophy. The decrease in the weight of the thymus for males was 42%, 56% and 94% in the 60, 100 and 300 mg/kg groups, respectively. Females showed decreases of 10%, 46%, and 91% in the corresponding dose groups. Significant changes in the white blood cell parameters included marked elevations in the number of leukocytes and segmented neutrophiles, as well as dramatic reductions in the number of lymphocytes."

(** According to CIBA-GEIGY, the actual chemical identity of Tinuvin® 144 is: propanedioic acid, ((3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl)methyl)butyl-, bis(1,2,2,6,6-pentamethyl-4-piperidinyl) ester.)

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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 the submitted study report, aspermatogenesis was observed in male rats exposed to Tinuvin® 144 at doses of 300, 600, and 1000 mg/kg. In addition, the study report states that increased blood clotting time was found in 1 male and 2 females in the 300 mg/kg dose group.

According to a submitted Material Safety Data Sheet (MSDS), Tinuvin® 144 was found to have an oral LD50 of 1500 mg/kg (rats), a dermal LD50 of >3100 mg/kg (rats); and a 4-hour LC50 of >0.46 mg/L (rats; exposure to an aerosol containing approximately 60% particles with sizes <7 microns). In addition, the provided MSDS indicates that studies in rabbits have shown that the product is non-irritating to the skin and only slightly irritating to the eyes. The MSDS states also that sensitization studies in guinea pigs showed the product to be negative following epidermal challenge but positive following intradermal challenge. Further, the MSDS states that a study involving 80 human subjects exposed to Tinuvin® 144 showed an apparent dose-related increased incidence of erythema but did not show sensitization. The Tinuvin® 144 MSDS states also that the product was found to be negative in a mouse phototoxicity study and in a guinea pig photosensitization study. Finally, the submitted MSDS states that the product was negative in an in vitro bacterial mutagenicity assay (Ames test).

Submission Evaluation

Immunosuppression is a very important and serious manifestation of systemic toxicity and can leave the affected individual open to 1) infection and/or 2) development of cancer; either can be life-threatening or life-shortening. Although CIBA-GEIGY's 28-day study of Tinuvin® 144 in rats is of too short a duration to evaluate whether tumor development was favored, it does show that the treated animals had an apparent susceptibility to infection (abscesses; poor general health) and that the chemical had an unmistakable dose-related impact on survival. Rats in the control group and the 60 mg/kg/day group lived through the 28-day study. At 100 mg/kg/day, 30% of the rats died in 11-27 days. At 300 mg/kg/day, 70% died in 5-10 days, while at 600 mg/kg/day, 80% died in 4-7 days. At 1000 mg/kg/day, all rats died in 3-6 days. The observed survival rates were approximately equal among males and females.

Female rats treated with 60 mg/kg/day gained weight at a rate similar to controls while males treated with 60 mg/kg/day gained weight at a similar rate for 21 days, and then leveled off. Rats of either sex treated with 100 mg/kg/day gained weight but at a much slower rate than the controls. Rats of either sex treated with the higher doses (i.e., 300, 600 or 1000 mg/kg/day) actually lost weight in a dose-related manner. The observed decreases in body weight correlated well with the observed decreases in food intake. Considering that this 28-day study involved exposure to the subject chemical by gavage, unpalatability of the food does not appear to be an issue.

The observed toxic signs reportedly included ataxia, muscular hypotonia, ptosis of the eyelids, hunched posture ("kyphotic carriage"), diarrhea, and gas in the intestines ("meteorism"). Neurohistochemical examinations of the sympathetic portion of the autonomic nervous system (presumably conducted because of the observed ptosis of the eyelids) did not reveal any difference between control animals and two rats each from both the 60 and 100 mg/kg/day dose groups. It is unclear why 60 mg/kg/day was chosen for examination in the neurohistochemical portion of the study rather than a higher dose, because ptosis was not reported in the 60 mg/kg/day group, but was reported in the higher-dose groups. This curiosity may not be vital, however, because the ataxia, hypotonia, and kyphotic carriage could be attributed alternatively to pain or malaise resulting either directly from treatment or secondarily from distention of the intestines with gas ("meteorism").

Histological examination and hematology showed a large-scale involvement of the reticuloendothelial immune system (thymus, lymph nodes, spleen, liver, and circulating white blood cells). The apparent increase in the total number of white blood cells may be either an artifact (e.g., as the result of serum-volume losses following diarrhea-induced dehydration) or due to a real increase in neutrophilic granulocytes (e.g., responding to acute infection, as indicated by the observed abscesses). Further, the observed depletion of circulating lymphocytes is consistent with immunosuppression. The observed atrophy of the thymus is also consistent with immunosuppression. The thymus is the source of T-lymphocytes that perform a variety of immune functions. The thymus is, however, a relatively insensitive indicator of immunosuppression. It is quite likely, therefore, that many other more sensitive but unmeasured immune-system changes occurred prior to the development of thymic atrophy.

A serious adverse effect observed in the 28-day gavage study but not mentioned in the submitted Tinuvin® 144 MSDS is the impaired spermatogenesis in male rats in the 300, 600, or 1000 mg/kg/day dose groups. Although this effect could be explained as being due to stress, ill health, or impaired nutrition if it were found in a 90-day study in rabbits for example, the rat testis is considered generally to be more hardy than the rabbit testis and a 28-day study covers only about half of the spermatogenic cycle. It is possible, therefore, that Tinuvin® 144 may have a direct adverse effect on the testis and testicular function. Further testing would be needed to sort out the cause(s) of the observed impairment of spermatogenesis.

Another serious adverse effect that deserves attention, although the submitted data are inadequate to permit its full appreciation at this time, is the prolongation of clotting time. This effect, which may have resulted from impaired liver function, could have contributed significantly to the hemorrhage that was observed in the lungs.

In general, the reported adverse immune-system effects appear to be of the type that one might expect to see in the first tier of the National Toxicology Program's tier-testing scheme for immunotoxic effects: screening tests based on hematology, body weight, organ weights (e.g., thymus, spleen, lymph nodes), and histology (e.g., cellularity of spleen and thymus). A wide variety of more specific and refined tests is available at the present time with which to pursue more in-depth immunologic questions (e.g., cell-mediated versus humoral immunity, effects on specific lymphocyte populations, or host resistance to bacterial, viral, or parasitic infection).

Finally, it should be noted that Tinuvin® 144 bears a striking structural resemblance to a chemical that was the subject of a TSCA Section 5 "Pre-Manufacture Notice" (PMN No. 81-495) submitted previously by CIBA-GEIGY. It would be of interest to know if CIBA-GEIGY has conducted, is conducting, or plans to conduct any studies to determine if that PMN chemical can cause adverse effects similar to those found in the 28-day study of Tinuvin® 144.

Current Production and Use

A review of the production range (includes importation volumes) statistics for CAS No. 63843-89-0, which is listed in the initial TSCA Chemical Substance Inventory, has shown that 1,000 to 10,000 pounds of this chemical were reported as produced and/or imported in 1977. This production range information does not include any production/importation data claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the information submitted to EPA for the initial TSCA Inventory, including the production range information, is subject to the limitations that are contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

In its submission, CIBA-GEIGY reported that the subject chemical has a molecular weight of 685 and "is an off-white crystalline powder having a melting point of 146-150°C and a vapor pressure of approximately 1×10^{-10} mm Hg at 20°C." CIBA-GEIGY reported also that Tinuvin® 144 "is an ultraviolet light stabilizer used in automobile coatings and polypropylene fibers." In addition, CIBA-GEIGY provided the following information with regard to the potential for exposure to Tinuvin® 144:

> "[The] workplace exposure to Tinuvin® 144 is generally limited to initial manual transfer operations. Subsequent mixing and master batch production operations are carried out mechanically in large scale mixing equipment.
>
> "The product is flowable and particles adhere to one another. Manual transfer operations thus produce minimal dusting.

"The [product's] moderately high molecular weight and limited water solubility should significantly reduce skin penetration.

". . . [CIBA-GEIGY's] five major customers using this product are health and safety conscious and already employ protective equipment to reduce exposure to solvents and other hazardous chemicals used in the same operations. One customer requires "space suits" to be worn when handling the product (because of [the] other chemicals used).

"Once formulated into polypropylene masterbatches, exposure to Tinuvin® 144 is precluded as the polyolefin pellets are generally 1/16 - 1/8" in diameter. User exposure further downstream is also largely precluded since the product is encapsulated within the plastic substrate.

"In automotive coatings, Tinuvin® 144 is completely enclosed in the dried vehicle of the coating system."

Comments/Recommendations

In order to "further reduce any risk to CIBA-GEIGY workers and downstream users," CIBA-GEIGY reported that the company has revised the Tinuvin® 144 Material Safety Data Sheet (MSDS) to reflect the reported toxicologic findings and has revised the Tinuvin® 144 product label to read in part:

"NOTICE: Liver, lymphoid, and blood system effects were seen in a feeding study conducted in laboratory animals. The relevance of these findings to humans is unknown."

CIBA-GEIGY stated also that in accordance with the Occupational Safety and Health Administration's (OSHA) Hazard Communication Standard (29 CFR 1910.1200), CIBA-GEIGY's "customers will be notified of these [toxicologic] findings via the revised MSDS and label within 90 days" and CIBA-GIEGY's "workers will be informed via the revised MSDS and the company's OSHA Hazard Communications Program."

In its submission, the CIBA-GEIGY Corporation requested EPA to address the TSCA Section 8(e)-applicability of immunotoxicologic findings. The purpose of the following discussion is to provide the basis for EPA's position with regard to the reportability of such findings under Section 8(e) of 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 [EPA] 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 TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978) 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 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 cancer, mutation, birth defects, or serious or prolonged incapacitation." (Emphasis added.) Information concerning these effects can be obtained directly or inferred from designed studies (e.g., in vivo animal studies) as described in Part VI of the TSCA 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 which reasonably supports that conclusion." In addition, Part VI explains that "not only should final results from such studies be reported, but also preliminary results from incomplete studies where appropriate."

With regard to the "fact or probability of its [i.e., the serious effect's] occurrence" criterion, Part V of Section 8(e) policy statement explains also that certain kinds of health effects are considered to be so serious that relatively little weight should be attached to exposure in determining whether a risk is substantial.

Based on the preceding discussion, it should be clear that if a company obtains (i.e., possesses or knows of) "new" information that offers reasonable support for a conclusion that exposure to a TSCA-covered chemical substance/mixture which that company manufactures, imports, processes or distributes in commerce can cause or ultimately result in serious immunomodulation (i.e., immunosuppression or immunostimulation), that company should report such information to EPA under Section 8(e) of TSCA within 15 working days in full accordance with the reporting procedures outlined in Part IX of EPA's March 16, 1978 Section 8(e) policy statement.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the CIBA-GEIGY Corporation to submit full copies of the final reports (including the actual experimental protocols, results of gross and histopathologic examinations, results of statistical analyses, etc.) from all studies cited in Part VI ("Health Hazard Data") of the company's Tinuvin® 144 Material Safety Data Sheet.

In view of the Agency's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity and/or exposure information, the Chemical Screening Branch will request CIBA-GEIGY to describe the nature and available results of all studies (other than the subject 28-day gavage study and those cited in the company's Tinuvin® 144 MSDS) about which CIBA-GEIGY is aware including those that the company has conducted, is conducting or plans to conduct to determine the toxicity of or the exposure to the subject chemical. CIBA-GEIGY will be asked also to describe the nature and available results of all studies (other than those submitted previously to EPA) about which CIBA-GEIGY is aware or that the company has conducted, is conducting, or plans to conduct to determine the toxicologic properties of the chemical which was the subject of PMN No. 81-495.

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, OW/EPA, OSWER/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) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: FEB 11 1986

SUBJECT: Status Report* 8EHQ-0186-0586 S

Approved: 2/12/86

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 and actual use of the subject chemical substance to be TSCA Confidential Business Information (TSCA CBI). Staff of the Information Management Division (IMD/OTS) will request the submitting company to substantiate these confidentiality claims. In its TSCA Section 8(e) notice, the company provided the following non-confidential generic name for the subject chemical substance: "2-chloro-N-methyl-N-substituted-acetamide." In addition, the submitter stated that 1) this chemical was the subject of a TSCA Section 5 "Premanufacture Notice" (PMN No. P-84-393), and 2) the performed toxicologic study was conducted under the terms of a TSCA Section 5(e) "Consent Order."

Submission Description

In its TSCA Section 8(e) notice, the submitting company provided the following summary information with regard to the conduct and results of a 90-day dietary feeding study of 2-chloro-N-methyl-N-substituted-acetamide in rats:

> "Male and female Sprague-Dawley rats were fed diets containing [the subject chemical substance] at levels which provided daily dosages of 0, 500, 1100 and 2500 ppm for 13 consecutive weeks. The dosing regimen was selected after evaluation of [the] results obtained in a preliminary study (28-Day Dose-Range Toxicity Study in Rats . . .), which indicated body weight and food consumption effects were likely in a 90-day toxicity study at levels of 2500 ppm and greater.

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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.

"Under the conditions of this study, [the chemical] did not cause mortality in either sex at any dose level studied. No treatment-related abnormalities, clinical signs of toxicity or behavioral changes were noted. Administration of [the chemical] did cause several statistically significant differences in one or both sexes when comparing body weight, body weight gain, food consumption, food conversion and/or relative organ weight data between [the] control and test groups. No compound-related hematology or clinical chemistry effects were demonstrated after 13 weeks among groups.

"Relative kidney weights of mid and high-dose males were significantly increased after 13 weeks when compared to the control group. Microscopic examination of urine sediment identified a significant increase in cast formation in [the] males at all treatment levels studied. No gross pathological lesions indicative of a treatment-related effect were noted among groups after the 13 weeks. Microscopic findings (intratubular protein casts, hyaline droplets and tubular regeneration) in the kidneys of males at one or all treatment levels, which were characteristic of protein nephropathy, were significantly increased when compared to the control groups.

"The onset of significant decreases in body weight and food consumption incurred by males at both the mid and high-dose levels with no meaningful differences in weekly food conversion (body weight gain per gram of food consumed) suggested, at least in part, the cause was due to decreased palatability of the test diets. However, since no significant or dose-related decreases in food consumption were noted for females during the entire study and no recovery in body weight gain during the second-half of the study period (weeks 7-13) was demonstrated in males, toxicity and not palatability was determined responsible for the decreases noted in the males. Toxicity is further supported by significant increases in relative kidney weights at both the mid and high-dose levels as well as by the significant increase of cast formation in the urine and the treatment-related pathological changes in the kidneys of [the] male animals at all dose levels.

"Thus, administration of [the subject chemical] at the dietary levels studied for 13 consecutive weeks produced toxicological and pathological effects in male rats. No toxicological effects were evident in female rats."

Submission Evaluation

Based on the submitted summary information, it does appear that the subject chemical has a deleterious effect on the kidney of male rats. Further evaluation of the reported findings should be possible upon the Agency's receipt of full copies of the final reports from the 28-day dose range-finding and 90-day dietary studies cited in the submission.

It should be noted that immediately upon receipt of this TSCA Section 8(e) notice, the Chemical Screening Branch (CSB/ECAD/OTS) provided complete copies of the submission to the Premanufacture Notice Management Branch (PNMB/CCD/OTS) and the Existing Chemical Control Branch (ECCB/CCD/OTS) for review.

Current Production and Use

According to the non-confidential version of PMN No. P-84-393, the proposed generic use of the subject chemical is as a starch modifier. In the Section 8(e) notice, the submitting company stated that 1) the substance "is currently being manufactured as an intermediate" and 2) to the best of the submitting company's knowledge, the submitting company is sole U.S. manufacturer of the chemical.

With regard to potential exposure to the subject chemical, the submitting company reported in its Section 8(e) submission that workers exposed to the chemical "are required to wear NIOSH, category 19c air-supplied, positive pressure respirators, impervious gloves and clothing which covers exposed areas of the arms, legs, and torso." In addition, the submitter reported that all workers who handle the chemical have attended "training programs" on the hazards of the chemical. Finally, the submitter stated that the product label reflects the reported toxicologic findings and presents safe handling recommendations.

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, the results of statistical analyses, etc.) from the 28-day and 90-day studies cited in the company's TSCA Section 8(e) submission.

   In view of the Agency's general interest in corporate actions that are taken on a voluntary basis in response to chemical toxicity or exposure information, the submitting company will be asked to describe the nature and available results of all studies (other than those reported already to the Agency) that the company has

conducted, is conducting, or is planning to conduct to determine the toxicity of and/or the exposure to the subject chemical substance.

b) As in the case of the initial TSCA Section 8(e) notice, the Chemical Screening Branch will immediately forward all additional information received on this chemical to the Premanufacture Notice Management Branch/CCD/OTS and the Existing Chemical Control Branch/CCD/OTS for review and appropriate followup action.

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, PNMB/CCD/OTS and ECCB/CCD/OTS. Copies of this status report will be sent also to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

DATE: FEB 13 1986

SUBJECT: 8EHQ-0186-0587

Approved: 2/18/86

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 Fragrance Materials Association (FMA) of the United States submitted the following information concerning the conduct and preliminary findings of oral and dermal teratologic studies of phenylethyl alcohol (PEA; CAS No. 60-12-8) in rats. (According to the submitted information, the dermal study was sponsored by the Research Institute for Fragrance Materials (RIFM) and the oral study was sponsored by the Flavor and Extract Manufacturers' Association (FEMA).)

> "In the oral study, rats were given microencapsulated PEA in the diet at levels of 0 (control), 1000, 3000, or 10,000 ppm during days 6 to 15 of pregnancy. In the dermal study (designed to maximize exposure by using undiluted material under 24 hour/day occlusion at the maximum possible dosage), doses of 0 (control), 0.14, 0.43 and 1.40 ml/kg of neat material were applied topically during days 6 to 15 inclusive of pregnancy. An occlusive bandage was used to minimize oral ingestion of the test material and to minimize evaporation. This bandage was put on immediately after dosing and not removed until the following day. In both . . . [the oral and dermal studies,] the animals were killed on day 20 of pregnancy and in utero development was assessed by determination of litter values and examination of the fetuses for soft tissue and skeletal changes.
>
> "At the high oral dose there was initial suppression of maternal appetite and a slight overall weight loss in dams during the first two days of treatment. A slightly higher incidence of fetuses with incomplete ossification of some skeletal elements was concluded to be a negligible detrimental effect. There were no effects at the lower doses.

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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.

"Dermal treatment at the 1.4 ml/kg level resulted in maternal toxicity as manifested by death of 3/35 animals, progressively marked clinical signs of reaction, suppression of [the] mean food intake and growth rate. This dose also resulted in total loss (resorption) of 5/23 litters and 50% or more embryofetal wastage in a further 4/18 litters. However, 7/18 animals carrying to term had less than 10% early resorptions so that there was obviously a marked difference between rats in their response to treatment. The general reduction in mean litter size resulting from these losses was also accompanied by depression of fetal weight assessed at day 20 of gestation. Additionally, morphological abnormalities were observed in virtually all fetuses. Both soft tissue and skeletal changes were observed; ossification was incomplete.

"At the 0.43 ml/kg dosage there was no clear evidence of any adverse effect on the parent animal and litter parameters were comparable with those of the control group. While the number of fetuses showing structural changes in soft tissue were slightly higher than [the] controls, no pattern was obvious. Skeletal examination revealed the number of fetuses with cervical rib(s) and those showing moderate degrees of reduced ossification were significantly less than in the high dose but were significantly higher than [in the] controls. These cervical ribs were extremely small, usually just a dot which was weakly stained. Studies are being planned that will investigate the likelihood that these effects would not persist into post-natal life or if they did, whether they would have any functional significance.

"The lowest . . .[dermal dose] did not produce any evidence of overt maternal toxicity or adverse effect on litter parameters. Neither the incidence nor distribution of structural changes recorded could be considered to provide conclusive evidence of association with treatment; incidences of such changes were slightly higher than control."

FMA's TSCA Section 8(e) submission also presented the following information concerning ". . . comparative dermal absorption, distribution, metabolism and excretion studies in humans and rats" recently initiated or planned by RIFM "to aid in determination of risk to humans."

"Studies are underway which are designed to obtain data allowing exact extrapolation of absorbed dose from the rat to the human. The initial results of these studies indicate that about 60% of the [PEA] dose applied neat and under occlusion to the rat is absorbed. Studies in humans should begin in the near future. (General knowledge of relative permeabilities of rat skin and human

skin combined with consideration of the extreme conditions of exposure used in the rat study would lead to the conclusion that the assumption of 10% absorption by humans under conditions of normal exposure is greatly exaggerated.)"

Submission Evaluation

Immediately upon receipt of this TSCA Section 8(e) notice, the Chemical Screening Branch (CSB/ECAD/OTS) provided a copy to the Risk Analysis Branch (RAB/ECAD/OTS) for inclusion in the ongoing RAB/ECAD review of available toxicologic and exposure information on phenylethyl alcohol. It should be noted that in 1985, the Chemical Screening Branch prepared a Chemical Hazard Information Profile (CHIP) on phenylethyl alcohol (CAS No. 60-12-8) and its acetate (CAS No. 103-45-7). In preparing that CHIP, CSB received several "For Your Information" (FYI) submissions on phenylethyl alcohol and its acetate.

Current Production and Use

A review of the production range (includes importation volumes) statistics for phenylethyl alcohol (CAS No. 60-12-8), which is listed in the initial TSCA Inventory, has shown that between 1.34 million and 13.4 million pounds were reported as produced and/or imported in 1977. This production range information does not include any production or importation data that were claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

According to secondary literature sources, phenylethyl alcohol is used as a fragrance in cosmetics, soaps, detergents, creams, lotions, air fresheners, perfumes (particularly rose perfumes), and possibly paper products; other uses reportedly include: synthetic flavoring agent, antimicrobial agent, preservative, mosquito and housefly repellant and chemical intermediate.

FMA's Section 8(e) submission contained the following information with regard to the potential for human exposure to phenylethyl alcohol:

"The best estimates of exposure are an average daily exposure of about 12 mg/day and a 90%ile use level exposure of about 32 mg/day. Assuming a weight of 50 kg and absorption of 10% of the dose, the 90%ile absorbed dose would be 0.064 mg/kg/day. This gives a safety factor of about 25,000 compared to the high dose and about 2,500 compared to the low dose."

Comments/Recommendations

Although EPA considers that anyone may submit information to the Agency under Section 8(e), the "substantial risk" information reporting provision of the Toxic Substances Control Act (TSCA), only certain persons are required to do so. In view of the fact that a number of TSCA Section 8(e) submissions have been received thus far by EPA from chemical trade/research associations, the purpose of the following discussion is to reiterate EPA's policy with regard to the TSCA Section 8(e) reporting obligation of such organizations and chemical companies that may be members of such organizations.

> 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."
>
> 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 the Agency considers the term "person" to include "any natural person, corporation, firm, company, joint-venture, sole proprietorship, association, or any other business entity . . . ." Therefore, the obligation to immediately report substantial risk information to EPA would apply to a chemical trade or research association only if that organization itself is engaged in the manufacture, importation, processing, or distribution of the chemical substance or mixture about which substantial risk information has been obtained. It is more likely, however, that a mandatory Section 8(e) reporting obligation would be incurred by a member or non-member company that obtains the results (including preliminary results) from studies conducted or sponsored by a chemical trade or research association, if the obtained results meet the reporting criteria outlined in the Agency's TSCA Section 8(e) policy statement and pertain to a chemical substance or mixture that the company manufactures, imports, processes, or distributes in commerce.
>
> Part III of the EPA's TSCA Section 8(e) policy statement explains that substantial risk information is obtained at that time when any company officer or employee who is capable of appreciating the significance of the information, either possesses, or knows of, that information. Except in situations involving "Emergency Incidents of Environmental Contamination" (EIECs), the obligation to immediately report substantial risk information to EPA

is considered discharged if EPA receives the information 1) in accordance with the reporting requirements outlined in Part IX of the Section 8(e) policy statement, and 2) not later than the 15th working day after the date the information was obtained. The information need not be reported to EPA, however, if the subject person has actual knowledge that the Agency has already been adequately informed about that information. Part VII of the TSCA Section 8(e) policy statement provides further guidance with regard to the types of information that need not be reported under Section 8(e). In addition, Section 3 of TSCA itself lists those substances (e.g., drugs, pesticides) that are not covered by TSCA.

Finally, it should be noted that a company that relies on some other party to submit information under Section 8(e) on the company's behalf, must ensure that EPA receives the information in a timely manner and in full accordance with the requirements outlined in Part IX of EPA's TSCA Section 8(e) policy statement.

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a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask FMA to ensure that the Agency receives complete copies of the final reports (including the actual experimental protocols, results of gross and histopathologic examinations, results of statistical analyses, etc.) from all studies cited in FMA's submission.

b) The Chemical Screening Branch will immediately forward all reported information on phenylethyl alcohol to the Risk Analysis Branch/ECAD/OTS for inclusion in their ongoing assessment of this chemical substance.

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, and RAB/ECAD/OTS. In addition, copies of this report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAR 19 1986

Approved: 3/19/86

SUBJECT: Status Report* 8EHQ-0286-0588

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 submitted a copy of the following published article: "Fertility of Male Workers Exposed to Mercury Vapor or to Manganese Dust: A Questionnaire Study" (R. Louwerys et al., American Journal of Industrial Medicine, Vol. 7, pages 171-176, 1985). In the cover letter to its Section 8(e) submission, Union Carbide stated that the company's rationale for submitting this published paper was that the company was unable to locate an abstract of the provided article in any of the six abstracting services listed in Part VII(c) of EPA's Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" March 16, 1978; 43 FR 11110; March 16, 1978). Union Carbide noted, however, that the submitted article was abstracted by other well-known abstracting services including BioSciences Information Service (BIOSIS).

Comments/Recommendations

Part VII(c) of EPA's TSCA Section 8(e) policy statement explains that information need not be reported to EPA under Section 8(e) if the subject information "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, [and/or] (6) National Technical Information Service." Considering that (1) BioSciences Information Service (BIOSIS) publishes both the printed and on-line computerized versions of Biological Abstracts, and (2) an abstract of the submitted scientific paper can be found in both the printed and computerized versions of Biological Abstracts, the Union Carbide Corporation's submission of the subject article was not warranted 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.

a) The Chemical Screening Branch will review the submitted article to determine the need for further OTS assessment of the reported findings.

b) The Chemical Screening Branch will send copies of this status report to OSHA, NIOSH, FDA, CPSC, 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 for further distribution.

DATE: MAR 28 1986

SUBJECT: Status Report* 8EHQ-0386-0589 S Approved: 3/31/86

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 CIBA-GEIGY Corporation has claimed the actual identity of the subject substance to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS) will request CIBA-GEIGY to substantiate this confidentiality claim. In its submission, CIBA-GEIGY did report non-confidentially that the subject chemical was an azo dye having the following Color Index (C.I.) name: C.I. Reactive Orange 12.

Submission Description

The CIBA-GEIGY Corporation reported that CIBA-GEIGY Ltd. (Basel, Switzerland) had been notified by Imperial Chemical Industries (ICI) PLC (Manchester, England) that C.I. Reactive Orange 12 was a human respiratory sensitizer. In its Section 8(e) submission, the CIBA-GEIGY Corporation reported that ICI had documented 10 cases of allergic symptoms (7 ICI employees and 3 employees in customer facilities). According to CIBA-GEIGY, ICI stated that the ICI Medical Officer's re-examination of ICI employee occupational records confirmed the ICI Medical Officer's opinion that all affected ICI employees suffered from acute allergic symptoms between 1968 and 1985 as the result of exposure to C.I. Reactive Orange 12. According to CIBA-GEIGY, ICI reported that in one case the finding was confirmed by an inhalation challenge test and confirmed in another case by the detection of elevated IgE antibody levels to C.I. Reactive Orange 12.

In its Section 8(e) submission, CIBA-GEIGY reported also that a CIBA-GEIGY product (Cibacron Golden Yellow 2R-A powder which contains C.I. Reactive Orange 12) had been tested by CIBA-GEIGY and found to be non-irritating to the skin or eyes and to have 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.

oral (rat) LD50 of greater than 5 g/kg. In addition, CIBA-GEIGY reported that Cibacron Golden Yellow 2R-A powder was found to be a skin sensitizer in guinea pigs but not in humans.

With regard to the relative risk of pulmonary sensitization posed by exposure to C.I. Reactive Orange 12 or to products containing this azo dye, CIBA-GEIGY reported that the company believes that the risk would be the highest in those circumstances involving "uncontrolled exposure to a finely divided powdered form," less serious under conditions involving exposure to granular material, and almost negligible in those cases involving exposure to liquid formulations. Finally, CIBA-GEIGY reported that the company "has imported [C.I. Reactive Orange 12] dyes for over 8 years and has never received any human health complaints from [CIBA-GEIGY] employees or from the user industry's employees."

Submission Evaluation

Immunologic sensitization is a systemic condition that can be initiated by either acute or chronic exposure to a chemical substance. Once sensitized, an affected individual may react mildly or severely to further acute or chronic exposure to the causative agent. The site of reaction is not necessarily predictable in that the reaction can occur at the site of exposure and/or at a site or sites in the body distant from the point of contact with the causative agent. The duration of reaction and consequences of reaction are not necessarily predictable either and may range from quite short to long-term. When a sensitization reaction takes place in the pulmonary system, for example, that reaction could have been provoked by inhalation or other (e.g., dermal) exposure to the causative agent and may manifest itself by a mild to severe asthmatic-like condition of unpredictable duration. In some cases, sensitization reactions can be extremely serious, debilitating and even life-threatening. It should be noted also that a sensitization reaction can occur as the result of exposure to a chemical structurally similar to the initial causative agent (cross-sensitization). Cross sensitization reactions involving C.I. Reactive Orange 12 may be of concern in that sensitization reactions involving other azo dyes have been well documented.

Current Production and Use

In view of the fact that CIBA-GEIGY claimed the exact identity of the subject azo dye to be TSCA CBI, no production/importation information derived from the non-confidential computerized version of initial TSCA Chemical Substance Inventory will appear in this status report. It should be noted that C.I. Reactive Orange 12 is listed in several publicly available computerized scientific data bases (e.g., TOXLINE, CHEMLINE) as having been assigned the following Chemical Abstract Service (CAS) Registry Numbers: 12225-84-2. It should be noted also that CAS No. 12225-84-2 replaced CAS No. 82600-93-9 for C.I. Reactive Orange 12. Neither of these CAS Registry Numbers was found, however, in the non-confidential computerized version of the TSCA Chemical Substance Inventory.

In its submission, CIBA-GEIGY reported non-confidentially that the company imports C.I. Reactive Orange 12 "as a component of 5 dyestuff mixtures consisting of two different physical forms: in granular or powder form as Cibacron Golden Yellow 2R-A, Cibacron Golden Yellow 2R and Cibacron Black GR-D; and in liquid form as Cibacron Golden Yellow 2R LQ 25 and Cibacron Black GR LQ 40." (Note: CIBA-GEIGY has asserted TSCA CBI claims for the amount of C.I. Reactive Orange 12 in these dyestuff products and the total volume of active ingredient C.I. Reactive Orange 12 imported by the company in 1985. The Information Management Division will request CIBA-GEIGY to substantiate these confidentiality claims as well.)

With regard to the use of C.I. Reactive Orange 12, CIBA-GEIGY stated that the dye is "used for piece dyeing of cellulosic knit fabrics by an atmospheric exhaust process in becks." According to secondary literature sources, C.I. Reactive Orange 12 can be used also to dye and/or print wool, silk or nylon.

Comments/Recommendations

In its submission, CIBA-GEIGY stated that the company plans to modify the Material Safety Data Sheet (MSDS) and label for all granular and powdered products containing C.I. Reactive Orange 12 to reflect the potential for human respiratory sensitization. In addition, CIBA-GEIGY stated that its employees as well as those customers who purchased powdered or granular products containing C.I. Reactive Orange 12 will be notified about this adverse human health effect and the need for appropriate engineering controls and/or personal protective equipment. Finally, CIBA-GEIGY stated that the company is planning to recommend to its customers that when "suitable controls are not feasible or practical, potential inhalation exposure, and therefore [the] risk of respiratory sensitization, can be reduced to negligible levels by switching to a liquid form of the dye."

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask CIBA-GEIGY to 1) provide to EPA a complete copy of the ICI notification letter to CIBA-GEIGY concerning the 10 cases of pulmonary sensitization observed in workers exposed to C.I. Reactive Orange 12, and 2) keep the Agency abreast of any further developments with regard to human pulmonary sensitization resulting from exposure to C.I. Reactive Orange 12 or products containing this dye. In addition, CIBA-GEIGY will be asked to provide to EPA 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 each study (including the human patch test) of Cibacron Golden Yellow 2R-A cited in the company's TSCA Section 8(e) submission.

In addition, the Chemical Screening Branch will request ICI Americas Inc. to submit to EPA all information in the company's possession or control which relates to the risk of human pulmonary sensitization posed by exposure to C.I. Reactive Orange 12.

Considering EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, CIBA-GEIGY and ICI Americas Inc. will be requested to describe the nature and available results of all studies (other than those already submitted to EPA or those published in the open scientific literature) about which the companies are aware or that the companies have conducted, are conducting, or plan to conduct to determine the toxicity of or exposure to C.I. Reactive Orange 12 or products containing this azo dye. In addition, ICI Americas Inc. will be asked to describe the actions that the company has taken or plans to take to 1) warn workers and others about the risk of respiratory sensitization posed by exposure to C.I. Reactive Orange 12, and 2) reduce and/or eliminate exposure to C.I. Reactive Orange 12 or products containing this dye.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of C.I. Reactive Orange 12.

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. Copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: MAR 26 1986

SUBJECT: Status Report* 8EHQ-0386-0590 S

Approved: 3/27/86

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 (TSCA CBI). The Information Management Division/OTS will request the submitter to substantiate these confidentiality claims. In its Section 8(e) submission, the company provided the following non-confidential generic name for the subject chemical: alkyl aryl phosphine. The submitting company reported that this chemical had been the subject of a TSCA Section 5 Premanufacture Notice (PMN No. 83-1023) and a TSCA Section 5(e) Consent Order.

Submission Description

The submitting company reported that a 28-day neurotoxicity study of the alkyl aryl phosphine in male and female rats was conducted pursuant to the conditions of a TSCA Section 5(e) Consent Order and provided the following summarized information concerning the conduct and preliminary histopathologic findings from that study:

> "The brain, spinal cord, and peripheral nerves from 10 control and 10 [alkyl aryl phosphine-]treated rats were evaluated microscopically. The treated rats received [alkyl aryl phosphine] at the rate of 25 mg/kg/day [for 28 days]. [The] microscopic evaluation of the tissues revealed slight axonal swelling and pyknotic debris in the reticular formation of the medulla and more prominent axonal damage in the spinal cord and peripheral nerves. In addition, there were foci of gliosis in the central grey column of the spinal cord. These central and peripheral lesions were present in 10/10 treated rats and in 0/10 control animals."

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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, the company stated that the 25 mg/kg/day dose "probably exceeded the maximum tolerated dose" for the chemical. The submitting company stated also that "no clear clinical neurological effects" were observed by the testing laboratory in the treated animals during the conduct of the 28-day study. Finally, the submitting company reported that the testing laboratory has been directed "to prepare and evaluate tissue slides for ten test animals in the mid dose group and ten test animals in the low dose group." (Note: The mid and low dose levels were not specified in the Section 8(e) submission.)

Submission Evaluation

Although no overt clinical neurotoxic signs were observed in the alkyl aryl phosphine treated-rats, it is clear from the submitted preliminary pathology report that the alkyl aryl phosphine caused neuropathologic effects when administered to rats at 25 mg/kg/day for 28 days. Immediately upon receipt of this TSCA Section 8(e) notice, the Chemical Screening Branch (CSB/ECAD/OTS) transmitted copies of the information to the Premanufacture Notice Management Branch (PNMB/CCD/OTS) and to the Existing Chemical Control Branch (ECCB/CCD/OTS) for review and appropriate followup attention.

Current Production and Use

According to the information contained in the non-confidential version of PMN No. 83-1023, the intended use of this new alkyl aryl phosphine is as an industrial catalyst. According to the non-confidential public docket for PMN No. 83-1023, the Agency has received a "Notice of Commencement" (NOC) of manufacture for this chemical substance.

Comments/Recommendations

In its TSCA Section 8(e) submission, the company stated that upon receipt of the preliminary report from this 28-day neurotoxicity study, the company notified its "customers and manufacturing personnel to share this information and to request that all handling of the PMN substance be done with the utmost care."

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the submitting company to ensure that EPA receives in a timely manner all future interim pathology reports and a complete copy of the final report (including the actual experimental protocol, results of gross/histopathologic examinations, results of statistical analyses etc.) from the company's 28-day neurotoxicity study of this alkyl aryl phosphine in rats.

b) Upon receipt of the requested information, the Chemical Screening Branch will send copies of that information immediately to the PNMB/CCD/OTS and ECCB/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/EPA, PNMB/CCD/OTS and ECCB/CCD/OTS. 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: APR 8 1986

SUBJECT: Status Report* 8EHQ-0386-0591 Approved: 4/9/86

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 Procter & Gamble Company provided the following information concerning the conduct and results of a repeated skin application study of dioctyl dimethyl ammonium chloride (CAS No. 5538-94-3) in rabbits:

> ". . .[This study in rabbits] involves examination of progressive electrocardiogram [(ECG)] changes after repeated dermal (occluded patch) exposure to dioctyl dimethyl ammonium chloride. This study is still in progress. However, a preliminary examination of the data, indicates that after 7-14 days, rabbits receiving 5-10 mg dioctyl dimethyl ammonium chloride/kg/day are displaying ECG changes. These changes include premature ventricular contractions and ventricular tachycardia. This treatment regimen has also resulted in the death of two animals after 7 and 11 days of [dermal] exposure to 10 mg/kg/day. A no-effect level for the cardiotoxic effects following [repeated] dermal exposure has not been established.
>
> "The results of . . .[previously conducted] preliminary in vitro skin penetration studies indicate that the rabbit may be uniquely sensitive to dermally administered dioctyl dimethyl ammonium chloride, in part because of a high rate of dermal absorption. It is widely recognized that this species exhibits greater dermal penetration than other species for a variety of chemical compounds. In addition, . . .[previously conducted] interspecies comparative studies have shown that the rabbit also may be especially sensitive to dioctyl dimethyl ammonium chloride-induced ECG alterations.

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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 the absorption and distribution of dioctyl dimethyl ammonium chloride, Procter & Gamble found] that following a single intravenous injection or dermal application, dioctyl dimethyl ammonium chloride (or metabolites) concentrates in the heart of rats and rabbits to a greater extent than other tissues. Results of tissue clearance studies show that after a single intravenous bolus injection, the half life of dioctyl dimethyl ammonium chloride and/or its metabolites from rat cardiac tissue is approximately 4-8 days."

Submission Evaluation

Based on the preliminary data on the cardiotoxic effects observed in rabbits following dermal exposure to dioctyl dimethyl ammonium chloride, several mechanisms of action can be postulated. For example, the chemical may act directly on the heart muscle (the heart appears to have the highest concentration of the chemical or a metabolite(s) thereof). Also, the chemical has a charged nitrogen and alkyl substitutions on that nitrogen which make the chemical structurally similar to drugs affecting the cholinergic nervous system. It is not clear from the submitted information if there were any adverse dermal effects due to treatment. If there was severe dermal irritation, the adverse heart effects could have been due to hyperemia and shock. In order for EPA to evaluate more thoroughly the reported cardiotoxic effects, the Procter & Gamble Company should be asked to provide a full copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, blood pressure measurements, identification of any metabolites, results of all statistical analyses, etc.) from the company's repeated dermal application study of dioctyl dimethyl ammonium chloride in rabbits. The company should be asked also to provide full copies of the final reports from all other studies cited in the submission.

Current Production and Use

A review of the production range (includes importation volumes) statistics for dioctyl dimethyl ammonium chloride (CAS No. 5538-94-3), which is listed in the initial TSCA Chemical Substance Inventory, shows that no 1977 production/importation was reported or that all of the production/importation information reported was claimed as TSCA Confidential Business Information (TSCA CBI) by the manufacturer(s) and/or importer(s) and cannot be disclosed (Section 14(a) of TSCA; U.S.C. 2613(a)). All of the information submitted for the TSCA Inventory, including the production range information, is subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

In its Section 8(e) notice, Procter & Gamble stated that dioctyl dimethyl ammonium chloride is "used in a number of microbiocidal products such as disinfectants, algicides and sanitizers, but the extent of such usage is not known to . . . [Procter & Gamble]." With regard to its use of dioctyl dimethyl ammonium chloride,

Procter & Gamble stated that the company "has been evaluating the safety of this material in research associated with the upstream development of an experimental product." No other information concerning the use(s) of dioctyl dimethyl ammonium chloride was located in the secondary literature sources consulted.

Comments/Recommendations

In its Section 8(e) submission, Procter & Gamble stated that its research program with dioctyl dimethyl ammonium chloride is not as yet completed and that the chemical has been handled and will continue to be handled with appropriate caution in the company's ongoing laboratory work.

a) The Chemical Screening Branch (CSB/ECAD/OTS/OPTS) will ask Procter & Gamble to submit to EPA a full copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, results of statistical analyses, etc.) from each study of dioctyl dimethyl ammonium chloride 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 chemical toxicity or exposure data, the Procter & Gamble Company will be requested also to describe the nature and available results of all studies (other than those published in the open scientific literature or submitted previously to EPA) about which Procter & Gamble is aware or that the company has conducted, is conducting, or plans to conduct to determine the toxicity of or the exposure to dioctyl dimethyl ammonium chloride. Procter & Gamble will be asked also to describe in greater detail the actions the company has taken or plans to take to 1) notify its workers and others about the reported toxicologic findings, and 2) reduce or eliminate exposure to dioctyl dimethyl ammonium chloride.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of dioctyl dimethyl ammonium chloride. In addition, copies of the reported information will be sent to the Office of Pesticide Programs (OPP/OPTS) for review and appropriate followup action under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

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: APR 7 1986

SUBJECT: Status Report* 8EHQ-0386-0592 Approved: 4/7/86

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 Celanese Corporation submitted a report concerning studies conducted by the Departments of Neuropathology, Pathology and Environmental Medicine at the New York University (NYU) Medical Center (New York, New York). According to the "Introduction" of the submitted report, these independently conducted studies were designed "to investigate 1) the effects of chronic dermal application of AA [(acrylic acid; CAS No. 79-10-7)], 2) its potential as a tumor promoter in two stage carcinogenesis, [and] 3) the ability of AA to bind to DNA in vitro." The submitted report contained the following information with regard to the conduct and results of a chronic in vivo study:

> "Thirty [4 week old] female ICR/Ha Swiss mice per group were randomly assigned to test and control groups [and then acclimatized for approximately 2 weeks].
>
> "Experiments began when animals were 6 weeks of age. Acrylic acid (4 mg) was applied to shaved dorsal skin by micropipette in 0.1 ml acetone, 3 times per week for 1.5 years. This dose of AA was determined to be near the maximum tolerated dose [(MTD)] in previous six week dose response testing. Mice in another group were first initiated with 20 ug DMBA [(dimethylbenzanthracene)]. . ., then began receiving AA two weeks later (3 times per week for 1.5 years). Control animals received acetone alone or DMBA followed by acetone alone as described above. Animals were observed daily and weighed every other month. At the time of sacrifice (1.5 years), animals were necropsied. Tissue from skin, kidney, liver, spleen, brain, bladder, and colon as well as any grossly abnormal tissue were examined histologically.

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"Acrylic acid produced skin tumors in both the DMBA/AA group and the AA alone group. Four tumors were observed in the DMBA/AA group. . . ($p<.05$; Fisher exact test). One of these tumors proved to be a squamous cell carcinoma. In the AA alone group, two tumors were oberved, both of which were squamous cell carcinomas. . . . This is marginally significant when compared to historical controls ($p<.07$; Fisher exact test). No skin tumors were observed in [the DMBA/acetone or acetone alone concurrent] control groups. There was no statistical difference in the numbers of tumors or latency of tumor appearance between the DMBA initiated group and the AA alone group. This suggests that AA may act as a complete carcinogen and not as a promoter. If these two acrylic acid groups are combined, irrespective of DMBA, the incidence of carcinoma is 5%.

"AA also produced an increase in leukemia which normally occurs in 20 to 40% of historical controls and occurred in 30% of the control groups in this study. Leukemia in AA treated animals was 86%. The tumor incidence for the sum total of all other tumor types was also significantly different from control ($p<.05$; Fisher exact test). However, other than those discussed above, no single tumor type alone was significant."

The submitted study report presented the following information concerning the conduct and results of the in vitro DNA binding assay:

"Acrylic acid was reacted with calf thymus DNA at 37°C and pH 7.0. DNA was hydrolyzed using acid and enzyme hydrolysis. . . . Adduct formation was detected by analytical paper chromatography and high performance liquid chromatography (HPLC). Adducts were isolated by preparative paper chromatography and purity [was] verified by HPLC and/or paper chromatography. Structures were elucidated by gas chromatography-mass spectrometry (GCMS) . . . .

"The adducts found by the in vitro reaction of AA with calf thymus DNA were 1-(2-carboxyethyl)adenine, 3-(2-carboxyethyl)cytosine, 7-(2-carboxyethyl)guanine, and 3-(2-carboxyethyl)thymine. The reaction time of AA is slow with a $t_{1/2}$ in the order of days."

Submission Evaluation

The reported findings show that chronic application of acrylic acid to the skin of mice resulted in 1) a substantial increase in the incidence of leukemia over that seen in either concurrent or historical control mice, and 2) a low and marginally significant

incidence of skin tumors when compared to either concurrent or historical control mice. The reported in vitro acrylic acid-DNA adduct formation results provide further support for an oncogenic concern for acrylic acid.

Current Production and Use

A review of the production range (includes importation volumes) statistics for acrylic acid (CAS No. 79-10-7), which is listed in the initial TSCA Chemical Substance Inventory, shows that between 221 million and 1.11 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) 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 TSCA Inventory Reporting Regulations (40 CFR 710).

According to secondary literature sources, acrylic acid is a colorless fuming liquid used primarily as a captive intermediate in the manufacture of acrylate esters. No information concerning the current production/importation volumes of acrylic acid was located in the secondary literature sources consulted.

Comments/Recommendations

The Chemical Screening Branch has received a number of TSCA Section 8(e) and "For Your Information" (FYI) notices on several acrylic acid derivatives. In addition, the Chemical Screening Branch has prepared Chemical Hazard Information Profiles (CHIPs) on acrylic acid, ethyl acrylate, ethylhexyl acrylate and neopentyl glycol diacrylate. The Office of Research and Development (ORD/EPA) has prepared Health and Environmental Effects Profiles (HEEPs) on acrylic acid and a number of acrylic acid derivatives. Also, the Risk Analysis Branch (RAB/ECAD/OTS) has been evaluating available toxicologic and exposure data (including TSCA Section 8(a) exposure data) on several acrylates. Finally, it should be noted that the Office of Toxic Substances (OTS/OPTS/EPA) has received and evaluated a number of TSCA Section 5 "Premanufacture Notices" (PMNs) on acrylates and is now assessing the potential risks posed by acrylates as a class.

a) The Chemical Screening Branch will consider revising the existing CHIP on acrylic acid to include the submitted findings and other toxicologic and exposure information that has become available since the preparation of that CHIP in 1981.

b) 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, CCD/OTS, HERD/OTS, RAB/ECAD/OTS/OPTS, and to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAR 31 1986

SUBJECT: Status Report* 8EHQ-0386-0593 Approved: 3/31/86

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 submitted a written followup report concerning an "Emergency Incident of Environmental Contamination" that occurred on February 28, 1986. In its report, Union Carbide provided the following information with regard to this incident:

> "A rail car containing 20,000 gallons of ethoxyethyl acetate (CAS No. 111-15-9) was reported to be derailed and overturned on a trestle crossing the Ouachita River near Grayson, Louisiana on the morning of February 18, 1986. Some material leaked from the dome of the tank car, estimated by someone to be approximately 5 gallons per minute, into the river. After the car was righted, it continued to leak, at a substantially reduced rate, apparently from a damaged bottom valve. Emergency response personnel from Union Carbide facilities at Taft, Louisiana and Seadrift, Texas were dispatched to the scene and succeeded in transferring the material in the tank car to an undamaged one. According to railroad personnel, Louisiana State Police were at the scene and authorities of the town of Grayson were notified.
>
> "Since the time of the incident, Union Carbide has received no reports of adverse ecological or environmental effects as a result of the incident. Based on the amount of material transferred to the undamaged tank car, an estimated 1000 gallons were lost during the event. The decision to . . .[immediately phone the EPA Region VI Office in Dallas, Texas] was made at the time the tank car was reported to be still leaking, and it was not possible to know if adverse ecological or environmental effects would occur."

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Comments/Recommendations

Animal studies of 2-ethoxyethanol and/or its acetate show that these chemical substances can cause developmental, testicular, hematologic, and/or neurologic effects. The Chemical Screening Branch (CSB/ECAD/OTS) has received a number of TSCA Section 8(e) and "For Your Information" (FYI) notices on glycol ethers and their derivatives, including 2-ethoxyethanol and its acetate. Also, the Chemical Screening Branch has prepared Chemical Hazard Information Profiles (CHIPs) on 2-ethoxyethanol, 2-methoxyethanol and their acetates. The Risk Analysis Branch (RAB/ECAD/OTS) has been evaluating available toxicologic and exposure data on glycol ethers and their derivatives. Finally, it should be noted that the Chemical Control Division (CCD/OTS) is considering various regulatory options with regard to reducing the risks posed by exposure to 2-ethoxyethanol, 2-methoxyethanol and their acetates.

Immediately upon receipt of Union Carbide's followup report, the Chemical Screening Branch sent copies of the report to the Office of Solid Waste and Emergency Response (OSWER/EPA), the Office of Water (OW/EPA), the Chemical Control Division (CCD/OTS), the Risk Analysis Branch (RAB/ECAD/OTS) and to EPA's Region VI Office in Dallas, Texas for review and any warranted followup action.

a) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, CCD/OTS, RAB/ECAD/OTS and to EPA's Region VI Office (Dallas, TX). A copy of this status report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: APR 16 1986

SUBJECT: Status Report* 8EHQ-0386-0594 S Approved: 4/16/86

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 4 of this status report)

The submitting company has claimed its name and the identity of the tested product to be TSCA Confidential Business Information (TSCA CBI). The submitter reported on a non-confidential basis, however, that 1) the product was a liquid mixture of octyltin esters, and 2) the product contained the following chemical substance as the predominant component: dioctyltin bis(thioglycolic acid), 2-ethylhexyl ester (CAS No. 15571-58-1). The Information Management Division (IMD/OTS) will request the submitting company to substantiate its TSCA CBI claims.

Submission Description

The company submitted a copy of the final report of a subchronic feeding study of the subject octyltin esters mixture in male and female rats. According to the provided study report, the subject product was administered to groups of 40 rats (20 males and 20 females) at dietary levels of 0, 25, 50 or 100 ppm for 90 days. These levels were reported to be equivalent to approximately 0, 1.6, 3.3, and 6.6 mg/kg/day, respectively. The study report states also that 10 male and 10 female rats from each group were held for a 15-30 day post-exposure recovery period. In the cover letter to its TSCA Section 8(e) submission, the company provided the following information with regard to the results of this 90-day feeding study:

> "The test material did not produce any detrimental effects in the following parameters: body weight gain, food consumption, clinical chemistry/hematology values, urine analysis and necropsy findings. Weights of the thymus gland (absolute and relative) showed a statistically significant dose-related reduction in the 3.3 and 6.6 mg/kg groups. In addition, 2/10 females in the 6.6

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> mg/kg group showed very mild changes consisting of a reduction in the cortical lymphocytes and a less clear distinction between the cortex and medulla in the thymus gland. In a post-dose recovery period lasting 15-30 days, the [adverse thymic] effects appeared reversible as no alterations were seen in the 6.6 mg/kg group with 10 males and 10 females."

In its TSCA Section 8(e) submission, the company noted that the "immuno-suppressive effects of dioctyltin compounds are generally well known and can be controlled by appropriate engineering controls and work practices." The submitter noted also that the current U.S. Occupational Safety and Health Administration (OSHA) Threshold Limit Value (TLV) is 0.1 mg/m^3 for organotin compounds.

Submission Evaluation

In view of the observed statistically significant dose-related thymic weight reduction in rats at the 3.3 and 6.6 mg/kg dose levels (the no-observed-effect level (NOEL) was 1.6 mg/kg), the submitter's concern that the tested chemical mixture may cause immunotoxic effects appears to be well-founded even though the adverse thymic effects were reported to be reversible in the high dose animals following a 15-30 day post-exposure recovery period.

Considering that the thymus is a principle source of circulating long-lived, immunologically competent lymphocytes, the thymic influence upon lymphocytes and immune competence is most critical in the later stages of fetal development and in young animals and is present but less critical in mature animals. It is important to note also that the thymus gland typically becomes atrophic and involuted with age. Based on the weight range (120-142 grams) of the rats at the beginning of the 90-day study, it is reasonable to predict that the immunologic system of these adult animals would continue to function normally even upon removal or atrophy of the thymus. Removal or destruction of the thymus in neonates or young animals, however, can lead to a failure of the body to become seeded with immunologically competent lymphocytes.

It would be of interest to know if the submitting company has conducted or is conducting studies designed to determine if adverse immunologic effects occur in the off-spring as the result of maternal exposure to the subject mixture or its components or if adverse immunologic effects occur in young animals exposed to the mixture or its components.

Current Production and Use

A review of the production range (includes importation volumes) statistics for the 2-ethylhexyl ester of dioctyltin bis(thioglycolic acid), which is listed in the initial TSCA Inventory, has shown that 0 to 2000 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 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).

In its Section 8(e) notice, the submitting company reported that it imported the tested product in 1981 and since that time has sent only one sample to one customer for development purposes. In addition, the submitting company reported that all remaining inventory of the product has been warehoused by the company since 1981 and will be "disposed of as waste, probably by incineration" in the near future.

The company did not provide any information concerning the actual or planned use(s) of the tested product nor was such information located in the secondary literature sources consulted.

Comments/Recommendations

The submitting company stated that it is planning to notify its warehouse workers about the reported toxicologic findings by way of a revised Material Safety Data Sheet (MSDS) and product label. The submitting company stated also that it is discontinuing all further development work with the product.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the submitting company to provide to EPA full copies of the MSDS and product label that the company has revised to reflect the reported toxicologic findings.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, the submitting company will be asked to describe the nature and available results of all studies (other than those in the open scientific literature) about which the company is aware or that the company has conducted or is conducting to determine the toxicity of or exposure to the subject product or its components.

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

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. Copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

Note

In a letter dated July 23, 1986 (8EHQ-0786-0594 FLWP Seq. D), the CIBA-GEIGY Corporation stated that the company no longer wished to maintain as TSCA CBI the company's name or the identity of the minor constituent of the subject product. According to the declassified version of CIBA-GEIGY's initial Section 8(e) notice, the minor component of the product is the 2-ethylhexyl ester of octyltin tris(thioglycolic acid) (CAS No. 27107-89-7).

A review of the production range (includes importation volumes) statistics for the 2-ethylhexyl ester of octyltin tris(thioglycolic acid), which is listed in EPA's initial TSCA Chemical Substance Inventory, has shown that between 0 and 1000 pounds of this chemical were reported as manufactured and/or imported in 1977. This production range information does not contain any data claimed to be 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 EPA's initial TSCA Inventory Reporting Regulations (40 CFR 710).

12/22/86

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: APR 29 1986

SUBJECT: Status Report 8EHQ-0386-0595 Approved: 4/29/86

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 Union Carbide Corporation provided summarized final results from a recently conducted cytogenetics test of 2,4-pentanedione (CAS No. 123-54-6) in cultured Chinese Hamster Ovary (CHO) cells. Based on preliminary tests to observe effects on cell division, CHO cells in the absence of an exogenous metabolic activation system were reportedly treated for 6 hours at 2,4-pentanedione concentrations of 0.08, 0.10 and 0.12 mg/ml and sampled 22 hours after start of treatment; in the presence of S-9 metabolic activation, CHO cells were treated for 2 hours at 2,4-pentanedione concentrations of 0.10, 0.12 and 0.14 mg/ml and sampled at 14 hours after treatment. In its Section 8(e) submission, Union Carbide presented the following information with regard to the results of this in vitro study:

> "Tests conducted in the absence of a metabolic activating system showed a high incidence of [CHO] cells with chromosome aberrations. The incidence of aberrant cells for the various concentrations of 2,4-pentanedione was 99% (0.08 mg/ml), 100% (0.10 mg/ml) and 95% (0.12 mg/ml). The incidence of aberrant cells in the controls was 2% for the negative control (medium), solvent (water), and 72% for the positive control material (triethylenemelamine). A large proportion of the severely damaged [CHO] cells consisted of multiple breaks and complex rearrangement figures. In contrast, tests conducted in the presence of the S-9 metabolic activating system did not show a statistically significant increase in the incidence of aberrant cells in comparison with the control cultures. Thus, the incidence for the various concentrations of 2,4-pentanedione was 6% (0.10 mg/ml), 3%

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(0.12 mg/ml) and 7% (0.14 mg/ml). For the various controls, the incidence of chromosome aberrations was 4% for the negative (medium), 3% for the solvent (water) and 26% for the positive control (cyclophosphamide). These studies indicate a high clastogenic activity of 2,4-pentanedione by in vitro testing in the absence of an activating system."

On a "For Your Information" (FYI) basis, Union Carbide submitted previously the results of 4 in vitro genotoxicity studies of 2,4-pentanedione (FYI-OTS-0186-0434 Sequence B and FYI-OTS-0286-0434 Sequence C). The compound was reported to be negative in Ames Salmonella typhimurium (bacteria) and CHO/HGPRT gene mutation assays both with and without metabolic activation. In a cytogenetics test in cultured CHO cells, 2,4-pentanedione reportedly produced small increases in the number of chromosomal aberrations. According to the provided final report, only one dose was statistically different from concurrent controls both under activation and non-activation conditions. These test results were considered equivocal by the performing laboratory and by Union Carbide, leading to a repeat of this study under different test conditions. (The repeated study is the subject of the present TSCA 8(e) submission.) In a Sister Chromatid Exchange (SCE) assay using cultured CHO cells, a "steep" 2,4-pentanedione dose-response was found with a statistically significant increase in SCE's above concurrent control values reported for each 2,4-pentanedione concentration tested either with or without metabolic activation.

In its initial FYI submission (FYI-OTS-0885-0434 Sequence A) on 2,4-pentanedione, Union Carbide provided the final report from a 14-week study of rats exposed via inhalation to 2,4-pentanedione vapor at concentrations of 0, 100, 300, or 650 ppm. According to the submitted final report, there was a high incidence of mortality accompanied by clinical abnormalities and tissue lesions (including acute degeneration in the thymus and brain) in the high dose animals.

In response to a written Agency request for information on the company's plans for additional toxicity testing, Union Carbide stated that it was conducting neurotoxicity studies involving acute exposure of rats to 2,4-pentanedione vapor at or near the lethal concentration (FYI-OTS-0386-0434 Sequence D). In its Section 8(e) submission, the company reported that in "a study currently nearing completion to determine the teratogenic potential from 2,4-pentanedione vapor to rats, there appears to be no evidence at concentration[s] up to 400 ppm of any teratogenic or embryotoxic effects."

In its TSCA Section 8(e) submission, Union Carbide offered the following comments concerning the overall significance of the positive in vitro cytogenetics test results reported to EPA under Section 8(e):

"In the absence . . . of in vivo genotoxicity studies, the possible adverse health effects of the recent[ly reported] studies should be viewed in the light of other recently conducted studies involving repeated exposure to 2,4-pentanedione vapor. In particular, the results from a subchronic inhalation study and a teratology study are relevant. In the subchronic inhalation study, the results of which have already been submitted to the Agency (FYI-OTS-0885-0434 [Sequence A]), there was no indication of testicular or bone marrow injury, which might be expected of a clastogen active in vivo. In a study currently nearing completion [designed] to determine the teratogenic potential from 2,4-pentanedione vapor [exposure] to rats, there appears to be no evidence at concentration[s] up to 400 ppm of any teratogenic or embryotoxic effects. These indications of a lack of in vivo clastogenic potential accord with the finding of no in vitro clastogenic potential in the presence of a metabolic activating system."

Submission Evaluation

According to the summarized results of the cultured CHO cell cytogenetics assay provided by Union Carbide in this Section 8(e) submission, 2,4-pentanedione was tested at doses higher than those tested in the original study (FYI-OTS-0186-0434 Sequence B and FYI-OTS-0286-0434 Sequence C) both with and without exogenous metabolic activation. In addition, the harvest times both with and without activation were longer than those of the original study (14 and 22 hours after initiation of treatment in the recent study as compared to 10 and 6 hours after initiation of treatment in the original study). The extended harvest times were used to compensate for the long mitotic delay induced by 2,4-pentanedione. Although no substantial increases in chromosomal aberrations were observed with exogenous metabolic activation in the recent study, no statistical analyses were provided in the 8(e) submission. Without exogenous metabolic activation, on the other hand, the incidences of 2,4-pentanedione-treated cells with chromosomal aberrations were increased substantially (99%, 100%, and 95% for the three dose levels tested versus 20% for the solvent control and 72% for the positive control (triethylene-melamine)).

The results from the other in vitro genotoxicity assays submitted in FYI-OTS-0885-0434 et seq. indicate that while 2,4-pentanedione is not mutagenic with or without exogenous metabolic activation in the Ames Salmonella typhimurium (bacteria) or CHO/HGPRT assay, the chemical did induce SCEs in cultured CHO cells when tested in the presence or absence of metabolic activation.

In discussing the significance of the submitted test results, Union Carbide stated that in view of the lack of data from in vivo genotoxicity studies with 2,4-pentanedione, the results from

the company's subchronic inhalation and inhalation teratology studies of 2,4-pentanedione are indicative of a lack of in vivo clastogenic activity for this chemical. It should be noted, however, that results from these particular types of studies are not necessarily indicative of the clastogenic potential of a chemical. A true evaluation of in vivo clastogenic potential would require that an in vivo study designed to measure such an end-point be conducted. Until results of a such a study become available, the in vitro cytogenicity test results submitted by Union Carbide thus far provide the best indication of the clastogenic potential of 2,4-pentanedione.

In order for EPA to evaluate better 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 experimental protocol, data, results of statistical analyses, etc.) from the in vitro cytogenetics study cited in this Section 8(e) submission. In addition, Union Carbide should be asked to ensure that EPA receives complete copies of the final reports (including the actual experimental protocols, results of gross and histopathologic examinations, results of statistical analyses, etc.) from the company's ongoing inhalation teratology and neurotoxicity studies of 2,4-pentanedione.

Current Production and Use

A review of the production range (includes importation volumes) statistics for 2,4-pentanedione (CAS No. 123-54-6), which is listed in the initial TSCA Chemical Substance Inventory, has shown that between 1.1 and 11.1 million pounds of this chemical were reported as produced/imported in 1977. This production range information does not include any production/importation data claimed as TSCA Confidential Business Information (TSCA CBI) by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise TSCA CBI. All of the information submitted for the TSCA Inventory, including the production range information, is subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

According to secondary literature sources, 2,4-pentanedione forms organometallic complexes which are used as gasoline and lubricant additives; driers for varnishes and printing inks; fungicides; insecticides; dyes; and can be used as a solvent for cellulose acetate and as an intermediate.

In FYI-OTS-0386-0434 Sequence D, Union Carbide reported that "2,4-pentanedione is a specialty chemical of which Union Carbide is the only domestic manufacturer; there are other producers in West Germany, the United Kingdom, and Japan." In addition, Union Carbide reported that "sales for a variety of applications, many of which are based on the chemical's metal-chelating properties, by Union Carbide were less than 5 million pounds in 1984 and 1985, including export sales." According to Union Carbide, 2,4-

pentanedione uses associated with the company's sales of this chemical "are all industrial, and consist of 62% as [a] chemical intermediate, 35% in industrial chelating uses (mostly as metal chelates), and 3% unknown; there are no solvent uses to . . .[the company's] knowledge."

With regard to worker exposure to 2,4-pentanedione, Union Carbide stated in FYI-OTS-0386-0434 Sequence D that the company does not have any data from its own operations or from users concerning the actual workplace concentrations of 2,4-pentanedione during routine processing or under exceptional circumstances.

Comments/Recommendations

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask Union Carbide to ensure that EPA receives in a timely manner a complete copy of the final report (including the actual experimental protocol, results of statistical analyses, etc.) from the in vitro CHO cell cytogenetics study that was cited in the company's TSCA Section 8(e) submission on 2,4-pentanedione. Union Carbide will be requested also to ensure that the Agency receives in a timely manner complete copies of the final reports (including the actual experimental protocols, results of gross and histopathologic examinations, etc.) from the company's ongoing neurotoxicity and teratology studies of 2,4-pentanedione.

   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, Union Carbide will be asked also to describe the nature and available results of all studies (other than those reported previously to EPA or those published in the open scientific literature) 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 2,4-pentanedione.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of 2,4-pentanedione.

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. In addition, copies for this status report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: APR 14 1986

SUBJECT: Status Report* 8EHQ-0486-0596 S Approved: 4/14/86

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 (TSCA CBI). However, the submitting company reported non-confidentially that the chemical was a halogenated aliphatic carboxanilide. The Information Management Divison (IMD/OTS) will request the company to substantiate all of the confidentiality claims made in its Section 8(e) submission.

Submission Description

The submitting company provided the following information with regard to the conduct and results of an acute eye irritation study of this halogenated aliphatic carboxanilide in rabbits:

> ". . .[A] 10% granular formulation of the compound, when placed in one eye of each of three New Zealand white rabbits at a dose of 66 mg (equivalent in volume to 0.1 cc), caused moderate corneal opacity, slight to moderate iritis, moderate conjunctivitis, and lens opacity with prominent lateral suture lines. Within 24 hours post-treatment, lens opacity with prominent lateral suture lines disappeared. An examination of treated eyes 48 hours post-exposure indicated faint lens opacity in one animal, accompanied by corneal edema and cloudiness, moderate corneal opacity and marked iritis, and normal lenses in the remaining two animals. Seven days after exposure, the treated eye of one rabbit was normal and the remaining two rabbits had mild to severe corneal opacity, mild to severe iritis, moderate conjunctivitis, and one animal had peripheral corneal vascularization."

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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 the Agency to evaluate the overall significance of the reported eye toxicity, the company should be asked to submit a complete copy of the final report (including the actual experimental protocol, results of gross/histopathologic examinations, etc.) from this acute eye irritation study in rabbits.

Current Production and Use

In view of the fact that the submitting company has claimed the exact identity of the subject chemical substance to be TSCA CBI, no information with regard to the TSCA Inventory status of the chemical will appear in this report. According to the submitting company, less than 50 kilograms of this chemical substance have been manufactured thus far. In addition, the submitting company reported that approximately 25 employees work with the chemical, and the exposure time averages 16 hours per year for each worker. Although the submitting company claimed its use of the chemical to be TSCA CBI, the company did state non-confidentially that 1) the chemical substance has not been patented as yet, and 2) the company is planning to apply for an Experimental Use Permit (EUP) for the chemical. It should be noted that EPA issues EUPs under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

Comments/Recommendations

The submitter reported that the subject chemical is "labelled as hazardous and all personnel who work with it are notified of the chemical's properties and that eye protection is necessary."

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the submitting company to provide to EPA at this time a complete copy of the final report (including the actual experimental protocol, results of both gross and histopathologic examinations, etc.) from the eye irritation 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 data, the submitting company will be asked to describe the nature and results, if available, of all other studies that the company has conducted, is conducting, or is planning to conduct to determine the toxicity of or the exposure to the subject chemical.

b) The Chemical Screening Branch will review the reported data to determine the need for further OTS assessment of the chemical at this time. In addition, the Chemical Screening Branch will send copies of the reported data to the Office of Pesticide Programs (OPP/OPTS/EPA).

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. 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: APR 22 1986

SUBJECT: Status Report* 8EHQ-0486-0597 S

Approved: 4/22/86

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 (TSCA CBI). In its submission, the company reported non-confidentially that the tested chemical was a "benzotriazole-2-yl substituted hydroxyphenylpropionate ester" or more simply a "substituted benzotriazole." The Information Management Division (IMD/OTS) will ask the submitting company to substantiate these confidentiality claims.

Submission Description

The submitting company provided a final report from a 28-day oral study of the substituted benzotriazole in male and female rats. In the cover letter to its submission, the company provided the following information with regard to the conduct and results of this sub-acute study:

> "The test[ed] chemical was administered daily by gavage for 28 days at doses of 0, 50, 200 and 1000 mg/kg body weight to groups of 5 male and 5 female rats. There was a consistent hepatotoxicity at the 1000 mg/kg level where there were significant increases in liver weight parameters, serum values (SGOT, SGPT, bilirubin, and urea) and 1/5 males had extensive liver necrosis (+++ severity). At the 50 mg/kg level, there were minimal elevations in serum values; however, there was a 60-75% increase in liver weight and two male rats had recent liver necrosis (+ to ++ severity)."

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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 a submitted Material Safety Data Sheet (MSDS), the chemical has an oral rat LD50 of greater than 5 grams/kg and a dermal rat LD50 of greater than 2 grams/kg. In addition, the MSDS reports that the chemical is non-irritating to the skin of rabbits following a 4-hour exposure and produces only slight and reversible (after 48 hours) eye irritation in rabbits. The MSDS reports further that the chemical was not found to produce skin sensitization in guinea pigs. With regard to genotoxic effects, the MSDS indicates that the chemical was negative in tests for mutagenicity and clastogenicity. Finally, the MSDS reports that the subject chemical 1) is not readily biodegradable (modified Sturm Test), 2) has a 96-hour LC50 of >100 parts per million for Zebra fish, and 3) has a 24-hour EC50 of >66 parts per million for Daphnia magna.

Submission Evaluation

The most significant toxicologic findings acknowledged by the submitter were in the high dose group and included increases in liver weight parameters and serum values (SGOT, SGPT, bilirubin and urea) and extensive liver necrosis in 1/5 male rats. At the 50 mg/kg dose level, the submitter noted that there were minimal elevations in serum values and a 60-75% increase in liver weight and liver necrosis in 2/5 male rats. The hepatomegaly reported in the submitting company's study appears to be consistent with that observed in a study in which administration of a substituted benzotriazole at oral doses of 300 mg/kg/day for 14 or 28 days caused an increase in liver weight in male rats. In this other study, however, the observed change in liver weight was found to be reversible.

In the summary presented by the submitting company in its cover letter, no mention was made about the significant increase found in both absolute and relative kidney weights of female rats in the mid and high dose groups (the kidney weights of the treated males did not show any marked alteration). In addition, the submitted pathology report states that in the high dose group there was a decrease in the size of the thymus glands in 3/5 male rats and small seminal vesicles in 2/5 male rats.

Current Production and Use

In view of the fact that the submitting company has claimed the exact identity of the tested chemical substance to be TSCA CBI, no information with regard to the TSCA Inventory status of the chemical will appear in this report.

According to the submitting company, the tested chemical is a site-limited intermediate imported for research and development (R&D) purposes at one of the company's research laboratories.

The amount of this R&D intermediate that the company imported during 1984-1985 has been claimed as TSCA CBI.** The submitting company reported that the R&D intermediate is present as an impurity (estimated by the company to be less than 1%) in a product imported by the company for the past 3 years, first for R&D purposes and then for commercial purposes. The submitting company claimed the identity of this commercial product and the amount imported during the last 3 years to be TSCA CBI.**

** The Information Management Division will request the submitter to substantiate these TSCA CBI claims as well.

Comments/Recommendations

In its submission, the company stated that the MSDS and label for the subject R&D chemical had been updated to reflect the reported liver toxicity and that the company's workers are being informed about this toxicity. It is not clear, however, why the MSDS and label were not revised to reflect also the other organ toxicities observed in the company's 28-day study.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the submitting company to provide to EPA a complete copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, results of statistical analyses, etc.) from each toxicologic study cited in the submitted MSDS.

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, the submitting company will be requested to describe the nature and available results of all studies (other than those cited in the submitted MSDS) that the company has conducted, is conducting, or is planning to conduct to determine the toxicity of or exposure to the site-limited R&D intermediate. In addition, the submitting company will be asked if it plans additional revisions to the MSDS and label for this chemical to reflect the other toxicologic findings from the company's 28-day oral study of the R&D substance.

Finally, the submitting company will be requested to describe the nature and available 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 the product reported to contain the subject R&D intermediate as a contaminant at a level estimated by the company to be less than 1%.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of the subject R&D intermediate or the product reported to contain that substance.

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: MAY 6 1986

SUBJECT: Status Report* 8EHQ-0486-0598 Approved: 5/6/86

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 summarized preliminary findings from an epidemiologic study of male workers at Du Pont's Camden, South Carolina plant site. According to the company, previous epidemiologic study reports (sent to the Agency on a "For Your Information" (FYI) basis in 1977, 1979 and 1984) "dealt with [Du Pont] employees assigned to [the Camden] plant areas where there was exposure to acrylonitrile." Du Pont stated that although the 1977 study report showed an excess of certain types of cancer, the company recognized that there was worker exposure to other chemicals as well. Du Pont stated also that "in an effort to examine [the] potential confounding by exposure to dimethylformamide, . . . [Du Pont's] data base has been extended to include all males at the plant." In its TSCA Section 8(e) submission, Du Pont provided the following information with regard to the conduct and preliminary results of the expanded epidemiologic study:

> "The total number of [male] employees in this study is about 5,000. Of these, approximately 1,100 constitute a non-exposed group, that is, they were exposed to neither acrylonitrile nor dimethylformamide. The number of workers exposed to dimethylformamide but not acrylonitrile was about 2,500; those exposed to both acrylonitrile and dimethylformamide number about 1,300. The [study] cohort includes only those employees with first exposure to dimethylformamide between 1950 and 1970. A small group (16) was exposed to acrylonitrile but not to dimethylformamide.
>
> "Preliminary findings from this [epidemiologic] study of the Camden employees exposed to dimethylformamide but not to acrylonitrile show no statistically significant

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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.

> excess in total cancers for the period 1956 through 1984 based on Du Pont rates (47 observed with 40 expected). Within this group, . . .[Du Pont has] observed 9 cases of cancer of the buccal cavity and pharynx with 1.6 cases expected. Of these, 8 were observed in the wage roll group with 1.0 expected and 1 was observed in the salary roll group with 0.6 expected. . . .[Du Pont has] not observed an increased incidence of buccal cavity and pharynx cancer in the [study] cohort exposed to both acrylonitrile and dimethylformamide (2 observed and 1.6 expected).
>
> "In reviewing the mortality of the cohort exposed to dimethylformamide but not acrylonitrile, compared to Du Pont rates, . . .[Du Pont has] observed 2 deaths from cancer of the buccal cavity and pharynx with 0.8 expected. . . .[Du Pont] did observe statistically significant excesses of deaths ($p<0.01$; 2-tailed) from the following categories: all causes, 225 observed with 160.2 expected; ischemic heart disease, 77 observed with 57.3 expected; external causes, 46 observed with 28.6 expected. However, when these observations are compared to the expected number based on U.S. rates, they are not statistically significant. . . . .
>
> "While the observed incidence of cancers of the buccal cavity and pharynx is statistically significant when compared to Du Pont Company rates, there are a number of factors which complicate the interpretation of these data. The findings are based on numerical data and do not take into consideration confounding factors such as cigarette smoking and alcohol consumption, both of which have been associated with cancer of the buccal cavity and pharynx. All 9 cases of cancer of the buccal cavity and pharynx were cigarette smokers."

In its TSCA Section 8(e) submission, Du Pont reported that the company "has reviewed the available animal and human toxicity data which suggest that the liver is the target organ for dimethylformamide toxicity" and has "seen no excess incidence of liver cancer in employees exposed to dimethylformamide at the Camden plant." Finally, Du Pont reported that based on available data, Du Pont has concluded that no change is necessary in the company's "10 ppm, 8-hour and 12-hour acceptable exposure limit value (AEL) used for these operations."

Submission Evaluation

This TSCA Section 8(e) notice reports the morbidity and mortality experience of 2,500 males exposed to dimethylformamide between 1950 and 1970. It is important to note that when compared to Du Pont rates, this group of workers was found to have a significant excess of buccal cavity and pharyngeal cancers (morbidity). In

all, 9 cases of such cancers were observed with only 1.6 expected (SMR=563; p=0.00005). Eight (8) of these cancer cases were among the wage roll workers as compared to 1.0 expected cases (SMR=800; p=0.00001). These 9 cancer cases contributed to the observed excess (not statistically significant) of total neoplastic deaths (47 observed, 40 expected; SMR=118; p=0.15). In the mortality analyses, Du Pont found 2 deaths due to buccal cavity/pharyngeal cancer giving a SMR of 250 (0.8 expected; p=0.18). Significant excesses in mortality in this study cohort were reported from all causes (SMR=140; 225 observed), ischemic heart disease (SMR=134; 77 observed); external causes (SMR=161; 46 observed).

All 8 of the wage roll cases and the 1 salary roll cases were reported to be smokers but comparisons do not reflect adjustments; this may be a limitation of the analyses. Considering that Du Pont uses company rates to calculate expected numbers, this is a serious limitation only in the two separate job classification analyses if the workers' smoking patterns differ from those of the average Du Pont wage roll or salary roll employee.

Current Production and Use

A review of the production range (includes importation volumes) statistics for dimethylformamide (CAS No. 68-12-2), which is listed in the initial TSCA Chemical Substance Inventory, shows that 50 million to 100 million pounds were reported as manufactured/imported in 1977. This production range information does not contain any information claimed as TSCA Confidential Business Information (TSCA CBI) by the persons reporting for the 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, dimethylformamide is used as a solvent in a wide variety of industrial applications and in production of a wide variety of chemical substances (e.g., acrylic and mod-acrylic fibers, vinyl-based polymers used as coatings). Some other applications of dimethylformamide include its use as a solvent component of certain pesticide products, and as a crystallization solvent (e.g., for pharmaceuticals).

Comments/Recommendations

EPA's Office of Toxic Substances (OTS) has received a number of TSCA Section 8(e) and/or "For Your Information" (FYI) submissions concerning acrylonitrile and dimethylformamide. In late 1981, the Chemical Screening Branch (CSB/ECAD/OTS) prepared a Chemical Hazard Information Profile (CHIP) on dimethylformamide. Finally, it should be noted that several other EPA Program Offices have assessed or are assessing available toxicologic and exposure information on acrylonitrile and/or dimethylformamide.

a) The Chemical Screening Branch will ask Du Pont to ensure that the Agency receives as soon as possible a complete copy of the final report (including the actual protocol, the results of all statistical analyses, etc.) from this expanded epidemiologic study.

b) Upon receipt and review of a complete copy of the final report from Du Pont's expanded epidemiologic study, the Chemical Screening Branch will consider updating the 1981 CHIP on dimethylformamide to include the reported information and other relevant toxicologic and exposure information that has become available since 1981.

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. 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: APR 29 1986

SUBJECT: Status Report* 8EHQ-0486-0599 Approved: 4/29/86

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 Eastman Kodak Company provided the following information with regard to the conduct and preliminary results of several ongoing acute oral and inhalation toxicity studies of the methyl ester of 3-methoxy propanoic acid (MMP) in rats:

> "Single dose oral LD50 and single exposure inhalation LC50 studies [of MMP] are being conducted on male and female rats. These [acute toxicity] studies are still in progress . . .[and all findings reported herein are preliminary]. In the oral LD50 study, all males at 1250 mg/kg appear normal. At 2500 mg/kg, 3 of 5 males appear normal, 1 of 5 died within a day, and 1 of 5 has shown severe hindlimb weakness. At 5000 mg/kg, 4 of 5 males died within one day, the single survivor showed hindlimb weakness. All females at 5000 mg/kg died within a day of dosing. All males and females that died during the first day of the study were narcotized and not evaluated for hindlimb weakness. After the first observation of hindlimb weakness, 5 males were dosed orally with 3500 mg/kg and 5 females at 1700 mg/kg. In males, 3 of 5 died within a day and 2 of 5 survived without apparent ill effects. One of the males exhibited hindlimb weakness before death. In females, 2 of 5 died within two days and 3 of 5 survived without apparent ill effects. The one male and one female exposed to MMP in the oral LD50 study and showing signs of hindlimb weakness have been partially examined histologically. Noteworthy effects include necrosis of the thoracolumbar spinal cord and brain stem. The necrotic lesions appear to be related to ischemia although no obstruction to blood flow has been observed. Lesser affected areas of the spinal cord and brain stem show perivascular hemorrhage. Peripheral nerves and dorsal root ganglia appear unaffected.

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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 inhalation study involved a single 6-hour exposure [of male and female rats] to [MMP] vapor concentrations of 965, 1968, or 3656 ppm. At the high dose, all males and all but one of the females died during the exposure period. The sole survivor was ataxic on removal from the cage and is exhibiting signs of hindlimb weakness. Rats exposed to the lower [MMP] concentrations have not exhibited hindlimb weakness."

Eastman Kodak also provided the following information concerning the conduct and preliminary results of acute single dose oral LD50 and single dose inhalation LC50 studies of the ethyl ester of 3-methoxy propanoic acid (EMP) in rats:

> "In the [acute] oral studies at 3500 mg/kg, 1 of 5 male rats and 1 of 5 female rats showed hindlimb weakness prior to death. At 5000 mg/kg, 1 of 5 males also showed the hindlimb weakness and was perfused with formalin. This animal has not yet been examined histologically. In the [acute] inhalation studies, groups of 5 male and 5 female rats were exposed to [EMP] vapor concentrations of 769 or 1571 ppm for a single 6-hour time period. No hindlimb weakness or other neurological signs have been observed."

Submission Evaluation

It is not clear from the submitted summarized information if EMP and MMP are primary neurotoxic agents or if the observed neurotoxic effects occurred secondarily (e.g., possibly as the result of hypoxia). In order for EPA to evaluate better the overall significance of the reported findings, the Eastman Kodak Company should 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 statistical analyses, etc.) from each toxicity study cited in the submission.

Current Production and Use

A review of the non-confidential computerized version of the initial TSCA Chemical Substance Inventory showed that the ethyl ester of 3-methoxypropanoic acid (CAS No. 10606-42-5) is not listed. A review of the production range (includes importation volumes) statistics for the methyl ester of 3-methoxypropanoic acid (CAS No. 3852-09-3), which is listed in the initial TSCA Inventory, showed that no 1977 production or importation was reported or that all of the production range information reported has been 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 information, including the production range information reported for the initial TSCA Chemical Substance Inventory is subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

Eastman Kodak reported in its Section 8(e) submission that the company uses both MMP and EMP for research and development (R&D) purposes. Eastman Kodak did not disclose, however, any information concerning the specific use(s) of the chemical substances. According to secondary literature sources, MMP may be used as an intermediate in the manufacture of acrylic esters via a process that avoids the use of propiolactone. No information concerning the use(s) of EMP was located in the secondary literature sources consulted by EPA.

Comments/Recommendations

In its submission, Eastman Kodak reported that the company has taken steps to warn its workers about the potential toxicity of the subject chemicals and has established appropriate handling precautions for the chemicals. In addition, Eastman Kodak stated that copies of the final reports from the reported studies will be sent to EPA upon completion of those reports.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the Eastman Kodak Company to ensure that EPA receives full copies of the final reports (including the actual experimental protocols, results of gross and histopathologic examinations, results of any statistical analyses, etc.) from all toxicity studies cited in the company's Section 8(e) submission.

   In view of the Agency's general interest in corporate actions that are taken on a voluntary basis in response to chemical toxicity or exposure information, Eastman Kodak will be asked to describe the nature and available results of all other studies that the company has conducted, is conducting, or plans to conduct to determine either the toxicity of or the exposure to the ethyl or methyl ester of 3-methoxypropanoic acid.

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 send copies of this status report to OSHA, NIOSH, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, and OPP/OPTS. 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 27 1986

SUBJECT: Status Report* 8EHQ-0486-0600 Approved: 5/27/86

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 submitted a copy of a scientific journal article entitled "Tumorigenic Effects in the Mucosa of the Forestomach of Rats in Feeding Experiments with Propionic Acid [(propanoic acid; CAS No. 79-09-4)]" which appeared in the Bundesgesundhbl. in November, 1985. The following information concerning the conduct and preliminary results of the study was presented in the English summary portion of the submitted paper:

> "In a feeding experiment which is still underway, 3 groups of male Wistar rats (90 in total) have been exposed to propionic acid. After 20 weeks, 10 animals from each group were sacrificed [and] the remaining ones will be observed until death. In the sacrificed rats of group I (4% propionic acid), pronounced hyperplasia, hyperplastic ulcers and papillomas were found in the mucosa of the forestomach. Histologically, proliferation of [the] basal cells and carcinomatous changes of the squamous epithelium could be demonstrated in the mucosa of the forestomach. There were erosive changes in the glandular epithelium of these animals. In the sacrificed rats of group II (0.4% propionic acid), hyperplastic changes were found in the region of the limiting ridge. The controls (group III) sacrificed did not exhibit any pathological changes of the mucosa of the stomach. It will be necessary to conduct further studies with short-chain fatty acids under modified experimental conditions to permit a re-assessment of the risk posed by propionic acid as a food additive."

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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.

Union Carbide submitted also a full copy of an anonymous English translation of a paper entitled "Communication from the [German] Federal Board of Health Concerning a Meeting of Experts on the Preservative Propionic Acid" which appeared in the January 1986 issue of the Bundesgesundhbl. The stated purpose of the meeting was to "clarify the question of whether the new findings place in question the harmlessness of the use of propionic acid for the preservation of foodstuffs."

Submission Evaluation

The submitted preliminary findings indicate that propionic acid, administered to rats at 4% in the feed, induced carcinomatous changes in the squamous epithelium of the forestomach after only 20 weeks of exposure. These results appear to be consistent with the weak oncogenic activity of pentanoic acid and marginal oncogenic activity of heptanoic acid toward the skin of mice observed following chronic dermal application (see 8EHQ-0584-0514 et seq). Overall, the results of these long-term studies of short-chain fatty acids suggest a need to systematically review this class of chemicals for potential proliferative, genotoxic, and oncogenic activities.

Current Production and Use

A review of the production range (includes importation volumes) statistics for propionic acid (CAS No. 79-09-4), which is listed in the initial TSCA Chemical Substance Inventory, has shown that from 61.2 million to 162 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) 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 Inventory Reporting Regulations (40 CFR 710).

According to secondary literature sources, propionic acid is used to produce propionate esters of which some are used as bread mold inhibitors and antifungal agents. In addition, propionic acid is reportedly used as an emulsifying agent and as a grain and wood chip preservative. Other reported uses include the manufacture of herbicides, perfumes, artificial food flavorings, drugs, and cellulose propionate thermoplastic.

Comments/Recommendations

According to Part VII(c) of EPA's March 16, 1978, Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110), information need not be reported to EPA under TSCA Section 8(e) if, for

example, the information has been 1) published by EPA in reports; 2) submitted already to EPA under a mandatory reporting provision of another authority administered by EPA; or 3) published in the open scientific literature and abstracted/referenced by Agricola, Biological Abstracts, Chemical Abstracts, Dissertation Abstracts, Index Medicus, or the National Technical Information Service. In its TSCA Section 8(e) submission, Union Carbide stated that the company had been unable to locate an abstract of either of the submitted articles in any of the abstracting services listed in Part VII(c) of the Section 8(e) policy statement or in any other abstracting services. EPA was equally unsuccessful in finding abstracts of the submitted articles in the listed or any other abstracting services. Therefore, Union Carbide's report to EPA under TSCA Section 8(e) was appropriate.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will review the reported findings in more detail to determine the need for further OTS assessment of the potential risks posed by exposure to propionic acid as well as other short-chain fatty acids.

b) 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. In addition, copies of this report will be transmitted to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUN 5 1986

SUBJECT: Status Report* 8EHQ-0586-0601 Approved: 6/5/86

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 its six member companies, the Smelter Environmental Research Association (SERA) provided a complete copy of the final report from a SERA-funded epidemiologic study that was conducted by the University of Pittsburgh Graduate School of Public Health. The "Executive Summary" section of the submitted report (entitled "Mortality Among Copper and Zinc Smelter Workers in the United States") presented the following information with regard to the conduct and results of the study:

> "This study of 14,562 white male workers from the copper and zinc smelting industries did not show any overall mortality excesses when the mortality of smelter workers was compared to the mortality of the total U.S. population. There was, in fact, a 14% deficit in mortality for all causes of death for both copper and zinc smelter workers. While there were variations in the all cause mortality experience among smelters, some of this was probably due to natural variation and is probably not important.
>
> "When diseases likely to be associated with smelting of copper and zinc were examined, only two associations were found that are probably of importance. First, an association was noted between sulfur dioxide exposure and emphysema mortality. This is not reported elsewhere and may be a new finding. Secondly, there was an association between arsenic exposure and lung cancer. This is not a new finding. Given the relatively low level of arsenic exposure in this study, however, the association was surprisingly strong and suggests that arsenic might be more potent as a carcinogen than has been suggested in other studies.

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> "Aside from these two findings, this extensive examination of the mortality experience of smelter workers in the United States is essentially negative. This conclusion is based on a very extensive analysis relating not only to [the] patterns of mortality but also to specific [the] responses to a wide variety of agents known to be present in copper [and zinc] smelters. . . . ."

In the cover letter to its Section 8(e) notice, SERA stated that the study investigators found "a statistically significant trend for emphysema mortality with increasing duration of exposure to sulfur dioxide at peak values exceeding 24.00 PPM (parts per million) in air." SERA stated also that "the finding is based on a small number of deaths and any confounding effects of cigarette smoking could not be examined under the original study design." SERA did not submit any comments on the arsenic-related findings.

Submission Evaluation

The subject epidemiologic study was organized into four phases which included 1) standardized mortality ratio (SMR) analyses by occupational job categories (e.g., mill workers, smelter only workers), 2) SMR analyses by occupational category for trends with duration of exposure and for time since first employed, 3) SMR analyses by specific chemical exposures, and 4) a nested case-control study of lung cancer. The SMR analyses of the various occupational job categories did not reveal any associations with specific causes of death, with duration of exposure, or with time since first employed. However, the third phase of the study showed 1) increased risks of emphysema for workers exposed to sulfur dioxide, 2) increased risks of lung cancer for workers exposed to arsenic, and 3) increased risks of lung cancer for workers exposed to sulfur dioxide. Further analyses of the lung cancer cases utilizing a nested case-control approach suggest that smoking and arsenic exposure may have been confounding factors that could explain the sulfur dioxide/lung cancer association. Further, logistic regression analyses, which examined the lung cancer and arsenic relationship and did control for smoking, suggest that lower level arsenic exposure might be a more potent lung carcinogen than has been suspected from previous studies.

A brief review of the various methodologies and the statistical analyses revealed that there are several factors that influence interpretation of the study results. These factors include 1) the choice of the control population (mill workers) potentially subject to some of the same adverse mortality effects as the study cohort, and 2) the potential misclassification of exposure levels due to use of a job description model rather than environmental monitoring data. However, given that misclassification in the submitted study would be random, the significant relationship between sulfur dioxide exposure and emphysema is noteworthy even though smoking histories were not obtained for emphysema deaths and smoking could confound that relationship. As noted in the case-control study, smoking did confound the sulfur dioxide/lung

cancer relationship. Also noteworthy is a concaved upward shaped dose-response curve for lung cancer and arsenic exposure while dose-response modelling from previous studies of this type have suggested a linear relationship. The submitted report, however, does not contain sufficient information with which to evaluate this finding adequately.

Comments/Recommendations

SERA stated in the cover to its Section 8(e) submission that full copies of the final report from the epidemiologic study had been sent to all SERA member companies (ASARCO Inc.; Cominco, Ltd.; Inspiration Consolidated Copper Company; Kennecott Newmont Mining Corporation; Phelps Dodge Corporation; and the St. Joe Minerals Corporation).

EPA's Office of Toxic Substances (OTS) has received a number of TSCA Section 8(e) and "For Your Information" (FYI) submissions concerning the results of epidemiologic studies involving worker exposure to a wide variety of heavy metals and/or other chemical substances.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will review the provided report in more detail to determine the need for further OTS assessment of the study findings.

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 and OPP/OPTS. 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: JUN 24 1986

SUBJECT: Status Report* 8EHQ-0586-0602 S

Approved: 6/24/86

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 identities of the tested materials as TSCA Confidential Business Information (TSCA CBI). Information Management Division (IMD/OTS) staff will request the submitting company to substantiate all of the company's TSCA CBI claims. In reporting under Section 8(e), the submitting company stated non-confidentially that the company was aware of the Agency's concerns about chemicals containing an acrylate moiety and that the submitted data were expected to aid the Agency in its ongoing efforts in evaluating possible adverse health effects of acrylates.

Submission Description

The submitting company provided 9/15 final reports from a battery of 5 genotoxicity studies conducted on each of 3 test materials. Specifically, the 3 materials (II, III, and IV) were studied in 1) an Ames/Salmonella typhimurium (bacteria) Assay, 2) an in vivo Mouse Micronucleus Chromosomal Aberration Assay, 3) an in vitro Rat Hepatocyte Primary Culture DNA Repair Assay, 4) an in vitro Mammalian Cell Forward Gene Mutation Assay;, and 5) an in vitro Hamster Ovary Cell Chromosomal Aberration Assay. According to the submitter, all of the performed genotoxicologic studies were negative with the exception of statistically significant positive results observed in the in vitro chromosomal aberration assays.

Submission Evaluation

An initial review of the submitted final reports shows that all 3 materials were negative in the Ames assay when tested with and without exogenous metabolic activation in bacterial strains TA98, TA100, TA1535, TA1537 and TA1538. Although test materials III and IV had originally showed some suggestive activity in strain TA1538, no activity was evident in repeated tests.

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The only final report submitted thus far from the in vivo mouse micronucleus tests was the one for material IV. No increased micronuclei were observed at sacrifice times of 30, 48 or 72 hours after a single intraperitoneal injection of 1000 mg/kg. Further, no alteration from study controls was observed with regard to the polychromatic erythrocyte (PCE)/normochromatic erythrocyte (NCE) ratio. At the administered dose of 1000 mg/kg, there were some signs of toxicity, however, and one of the test animals died.

The company provided the final reports for the DNA repair assays conducted on materials II and III. Both materials were negative at test concentrations of up to 167 ug/ml and toxicity was seen at higher doses.

Finally, the company submitted the final study reports from the cultured Chinese Hamster Ovary (CHO) cell chromosomal aberration assays on materials II, III and IV. All 3 of the test materials produced dose dependent increases in chromosomal aberrations both with and without exogenous metabolic activation. The top 1 or 2 test material concentrations generally produced responses that were statistically significant. Only with test material II under activated conditions was the increase in aberrations found to be just at the level of statistical significance. The rest of the observed responses were clearly positive.

Further evaluation of the overall significance of the reported genotoxicity findings should be possible upon EPA's receipt of the remaining 6 final reports from the performed studies.

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 tested materials will appear in this status report.

Comments/Recommendations

The submitting company stated that the 6 remaining final reports will be sent to EPA as soon as the company receives the reports.

The Chemical Screening Branch has received numerous TSCA Section 8(e) and For Your Information (FYI) notices on acrylic acid and its derivatives. Further, the Chemical Screening Branch has prepared Chemical Hazard Information Profiles (CHIPs) on acrylic acid, ethyl acrylate, ethylhexyl acrylate and neopentyl glycol diacrylate. Also, the Risk Analysis Branch (RAB/ECAD/OTS) has been evaluating available toxicologic/exposure data on several acrylates. Finally, EPA's Chemical Control Division/Office of Toxic Substances (CCD/OTS) has received a number of TSCA Section 5 "Premanufacture Notices" (PMNs) on acrylates and is assessing the potential risks posed by exposure to acrylates as a class.

a) The Chemical Screening Branch (CSB/ECAD) will ask the submitting company to report to EPA the exact chemical identity (including the CAS Registry Number, if known) and amount (if known) of each constituent in each of the tested materials cited in the company's initial Section 8(e) notice.

b) The Chemical Screening Branch will review the reported information in order to determine the need for separate assessment of the tested materials and/or inclusion of the reported findings into ongoing OTS assessments of acrylates.

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUN 17 1986

SUBJECT: Status Report* 8EHQ-0686-0603 Approved: 6/17/86

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 with regard to the conduct and preliminary results of a short-term repeated inhalation exposure study of 1-propoxy-2-propanol vapor (Propasol® Solvent P; CAS No. 1569-01-3) in male and female rats:

> "Fischer 344 rats, in groups containing 10 males and 10 females, were exposed [via inhalation] to target concentrations of 1-propoxy-2-propanol vapor of 0 (air control group), 500, 1000 and 2000 ppm. Only [those] animals free of ophthalmic abnormalities on visual inspection were included in the study. Exposures were 6 hours a day, for 9 days over 2 weeks. During this period, the analytically measured concentrations of vapor, expressed as mean ± SD, were 0 (air control), 503 ± 21, 983 ± 65, and 2000 ± 101 ppm. During routine daily inspection of the animals for signs of [overt] toxicity, opacification of the cornea was observed at 2000 ppm; this was seen in 13 of 20 rats after 4 days of exposure and in 17 of 20 rats after 9 days of exposure. Signs of sensory irritation of the eye, such as periocular wetness, were seen only in 3 of the 20 animals exposed to 2000 ppm of the vapor, and in these [3] animals only after the first exposure day. On standard daily clinical inspection of the animals exposed to 503 or 983 ppm of vapor, there were no signs of corneal injury or sensory irritation of the eye. A more detailed examination of the eyes was conducted on the morning of the ninth day of exposure by use of a magnifying lens. No corneal abnormalities were seen in the control, 503, or 983 ppm groups. At 2000 ppm, one of the 20 exposed animals had normal eyes, 17 had corneal opacities, one had cloudy corneas, and one had central corneal ulcers. Histological examination 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.

> the eyes showed lesions in the corneas at all exposure concentrations, but none in the air-alone controls. The lesion was limited principally to the anterior portion of the cornea, and [was] characterized by separation of the epithelium from the underlying substantia propria, patchy loss of the epithelium producing ulceration, inflammatory cell infiltration and vascularization of the other substantia propria. There was also mineralization of the outer stroma. . . . ."

In its TSCA Section 8(e) submission, Union Carbide reported that during the "more than 20 years of manufacturing and marketing of 1-propoxy-2-propanol, . . .[the company has] received no reports of chronic eye injury ascribed to the chemical."

Submission Evaluation

Although the submitted summarized information does indicate that inhalation exposure to 1-propoxy-2-propanol can result in adverse ocular effects, a more complete assessment 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 cited study.

Current Production and Use

A review of the production range (includes importation volumes) statistics for 1-propoxy-2-propanol (CAS No. 1569-01-3), which is listed in the initial TSCA Chemical Substance Inventory, shows that no 1977 manufacture/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 manufacturer(s) and/or importer(s) and cannot be disclosed (Section 14(a) of TSCA, U.S.C. 2613(a)). All of the information provided for the initial TSCA Inventory, including the production range information, is subject to the limitations that are contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

Union Carbide did not submit any information with regard to the current production/importation volume or the specific use(s) of 1-propoxy-2-propanol; no information relating to current production or importation volumes or specific use(s) of this chemical was located in the secondary literature sources consulted.

Comments/Recommendations

Union Carbide stated that the company plans to submit to EPA a full copy of the final report from the cited inhalation study as soon as that report is received and reviewed by the company. In addition, Union Carbide stated that the company is 1) notifying employees and customers about the reported toxicologic findings, and 2) revising the label and Material Safety Data Sheet for 1-propoxy-2-propanol to reflect the reported toxicologic findings.

EPA's Office of Toxic Substances (OTS) has received a number of TSCA Section 8(e) and "For Your Information" (FYI) submissions on glycol ethers and their derivatives. In addition, the Chemical Screening Branch prepared Chemical Hazard Information Profiles (CHIPs) on 2-ethoxyethanol, 2-methoxyethanol and their acetates. Further, the Test Rules Development Branch has been evaluating available toxicologic and exposure information on 3 triethylene glycol ether derivatives designated by the Interagency Testing Committee (ITC) for health effects testing under Section 4 of TSCA. Finally, it should be noted that following consideration of the various regulatory options for reducing the risks posed by exposure to 2-ethoxyethanol, 2-methoxyethanol and their acetates, the Agency recently referred these chemicals to the Occupational Safety and Health Administration (OSHA) under Section 9 of TSCA (see 51 FR 18488; May 20, 1986).

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask Union Carbide to ensure that EPA receives a full copy of the final report (including the actual experimental protocol, results of gross/histopathologic examinations, etc.) from the inhalation study cited in the company's TSCA Section 8(e) notice. In addition, Union Carbide will be asked to provide to EPA copies of the 1-propoxy-2-propanol label and Material Safety Data Sheet revised to reflect the reported toxicologic findings.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity and/or exposure data, the Chemical Screening Branch will request the Union Carbide Corporation to describe the results of all studies (other than those published 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 determine the toxicity of or the exposure to 1-propoxy-2-propanol.

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

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUN 13 1986

SUBJECT: Status Report* 8EHQ-0686-0604 Approved: 6/13/86

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 Amoco Chemicals Company (a wholly owned subsidiary), the Amoco Corporation provided the following summarized information with regard to the conduct and preliminary findings from a lifetime mouse skin painting study of a "heavy aromatic bottoms stream from a paraxylene unit" (**):

> "[Fifty (50)] microliters of undiluted test material were applied to the dorsal skin of 50 male mice, twice per week, for the intended lifetime of the animals. The results reported here are those found after 93 weeks of dosing. Thirteen mice developed tissue mass(es) at the application site, with a median latency period of 85.0 weeks. Of those, eight mice have been observed with a single mass each, and five mice have multiple masses per animal. Histopathological examinations of those masses will be done at the end of the study. A concurrent control group of 120 mice is free of dermal masses through 93 weeks."

** According to the submitter, the identity of the test material was submitted to EPA in 1978 for inclusion to the initial TSCA Chemical Substance Inventory as a heavy aromatic solvent naphtha (CAS No. 64742-94-5). The submitter stated, however, that the "current Inventory description for this material may not be the most accurate one" and that the company "is in the process of evaluating the composition of this stream and will supply the Agency with a more accurate description, if one is warranted, under separate correspondence."

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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 the submitted summarized information indicates that the tested material may possess some degree of oncogenic activity toward the skin of male mice, an 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 ongoing mouse skin application study.

Current Production and Use

Appendix A in Volume 1 of the new (1985) printed version of the initial TSCA Chemical Substance Inventory contains the following definition for CAS No. 64742-94-5 (heavy aromatic solvent naphtha (petroleum)):

> "A complex combination of hydrocarbons obtained from distillation of aromatic [petroleum] streams. It consists predominantly of aromatic hydrocarbons having carbon numbers predominantly in the range of C9 through C16 and boiling in the range of approximately 165°C to 290°C (330°F to 554°F)."

A review of the production range (includes importation volumes) statistics for CAS No. 64742-94-5, 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 cited 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 contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

Comments/Recommendations

In its Section 8(e) notice, the Amoco Corporation stated that the company will submit a copy of the final report from the ongoing lifetime mouse skin application study once the final report from the study is completed in mid-1987. Amoco stated further that, in the interim, the company 1) is informing its employees about the reported findings, and 2) "will revise the material safety data sheets as necessary for this substance, and for products containing this material, to reflect the potential hazard."

It should be noted that the Office of Toxic Substances (OTS) has received numerous TSCA Section 8(e) and "For Your Information" (FYI) submissions containing toxicologic and/or exposure data on a number of petroleum, coal, and shale oil process streams.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the Amoco Corporation to ensure that EPA receives a full copy of the cited chronic mouse dermal application study final report (including the actual experimental protocol, results of gross and histopathologic examinations, results of any statistical analyses, etc.) immediately upon the company's receipt of that final report. In addition, Amoco will be asked to keep EPA apprised of significant results obtained from all future sacrifices in this study.

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

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

DATE: JUL 7 1986

SUBJECT: Status Report* 8EHQ-0686-0605 S Approved: 7/8/86

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 claimed its company name as well as the exact identities of the tested chemicals to be TSCA Confidential Business Information (CBI). The Information Management Division (IMD/OTS) staff will ask the submitting company to substantiate these TSCA CBI claims. In its Section 8(e) notice, the company stated non-confidentially that the test material was a mixture of two complex organosilane oligomers which were the subject of "Premanufacture Notices" (PMNs) submitted to EPA previously under Section 5 of TSCA. The company stated also that it had received the submitted Section 8(e) information verbally.

Submission Description

The company submitted the following summarized information with regard to the conduct and preliminary results of a sub-acute inhalation toxicity study of the subject mixture in rats:

> "This [organosilane oligomer] mixture was the subject of a repeated 28-day inhalation study in which male and female Fisher 344 rats were exposed to 0, 10, 40 or 150 mg/m^3. The duration of the test was [for] six hours a day, five days a week for four weeks. At the conclusion of the study, [the] animals were necropsied and subject[ed] to an extensive histopathological evaluation. The relevant findings from this investigation revealed that the larynges of animals exposed at 150 mg/m^3 [had] suffered necrosis and ulceration. At the two lower concentrations (10 or 40 mg/m^3), lesser effects were noted. However, there was a clear concentration response relationship in these two [lower] exposure groups which was characterized as squamous metaplasia and coincided with the site of ulceration and necrosis seen in the animals exposed to 150 mg/m^3. . . . ."

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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 the reported findings do provide additional support for EPA's concerns about the potential health risks posed by exposure to organosilanes, an evaluation 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 submitting company's 28-day repeated inhalation exposure study in rats.

Current Production and Use

Considering the submitter's TSCA CBI claims, no information with regard to the production or use of the tested mixture or its constituents will appear in this status report.

Comments/Recommendations

The Office of Toxic Substances has received a number of TSCA Section 8(e) and/or "For Your Information" (FYI) submissions on organosilanes. In addition, the Chemical Screening Branch has prepared a Chemical Hazard Information Profile (CHIP) on 3,4-epoxycyclohexylethyltrimethoxy silane and is in the process of preparing a CHIP on other selected organosilanes. Further, the Risk Analysis Branch (RAB/ECAD/OTS) has been reviewing available toxicologic/exposure data on 3,4-epoxycyclohexylethyltrimethoxy silane. Finally, the Office of Toxic Substances has received a number of TSCA Section 5 PMNs on organosilanes.

a) The Chemical Screening Branch will request the submitter to ensure that the Agency receives a complete copy of the final report (including the actual experimental protocol, the results of both gross and histopathological examinations, etc.) from the 28-day inhalation toxicity study cited in the company's Section 8(e) submission.

   In view of the Agency's general interest in corporate actions that are taken on a voluntary basis in response to chemical toxicity or exposure data, the submitting company will be asked also to describe the nature and available results of 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 determine the toxicity or the exposure to the tested mixture or its individual components. In addition, the submitting company will be asked to describe the actions the company has taken or is planning to take to 1) notify its workers and others about the reported toxicologic findings, and 2) reduce or eliminate exposure to the tested mixture or its components.

b) The Chemical Screening Branch will review the submitted information and consider inclusion of that information in the organosilane CHIP now in preparation.

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. Copies of this status report will be transmitted also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: JUL 11 1986

SUBJECT: Status Report* 8EHQ-0786-0606 S Approved: 7/11/86

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 CIBA-GEIGY Corporation claimed the exact chemical identity of the tested substance to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS) will be requesting the company to substantiate this TSCA CBI claim. CIBA-GEIGY provided the following non-confidential generic name for the tested chemical: "heteromonocyclic carbomonocyclic urea."

Submission Description

CIBA-GEIGY submitted the following summarized information with regard to the conduct and preliminary results from a two-year dietary oncogenicity/chronic toxicity study of this heteromonocyclic carbomonocyclic urea in male and female mice:

> "The dose levels for the two-year dietary . . . study were 10, 100, 750 and 1,500 ppm. Microscopic findings in the second year of study showed an increase in incidence of hepatocellular adenomas in males at the 100, 750 and 1,500 ppm dosage levels and in females at the 1,500 ppm dosage level. Because the [tested] compound had been dropped [in late 1984] from further development [by CIBA-GEIGY as a research and development chemical intended solely for use as a pesticide product], microscopic pathology was conducted only on liver masses and nodules noted during the macroscopic examination. No significant increase in the incidence of hepatocellular carcinoma was evident in the test article treated mice."

In its submission, CIBA-GEIGY stated that no oncogenic response has been noted for the subject chemical substance in a two-year dietary feeding study in rats. In addition, CIBA-GEIGY reported that the chemical was negative in an Ames Salmonella typhimurium (bacteria) mutagenicity assay.

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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 the provided summarized preliminary findings indicate that the tested chemical caused an increase in the incidence of hepatocellular adenomas in male mice at the upper doses and in female mice at the highest dose, a more complete evaluation of the reported results should be possible upon EPA's receipt of a complete copy of the final report from the performed study.

Current Production and Use

The CIBA-GEIGY Corporation stated that the tested substance was a research and development (R&D) chemical that was under evaluation by the company solely for use as a pesticide product. According to CIBA-GEIGY, the subject chemical substance had been tested by "technically qualified personnel, knowledgeable in handling potentially hazardous chemicals." Finally, CIBA-GEIGY stated that the tested chemical "was dropped in November 1984 as a possible pesticide due to lack of sufficient pesticidal activity."

Comments/Recommendations

In its submission, CIBA-GEIGY stated that upon the company's receipt and review of the final report of the two-year dietary feeding study in mice, the company would submit a copy of that report and the company's assessment of the results. CIBA-GEIGY stated also that "notifications to persons working with [the heteromonocyclic carbomonocyclic urea] will not be necessary as supplies of the material no longer exist."

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask CIBA-GEIGY to ensure that EPA receives a full copy of the final report (including the actual experimental protocol, results of gross/histopathologic examinations, etc.) from the two-year mouse dietary oncogenicity and chronic toxicity study cited in the company's initial TSCA Section 8(e) submission.

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUL 15 1986

SUBJECT: Status Report* 8EHQ-0786-0607 S Approved: 7/15/86

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 name and the specific use of the subject chemical as TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS) will request the submitting company to substantiate all of the TSCA CBI claims made in the submission.

Submission Description

The submitting company reported the following summary information with regard to the conduct and results of a series of short-term in vivo toxicity studies of 2,2,6,6-tetramethylpiperidine-1-oxyl (CAS No. 2564-83-2):

"Inhalation LC50-Limit Test

Five female and five male Sprague-Dawley rats were exposed to the vapors of the test chemical, obtained by slowly heating the test material to 100°C. All ten of the exposed rats died within 2 hours of the initiation of the intended 4-hour exposure. A nominal concentration of 4.5 - 6.6 mg/liter was delivered, but, because the material condensed on the surfaces of the delivery apparatus and inhalation chamber during delivery, it is estimated that the rats were actually exposed to vapor concentrations at least 10-fold less than the nominal concentration.

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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.

Dermal LD50-Limit Test

The test chemical was applied, undiluted, to the backs of two male and two female rabbits at a dose of 2.0 gm/kg body weight, and the application site was wrapped. Two females and one male died within 24 hours after application. The remaining male rabbit showed overt signs of toxicity (i.e., lethargy, hypoactivity) at first, but subsequently recovered.

Dermal Irritancy/Corrosivity Study

A 0.5 gm quantity of the chemical was applied to the shaved back of each of 6 rabbits for a 4-hour period, and the skin reaction was scored at 24 and 72 hours after removal of the test material. A primary skin irritation score of 6.5/8.0 was obtained.

Eye Irritation Study (Draize)

A 0.1 gm quantity of the [subject] chemical was placed in the everted eyelid of each of 6 rabbits. After 24 hours, the maximum primary eye irritation score was 60.2/110.0."

In reporting this information under Section 8(e), the submitter stated that "taken together, these results indicate a toxicity profile for 2,2,6,6-tetramethylpiperidine-1-oxyl that warrants concern because of its potential to cause harm in humans."

Submission Evaluation

Based on an initial review of the provided summarized results, the subject chemical appears to be very toxic (at minimum) via inhalation, can penetrate unabraded skin in sufficient amounts to cause death, is extremely irritating upon dermal application, and is severely irritating to the eyes. An evaluation of the overall significance of the reported findings should be possible upon receipt of the final reports from the cited acute toxicity studies.

Current Production and Use

The subject chemical was not located in the non-confidential computerized version of initial (1977) TSCA Chemical Substance Inventory. As stated previously, the submitting company has claimed the information pertaining to the company's use of this chemical to be TSCA CBI.

Comments/Recommendations

In its TSCA Section 8(e) notice, the submitting company stated that "persons who handle this substance have been informed of its toxicity, and procedures have been reviewed to ensure safe workplace practices." The company stated also that the final reports from the cited acute toxicity studies will be sent to EPA as soon as those reports are available.

a) The Chemical Screening Branch (CSB/ECAD) 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 and histopathologic examinations, etc.) from each study that was cited in the company's initial 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 data, the submitting company will be requested to describe the nature and available results of all studies (other than those cited in the open scientific literature or those submitted already to the Agency) 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 2,2,6,6-tetramethylpiperidine-1-oxyl.

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

DATE: JUL 21 1986

SUBJECT: Status Report* 8EHQ-0786-0608 S Approved: DK 7/21/86

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 claimed its name and the exact identity, use, and production volume of the subject chemical substance to be TSCA Confidential Business Information (TSCA CBI). Staff of the Information Management Division (IMD/OTS) will request the submitting company to substantiate all of the TSCA CBI claims made in the company's TSCA Section 8(e) submission. In its submission, the company stated non-confidentially that the subject chemical was a "metal salt of a phosphoric acid ester."

Submission Description

The submitting company provided the final results from an Ames Salmonella typhimurium (bacteria) mutagenicity assay, an in vitro Chinese Hamster Ovary (CHO) cell sister chromatid exchange (SCE) assay and a 28-day repeated skin application study of the subject chemical in rats. According to the submitting company, the Ames assay (with or without exogenous metabolic activation) as well as the 28-day dermal application study were negative. With regard to the results of the SCE assay, the submitting company stated that a "positive dose-related response" was observed. (The submitted final report from the SCE assay states that a significant concentration-dependent increase in SCEs was observed in the presence but not in the absence of exogenous metabolic activation.)

Submission Evaluation

Although the submitting company stated that the 28-day dermal study in rats was negative, the company provided only the protocol and narrative results sections of the final report. Without the actual data tables, the Agency cannot evaluate the reportedly "negative" findings from this in vivo 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.

With regard to the performed genotoxicity assays, the Ames assay was negative in the presence and absence of exogenous metabolic activation in Salmonella typhimurium (bacteria) strains TA98, TA100, TA1535, TA1537 and TA1538 up to toxic doses of the subject chemical (dose range was from 0.3 - 1.0 mg/plate). The SCE assay was negative under non-activation conditions up to a dose of 3.0 ug/ml (5.0 ug/ml was found to be toxic). Under activated conditions, there was a small but significant concentration dependent increase in SCEs at test chemical concentrations up to 5.0 ug/ml (10.0 ug/ml was found to be toxic). Although this increase is statistically significant, it may be of marginal biological significance especially when one considers that the submitted final report for the SCE assay states that a "repeat" SCE assay did not duplicate the positive findings of the first SCE assay.

Current Production and Use

In light of the submitter's TSCA CBI claims, no information with regard to production volume, use, or TSCA Inventory status of the subject chemical will appear in this status report. According to the submitter, the tested material "is currently being used for a limited number of products. . ." The submitter stated also that to the extent the subject chemical is contained in such products, exposure to the subject chemical can and should be controlled or minimized as the result of already reported concerns about the potential oncogenic risks posed by exposure to the products themselves.

Comments/Recommendations

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 define better the toxicity of or exposure to that chemical or mixture. The results of such additional studies should be considered also for possible submission to EPA pursuant to Section 8(e) of TSCA.

a) The Chemical Screening Branch (CSB/ECAD) will ask the submitting company to provide to EPA a complete copy of the final report from the "repeat" SCE assay cited in the SCE assay final report contained in the company's initial TSCA Section 8(e) submission. In addition, the

submitting company will be asked to provide a full copy of all data tables from the "negative" 28-day dermal application study cited in the initial 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 submitting company will be asked to describe the nature and results, if available, from all studies (other than those submitted already to EPA) that the company 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 "metal salt of a phosphoric acid ester."

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, CCD/OTS/OPTS and OPP/OPTS. In addition, copies of this status report will be provided to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JUL 21 1986

SUBJECT: Status Report* 8EHQ-0786-0609 S Approved: 7/21/86

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

R. T. Vanderbilt Company, Inc. has claimed the exact identity of the subject chemical to be TSCA Confidential Business Information (TSCA CBI). The company has reported non-confidentially by phone that the chemical is a "heterocyclic derivative." Staff of the Information Management Division (IMD/OTS) will be requesting the company to substantiate this confidentiality claim.

Submission Description

R. T. Vanderbilt Company, Inc. provided the following information with regard to the conduct and preliminary findings of an acute (4-hour) inhalation study of the heterocyclic derivative in rats:

> "Five male and five female Sprague-Dawley rats were exposed to a liquid droplet aerosol of [the heterocyclic derivative] at an average actual concentration of 5.2 mg/L for four consecutive hours. The animals were observed periodically during and post-exposure for pharmacotoxic signs and mortality. Under the conditions of this study, the . . .[heterocyclic derivative] produced 100% mortality."

Submission Evaluation

An EPA evaluation of the overall significance of the reported toxicity should be possible upon EPA's receipt of a full copy of the final report from this study. The submitting company stated in its submission that the final report would be sent to EPA as soon as the company receives that report.

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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 submitting company's confidentiality claims, no information concerning the TSCA Inventory status of the subject chemical will be presented in this status report. According to the submitting company, the subject chemical substance is an "experimental compound" that "is being synthesized in small quantities at . . . [the company's] Research and Development facilities and is handled by technical personnel." In addition, the company reported that "the risk of exposure to airborne dust is minimal."

Comments/Recommendations

a) The Chemical Screening Branch (CSB/ECAD) will request R. T. Vanderbilt Company, Inc. to ensure that the Agency receives a full copy of the final report (including the actual experimental protocol, the results of gross and histopathologic examinations, etc.) from the acute inhalation 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, R. T. Vanderbilt Company, Inc. will be asked to describe the actions that the company has taken or plans to take to notify its workers about the reported toxicologic findings. In addition, the company will be requested to describe the nature and results, if available, from all other studies 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 this heterocyclic derivative.

c) The Chemical Screening Branch will send a copy of this status report to OSHA, NIOSH, 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: AUG 12 1986

SUBJECT: Status Report* 8EHQ-0786-0610 Approved: 8/12/86

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

Total Petroleum, Inc. provided full copies of the final reports from an Ames Salmonella typhimurium (bacteria) mutagenicity assay and an in vitro BALB/c-3T3 cell transformation assay of a mineral seal oil. According to the submitter, both assays were positive. In addition, the company reported that an in vitro chromosomal aberration study had been conducted and found to be negative (the company did not include a copy of the final report from this particular study in its submission). Total Petroleum, Inc. reported by phone that the tested mineral seal oil is a hydrodesulfurized middle (petroleum) distillate (CAS No. 64742-80-9). In addition, it should be noted that Total Petroleum, Inc. obtained the submitted study reports from the Pennzoil Products Company for whom the studies had been conducted by a contract laboratory.

Submission Evaluation

The subject mineral seal oil (as an emulsion) was assayed only in Salmonella typhimurium (bacteria) strain TA98 in the presence of exogenous metabolic activation. A 2-3 fold increase in revertant frequencies over background was found at almost all doses tested regardless of the type of emulsifier used (10% F68 Pluronic or 10% Tween 80). The provided data show that this mineral seal oil was mutagenic under the conditions of the performed Ames assay.

With regard to the in vitro BALB/c-3T3 mouse cell transformation assay, the mineral seal oil was tested as an emulsion in culture medium containing 1% F68 Pluronic. Based on the provided data, the mineral seal oil was weakly active in this assay. Further, it is unlikely that the observed activity was due to either the F68 Pluronic emulsifier or the relatively high concentrations of mineral seal oil tested (indicated by the lack of cytotoxicity).

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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

According to the printed version of the initial TSCA Chemical Substance Inventory, CAS No. 64742-80-9 is a complex combination of hydrocarbons obtained from a petroleum stock by treating with hydrogen to convert organic sulfur to hydrogen sulfide which is removed; it consists of hydrocarbons having numbers predominantly in the range of C11 to C25 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. 64742-80-9, which is listed in the initial TSCA Chemical Substance Inventory, shows that over one billion pounds were reported as manufactured and/or imported in 1977. This production range information does not contain any production/importation range data claimed as TSCA Confidential Business Information (TSCA CBI) by those persons reporting for the initial TSCA Inventory, nor does it include any information that would compromise TSCA CBI. All of the data submitted 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).

Total Petroleum, Inc. did not provide any information on the specific use(s) of this mineral seal oil nor was such information located in the secondary literature sources consulted by EPA.

Comments/Recommendations

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 substance or mixture. Also, EPA believes that a positive genotoxicity test result, in combination with additional relevant information (e.g., the 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 define better the toxicity of or the exposure to that chemical or mixture. The results of such additional tests 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) previously received and evaluated a TSCA Section 8(e) submission on another mineral seal oil. In 8EHQ-0683-0480 et seq., Exxon Company, U.S.A. reported that benign and malignant skin tumors were found in a chronic mouse skin painting study of a chemically neutralized middle (petroleum) distillate (CAS No. 64742-30-9).

It should be noted also that OTS has received and evaluated many TSCA Section 8(e) and "For Your Information" (FYI) notices concerning petroleum, shale, and coal oils and process streams.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask Total Petroleum, Inc. to provide to EPA a complete copy of the final report (including the actual experimental protocol, data, etc.) from the chromosomal aberration assay 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 chemical toxicity or exposure data, Total Petroleum, Inc. will be requested to describe the actions the company has taken or is planning to take to 1) notify workers and others about the reported toxicologic findings, and 2) reduce or eliminate exposure to Total's mineral seal oil. In addition, Total Petroleum, Inc. will be requested to describe the nature and results, if available, from 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 either the toxicity of or the exposure to this mineral seal oil.

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

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. Copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: AUG 13 1986

SUBJECT: Status Report* 8EHQ-0786-0611 S Approved: 8/13/86

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 TSCA CBI claim.

Submission Description

The submitting company reported that it learned recently (via a private communication) about the as yet unpublished results of a clinical study involving 8 ethylene oxide-exposed workers and 8 matched control workers. According to the submitter, the study had been conducted independently by scientists at the University of California's San Francisco General Hospital. The submitter stated further that the performed study included central and peripheral nervous system function tests designed to detect possible neurotoxicity. The submitter stated also that the investigators conducted a computerized psychometric test battery, nerve conduction studies, P-300 event potentials, EEG spectral analyses, and neurological and physical examinations. Finally, the submitter provided the following information with regard to the primary investigator's statements about the study findings which are expected to appear soon in the published scientific literature:

> "The findings of . . . [the performed] study suggest that in addition to the well documented peripheral neuropathological manifestations [associated] with chronic [exposure to] ethylene oxide, there are subtle central nervous dysfunctions which may result from chronic low level exposure [to the chemical]. These effects may occur at exposure levels believed to be historically common to hospital sterilizing operations."

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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 the conducted tests are of the type that would allow for detection of CNS dysfunction (including subtle changes), further information concerning the conduct and results of the performed tests is necessary in order for EPA to evaluate properly the overall significance of the reported findings. (In its Section 8(e) notice, the submitting company provided the name and address of the primary investigator in order for the Agency to contact the investigator directly for additional information pertaining to the conduct and results of the performed tests.)

Immediately upon EPA's receipt of this submission, the Chemical Screening Branch (CSB/ECAD/OTS/OPTS/EPA) provided copies of the notification to the Occupational Safety and Health Administration (OSHA), National Institute for Occupational Safety and Health (NIOSH), Food and Drug Administration (FDA) and EPA's Office of Pesticide Programs (OPP/OPTS/EPA). It should be noted that on June 22, 1984, OSHA promulgated (49 FR 25734) a final standard for occupational exposure to ethylene oxide (Permissible Exposure Level (PEL) = 1 part per million (ppm) as an 8 hour Time Weighted Average (TWA).

Current Production and Use

According to Chemical & Engineering News (July 9, 1986 issue), approximately 5.7 billion and 5.8 billion pounds of ethylene oxide were produced in the U.S. in 1984 and 1985, respectively.

Ethylene oxide is used mainly as a chemical intermediate (e.g., in the production of ethylene glycol) and as a chemosterilant/fumigant (e.g., medical and surgical equipment/devices, packaging materials, dried foods). According to staff of EPA's Office of Pesticide Programs (OPP/OPTS/EPA), ethylene oxide is present as the active ingredient in 38 pesticide products registered under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

Comments/Recommendations

It should be noted that EPA's Office of Toxic Substances (OTS) has received a number of Section 8(e) and "For Your Information" (FYI) notices on ethylene oxide. Further, the Chemical Screening Branch prepared a Chemical Hazard Information Profile on ethylene oxide in 1982. In addition, OTS has promulgated Section 8(a) and 8(d) information reporting rules on ethylene oxide.

a) The Chemical Screening Branch will attempt to obtain further information concerning the conduct and results of the reported studies directly from the investigator.

b) The Chemical Screening Branch will review the reported findings in order to determine the need for further OTS assessment of ethylene oxide or possible inclusion of the reported findings into any ongoing EPA and/or other Federal agency assessments of the potential risks posed by exposure to ethylene oxide.

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. Copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

Note

In a letter dated August 14, 1986 (8EHQ-0886-0611 FLWP Seq. B), the Union Carbide Corporation stated that the company no longer wished to maintain its company name as TSCA CBI.

12/22/86

DATE: AUG 20 1986

UBJECT: Status Report* 8EHQ-0786-0612 Approved: 8/21/86

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

ALCOLAC has reported that the company recently received a letter from an English physician who provided the following information regarding diallyl maleate (CAS Number: 999-21-3):

> " . . . [The physician has] just seen a patient with dermatitis and the clinical picture suggests that he may have become sensitized to the above chemical. From the literature and . . .[ALCOLAC's diallyl maleate Material] Safety Data Sheet, it is clear that the chemical is a primary irritant both in the experimental animal and man. There is no information with regard to its skin sensitization properties. . . ."

Submission Evaluation

In order for EPA to evaluate the significance of the reported finding, additional information would be needed (e.g., duration of exposure(s), route(s) of exposure(s), time to onset of the symptoms, results of clinical chemistry tests that may have been performed, employment history including previous or concomitant exposure(s) to other 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.

Current Production and Use

A review of the production range (includes importation volumes) statistics for diallyl maleate (CAS Number: 999-21-3), which is listed in the initial TSCA Chemical Substance Inventory, shows that 110 thousand to 1.1 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 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 data, is subject to the limitations that are contained in the initial TSCA Inventory Reporting Regulations (40 CFR 710).

ALCOLAC did not provide any information concerning the specific use(s) of diallyl maleate. According to secondary literature sources, diallyl maleate is a monomer used in the production of certain polymers/copolymers and certain insecticides.

Comments/Recommendations

In its submission, ALCOLAC reported that the company has asked the English physician for additional details on the reported case of sensitization and to keep the company apprised of all further developments with regard to this case.

Based on EPA's initial review of the summarized information as presented in ALCOLAC's submission, it is not entirely clear that the information provided by the company is of the type required for submission to EPA under Section 8(e), the substantial risk information reporting provision of TSCA. It is quite probable, on the other hand, that the subject information is of the type required to be maintained by ALCOLAC under the Section 8(c) mandatory recordkeeping provision of TSCA. On August 22, 1983, the Agency published (48 FR 38178) a final rule that required full compliance with TSCA Section 8(c) as of November 21, 1983. In general, the final TSCA Section 8(c) rule requires chemical manufactures, importers, and certain processors to maintain records of significant adverse reactions alleged to have been caused by TSCA-covered chemical substances or mixtures. The final TSCA Section 8(c) rule also requires that allegations involving significant adverse reactions in employees be kept for 30 years and that all other allegations be kept for 5 years. It should be noted that EPA is empowered to both inspect and require the submission of Section 8(c) records. On several occasions to date, EPA has required certain chemical companies to submit their TSCA Section 8(c) records on specific chemical substances of concern to the Agency.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask ALCOLAC to ensure that the Agency is apprised in a timely manner about all further information received by the company concerning this case.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, ALCOLAC will be asked to describe the actions the company has taken or plans to take to 1) notify workers and others about the reported findings, and 2) reduce or eliminate exposure to diallyl maleate. In addition, ALCOLAC 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 ALCOLAC is aware or that ALCOLAC has conducted, is conducting, or plans to conduct to determine the toxicity of or the exposure to diallyl maleate.

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

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 to OPP/OPTS/EPA. Copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: AUG 19 1986

SUBJECT: Status Report* 8EHQ-0786-0613 S Approved: 8/21/86

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 tested chemical as TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS) will request the company to substantiate this confidentiality claim. In its submission, CIBA-GEIGY provided the following non-confidential generic name for the chemical: "heterocyclic thiophosphate."

Submission Description

The CIBA-GEIGY Corporation submitted copies of the final reports from a wide variety of in vitro and in vivo genotoxicity assays of a heterocyclic thiophosphate. In summary, the tests included 1) several Ames Salmonella typhimurium (bacteria) mutagenicity assays conducted with exogenous or host-mediated metabolic activation, 2) an in vitro L5178Y/TK± mouse cell mutagenicity assay, 3) DNA repair assays in cultured human fibroblasts or cultured rat hepatocytes, 4) a Saccharomyces cerevisiae (yeast) cell/mammalian microsome mutagenicity assay, 5) a cell transformation assay in cultured BALB/c-3T3 mouse cells, 6) a Sister Chromatid Exchange (SCE) assay in Chinese hamster bone marrow cells, 7) a nucleus anomaly assay in Chinese hamster bone marrow cells, and 8) a dominant lethal study in mice. CIBA-GEIGY reported that in summary the provided results "indicate that the compound is positive in several short-term in vitro assays for mutagenic activity but is negative when tested for mutagenic activity in vivo."

In addition to submitting the genotoxicity findings, CIBA-GEIGY reported that to help clarify the significance of the observed positive in vitro mutagenicity results, this heterocyclic thiophosphate is now being studied "in a number of other toxicity tests, including lifetime dietary and oncogenicity studies in the mouse and rat."

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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

Three separate Ames tests were performed each using strains TA98, TA100, TA1535 and TA1537 with and without exogenous metabolic activation. The top concentration used in any of the assays was 6250 ug/plate. The obtained data show that the subject chemical induced the mutant frequency in strain TA100 to over 2 times the background at the higher concentrations used. This response was seen both with and without exogenous metabolic activation. (The third assay was performed several years prior to the other two and did not have high enough test material concentrations which may explain the observed negative finding.) The subject chemical was negative in the other strains with and without activation in all assays. Overall, the test chemical induced activity in TA100 to over 2 times background both with and without exogenous metabolic activation.

Two separate host-mediated assays were conducted in male albino mice with Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 as indicator organisms. In the first trial of the first assay, a slight but significant increase in mutant frequency with TA98 at the top dose was observed (400 mg/kg; gavage; one administration). However, this was not repeatable in the second trial or in the second assay performed at higher doses. The several animals that died during the experiments indicate that adequate toxicity was probably attained. It should be noted, however, that no details concerning these deaths were provided. Overall, the subject chemical appears to be negative in these assays.

In the cultured L5178Y/TK± mouse lymphoma cell assay, the subject chemical was tested at concentrations up to 700 ug/ml without exogenous metabolic activation and up to 100 ug/ml with activation. These dose ranges produced adequate toxicities (10-20% survival). There was an induced mutant frequency at one concentration (175 ug/ml; 4.7% survival) under non-activated conditions, but this response was at a very high toxicity and was not subsequently repeatable. Overall, the test substance appears to be negative in this assay under the experimental conditions employed.

Two Unscheduled DNA Synthesis (UDS) assays were submitted, one conducted in cultured rat hepatocytes and the other in cultured human fibroblasts. The subject chemical induced concentration dependent increases in UDS to 2.91 times background (net gain of 8.52 nuclear grains over vehicle control) in rat hepatocytes and to 8.49 times background (net gain of 5.94 nuclear grains over vehicle control) in human fibroblasts. These results indicate a positive response in both assays.

In the Saccharomyces cerevisiae (yeast) strain D7 assay, mitotic crossing over, mitotic gene conversion and mutation induction was examined both with and without exogenous metabolic activation. The subject chemical induced a concentration dependent increase in convertants without activation (up to the 400 ug/ml top concentration). Some inconsistent increases in revertants were seen

also in the three separate trials reported. Overall, the tested chemical was active for gene conversion with metabolic activation and it appears that added metabolic activation reduces this gene conversion activity.

Two separate trials were performed with the subject chemical in the cultured BALB/c-3T3 mouse cell transformation assay. In the first trial, increased transformation frequencies were observed at all doses (up to 8.4 ug/ml). These increases were not statistically significant, however, due probably to abnormally high solvent control values. In the second trial, a statistically significant increased transformation frequency (with an apparent dose-dependent trend) was observed at the top four concentrations tested. Overall, the subject chemical appears to be positive in the BALB/c-3T3 mouse cell transformation assay.

In the Sister Chromatid Exchange (SCE) assay, Chinese hamsters were dosed orally to up to 134 mg/kg of the test chemical for a 24 hour exposure. Higher doses (268 mg/kg and greater) killed the majority of the animals. In view of the fact that 147 mg/kg was lethal to the animals in the nucleus anomaly test (described in the following paragraph), an appropriate high dose may have been used. There was no evidence of increase SCEs at any of the doses used. However, no data were presented to indicate any possible adverse effect related to cell cycle.

In the nucleus anomaly test, Chinese hamsters were exposed orally to up to 135 mg/kg of the test substance once daily for two days. Several animals died at the top dose indicating adequate dosing (147 mg/kg was a lethal dose). The surviving animals were sacrificed 24 hours after the second dose. There was no evidence of increased nucleus anomalies (e.g., Jolly bodies, micronuclei) in any of the survivors. In light of the fact that only one time point following the last dosing was examined, however, an effect that may be either time dependent or cell cycle dependent cannot be ruled out at this time. Evidence pertaining to the cell cycle effects by the subject chemical may alleviate this inadequacy.

In the dominant lethal study, male albino mice were dosed orally with either 120 mg/kg or 360 mg/kg of the test substance and then mated to females (3 females/week) over a 6 week period. There were no apparent effects on pre-implantation loss or on embryonic deaths. It should be noted, however, that there were no signs of toxicity reported in the dosed males, which indicates that higher doses could have been used in this assay to determine possible dominant lethal effects.

In conclusion, the results for any individual genotoxicity assay are either negative or moderately positive. Due to the positive responses observed in several of the performed assays, however, this heterocyclic thiophosphate appears to possess an intrinsic genotoxic activity, albeit not an overwhelming activity.

Current Production and Use

According to CIBA-GEIGY, the subject chemical "is a research and development compound being investigated solely for pesticidal purposes." CIBA-GEIGY reported further that "these evaluations are being conducted under the supervision of technically qualified personnel, knowledgeable in handling potentially hazardous chemicals."

Comments/Recommendations

In its Section 8(e) notice, CIBA-GEIGY reported that the company plans to 1) submit to EPA copies of the final reports from the ongoing studies, 2) notify all persons working with the subject chemical about the submitted toxicologic findings, and 3) label the chemical to reflect the reported findings.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask CIBA-GEIGY to ensure that EPA is apprised about any significant interim findings from the ongoing studies cited in the submission. In addition, CIBA-GEIGY will be asked 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 ongoing studies cited in the submission.

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

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

Note

In a letter dated October 7, 1986, (8EHQ-1086-0613 FLWP Seq. B), CIBA-GEIGY reported that the company no longer wished to maintain the specific identity of the subject chemical to be TSCA CBI. According to the declassified version of the company's initial Section 8(e) notice, the tested chemical is "O,O-dimethyl-S-(6-chlor-oxazolo(4,5-b)pyridin-2(3H)-on-3-yl-methyl)-thiophosphate."

12/22/86

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: SEP 15 1986

SUBJECT: Status Report* 8EHQ-0786-0614 S

Approved: JFD for Frank D. Kover 9/15/86

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 name and the name of the company that performed the provided study to be TSCA Confidential Business Information (CBI). In addition, the submitter claimed the amounts of the individual components in the tested mixture as TSCA CBI. The Information Management Division (IMD/OTS/OPTS/EPA) will request the submitter to substantiate these TSCA CBI claims.

Submission Description

The submitting company provided the final results from a 2-year oncogenicity study of a mixture of octyltin trichloride (CAS No. 3091-25-6) and dioctyltin dichloride (CAS No. 3542-36-7) in rats. According to the submitted report, this mixture was administered to groups of 120 Tif:RAIf(SPF) rats (60 males and 60 females per group) at doses of 0, 5.0, 15, 50 and 150 parts per million (ppm) in the feed. In addition, the submitted report states that the "calculated mean daily intake based on the actual concentration of [the test mixture] was approximately 0.24, 0.69, 2.2, and 5.5 mg/kg b.w. in males and 0.26, 0.74, 2.3, and 6.0 mg/kg b.w. in females." The following information concerning the results of the study was presented in the "Conclusion" section of the submitted report:

> "Under the conditions of this test, no relevant differences were found between treated and control animals for mortality distribution, clinical observations and examinations, body and organ weights, food and water consumption, as well as in hematology, except an increased number of white blood cells in female groups treated with 50 and 150 ppm [of the test mixture,] 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.

"A significantly increased frequency of primary tumors of the thymus, especially thymic lymphomas, was noted in females treated with 150 ppm [of the test mixture]. Further, an increased incidence of generalized malignant lymphomas in [the] males of the upper dose levels and in [the] females of the top dose group was observed. In [those] animals treated at the low dose levels (5.0 and 15 ppm), no increase was observed, either in the incidence of primary thymic tumors or generalized malignant lymphomas."

Submission Evaluation

The provided information indicates that the tested mixture (or one of its components) is oncogenic when administered chronically in the feed of male and female rats. In order for the Agency to evaluate the overall significance of the reported findings, however, the submitting company should be requested to provide a complete copy of the final report (including information such as the survival data, "time to tumor" data, individual animal tumor data, individual animal weight data, food consumption data, etc.) from this 2-year feeding study in rats.

Current Production and Use

A review of the production range (includes importation volumes) statistics for octyltin trichloride (CAS No. 3091-25-6) and dioctyltin dichloride (CAS No. 3542-36-7), which are listed in the initial TSCA Chemical Substance Inventory, has shown that no 1977 manufacture/importation of these chemicals was reported or that all manufacture and/or importation data reported were claimed as TSCA CBI by the person(s) reporting for 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 TSCA Inventory Reporting Regulations (40 CFR 710).

According to the submitting company, both octyltin trichloride and dioctyltin dichloride "are present in tetraoctyltin as minor ingredients in the intermediate stage of the manufacture of dioctyltin stabilizers currently used for indirect food additives." The submitting company stated also that octyltin trichloride is present in "trace quantities" and that dioctyltin dichloride "is present to a maximum of 1.5%." The submitting company reported further that the company does export the chemicals for a "limited number of non-food applications."

Comments/Recommendations

According to the submitter, the company that performed the 2-year study has already notified the U.S. Food and Drug Administration (FDA) about the results of the study.

It should be noted that EPA's Office of Toxic Substances (OTS) has received a number of Section 8(e) and "For Your Information" (FYI) submissions on various organotin compounds. In addition, staff of the Test Rules Development Branch (TRDB/ECAD/OTS) has evaluated available toxicity and exposure information on several alkyltin compounds recommended to EPA by the Interagency Testing Committee (ITC) for testing under Section 4 of TSCA. Further, EPA has published TSCA Section 8(a) and (d) information reporting rules on those alkyltins considered for testing under Section 4 of TSCA.

a The Chemical Screening Branch will request the submitter to provide to EPA a complete copy of the final report, including all experimental data (such as those listed in the Submission Evaluation section of this report), from this 2-year feeding study in rats.

In view of EPA's general interest in company actions that are taken on a voluntary basis in response to chemical toxicity or exposure information, the submitting company will be requested to describe the actions the company has taken or plans to take to notify its workers about the reported toxicologic findings. In addition, the submitting company will be asked to describe the nature and results, if available, of all studies (other than those published in the open 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 and/or the exposure to dioctyltin dichloride or octyltin trichloride or to mixtures that contain these chemical substances.

b The Chemical Screening Branch (CSB/ECAD/OTS) will review the submitted information in order to determine the need for further OTS assessment of the subject organotin compounds.

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 TRDB/ECAD/OTS/OPTS/EPA. In addition, copies of this report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

DATE: AUG 19 1986

SUBJECT: Status Report* 8EHQ-0786-0615 Approved: 8/22/86

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

Texaco Inc. provided a copy of a report entitled "Mortality Among Workers at a 1,3-Butadiene Production Facility." According to Texaco, the submitted report is "based on a cohort mortality study of 2586 male employees at the [Port Neches, TX] facilities of [the] Neches Butane Products Company, a subsidiary of [the] Texaco Butadiene Company." Texaco reported further that the subject epidemiologic study "is important because this plant is the monomer-producing facility in a complex of plants including two styrene/butadiene rubber (SBR) production units" at which the National Institute for Occupational Safety and Health (NIOSH) had previously conducted a cohort mortality study. Texaco provided the following information concerning the submitted report:

> "The authors [of the study] noted increased standardized mortality ratios (SMR's) for lymphosarcoma and reticulum cell sarcoma which were statistically significant when compared with the U.S. population but not [statistically] significant when compared to a local seven-county population. In addition, there were elevated SMR's for other lymphatic cancers which did not correlate with exposure to butadiene. For these reasons, the authors of the study stated that nothing conclusive can be stated concerning an association between butadiene exposure and any of these diseases."

Submission Evaluation

Immediately upon EPA's receipt of the submitted information, the Chemical Screening Branch (CSB/ECAD/OTS/OPTS) sent copies to the Occupational Safety and Health Administration (OSHA), National Institute for Occupational Safety and Health (NIOSH), Office of Air and Radiation (OAR/EPA), Exposure Evaluation Division/OTS, Chemical Control Division/OTS and Risk Analysis Branch/ECAD/OTS for inclusion in any ongoing 1,3-butadiene assessments.

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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 1,3-butadiene (CAS No. 106-99-0), which is listed in the initial TSCA Chemical Substance Inventory, has shown that between 2.1 billion and 7.3 billion pounds were reported as manufactured/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 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, the primary use of 1,3-butadiene is as a raw material in the manufacture of synthetic rubber and fibers. According to the June 9, 1986, issue of Chemical & Engineering News, 2.45 and 2.53 billion pounds of rubber grade 1,3-butadiene were produced in the U.S. in 1984 and 1985, respectively.

Comments/Recommendations

EPA's Office of Toxic Substances (OTS/OPTS/EPA) has received and evaluated several TSCA Section 8(e) and "For Your Information" (FYI) notices on 1,3-butadiene. Also, the Chemical Screening Branch (CSB/ECAD/OTS) did prepare (in 1981) a Chemical Hazard Information Profile (CHIP) on this chemical. EPA's Office of Pesticides and Toxic Substances (OPTS/EPA), via Section 9 of TSCA on October 10, 1985 (50 FR 41393), referred 1,3-butadiene to OSHA for regulation of workplace exposure. Further, the Office of Air and Radiation (OAR/EPA) has published an "intent to list" 1,3-butadiene as a hazardous air pollutant under the Clean Air Act.

a) The Chemical Screening Branch will transmit copies of this status report to OSHA, NIOSH, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS/EPA, EED and CCD/OTS/OPTS/EPA, 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: AUG 26 1986

SUBJECT: Status Report* 8EHQ-0786-0616 Approved: 8/26/86

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

R. T. Vanderbilt Company, Inc. provided the following summarized information concerning the conduct and preliminary results of an acute inhalation toxicity study of copper dimethyldithiocarbamate (CAS No. 137-29-1) in rats:

"Groups of five male and five female Sprague-Dawley rats (approximately 230-280 grams) were exposed to atmospheres of copper dimethyldithiocarbamate dust for four hours. Six exposure levels were used (0.052 - 2.98 mg/L) and in all cases approximately 90 percent of the particles were less than 5.5 microns.

"Signs noted during exposure at all levels comprised slow irregular respiratory patterns, hunched appearance, and closed eyes. The incidence and severity of these signs was broadly exposure-level related. A no-effect-level was not determined.

"All rats exposed to levels of 0.21 mg/L and above died within 2 - 24 hours. No deaths occurred at 0.052 mg/L and nine rats are expected to survive at 0.068 mg/L.

"Survivors at the two lower levels lost weight through day 3 but subsequently showed normal bodyweight increments. Survivors were essentially asymptomatic from day 2 onwards and there was no evidence of any delayed or residual pathology at sacrifice on day 14 (0.052 mg/L).

"The LC50 is estimated to be in the range of 0.08 - 0.12 mg/L and will be calculated more precisely when the study is 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.

In its submission, R. T. Vanderbilt reported that this study had been conducted in England and co-sponsored by R. T. Vanderbilt, the Pennwalt Corporation, and several un-named foreign companies.

Submission Evaluation

In order for the Agency to evaluate the overall significance of the reported toxicologic findings, a complete copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, etc.) from the cited acute inhalation study should be requested from the submitter.

Current Production and Use

A review of the production range (includes importation volumes) statistics for copper dimethyldithiocarbamate (CAS 137-29-1), 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 production range information reported was claimed to be TSCA Confidential Business Information (TSCA CBI) and cannot be disclosed (see Section 14(a) of TSCA; U.S.C. 2613(a)). All of the information reported for the initial TSCA Chemical Substance Inventory, including the production range information, is subject to the limitations that are contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

In its Section 8(e) submission, R. T. Vanderbilt provided the following information with regard to worker exposure to copper dimethyldithiocarbamate:

> "At R. T. Vanderbilt, worker exposure to airborne [copper dimethyldithiocarbamate] powder is not expected. The com-ound is manufactured in an automatic system, wherein the powder is compounded with binders and converted to rod-form. A small percentage of the powder is treated with anti-dusting oil before drying and grinding. Prior to conversion to the automatic system, the material was manufactured by a batch type method since 1950. No complaints as a result of exposure to the material have been received during more than three decades of manufacture. Because of the special treatment of the material, the risk of exposure to airborne [copper dimethyldithiocarbamate] dust should be minimal within the manufacturing facility as well as in the processing plant."

R. T. Vanderbilt did not submit any information regarding the use of copper dimethyldithiocarbamate. According to secondary literature sources, this chemical is used primarily as an accelerator for styrene/butadiene rubber (SBR).

Comments/Recommendations

It should be noted that EPA's Office of Toxic Substances (OTS) has received several "For Your Information" (FYI) submissions on zinc dimethyldithiocarbamate, a rubber accelerator and fungicide for fruits and vegetables. In addition, the Chemical Screening Branch (CSB/ECAD/OTS) did prepare (in 1983) a Chemical Hazard Information Profile (CHIP) on zinc dimethyldithiocarbamate. Zinc dimethyldithiocarbamate was selected for CHIP preparation on the basis of a National Toxicology Program (NTP) study that showed carcinogenic effects on the male rat thyroid following chronic oral administration of the chemical. The Risk Analysis Branch (RAB/ECAD/OTS) has been evaluating available toxicologic and exposure information on zinc dimethyldithiocarbamate.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will request R. T. Vanderbilt to submit to EPA a complete copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, etc.) from the co-sponsored acute rat inhalation toxicity study cited in the company's submission.

   In view of EPA's general interest in company actions that are taken on a voluntary basis in response to chemical toxicity or exposure data, R. T. Vanderbilt will be asked to describe the actions the company has taken or plans to take to notify workers about the reported toxicologic findings. In addition, R. T. Vanderbilt will be asked to describe the nature and results, if available, from all studies (other than those submitted to the Agency already or those cited in the open scientific literature) about which R. T. Vanderbilt is aware or that the company has conducted, is conducting, or plans to conduct to determine the toxicity of or the exposure to copper dimethyldithiocarbamate.

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

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 provided to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

DATE: AUG 15 1986

SUBJECT: Status Report* 8EHQ-0786-0617 Approved: 8/15/86

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 submitted information concerning an "emergency incident of environmental contamination" (ECIC) that occurred at 10:00 A.M. on July 9, 1986 at Conrail's railroad yard located in Port Reading, New Jersey. According to Union Carbide, the incident occurred when two tank cars, one containing ethanol (CAS No. 64-17-5) and the other containing butyraldehyde (CAS No. 123-72-8), were punctured by the shelf couplers as the cars were being humped. Union Carbide reported further that personnel from the company's "HELP" team "went to the scene of the incident to give necessary aid in containment, clean-up, and removal." Union Carbide also provided the following details of the incident:

> "The chemicals were contained within the railroad yard, vapors were held down, no evacuation took place, nor were any exposures reported. [The] estimated loss of butyraldehyde was 25,000 gallons, and [the] estimated loss of ethanol was 18,000 gallons; both liquid releases were to the ground. The spill was contained by use of soda ash and, at the time of submission of this [written Section 8(e)] report, final clean-up of the spill was taking place. Since the time of the incident, Union Carbide has received no reports of adverse ecological or environmental effects, or of health effects resulting from the chemicals. . . . . The decision to notify the . . .[the Agency's Region II Office by phone on the day of the incident] was made at the time the leakage was occurring, at which time it was not possible to know if adverse effects would or would not result."

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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

Immediately upon receipt of this TSCA Section 8(e) submission, staff of the Chemical Screening Branch (ECAD/OTS/OPTS/EPA) sent copies of the submission to EPA's Region II Office and to EPA's Office of Solid Waste and Emergency Response (OSWER/EPA).

a) The Chemical Screening Branch will send copies of this status report to NIOSH, OSHA, OSWER/EPA, OW/EPA, OAR/EPA and to EPA's Region II Office. In addition, copies of this report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution

DATE: AUG 25 1986

SUBJECT: Status Report* 8EHQ-0886-0618 S Approved: 8/26/86

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

Submission Description

The submitting company provided the following information with regard to the inhalation toxicity of certain cadmium compounds:

> "It has come to . . .[the submitting company's] attention from a phone conversation with the Fraunhofer Institute of Aerosol Research and Toxicology in Hannover, West Germany, that additional preliminary study results have recently become available concerning the inhalation toxicity of cadmium compounds. These results, which are currently being presented at a toxicology meeting in Japan, indicate that lung tumors have been observed in rats following exposure to cadmium compounds other than cadmium chloride. It is believed these compounds are cadmium oxide, cadmium sulfate, and cadmium sulfide. The inhalation regimen involved exposures of about 20 hours/day, 7 days/week for 18 months. Previous results indicate that lung tumors have not been seen in mice or hamsters."

Submission Evaluation

Complete copies of the actual experimental protocol(s), results of gross and histopathologic examinations, etc. are needed in order for the Agency to evaluate the overall significance of the reported oncogenicity 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.

Current Production and Use

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

CHEMICAL NAME	CAS NO.	PRODUCTION RANGE
Cadmium Oxide	1306-19-0	2.72 million to 27.2 million
Cadmium Sulfide	1306-23-6	464 thousand to 4.65 million
Cadmium Sulfate	10124-36-4	232 thousand to 2.32 million

(Note: The above 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 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, the cadmium compounds cited above are used in a wide variety of industrial, pesticidal, medicinal and/or veterinary applications.

Comments/Recommendations

EPA's Office of Toxic Substances (OTS) has received several TSCA Section 8(e) and "For Your Information" (FYI) notices on cadmium compounds. In addition, a number of EPA Program Offices as well as other Federal agencies have assessed or are in the process of assessing the potential risks posed by exposure to cadmium and cadmium compounds. Also, the International Agency for Research on Cancer (IARC) has published two "Monographs" (1972 and 1976) on cadmium and cadmium compounds.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the submitting company to provide additional information that would allow EPA to obtain further information about and/or evaluate the significance of the reported findings.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment or referral of the information to another EPA Office or other Federal agency for consideration in any ongoing assessment of cadmium and cadmium compounds.

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 provided to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: AUG 19 1986

SUBJECT: Status Report* 8EHQ-0386-0619 Approved: 8/19/86
8EHQ-0586-0619 FLWP

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

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

Submission Description

On a "For Your Information" basis (FYI-OTS-0386-0486 Initial), the Monsanto Company provided the following information with regard to the conduct and preliminary findings from a recently completed intrapleural implantation study of calcium sodium metaphosphate (CAS No. 23209-59-8) fibers in rats:

> "In this test,. . .[calcium sodium metaphosphate] fibers in gelatin pledgets were surgically implanted in the pleural space of experimental rats. Each of 3 groups consisted of approximately 75 males and 75 females at the outset; sub-groups of 5 males and 5 females from each group were sacrificed at 6, 12, and 18 month intervals. No [calcium sodium metaphosphate] fiber-induced fibrosarcomas were detected at these interim periods. After the final sacrifice at 24 months, 3 of [the] 120 [calcium sodium metaphosphate fiber-exposed] animals had fibrosarcomas. Also, at the final sacrifice in the positive control group, in which chrysotile asbestos had been implanted, 5 of 121 animals had fibrosarcomas. In the negative control group, no fibrosarcomas were observed." [Note: Monsanto reported by phone that gelatin pledgets were surgically implanted in the pleural space of the negative control rats.]

In the initial FYI submission, Monsanto provided the following comments with regard to evaluating the reported results:

> "The finding of pleural sarcomas means that long (greater than 8 microns), thin (less than 1 micron) fibers were present in the pleural space. Prior "in vitro" testing results has led . . . [Monsanto] to hypothesize that phosphate fiber would biodegrade through enzymatic 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 is . . .[Monsanto's] opinion that the gelatin matrix decreased the rate of dissolution and biodegradation of the phosphate fiber due to chemical interaction with the matrix.

"The incidence of pleural sarcomas seen in the phosphate fiber study group approximated historical background levels and was low compared to [the] results reported for other fibrous materials. . . . These results could well reflect the biodegradability of the phosphate fiber despite any reaction with the gelatin matrix.

"The tissue responses seen in the present study with phosphate fiber were significantly different from those observed with asbestos. [The] phosphate fiber produced a very cellular, granulomatous reaction indicative of an inflammatory response, while asbestos produced an acellular lesion with a high collagen content."

In its initial FYI submission, Monsanto stated also that there is a study now underway in which rats (80 rats/sex/exposure group) are being exposed by inhalation to phosphate fiber at dose levels of 0, 1, 5, or 25 mg/m^3 for 6 hours/day, 5 days/week for 2 years. Monsanto noted that this study "was undertaken to evaluate the carcinogenic potential of inhaled phosphate fiber, representing the most likely route of human exposure." Monsanto noted also that the high dose level (25 mg/m^3) is 5 times greater than that which would be considered "nuisance dust." Finally, Monsanto stated that while preliminary results from the ongoing 2-year inhalation study were not expected until late 1987, the company was "encouraged" by the fact that rats sacrificed after 3 months of exposure show "no treatment-related pathological changes nor any indication of fibrosis."

Following a review of the summarized information presented in Monsanto's initial FYI notice, EPA informed Monsanto in writing (EPA letter dated April 14, 1986) that the Agency believed that the company's oncogenicity findings for calcium sodium metaphosphate fibers constituted "substantial risk" information and, as such, should have been submitted formally to the Agency pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). In EPA's April 14, 1986 letter, Monsanto was requested to provide the company's rationale as to why the subject cancer findings had not been submitted under Section 8(e) of TSCA.

In a followup response letter dated May 15, 1986 (FYI-OTS-0586-0486 Followup Response), Monsanto responded to EPA's questions concerning the Section 8(e)-applicability of the cancer findings from the company's 2-year intrapleural implantation study of calcium sodium metaphosphate fibers in rats. In this followup response letter, Monsanto stated that the company "remains convinced" that the reported findings "do not support the conclusion that Phosphate Fiber presents a substantial risk of injury to

health. . ." and offered a number of comments and citations to support the company's position. In addition, Monsanto provided a complete copy of the final report from the 2-year intrapleural implantation study and full copies of final reports from studies designed to measure chemical dissolution, in vitro biodegradation and in vivo animal lung clearance of phosphate fibers.

The following information concerning the conduct and results of the 2-year intrapleural implantation study was contained in the SUMMARY section of the submitted final report from that study:

> "A 24-month pulmonary oncogenicity study was conducted with Osborne-Mendel strain [male and female] rats to determine the effects of the test compound, calcium sodium metaphosphate [fibers], when implanted into the pleural cavity. . ." Responses induced by the test compound were compared to those induced by implantation of the positive control compound, chrysotile asbestos. The study also consisted of a negative control group (gelatin plegdets). Gelatin pledgets containing 40 mg of the test compound or asbestos (positive control) were implanted [surgically] into the pleural cavity of rats; the negative control group animals were implanted with sterilized gelatin pledgets [alone]. Each experimental group consisted of 75 male and 75 female rats except the negative and positive control female groups which contained 74 and 76 animals, respectively. The surgical implantation procedure [used] required two weeks. After implantation, all animals were observed twice daily for signs of mortality or morbidity or signs of toxicity. A more detailed examination, including palpation for masses, was conducted at the time of determination of body weights. Body weights were determined on each animal prior to dosing and biweekly (once every two weeks) during the first 14 weeks and every 4 weeks thereafter throughout the remainder of the study. Animals found dead or sacrificed moribund were subject[ed] to a complete necropsy and gross examination; [the] tissues were retained in 10% neutral buffered formalin for subsequent histological examination. Interim sacrifices, 5 males and 5 females in each group, were conducted after 26, 52 and 78 weeks; surviving animals were necropsied after the [end of the] 24-month experimental period. Tissues of all animals at necropsy were retained for subsequent histological examination.
>
> "Mortality of males and females receiving the test fiber was essentially similar to that of the respective negative controls (gelatin pledget only) and to the positive control animals (chrysotile asbestos). However, [the] mortality of males was higher than females. Likewise, mean body weights of males and females treated with the test fiber were essentially similar to that of the negative and positive control animals throughout the study.

"Gross examination of tissues at necrospy revealed no lesions considered unique to the test fiber or asbestos. Microscopic examination revealed the tissue response to the test fiber to be cellular, while the tissue response to the asbestos fiber was acellular, mostly collagenous. In addition, microscopic examination revealed pleural fibrosarcomas in near equal incidence in the test fiber and asbestos males and females. Morphologically, the fibrosarcomas induced by the test fiber were also more cellular compared to asbestos in that the acellular collagenous response characteristic of asbestos-induced fibrosarcomas was not seen in the test fiber group. The fibrosarcomas induced by the test fiber were probably related to the continued presence of long thin fibers. Other microscopic lesions observed were considered to be normal findings expected in rats in chronic studies."

[NOTE: In the followup response cover letter, Monsanto stated that the incidence of pleural fibrosarcomas in the asbestos exposed rats was 4 and not 5 as reported initially by the company. In addition, Monsanto stated that a consulting pathologist who reviewed the slides from the study stated that "matted masses of fibers were seen two years after their introduction" and "processes of clearance by solution and metabolism cannot and did not take place after this massive intrapleural dosage."]

The following information with regard to the conduct and results of a study designed to determine the in vitro biodegradability of radiolabelled calcium sodium metaphosphate fibers was presented as an ABSTRACT in the submitted final report from that study:

"The biodegradability of calcium sodium metaphosphate fibers (phosphate fibers) was studied in cultured lung cells. ^{32}P[phosphorus]-radiolabelled phosphate fibers were incubated for 0-7 days in culture medium in the presence and absence of cultured rat lung epithelial cells (LEC) and rat alveolar macrophages (RAM). The degree of fiber solubilization was estimated daily by filtering the extracellular medium and NaOH solubilized cells through a 0.45 um filter and monitoring radioactivity in the filtrate. The [phosphate] fibers were found to have limited solubility in culture media at 37 degrees C, with approximately 3% dissolved in seven days (from approximately 1% on day 0). Both LEC and RAM increased the solubility of the fibers, reaching 7% and 20%, respectively, for the two cell types in 7 days. [Monsanto's] results therefore suggest that phosphate fibers are degradable by lung cells."

The following information concerning the conduct and results of a study designed to determine the ability of phosphate fibers to be cleared from the rat lung in vivo was contained in the ABSTRACT section of the submitted final report from that study:

"Groups of 8 rats were exposed to calcium sodium metaphosphate (CSM) fibers by an inhalation technique that allowed [the study investigators] to bypass the nasal turbinates or by intratracheal instillation. Control rats were instilled with saline or sham-exposed via inhalation. Comparable lung burdens were detected at 1 day post-exposure in rats exposed by inhalation or [by] instillation. No statistically significant differences were detected in lung fiber-burdens measured at 1, 7, 21 or 57 days post-exposure. However, after 176 days the pulmonary concentration of inhaled CSM fibers was less than the pulmonary concentration of [the] instilled CSM fibers. Histopathologic examination of the lungs of the same rats did not reveal any acute inflammatory response or any evidence of a fibroproliferative response. Semi-quantitative evaluation of the regional distribution indicated a decreasing percentage of fibers in the conducting airways and an increasing percentage of fibers sequestered in the interstitium and alveolar ductal septa with time. Biochemical assessment of hydroxyproline, elastin, DNA and protein did not reveal the presence of a fibrotic response to the fibers. The CSM fibers were cleared from the conducting airways and alveoli such that at 6 months, most of the remaining fibers (7-16% of [the] fiber burden on day 1) were sequestered within the interstitium with a minimal histiocytic response. The [CSM] fibers did not demonstrate any inherently toxic properties when deposited in the lungs of rats under the exposure regimen used in these [in vivo] studies."

According to a submitted memorandum concerning the results of a fiber leaching/dissolution study, the total half-life (weight basis) of phosphate fiber, in a non-stagnant situation, may be "in the range of 2 to 16 months . . .from chemical and mechanical forces in the absence of any biological mechanisms." In addition, the memorandum states that the leaching procedure "produced a measurable increase in average fiber diameter and a decrease in surface area." These findings are reportedly "consistent with the [observed] weight loss being due to preferential dissolution of the smaller particles which have a larger surface to volume ratio." The submitted memorandum states also that the findings from this leaching study indicate that "some of the large fibers among the standard broad particle size distribution could be expected to remain undissolved for several half-lives (i.e., many months or a few years)."

In its followup response letter, Monsanto provided the following discussion summarizing Monsanto's position on the Section 8(e)-reportability of the cancer findings from the company's 2-year intrapleural implantation study of calcium sodium metaphosphate in rats:

"In summary, Monsanto's position is that the results of the intrapleural implant study cannot be extrapolated to cancer risks in man. . . .[The company has] provided evidence that this position is universally accepted by investigators who have conducted this test and also by many governmental agencies. Moreover, . . .[Monsanto feels that the company has] other data to show that Phosphate Fiber will be cleared from the body under normal routes of exposure and thus will not approach the high concentrations placed in the pleural cavity in this [implantation] study. . . .[Monsanto's] in vitro data has also shown that Phosphate Fiber is an order of magnitude less toxic than asbestos."

Submission Evaluation

In reviewing the summarized information contained in Monsanto's initial FYI notice, it was apparent to the Agency that surgically implanted gelatin-enclosed calcium sodium metaphosphate fibers and chrysotile asbestos fibers induced low but essentially equal incidences of fibrosarcomas in rats. Although Monsanto speculated that the gelatin had decreased the expected dissolution and enzymatic degradation (per the results of other studies) of the phosphate fiber, EPA's position was then and is now that it is equally plausible that the gelatin decreased substantially the carcinogenic activity of both types of fibers by 1) effectively reducing the pleural exposure to the fibers, and/or 2) altering the biological activity of the fibers.

Monsanto's followup response provides additional information that may be relevant to interpreting the extent to which the findings reported initially should be relied upon in assessing human risk posed by exposure to calcium sodium metaphosphate fibers. However, Monsanto has not provided any new information that refutes the low but essentially equal incidences of malignant pleural tumors observed in the calcium sodium metaphosphate and asbestos exposed rats but not in the concurrent control rats. In fact, several documents provided by Monsanto state that the malignant pleural tumors found in the calcium sodium metaphosphate fiber-treated rats were considered to be treatment-related.

In considering all of the information provided by Monsanto in its initial and followup response FYI notices, the Agency's position concerning the nature of the findings from the company's two-year pleural implantation study is not changed. EPA believes that the results of the performed study show clearly that calcium sodium metaphosphate fiber, when implanted surgically into the pleura of rats, produced a low incidence of fibrosarcomas.

Immediately upon receipt of Monsanto's initial and followup FYI notices, the Chemical Screening Branch (CSB/ECAD/OTS) provided copies to the Risk Analysis Branch (RAB/ECAD/OTS), Regulatory Program Development Branch (RPDB/CCD/OTS), and Asbestos Action Program/OPTS for inclusion in the ongoing reviews of available toxicologic/exposure information on fibrous materials.

Current Production and Use

According to a pamphlet entitled "Phosphate Fibers" provided to the Agency previously by Monsanto, calcium sodium metaphosphate fibers are cylindrical and are more like the chrysotile form of asbestos rather than the ribbon-like amphibole form of asbestos. The provided pamphlet states further that due to the tendency of crystalline calcium sodium metaphosphate to "split lengthwise into long fragments of smaller diameter," the fibers will open further and their surface area will increase upon application of mechanical stress. The pamphlet states also that this particular property is important "in applications which require high surface areas, such as paper products."

In its followup response letter, Monsanto provided the following information with regard to the potential for worker exposure to phosphate fibers:

> ". . .[The Monsanto Company] is reassured by the low exposure in the workplace to Phosphate Fiber. The use of Phosphate Fiber does not produce airborne dust since the finer fibers have a natural tendency to adhere to larger fibers due to coulombic forces.
>
> "Industrial hygiene monitoring conducted in the pilot plant supports this hypothesis in that exposures are at or below 0.04 fibers/cc. . . .[The Monsanto Company has] adopted an internal guideline of 2 fibers/cc and this limit has been communicated to . . .[Monsanto's] customers via . . .[the] Material Safety Data Sheet."

Comments/Recommendations

In its initial FYI submission, Monsanto reported that copies of that submission were being transmitted to all customers who were participating in Monsanto's sampling program. In its followup response letter, Monsanto stated the company had taken "prudent action" by 1) notifying EPA in a timely manner about the preliminary results of the 24-month intrapleural implantation study, 2) establishing a conservative interim phosphate fiber exposure guideline, and 3) increasing industrial monitoring efforts to assure that minimal phosphate fiber exposure levels have been attained. Finally, Monsanto reported that the company is continuing its safety evaluation of phosphate fibers and plans to utilize the results of the ongoing phosphate fiber inhalation study in rats in that regard.

Following a review of the information presented in FYI-OTS-0386-0486 and FYI-OTS-0586-0486 Followup Response, EPA's position is unchanged with regard to the TSCA Section 8(e)-applicability/-reportability of the observations from the Monsanto Company's intrapleural implantation study of calcium sodium metaphosphate fibers in rats. The basis for EPA's position is as follows:

Section 8(e) of the Toxic Substances Control Act states:

"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 March 16, 1978 Section 8(e) policy document ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110) 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 [i.e., the serious effect's] occurrence."

With regard to the seriousness of the effect, Part V of the 8(e) policy statement 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 or mixture can produce cancer. . ." [emphasis added] Information regarding this effect can be obtained directly or inferred from designed studies (e.g., in vivo studies) as described in Part VI of the 8(e) policy statement. Part VI states 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." In addition, Part VI of the 8(e) policy statement explains that "not only should final results from such studies be reported, but also preliminary results from incomplete studies where appropriate."

With regard to the "fact or probability of its [i.e., the serious effect's] occurrence" criterion, Part V of the 8(e) policy statement explains that certain types of adverse health effects (e.g., cancer) are so serious that relatively little weight should be given to the chemical's exposure in determining whether a risk is substantial.

Finally, Monsanto offers some apparently sound arguments concerning the adequacy of the company's cancer findings for risk assessment and extrapolation of those findings to humans. Although these particular types of arguments are important and are typically considered by EPA during the overall cancer risk assessment process, they do not alter the fact that a treatment-related carcinogenic

activity was observed in the performed study. In light of the fact that Section 8(e) is a statutory reporting requirement by which the Agency is to be notified immediately about any new health risk-related information that simply offers reasonable support for a conclusion of substantial risk, arguments of the type contained in Monsanto's FYI notices are not relevant to any great extent in determining Section 8(e)-reportability of cancer findings. The Monsanto Company's cancer findings, in and of themselves, provide a sufficient basis for submitting the findings to EPA under Section 8(e) of TSCA.

In view of the preceding policy discussion and EPA's review of the information contained in Monsanto's initial and followup FYI notices, EPA believes that the evidence obtained from Monsanto's two-year intrapleural implantation study in rats offers reasonable support for the conclusion that calcium sodium metaphosphate fibers can cause cancer. It is EPA's decision, therefore, that the subject cancer findings should have been submitted to the Agency under Section 8(e) of TSCA.

a) The Existing Chemical Assessment Division (ECAD/OTS) will notify Monsanto in writing about EPA's decision concerning the TSCA Section 8(e)-reportability of the cancer findings presented in FYI-OTS-0386-0486 and FYI-OTS-0586-0486 Followup Response. In view of this EPA decision, the Chemical Screening Branch (CSB/ECAD/OTS) has delivered all information contained in FYI-OTS-0386-0486 and FYI-OTS-0586-0486 Followup Response to the OTS Document Control Officer for appropriate handling/public filing under Section 8(e) of TSCA.

   The Monsanto Company will be asked to ensure that EPA receives in a timely manner 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 ongoing phosphate fiber inhalation study in rats.

b) Upon receipt of the final report from the inhalation study of calcium sodium metaphosphate fibers in rats, the Chemical Screening Branch (CSB/ECAD/OTS) will send full copies of that report immediately to RAB/ECAD/OTS, RPDB/CCD/OTS, and to the Asbestos Action Program/OPTS.

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, RAB/ECAD/OTS, RPDB/CCD/OTS, OCM/OPTS, and the Asbestos Action Program/OPTS. Copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: AUG 25 1986

SUBJECT: Status Report* 8EHQ-0886-0620 Approved: 8/25/86

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 individual industry members of the Phthalate Esters Panel, the Chemical Manufacturers Association (CMA) provided the following summary information regarding the preliminary results of several recently conducted genotoxicity studies:

> "As part of its negotiated [Section 4] testing program for phthalate esters, CMA agreed to perform [in vitro L5178Y] Mouse Lymphoma [cell forward mutagenicity] and in vitro [mouse cell] transformation assays on certain commercially significant [phthalate] esters. It was originally contemplated that CMA would also sponsor Ames . . . [bacterial mutagenicity] assays on the substances, but such testing had been previously performed by the National Toxicology Program (NTP).
>
> "[The cell] transformation and Ames assays for all [of] the test substances have been completed and were negative. On July 22, 1986, CMA was informed by the laboratory that [di-n-butyl phthalate (DBP; CAS No. 84-74-3)] gave weak, dose-related increases in the mutant frequency of L5178Y cells when tested in the standard Mouse Lymphoma forward mutation assay. . . . Responses were observed only in the presence of an Aroclor-induced rat liver S-9 fraction, indicating some participation of this system in the observed activity. . . . . Results of a previous trial assay with DBP gave weakly positive increases; however, these results did not represent a clear dose-related response. . . . [CMA was recently informed]. . . that [dimethyl phthalate (DMP; CAS No. 131-11-3)] gave weak dose related increases in mutant frequency in this assay in the presence of [the] Aroclor-induced rat liver S-9."

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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

Immediately upon receipt of this notice, the Chemical Screening Branch (CSB/ECAD/OTS) sent copies to the Test Rules Development Branch (TRDB/ECAD/OTS) and Risk Analysis Branch (RAB/ECAD/OTS) for inclusion in ongoing OTS assessments of phthalate esters.

Current Production and Use

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

CHEMICAL NAME	CAS NO.	PRODUCTION RANGE
Di-n-Butyl Phthalate	84-74-2	15 million to 100.4 million
Dimethyl Phthalate	131-11-3	2.2 million to 22 million

(Note: The above production range information does not include any data 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 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) notice, CMA stated that the "producers of DBP who are members of the [Phthalate Esters] Panel are BASF Corporation, Eastman Kodak Company and [the] US Diversified Group (formerly USS Chemicals, a division of US Steel Corporation, now USX)." CMA stated also that the Eastman Kodak is the Phthalate Esters Panel member who produces DMP. According to secondary literature, DMP and DBP are used primarily as plasticizers.

Comments/Recommendations

CMA stated that complete copies of the final genotoxicity study reports will be sent to EPA when those reports become available.

EPA's Office of Toxic Substances has received a number of TSCA Section 8(e) and "For Your Information" (FYI) notices concerning alkyl phthalates. In addition, the Chemical Screening Branch recently prepared Chemical Hazard Information Profiles (CHIPs) on diallyl phthalate and dimethoxyethyl phthalate. Further, EPA has published TSCA Section 8(a) and (d) rules on alkyl phthalates.

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 to 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: SEP 4 1986

SUBJECT: Status Report* 8EHQ-0886-0621 S Approved: 9/5/86

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 name and exact identity of the subject chemical to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS) will ask the submitter to substantiate the company's confidentiality claims. In the "sanitized" version of the notice, the submitter reported non-confidentially that the subject chemical substance is an alkylated aniline.

Submission Description

The submitting company provided summarized preliminary results of a battery of in vitro genotoxicity studies and several acute in vivo toxicity studies conducted with this alkylated aniline. According to the submitted information, the subject chemical was found to be active in an Ames Salmonella typhimurium (bacteria) mutagenicity assay, a DNA repair assay using cultured rat hepatocytes, and a cytogenetics assay in cultured Chinese Hamster ovary (CHO) cells; the chemical was reported to be inactive in an in vitro BALB/c-3T3 mouse cell transformation assay and an in vitro CHO cell point mutation assay. With regard to in vivo toxicity, the submitter reported that this chemical was non-irritating to eyes or skin (the test species was not specified). The submitter reported further that the alkylated aniline was found to have an oral LD50 (rats; combined sexes) of 742.8 mg/kg and a dermal LD50 (rabbits) of 2000 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.

Submission Evaluation

Although the submitted information indicates that this alkylated aniline is not irritating to skin or eyes and is not extremely toxic in terms of lethality, the reported *in vitro* test results indicate that the chemical does possess some degree of genotoxic activity. In order for EPA to assess the overall significance of the reported findings, however, the submitting company should be asked to ensure that the Agency receives complete copies of the final reports from all studies that were cited in the company's 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 of this alkylated aniline will appear in this report. According to the submission, the submitting company is not a commercial producer of the chemical nor does the company have any current plans to commercialize the substance.

Comments/Recommendations

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

   In view of EPA's general interest in company actions taken on a voluntary basis in response to chemical toxicity or exposure information, the submitting company will be asked to describe the actions the company has taken or plans to to take to notify workers and/or others about the reported findings.

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

c) The Chemical Screening Branch will provide 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 provided to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: SEP 4 1986

SUBJECT: Status Report* 8EHQ-0886-0622 S Approved: 9/5/86

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 the company's 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 submitter reported that information recently brought to the company's attention indicates that two (2) "employees exhibited a reaction to workplace exposure, resulting in temporary headaches, disorientation, chest tightness and a continuing inability to consume alcoholic beverages without a return of the headaches." The submitter also provided the following information concerning this situation:

> "The employee reactions are possibly due to sensitization or some other undetermined mechanism. These reactions appear to result from exposure to chemical mixtures used in electron beam cured coatings on paper or polymer film substrates or [to] an unknown chemical(s) generated in the process. [The company] has yet to determine what specific chemical or chemicals may be responsible for the symptoms being reported. The source of this information stems from employee verbal complaints of reported symptoms."

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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 EPA has received a number of Section 8(e) submissions regarding cases of possible sensitization among chemical workers, this is the second Section 8(e) submission concerning workers who experienced apparent alcohol/workplace chemical-related adverse effects. In Section 8(e) submission number 8EHQ-0880-0355, the Allied Chemical Corporation stated that several Allied employees who worked with methylthioacetaldehyde oxime (CAS No. 10533-67-2) developed red splotches on the face and upper trunk, headaches, and tachycardia following alcohol consumption. In this previous Section 8(e) notice, Allied stated also that the observed effects resembled those found following alcohol ingestion by persons receiving Antabuse® (tetraethylthiuram disulfide), a drug used in the treatment of alcoholism. In the preliminary evaluation of Allied's TSCA Section 8(e) submission, EPA noted that there are a number of chemicals/drugs capable of inhibiting the enzyme that converts acetaldehyde to acetic acid. (The first step in alcohol metabolism involves the conversion of the alcohol to acetaldehyde in the body.) EPA noted also that 1) introduction of alcohol in the presence of such enzyme inhibitors can result in an excess of acetaldehyde in the body, and 2) this acetaldehyde excess can bring about adverse symptoms and signs related to circulatory, respiratory, liver, and nervous system functions.

Comments/Recommendations

The submitting company stated that it is currently investigating the situation and "until a determination is made as to the exact cause of these symptoms, precautions are being taken to isolate the two employees that appear to be sensitized and to provide respiratory and skin protection for other employees in the workplace." The company stated also that EPA would be apprised of any new information obtained during the company's investigation.

Based on EPA's initial evaluation of the information presented in this notice, it is not entirely clear that the information provided by the company is of the type required for submission to the Agency under Section 8(e), the substantial risk information reporting provision of TSCA. It is quite probable, on the other hand, that the subject information is of the type required to be maintained by the submitting company under Section 8(c), the mandatory recordkeeping provision of TSCA. On August 22, 1983, EPA published (48 FR 38178) a final rule that requires chemical manufacturers, importers and certain processors to maintain records of any significant adverse reaction alleged to have been caused by TSCA-covered chemicals. The final TSCA Section 8(c) rule also requires that allegations involving significant adverse reactions in workers be kept for 30 years and that other recordable allegations be kept for 5 years. It should be noted that the Agency is empowered to both inspect and require submission of Section 8(c) records and has done so on a number of occasions to date.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will request the submitter to ensure that EPA is informed immediately about all significant findings from the company's investigation into the causative agent(s) of the adverse effects seen in two of the company's employees.

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

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 provided to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: SEP 30 1986

SUBJECT: Status Report* 8EHQ-0986-0623 S

Approved: James F. Darr for Frank D. Kover 9/30/86

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 the company's name and the exact identity of the tested chemical to be TSCA Confidential Business Information (TSCA CBI). Staff of the Information Management Division (IMD/OTS/OPTS) will request the submitting company to substantiate these TSCA CBI claims. In the sanitized version of the TSCA Section 8(e) notice, the submitting company reported non-confidentially that the tested chemical was a substituted diphenyl ether.

Submission Description

The submitting company provided the following summary information with regard to the conduct and preliminary findings from an oral teratology study in rats:

> "Groups of 30 bred Fischer 344 rats were administered the [substituted diphenyl ether] in aqueous solution by oral gavage on days 6 through 15 of gestation at dose levels of 0, 0.3, 1.0, or 7.5 mg/kg body weight/day. Each fetus was examined externally and approximately 50% of the fetuses from each litter were examined for visceral alteration by the Staples technique. . . . . [Skeletal examination] of fetuses is in progress.
>
> "Indications of maternal toxicity were evidenced by an increase in absolute and relative liver weights in high dose (7.5 mg/kg/day) females. Accompanying the maternal

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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.

toxicity at the high dose was a significant decrease in fetal body weight. In addition, visceral examination revealed an increased incidence (not statistically identified) of a great vessel malformation in the high dose group. This malformation involved a displacement of the ascending aortic arch which occurred in one fetus in the control group, two fetuses in the 1.0 mg/kg/day group and 4 fetuses in the 7.5 mg/kg/day group. Although the increased incidences of great vessel malformation were not statistically identified, the clustering of 4 fetuses from 4 different litters at the top dose level suggests a possible teratogenic response."

The submitting company also provided the following summarized information with regard to the conduct and preliminary results of a two-generation reproduction study of the subject chemical substance in rats:

". . . [G]roups of 30 rats/sex/dose level were given the compound in the diet at dose levels of 0, 0.1, 0.3, 1.5 (males) or 3.0 (females) mg/kg/day for a period of 10 weeks. These animals were then bred (1 male : 1 female) within dose groups for 3 weeks or until a sperm positive vaginal smear was obtained. Females were allowed to deliver their litters and the offspring were evaluated for growth and survival during lactation through weaning at 28 days of age. . . . .

"[Through 21 days of age,] there were no adverse effects noted among the f_0 adults in either body weights or feed consumption during the pre-mating, gestation, or lactation periods. Mating indices were also unaffected in all of the dose groups.

"Among [those] litters in the 3.0 mg/kg/day dose level, a significant increase in the mortality of pups through day 4 of lactation was observed. In addition, pup body weights in the 3.0 mg/kg/day dose group were significantly lower than the control group from birth through day 21 of lactation. These effects were considered to be a result of administration of the test compound. Statistically identified differences in pup body weights in the 0.1 and 0.3 mg/kg/day dose groups were also observed; however, these [observed] differences may have been secondary to the larger litter sizes seen in these groups when compared to the control group. Further conclusions regarding these data await completion of the lactation phase of the study."

It should be noted that on a "For Your Information" (FYI) basis (FYI-OTS-0286-0483), the submitting company provided previously the following summarized information with regard to the conduct and results of a "probe" teratology study in rats:

"Groups of ten [(10)] bred female Fischer 344 rats were administered [the test compound] by oral gavage on days 6 through 15 of gestation. Dose levels were 0, 3, 10 and 30 mg/kg body weight/day. On day 16, all animals were sacrificed and examined for gross pathological changes. The ovary and uterus of all animals were also examined at this time.

"Evidence of maternal toxicity was observed in the 3, 10 and 30 mg/kg[/day] dose groups. The degree of maternal toxicity was dose-related. Pregnant rats in the 30 mg/kg[/day] dose group exhibited a decrease in body weight on gestation day 16, a decrease in body weight gain during gestation days 6 through 8, 10 through 16, and 6 through 16, and an increase in kidney and liver weights. Pregnant rats in the 10 mg/kg[/day] dose group exhibited a decrease in body weight gain during gestation days 6 through 8 and an increase in kidney and liver weights. Pregnant rats in the 3 mg/kg[/day] group exhibited an increase in kidney and liver weights.

"Embryotoxic effects were observed in the high dose females. Pregnant rats in the 30 mg/kg[/day] dose group exhibited an increase in the percent of implantations undergoing resorption and the percent of litters with resorptions. At the two lower dose levels, the resorption rates were comparable with the controls."

It should be noted that on September 8, 1986, the submitting company provided to EPA a complete copy of the protocol from the oral teratology study cited in the company's TSCA Section 8(e) submission and a complete copy of the final report of the above referenced "probe" teratology study (FYI-OTS-0986-0483 S Followup Response). The Introduction and Purpose section of the final report from the "probe" teratology study presented the following information regarding the results of other studies conducted with the subject chemical substance:

"A range-finding acute oral toxicity study in male and female rats indicated the LD50 [of the substituted diphenyl ether] to be approximately 500 mg/kg in both sexes. . . . Administration of 0, 10, 50, or 100 mg/kg body weight/day to male Fischer 344 rats for 4 days via gavage resulted in statistically increased liver and kidney weights [observed] at all dose levels relative to controls. . . .

"[The] preliminary results of a 2-week dietary probe in which male Fischer 344 rats were given targeted doses of 0, 0.1, 1.0 or 10 mg/kg body weight/day and female rats were given 0, 1.0, 10 or 100 mg/kg body weight/day identified the liver and the kidneys as potential target tissues. Increases in absolute and relative liver and kidney weights were observed in male rats administered

> 10 mg/kg body weight/day. Absolute and relative liver weights were increased in females given 10 or 100 mg/kg body weight/ day. Microscopic examination of the liver revealed diffuse hepatocellular hypertrophy and altered cytoplasmic tinctorial properties in male and female rats receiving the highest dose level. Similar changes were also observed in female rats given 10.0 mg/kg body weight/day and males given 1.0 mg/kg body weight/day. A 12% depression in body weights relative to controls was also observed in top dose group female rats. Preliminary data reported for this [2-week] study suggest that the no-observed-effect-level (NOEL) was between 1.0 to 10 mg/kg body weight/day for female rats and 0.1 to 1.0 mg/kg body weight/day for male rats."

Finally, it should be noted that the final report from the "probe" teratology study states that the oral route of exposure had been selected for the "definitive" teratology study because the oral route is "a potential route of human exposure."

Submission Evaluation

According to the submitted findings from the recently conducted teratology study, soft tissue and external examination of the fetuses showed a great vessel defect, the incidence of which, while not statistically significant, was dose dependent (1 in controls, 0 at 0.3, 2 at 1.0 and 4 at 7.5 mg/kg). At the highest dose, there was also an observed increase in relative and absolute maternal liver weights and a decrease in fetal body weights. Further evaluation of the overall significance of the apparent teratologic effect should be possible upon EPA's receipt of a full copy of the final report from this study.

With regard to the two-generation reproduction study in rats, the submitter reported that no effects were seen in the parents at oral dose levels up to 3.0 g/kg/day. It should be noted, however, that the F_1 generation from the 0.3 and 3.0 mg/kg exposure groups showed a decreased body weight prior to weaning and an increased mortality prior to day 4 (at 3.0 mg/kg only). As in the case of the oral teratology study, further evaluation of the overall significance of the results of this reproduction study should be possible upon EPA's receipt of the final report.

Current Production and Use

In view of the submitting company's TSCA CBI claims, this status report will not contain any information with regard to the TSCA Chemical Substance Inventory status of the subject chemical substance. In its Section 8(e) notice, the company reported nonconfidentially that the tested chemical "is at the research stage and is being evaluated for use as a pesticide." According to the Introduction and Purpose section of the final report of the oral "probe" teratology study (FYI-OTS-0986-0483 S Followup Response), the chemical is undergoing evaluation as a potential herbicide.

Comments/Recommendations

The submitting company stated that in accordance with its long-standing corporate policy, the company plans to inform "relevant employees" about the results of the reported studies.

a) The Chemical Screening Branch (CSB/ECAD/OTS) 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 histopathologic examinations, results of statistical analyses, etc.) from the "definitive" oral teratology study that was cited in the company's Section 8(e) and FYI submissions on this substituted diphenyl ether.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, the submitting company will be requested also to describe the nature and results, if available, from all other studies that the company has conducted, is conducting, or is planning to conduct to determine either the toxicity of or the exposure to 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 this substituted diphenyl ether.

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. Copies of this status report will be transmitted also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: SEP 24 1986

BJECT: Status Report* 8EHQ-0986-0624/5 S Approved: James F. Darr for Frank D. Kover 9/24/86

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 identities of the tested chemicals as TSCA Confidential Business Information (TSCA CBI). Information Management Divsion (IMD/OTS) staff will request the submitter to substantiate these TSCA CBI claims. The submitter provided the following non-confidential generic names for the subject chemical substances: a substituted nitrobenzene (8EHQ-0986-0624 S) and a substituted chlorobenzene (8EHQ-0986-0625 S).

Submission Description

The submitting company provided the following summarized interim findings from a dietary feeding study of the subject chemicals in male and female Sprague-Dawley rats:

> "A significant increase in corneal opacity (milky or cloudy eye condition) has been observed in some of the treated animals at all [of] the dose levels employed in the study. Microscopic examination of opaque cornea revealed ulceration of the epithelium (outer layer of the cornea) in some of the treated animals. Vascularization including both capillaries and larger vessels was seen in some affected areas. A dose response relationship is not apparent at present for this lesion. Spontaneous repair and reversal of the lesion is occurring in some animals even though they continue to receive the test diets. It is too early to determine whether the lesion will completely reverse."

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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) submissions, the company noted that "while corneal toxicity is unusual, it is not unique to . . . [the tested chemical substances] but has been reported to occur from the administration of several drugs, including indomethacin, chloroquine, amiodarone and others." In its Section 8(e) submissions, the company also provided the results of ophthalmoscopic and biomicroscopic examinations associated with the performed studies. With regard to either the substituted nitrobenzene or the substituted chlorobenzene, the provided ophthalmoscopic/biomicroscopic examination reports presented the following summary information:

> "In many of the rats, an inflammatory corneal syndrome was seen. Observations seem to indicate the following stages in the syndrome. In its least severe stage, the corneal syndrome was characterized by the presence of fine granular deposits scattered throughout the corneal epithelial cells or the basement membrane area subepithelially. In this stage, the perilimbal area of the cornea was spared. In its moderate stage, a central corneal area, approximately half the surface, acquired a somewhat roughened surface, apparently associated with inter- or intraepithelial edema, and associated with [a] dessication of the affected [corneal] surface. There was a tendency for corneal ulceration to occur within the edematous zone. In the severe stage [of the syndrome], the superficial lesion seemed to induce corneal vascularization, which eventually encroached from every quadrant of the cornea to invest the edematous and dessicated zone. The vascularization often became severe enough to impede intraocular examination. The vascularization in many cases seemed to meet resistance when it reached the area of the dessicated zone. In a few [of the] cases, there seemed to be a partial recovery, with partial clearing of the cornea and shutdown of the engorged corneal vessels, leaving only ghost vessels. The syndrome occurred both uni- and bilaterally, and was often asymmetric when bilateral. . . . . Biomicroscopic examination of clinically unaffected eyes revealed that many had coarse granular surface deposits in the medial quadrant, generally forming an elliptical pattern. This occurred in both treated and untreated animals, and is a common finding in laboratory rats [that are] examined by this method."

The ophthalmoscopic/biomicroscopic examination report for the substituted nitrobenzene presented the following information unique to that chemical:

> "The [observed corneal] syndrome was compound related, though apparently not dose related. [The] males were more frequently and more severely affected [than were the females]. Four of 10 females (previously observed to have the syndrome), but no males, were observed to be

> in the healing stages of the disease, even though they are still receiving the test compound. In a group of treated rats not previously observed to have the corneal syndrome, [the] biomicroscopic examination revealed its presence to a mild degree, affecting [the] males more frequently than [the] females. . . . . Cataracts were present in 2 treated males previously observed to have [the] corneal disease. The cataracts are probably not treatment related. The corneal disease syndrome may be the result of toxic interference to the lacrimal glands and tear film, but is more likely to be the result of accumulation of toxic material in the corneal epithelial layer. The site of accumulation may be determinable by electron microscopic examination."

The ophthalmoscopic/biomicroscopic examination report for the substituted chlorobenzene presented the following information unique to that chemical:

> "The [observed corneal] syndrome was compound related, though apparently not dose related. [The] males are frequently and more severely involved than [are the] females. In a group of high dose rats not previously observed to have the corneal syndrome, many have the early stages of the disease, visible only biomicroscopically. Males were more frequently affected in this group also. Some of the affected rats also had an unusual form of retinal degeneration, involving the upper quadrants of the retina. This may be treatment related. This type of retinal degeneration generally occurs in much older rats. Three rats had cataracts, including two previously reported to be affected with the corneal degeneration syndrome. The cataracts do not appear to be treatment related. . . . . The corneal syndrome may be related to disease processes involving the lacrimal glands and tear film, but more probably deposition of toxic material in the corneal epithelial tissue. The site of abnormal inclusions may be visible . . . [by electron microscopy]."

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 EPA receives a full copy of the final report (including the actual experimental protocol, data, results of gross and histopathological examinations, results of statistical analyses, etc.) from the ongoing dietary study cited in the company's TSCA Section 8(e) submissions.

Current Production and Use

In view of the fact that the submitting company has claimed the exact identities of the subject chemical substances to be TSCA CBI, no information pertaining to the TSCA Inventory status of those chemicals will appear in this report.

In its Section 8(e) notices, the submitting company stated that the subject chemical substances were experimental pesticide candidates that have been "manufactured in small quantities with limited, controlled distribution." In addition, the company reported that the chemicals are "handled only by technically qualified persons including consulting scientists and company scientific personnel using prudent laboratory practices."

Comments/Recommendations

The submitting company stated that 1) all persons working with the subject chemicals will be notified immediately about the reported toxicologic findings, and 2) the existing practices for handling of these chemicals "will be evaluated and modified if necessary."

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the submitter to ensure that 1) the Agency is informed in a timely manner about any further significant interim findings from the ongoing dietary study cited in each of the company's Section 8(e) submissions and 2) the Agency receives a full copy of the final report (including the actual experimental protocol, data, results of gross and histopathologic examinations, results of any statistical analyses, etc.) from the 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 information, the submitting company will be asked also 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 is planning to conduct to determine the toxicity of or the exposure to the subject chemicals.

b) The Chemical Screening Branch will review the submitted 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, NTP, FDA, OSWER/EPA, OW/EPA, OAR/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.

DATE: OCT - 8 1986

SUBJECT: Status Report* 8EHQ-0986-0626 S

Approved: 10/1986

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

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

NOTE:

The submitting company has claimed its company name and the exact identity of the tested chemical to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS) will ask the submitting company to substantiate these confidentiality claims. The submitting company has stated non-confidentially that the chemical is a halogenated pyridine.

Submission Description

The submitting company provided the following summarized results of an oral teratology study of the halogenated pyridine in rats:

> "[G]roups of 29 bred Fischer 344 rats were administered the test material on days 6 through 15 of gestation at dose levels of 0 or 75 mg/kg/day. The fetuses were removed and all [of the] live fetuses were examined for external alterations. In addition, the tissues within the thoracic cavity were examined . . . in order to detect any vascular anomalies. . ."
>
> "At 75 mg/kg/day, decreased maternal weight gain during dosing, decreased feed consumption and increased water consumption were observed. . . Statistically significant differences in [the] maternal weight gain during the dosing period. . . Fetal body weights were also decreased. . . Visceral examination of tissues in the thoracic cavity revealed a statistically significant increased incidence of persistent right fourth aortic arch in the treated group. No evidence of this malformation was observed in the control 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.

In its TSCA Section 8(e) submission, the company also provided the following information with regard to the observed vascular anomaly:

> "During normal embryologic development, the left aortic arch persists to become the true aortic arch, and the right aortic arch combines with the right paired dorsal aorta to become the right subclavian. The persistence of the right aortic arch resulted in a vascular ring surrounding the esophagus and trachea."

In its TSCA Section 8(e) notice, the submitting company stated that the reported findings confirmed those provided previously to EPA on a "For Your Information" (FYI) basis (FYI-OTS-1085-0407 S Supplement). In FYI-OTS-1085-0407 S Supplement, the submitting company provided the following summarized information about the results of an oral teratology study of the halogenated pyridine in rats:

> "Groups of 24-28 bred Fischer 344 rats were administered the test material on days 6 through 15 of gestation and the fetuses removed by Cesarean section on day 21 of gestation. Dose levels were 0, 5, 25 and 75 mg/kg/day. Each fetus was examined externally, and approximately half of the fetuses in each dose group were examined for visceral alterations by the Staples technique. At the top dose level (75 mg/kg/day), decreased food consumption throughout gestation and increased water consumption during the first 3 days of dosing were the only indications of maternal effects. Fetal body weights were significantly lower than controls in the top dose group. Visceral examination revealed a cardiovascular malformation among fetuses in the top two dose groups which had not previously been observed in this strain within this laboratory. This malformation involved a displacement or absence of the ascending aortic arch which occurred in two fetuses in the 25 mg/kg/day dose group, and 5 fetuses in the 75 mg/kg/day dose group. Though the incidence of this [vascular] anomaly was not statistically elevated when compared to controls, the clustering of 5 fetuses at the top dose level with this unusual malformation suggests a teratogenic response at a dose level which does not produce maternal toxicity."

In the above referenced FYI supplement, the submitting company stated also that it had previously reported to EPA the results of a "probe" teratology study of this halogenated pyridine in rats (FYI-0585-0407 S Initial). In FYI-OTS-0585-0407 S Initial, the submitting company provided the following summarized information concerning the results of this "probe" study in Fischer 344 rats:

> "Ten bred females per dose level were dosed on days 6 through 15 of gestation by oral gavage. Dose levels were 0, 50, 100 and 150 mg/kg/day. Necropsy occurred on

day 16 of gestation. Parameters measured included: body weights and gains, food and water consumption, organ weights (liver and kidneys), corpora lutea, implantations, resorptions and litter size. At the top dose, there was a statistically significant increase in resorptions and a statistically significant decrease in litter size. The maternal animals showed a statistically significant decrease in body weight gain during days 6 through 16 and a statistically significant increase in relative liver weight at the top dose. The maternal animals also showed a statistically significant decrease in body weight gain over days 6 through 16 at the next to top dose." [Note: According to the submitted data, there was a dose-response trend in increased resorptions and decreased litter size, although these differences were statistically significant over controls only in the high dose group.]

Submission Evaluation

According to the probe teratology study, which was the subject of FYI-OTS-0585-0407 S Initial, oral administration of 100 mg/kg/day produced minimal maternal effects and no adverse effects in the fetus. In view of these findings, it may have been more prudent to use 100 mg/kg/day as the highest dose level (instead of 75 mg/kg/day) for the oral teratology study that was the subject of FYI-OTS-1085-0407 S Supplement; selection of 75 mg/kg/day as the highest dose level could have resulted in an under-estimation of the potential developmental toxicity of the test material.

The cardiovascular malformations reportedly observed in the oral teratology study (which was the subject of FYI-OTS-1085-0407 S Supplement), although not statistically different from controls, are considered toxicologically significant because they are rare malformations and were not observed in concurrent control rats or historical control rats in the performing laboratory. It should be noted also that the observed cardiovascular defects were dose-related, occurring in 0, 2 and 5 fetuses in the low, middle and high doses, respectively. In addition, these effects were found in more than one litter (0, 2 and 4 litters, respectively), and thus were not due to random occurrence in a single dam. On the basis of these data alone, therefore, it is apparent that the tested halogenated pyridine produced serious adverse effects on the fetus at doses below those causing overt maternal toxicity.

In FYI-OTS-1085-0407 S Supplement, the submitter stated that further work was planned to investigate the reproducibility of the findings reported in that supplemental FYI notice. The present TSCA Section 8(e) submission presents the results of this further work.

The summarized data submitted under TSCA Section 8(e) show that at the 75 mg/kg/day dose level, the tested chemical produced significant increases in persistent right 4th aortic arch, total

cardiovascular malformations (which included retroesophageal right subclavian artery and hypoplastic atrium) and incomplete diaphragm when compared to concurrent control rats. Overall, the results of the studies cited in the FYI supplement and the TSCA Section 8(e) notice both indicate that the subject chemical substance when administered orally to pregnant Fischer 344 rats at 75 mg/kg/day on days 6 through 15 of gestation produced uncommon cardiovascular malformations in the offspring. Although there was some toxicity seen in the dams, the rarity and apparent dose and litter response nature of the observed malformations suggests that the malformations were primary toxic effects due to exposure to the chemical and not due secondarily to maternal malaise.

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 report.

Comments/Recommendations

In its initial FYI submission, the submitter stated that all persons engaged in research on the subject chemical were being notified by the company about the reported findings.

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At the time of EPA's receipt of this Section 8(e) notice, EPA was in the process of preparing a statement outlining the Agency's initial position on the Section 8(e)-applicability/reportability of the findings from the teratology study cited by the company in FYI-OTS-1085-0407 S Supplement. It is appropriate, therefore, that this status report will serve as the forum for EPA to present its position.

Following an EPA review of FYI-OTS-1085-0407 S Supplement, it is EPA's initial position that the teratological findings presented therein should have been reported to EPA 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 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 . . . 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 of the Section 8(e) policy statement.

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 health effects (e.g., birth defects, cancer) are considered by EPA to be so serious that relatively little weight should be attached to the chemical's exposure in determining whether a risk is substantial. Further, EPA's response to Comment 31 (see Appendix B of the TSCA Section 8(e) policy document) states that the occurrence of serious effects such as those described in Part V(a) of the policy statement (e.g., birth defects) presupposes exposure to the tested chemical or mixture and must be submitted to EPA pursuant to 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."

In light of the preceding discussion and EPA's review of the information presented in the submitting company's supplemental FYI notice (FYI-OTS-1085-0407 S Supplement), EPA believes that the teratologic findings contained therein can "stand alone" in their ability to offer reasonable support for a conclusion that this TSCA-covered substance can cause birth defects and as such should have been submitted formally to EPA under Section 8(e) of the Toxic Substances Control Act.

a) The Chemical Screening Branch (CSB/ECAD) will ask the submitting company to provide its rationale as to why the results from the oral teratology study cited in FYI-OTS-1085-0407 S Supplement were not provided formally to EPA under TSCA Section 8(e). Following a review of the submitting company's response, the Chemical Screening Branch (CSB/ECAD/OTS) will, if appropriate, deliver all information contained in the submitter's supplemental FYI notice to the OTS Document Control Officer (DCO) for proper handling and filing under Section 8(e) of TSCA.

In addition, the Chemical Screening Branch will ask the submitting company to provide full copies of the final reports from all studies cited in FYI-OTS-0585-0407 S Initial, FYI-OTS-1085-0407 S Supplement and 8EHQ-0986-0626 S Initial.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure information, the submitting company will be asked also to describe the nature and results, if available, from all studies (other than those that have been reported 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 or the exposure to this halogenated pyridine.

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

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 report will be provided also to the TSCA Assistance Office (TAO/OTS/EPA) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: SEP 30 1986

SUBJECT: Status Report* 8EHQ-0986-0627 Approved: James F. Darr for Frank D. Kover 9/30/86

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 reporting the following information under Section 8(e) of TSCA, the CIBA-GEIGY Corporation stated that Tinuvin® 1130 (the reaction product of the methyl ester of beta-[3-(2H-benzotriazol-2-yl)-4-hydroxy-5-tert-butylphenyl]propionic acid and polyethylene glycol) was the subject of a TSCA Section 5 Premanufacture Notice (PMN 85-812) for which EPA's PMN review period had expired and for which the company had submitted (on December 17, 1985) a Notice of Commencement (NOC) of manufacture.

Submission Description

The CIBA-GEIGY Corporation submitted a complete copy of the final report from a 28-day oral gavage study of Tinuvin® 1130 in rats. In the cover letter to its submission, CIBA-GEIGY presented the following information with regard to the conduct and results of this 28-day study:

> "The test material was administered by gavage for a period of 28 days to [groups (5 males and 5 females/group) of Crl CD (SD) Br] rats. The dose levels were 0, 10, 50, 200 and 1000 mg/kg/BW. The major findings were foci of liver necrosis, focal liver hemorrhages, and marked renal tubular degeneration. The renal effects were only seen in the high dose males, and the liver effects had a NOEL [(no-observed-effect-level)] of 10 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.

In its submission, CIBA-GEIGY stated also that "a substituted benzotriazole, CG-571, that was the subject of 8EHQ-0486-0597 S, is an impurity in Tinuvin® 1130 (<1%)." It should be noted that in that previous Section 8(e) notice, the submitter reported that this substituted benzotriazole (identified non-confidentially as a "benzotriazole-2-yl substituted hydroxyphenylpropionate ester") had been found to cause hepatotoxicity, as well as other serious toxic effects, in male and female rats in a 28-day oral gavage study.

In the present Section 8(e) submission, CIBA-GEIGY also provided copies of the Tinuvin® 1130 Material Safety Data Sheet (MSDS) and product label. According to the submitted MSDS, Tinuvin® 1130 has an oral (rat) LD50 in excess of 5 grams/kg and a dermal (rat) LD50 in excess of 2 grams/kg. In addition, the MSDS reports that Tinuvin® 1130 is non-irritating to non-abraded rabbit skin and only slightly irritating to rabbit eyes. The MSDS does report, however, that Tinuvin® 1130 has a "strong grade of sensitizing potential" based on results obtained from a maximization test in guinea pigs (70% of the treated animals became sensitized to the product). With regard to genotoxicity, the submitted MSDS states that Tinuvin® 1130 was negative in an Ames Salmonella typhimurium (bacteria) test, a nucleus anomaly test in Chinese hamsters, and a micronucleus test in Chinese hamsters.

Submission Evaluation

Although the information received to date on Tinuvin© 1130 does indicate that the chemical is not particularly acutely toxic, the data from the 28-day repeated oral (gavage) exposure show that Tinuvin® 1130 induces liver and kidney toxicity, as well as other organ toxicities. Specifically, the 28-day study shows that when rats of both sexes were given oral dose levels of 0, 10, 50, 200 or 1000 mg/kg/day for 28 days, there was an observed increase in liver weights in a dose-responsive manner. For liver toxicity the no-observed-effect-level (NOEL) was 10 mg/kg/day and the hepatic findings included liver foci and focal liver hemorrhages. With regard to kidney toxicity, male rats receiving 1000 mg/kg dose had renal tubular degeneration (the NOEL was 200 mg/kg/day).

In terms of mortality, the treated animals experienced a high death rate at the highest dose level. Five of 10 treated animals died with males appearing to be more susceptible (4/5 died) than females (1/5 died). With regard to other toxicologic findings, the submitted data show that at 200 and 1000 mg/kg/day, the male rats had a decrease in size or weight of the seminal vesicles; females receiving 200 and 1000 mg/kg/day showed a decrease in spleen weights and females receiving 1000 mg/kg/day showed a decrease in thymus gland weights. The submitted data indicate, however, that the thymus and spleen weight decreases observed in the higher dose females were not accompanied by any microscopic abnormalities.

Current Production and Use

In the cover letter to its Section 8(e) submission, CIBA-GEIGY stated that Tinuvin® 1130 "is a relatively low volume product in an early stage of commercialization." According to the provided MSDS, Tinuvin® is an ultraviolet (UV) light absorber; according to EPA's public file (non-confidential) records for PMN 85-812, Tinuvin® 1130 is a light stabilizer imported as an additive for coatings. CIBA-GEIGY stated in its Section 8(e) submission that Tinuvin® 1130 "is a light yellow liquid with a boiling point of greater than 300°C and a vapor pressure of 6.8×10^{-7} mm Hg at 25°C." The provided MSDS reports also that Tinuvin® 1130 has "no discernible odor."

In its TSCA Section 8(e) submission on Tinuvin® 1130, CIBA-GEIGY also provided the following information concerning the potential for exposure to this product:

> "There is little likelihood of exposure by vapor inhalation because of the high boiling point and the very low vapor pressure of the liquid substance. Dermal exposure will be mitigated because the product has a strong dermal sensitizing potential, and protective equipment, impervious gloves, are already recommended in the MSDS. Based on theoretical considerations of the high molecular weight and chemical structure/properties of the test substance, dermal absorption would be expected to be negligible."

Comments/Recommendations

In the cover letter to its Section 8(e) submission, CIBA-GEIGY reported that based on the submitted toxicologic findings, the company has 1) revised the Tinuvin® 1130 MSDS and label, and 2) notified the company's laboratory staff and customers about the toxicologic findings.

a) 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 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 determine the toxicity of or the exposure to Tinuvin® 1130.

b) The Chemical Screening Branch will review the submitted 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, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA, OPP/OPTS, and CCD/OTS/OPTS. Copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

DATE: OCT 9 1986

JBJECT: Status Report* 8EHQ-0886-0628 Approved: 10/9/86

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 a full copy of a pre-publication manuscript entitled "Behavioral Toxicity of Nitrous Oxide in Rats Following Prenatal Exposure." According to the provided manuscript, the results of this study (which was conducted independently by investigators from the Forsyth Dental Center (Boston, MA) and the University of Pittsburgh (Pittsburgh, PA)) "emphasize the fact that exposure to . . .[nitrous oxide] in utero during a period beyond major organogenesis can result in permanent alterations in brain function." The submitted manuscript states also that previously conducted "teratological studies have focused on the physical malformations associated with early prenatal exposure [to nitrous oxide], leaving the false impression that no serious consequences occur as a result of exposure late in gestation. The submitted manuscript states further that "neurobehavioral deficits unaccompanied by physical deformities, such as those [behavioral deficits] induced by . . . [nitrous oxide] in this study, are lasting effects in need of further consideration."

According to the submitted draft manuscript, the performed study involved 40 timed-pregnant Sprague-Dawley rats of which 15 were exposed to a 75% nitrous oxide/25% oxygen mixture for 8 hours on day 15 of gestation; 15 were exposed to air only for 8 hours on day 15 of gestation (sham air control); 5 were exposed to the 75% nitrous oxide/25% oxygen mixture for 8 hours on both days 14 and 15 of gestation; and 5 were exposed to air only for 8 hours each on both days 14 and 15 of gestation (sham air control).

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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 submitted manuscript reports that "at parturition, all litters were reduced to eight pups; 4 males and 4 females were randomly selected whenever possible" for use in studies involving 1) exploratory, diurnal and nocturnal locomotor activity in a residential maze, and 2) spontaneous diurnal primary behaviors (e.g., lying down, standing, walking, rearing) and secondary behaviors (e.g., grooming, sniffing, scratching) as measured by time-lapse photography of rats exposed to a novel environment.

The Results section of the manuscript presents the following information regarding the findings of the maze study:

> ". . . . In 1 month old males and females exposed [to 75% nitrous oxide] only on gestational day 15, no significant changes in group activity were detected. By 5 months of age, however, the females had developed significant hypoactivity during the exploratory period. Males, in contrast, displayed significant diurnal activity. Extending the prenatal [nitrous oxide] treatment to include gestational day 14 as well as day 15 resulted in significant exploratory and diurnal hyperactivity in the females at both ages tested. Hyperactivity also appeared in the males receiving two days of [nitrous oxide] exposure in utero, but it was detectable in the residential maze only at the early age and not at 5 months."

The Results section of the submitted manuscript provided the following information regarding behavioral activity as measured by time-lapse photography in the male rats:

> "Examination of nitrous oxides's effect on behavior in one month-old males revealed little change. Whether exposure lasted one or two days, no significant changes in the frequency, duration or distribution of the primary motor acts . . . were found. Only a few secondary or modifier acts were affected in males at this age, and these changes were specific to the day/days of exposure . . . . Males exposed on gestational day 15 exhibited fewer occurrences and a shorter duration . . . of sniffing, marginally fewer occurrences of scratching and a greater frequency of looking. The average duration of turning in these young . . . males . . . tended to be shorter than in the simultaneously filmed controls. . ., but the difference [observed] was not statistically significant. . . . Males exposed on gestational days 14 and 15 did not show any significant changes in their motor acts, although they too showed slight tendencies of change in turning (frequency) and sniffing (frequency and duration).

"Altered male behavior was most obvious in the five month-old rats exposed [to nitrous oxide on days 14 and 15 of gestation]. In that group, changes in body position were detected, consisting of a decreased frequency of standing . . . and a corresponding increase in the average duration of rearing. . . . In addition to [the] changes in body position, there were fewer incidences when no secondary . . . [motor acts were observed]. All [nitrous oxide-]treated males displayed effects on face washing behavior; males exposed for one day did not wash their faces as often, whereas males exposed for two days displayed face washing more randomly over time. . . . In general, all of these changes make the adult males appear slightly hyperactive, especially those exposed for two days in utero."

The Results section of the manuscript presented the following information with regard to behavioral activity as measured by time-lapse photography of the female rats:

"Induction of hyperactivity by prenatal [nitrous oxide] exposure is demonstrated clearly in data from females. Even at one month, evidence for hyperactivity could be found. The females exposed [to nitrous oxide] in utero on days 14 and 15 had increased rearing and walking frequencies . . . that accompanied significantly shorter durations of standing . . . and sitting. . . . At five months of age, hyperactivity in the females was even more evident. The frequencies of turning and smelling increased, whereas those of sitting, washing face and grooming decreased. . . . The average durations of sitting, grooming, looking and rearing were more randomly distributed in time. In contrast, [the observed] occurrences of sitting and face washing were more clustered in time. . . .

"Females exposed [to nitrous oxide] on only gestational day 15 did not exhibit the same behavioral abnormalities, although they too had been affected. At one month of age, [the females] exhibited more occurrences of head turning . . . and a more random . . . distribution of body turning . . . when compared to air controls. . . ." At five months [of age], these females displayed a tendency toward hypoactivity as indicated by a greater number of instances when no secondary [motor] acts . . . were performed . . . and the duration of rearing was shortened. . . ."

The Discussion section of the submitted manuscript presented the following statements with regard to the overall interpretation of the data obtained from the performed studies:

"The time-lapse photographic and residential maze data demonstrated that prenatal exposure [of rats] to 75[%] nitrous oxide for 8 hours can permanently alter the neurobehavioral output of the CNS. This [nitrous oxide] effect was easier to detect in mature, 5 month old rats than it was in younger animals only one month old. Females exhibited more changes than males, and two day exposures spanning gestational days 14 and 15 altered behavior more than a one day exposure on gestational day 15. When hyperactivity was the clearcut outcome, it was typically characterized by the grooming behaviors (sit, wash face, groom) decreasing in frequency, shortening in duration and clustering in distribution in time. Concurrently, exploratory and attentive acts increased in frequency (turn and smell) and become more randomly distributed in time (stand, smell, look and rear)."

Submission Evaluation

Although there are several limitations of the performed study, the submitted findings do suggest that prenatal exposure to nitrous oxide results in a pattern of hyperactivity postnatally. (It should be noted that the reported results are supported by published studies, the results of which indicate that altered behavior occurred in mice following prenatal exposure to nitrous oxide.) Some of the limitations of the present behavioral teratology study include, for example: 1) use of too few animals; 2) use of the pup as opposed to the litter as the statistical unit; and 3) use of a technique (time-lapse photography) that is not as yet well established for assessment purposes (the results obtained using this technique do appear to support, however, the findings of the maze study). Further, it is quite difficult to interpret some of the reported findings because the experimental methodology was not described in sufficient detail. For example, there was no indication as to whether the same rats were tested at 1 month and 5 months of age. Also, the residential maze study findings were presented for only 4 or 5 litters although there were 15 litters exposed to nitrous oxide on day 15 of gestation. In addition, there is no way to determine how many different litters were analysed in the time-lapse photography portion of the study because the data are presented only in terms of numbers of animals. Finally, the information presented in the manuscript does not allow for a determination of whether the rats tested in the residential maze were the same as those tested via time-lapse photography.

In conclusion, while there are a number of limitations regarding study design and presentation of the findings, the submitted data suggest that altered post-natal behavior occurred as the result of exposure to nitrous oxide in utero. In order to reach a firm conclusion regarding this apparent toxicity, however, additional research is clearly necessary.

Current Production and Use

A review of the production range (includes importation volumes) statistics for nitrous oxide (CAS Number 10024-97-2), which is listed in the initial TSCA Chemical Substance Inventory, shows that between 101 million and 211 million pounds of this chemical were reported as being manufactured and/or 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 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 secondary literature sources, nitrous oxide (which is known also as laughing gas) is a colorless, non-combustible gas with a "sweet" odor/taste. The applications of nitrous oxide include its use as a general anesthetic in dentistry/medicine, as a propellant in certain types of aerosol food products, as a leak detector, as a component in carbon disulfide-containing rocket fuels, and as an oxidizing agent.

Comments/Recommendations

In its Section 8(e) submission, Union Carbide provided EPA with the name, address and phone number of the lead author of the submitted manuscript in order for the Agency to obtain further information directly from the investigator(s).

a) The Chemical Screening Branch will contact the lead investigator in order to obtain additional information with regard to the conduct/results of this behavioral teratology study of nitrous oxide in rats.

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

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. Copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: OCT 14 1986

SUBJECT: Status Report* 8EHQ-0986-0629 Approved: 10/14/86

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 submitted a copy of draft final report entitled "Epidemiologic Study of Vinyl Chloride Workers." (According to Union Carbide, the study had been conducted for the Chemical Manufacturers Association (CMA).) The "Summary" section of the submitted report presented the following information with regard to the conduct and results of the performed epidemiologic study:

> "The cohort consisted of 10,173 men who had worked for at least one year in jobs involving exposure to vinyl chloride prior to January 1, 1973. These men were employed at 37 plants in the U.S. belonging to 17 companies. Observation of the mortality experience of the cohort was extended to December 31, 1982. A total of 1536 cohort members were identified to have died. The observed mortality, by cause, was compared with the expected based on U.S. mortality rates, standardized for age, race and calendar time. Analyses by length of exposure, latency, age at first exposure, calendar year of first exposure and type of products were performed. The [performed epidemiologic] study confirmed that the vinyl chloride workers [had] experienced significant mortality excesses in angiosarcoma (15 deaths), cancer of the liver and biliary tract (SMR = 641), and cancer of the brain and other central nervous system (SMR = 180). In addition, the study also found a significant mortality excess in emphysema (SMR = 179). On the other hand, the study did not find any excess in either respiratory cancer or lymphatic and hematopoietic cancer."

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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 this report to EPA, Union Carbide stated that "the information on excess emphysema observed in [the] vinyl chloride workers is not reliably ascribed in the report to exposure to vinyl chloride because of: (1) potential problems involved in the cause of death coding for emphysema; (2) the manner in which the diagnosis of emphysema was made (clinically or pathologically; (3) the possible contribution of other factors such as smoking and geographical variation; and (4) the absence of precedents in experimental animals." In addition, Union Carbide stated that the apparent excess of biliary tract cancer "may be explained by failure to diagnose angiosarcoma properly."

Submission Evaluation

The submitted epidemiological study continued the follow-up of 10,173 workers who were exposed to vinyl chloride for 1 year or more between 1942 (or on initiation of complete recordkeeping systems at the studied plant) and December 31, 1972. The vital status of 9200 members was characterized as of December 31, 1982. Within the period of the study, 1536 (16.7% of the cohort) died. When compared to the mortality experience of U.S. white males, this cohort had a statistically significant deficit in total mortality. Statistically significant increases in mortality were observed from neoplasms of the liver and biliary tract (Standard Mortality Ratio (SMR)=641.2; $p<0.001$; 37 observed), brain and central nervous system (SMR=180.2; $p<0.05$; 23 observed) as well as emphysema (SMR=179.6; $p<0.01$; 41 observed).

The excesses in liver and brain cancers have been reported in other epidemiological studies of vinyl chloride-exposed workers, while the excess in emphysema deaths appears to be the first of its kind. Liver cancers and angiosarcomas have been causally linked to vinyl chloride exposure and several studies have reported significant excesses in brain cancer mortality. In this TSCA Section 8(e) submission, the liver and biliary cancer SMR's showed a highly significant increasing trend in analyses with increasing length of exposure and with increasing latency since first exposure. These trends appear also in the the analyses of the brain cancer deaths. By contrast, analyses of the emphysema deaths showed a decreasing trend with length of exposure with the SMR being statistically significantly elevated for workers with exposures of less than 10 years. The excess in emphysema deaths was limited to polyvinyl chloride manufacturing and to workers who were 35+ years of age when first exposed. The observed emphysema excess was not associated with the year of first exposure or with latency since first exposure.

The limitations of the reported study include the lack of control for confounding exposure such as smoking or other occupational agents. In addition, bias may have been introduced because the deaths were not histologically confirmed. It should be noted, however, that these particular limitations (and others listed by Union Carbide) are insufficient to explain the observed excess in emphysema deaths.

In conclusion, this epidemiological study appears to have been conducted carefully and the results are presented in an unbiased fashion. The excesses in liver and brain cancers observed in the cohort could be used possibly to estimate low-level human cancer risks. The observed excess in emphysema deaths is a finding that deserves further attention. For example, an in-depth evaluation of the existing epidemiologic information on vinyl chloride could be conducted in order to determine the ability of previously performed studies to detect emphysema excesses.

Current Production and Use

A review of the production range (includes importation volumes) statistics for vinyl chloride (CAS No. 75-01-4), which is listed in the initial TSCA Chemical Substance Inventory, has shown that between 3.8 and 10 billion pounds of this chemical were reported as manufactured and/or imported in 1977. This production range information does not include any manufacturing/importation 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 information reported for the initial TSCA Inventory, including the production range information, is subject to the limitations that are contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

According to Chemical & Engineering News (June 9, 1986 issue), U.S. production of vinyl chloride was 6.09 billion pounds and 7.78 billion pounds in 1984 and 1985, respectively.

According to secondary literature sources, applications of vinyl chloride include the chemical's use in the production of polyvinyl chloride, as a refrigerant, and as a plastics adhesive.

Comments/Recommendations

In its Section 8(e) submission, Union Carbide stated that any questions concerning the submitted report should be addressed to the Chemical Manufacturers Association.

It should be noted that the Office of Toxic Substances (OTS) has received several Section 8(e) and "For Your Information" (FYI) notices on vinyl chloride. It should be noted also that several EPA Program Offices (e.g., Office of Air and Radiation (OAR)) have evaluated or are currrently evaluating available toxicologic and exposure data on vinyl chloride.

a) In view of EPA's general interest in corporate actions taken on a voluntary basis in response to toxicologic or exposure data, the Chemical Screening Branch (CSB/ECAD) will request Union Carbide to describe the actions the company has taken or plans to take to notify workers or others about the reported epidemiologic findings.

b) The Chemical Screening Branch will review the reported information in greater detail in order to determine the need for further OTS assessment of vinyl 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. Copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: SEP 24 1986

SUBJECT: Status Report* 8EHQ-0986-0630

Approved: James F. Darr for Frank D. Kover 9/24/86

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 Celanese Corporation provided the following information with regard to the conduct and preliminary results of two genotoxicity studies on pentaerythritol-tris-(B-(N-aziridinyl)propionate) (CAS No. 57116-45-7:

> "The tests conducted were in vitro chromosome aberration and in vitro cell transformation assays. Both [of the] tests were positive. The chromosome aberration test was positive with and without metabolic activation. These results are from an oral report, and full reports will be available shortly . . . [and will be sent to EPA]."

Submission Evaluation

The submitted summarized information indicates that the tested chemical does possess some degree of genotoxic activity. In order for the Agency to evaluate the overall significance of the reported findings, however, full copies of the final reports (including the actual experimental protocols, data, results of any statistical analyses, etc.) from the cited studies are needed.

Current Production and Use

A review of the production range (includes importation volumes) statistics for CAS No. 57116-45-7, which is listed in the initial TSCA Chemical Substance Inventory, has shown that between 10,000 and 100,000 pounds of this chemical were reported as manufactured and/or imported in 1977. This production range information does

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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.

not contain any manufacturing or importation 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 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 Celanese Corporation, this chemical is being manufactured in Japan and is imported for commercial purposes by Virginia Chemicals, Inc., a Celanese subsidiary. In addition, Celanese stated that the chemical's "primary end use application is as a cross-linker in coating systems."

Comments/Recommendations

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 chemical or mixture. Also, the Agency believes that a positive genotoxicity test result, in combination with additional information (e.g., the knowledge of potential exposure to and/or high production of the tested chemical or mixture), would suggest the need, in many cases, to conduct other studies designed to determine better the toxicity of or the exposure to that chemical or mixture. The results of such additional studies should be considered also for submission to EPA under Section 8(e) of TSCA.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the Celanese Corporation to ensure that EPA receives a full copy of the final report (including the actual experimental protocol, data, results of any statistical analyses, etc.) from each 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, Celanese will be requested also to describe the actions that the company has taken or plans to take to notify workers or others about the reported toxicologic findings. In addition, Celanese 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 EPA) about which Celanese is aware or that Celanese has conducted, is conducting, or plans to conduct to determine the toxicity of or the exposure to this chemical.

b) The Chemical Screening Branch will review the reported findings 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, 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: SEP 29 1986

SUBJECT: Status Report* 8EHQ-0986-0631 S Approved: James F. Darr for Frank O. Kover 9/29/86

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 claimed its company name and the exact identities of the subject chemicals to be TSCA Confidential Business Information (TSCA CBI); the Information Management Division (IMD/OTS) will request the submitter to substantiate these claims. In its submission, the company did state non-confidentially that the subject chemicals, which were tested as a mixture in mineral spirits, were perfluoroalkyl resins that had been the subject of the following TSCA Section 5 Premanufacture Notifications: (PMN 85-1053 and PMN 85-1054). According to the non-confidential versions of these PMNs (which were obtained from the Agency's public TSCA Section 5 files), the tested resins are "perfluoroalkyl methacrylate copolymers."

Submission Description

The submitting company provided summarized preliminary findings from acute inhalation studies in rats exposed for 4 hours to a respirable aerosol (1 um mass medium aerodynamic diameter or less) of mineral spirits alone (solvent control) or a mixture consisting of 0.5% perfluoroalkyl resins (total content), 4.5% chlorofluorocarbon 113, and 95% mineral spirits. According to the submitter, these acute inhalation studies showed the mixture to be more toxic than mineral spirits alone (10/10 deaths were observed following exposure to 544 parts per million (ppm) of the mixture while no deaths were observed following exposure to 488 ppm of mineral spirits (the published 4-hour rat inhalation LC50 value for mineral spirits is 3400 ppm). The submitter reported also that no deaths were observed for rats exposed for 4 hours via inhalation to 102 ppm of the mixture. According to the non-CBI versions of PMN 85-1053 and PMN 85-1054, the subject resins have acute oral LD50's of approximately 15 grams/kg each in mice.

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Submission Evaluation

Immediately upon receipt of this TSCA Section 8(e) submission, the Chemical Screening Branch (CSB/ECAD/OTS) provided copies of the submission to the Premanufacture Notice Management Branch (PNMB/CCD/OTS) and the Risk Analysis Branch (RAB/ECAD/OTS) for review. It should be noted that EPA's Office of Toxic Substances (OTS) has received a number of TSCA Section 8(e) submissions on perfluoroalkyl compounds. It should be noted also that the Risk Analysis Branch is currently reviewing available toxicologic and exposure data on this class of chemicals. Finally, it should be noted that EPA's 90-day PMN review period for PMN 85-1053 and PMN 85-1054 has been halted to date due to the company's voluntary testing of the subject perfluoroalkyl methacrylate copolymers.

Current Production and Use

According to the non-CBI versions of PMN 85-1053 and PMN 85-1054, the subject perfluoroalkyl methacrylate copolymers are imported. In addition, the non-CBI PMN's state that the substances are for use as "fabric stain repellents." In its Section 8(e) notice, the submitting company stated that because "the resins tested in the mixture are not commercial products, only very small numbers of people have been potentially exposed in development work." The submitter stated further that this development work "has been carried out with the usual safeguards employed in the conduct of research activities" and it is the company's belief "that the risk to these individuals has been minimal."

Comments/Recommendations

In its Section 8(e) notice, the submitting company stated that the company's development program employees and the overseas supplier of the resins have been notified about the reported toxicologic findings.

a) The Chemical Screening Branch will ask the submitting company to ensure that EPA receives complete copies of the final report (including the actual experimental protocol, results of gross and histopathologic examination, results of statistical analyses, etc.) from each 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 submitting company will be requested also 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 is planning to conduct to determine the toxicity of or the exposure to the subject resins alone or in combination with other chemical substances.

b) As in the case of the initial Section 8(e) submission, all reported information will be transmitted immediately to RAB/ECAD/OTS and PNMB/CCD/OTS for evaluation.

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, PNMB/CCD/OTS, and RAB/ECAD/OTS. In addition, copies of this report will be sent to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: OCT 22 1986

SUBJECT: Status Report* 8EHQ-0986-0632 Approved: 10/23/86

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

Hercules Incorporated reported that the company received letters in which two physicians indicated that a Hercules employee's susceptibility to ear infections was increased due to the inhalation of siliceous muscovite mica dust. In its notification, Hercules stated that its decision to submit this information to EPA under Section 8(e) of TSCA was based on 1) the possible sequelae of ear infections leading to serious impairment of normal activities, 2) the widespread environmental occurrence of mica dust, and 3) the concurrence by two doctors that exposure to mica dust resulted in the employee's ear infections.

In its TSCA Section 8(e) submission, Hercules reported that it reviewed the available toxicological literature, including the supplier's Material Safety Data Sheet (MSDS), and did not locate any information that links mica dust exposure and ear infections. In addition, Hercules stated that although the affected employee has been exposed to mica dust only on an intermittent basis in the workplace, the employee is "now wearing a respirator during his worktime when he might be exposed to mica dust."

Submission Evaluation

The information provided to the Agency by Hercules does indicate that the affected employee's ear infections are the result of or are at least exacerbated by the employee's exposure to mica dust in the workplace. Hercules should be asked to keep EPA apprised of any further significant developments regarding this matter.

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Current Production and Use

In its TSCA Section 8(e) submission, Hercules reported that it processes mica as that term is defined in TSCA Section 3(10)(B). According to secondary literature sources, mica can be obtained from natural sources (muscovite, phlogopite, and pegmatite) as well as from synthetic routes (i.e., single mica crystals can be "grown" by an electrothermal process). Synthetic or naturally occurring micas are used in a variety of applications including a number of electrical and building applications (e.g., electrical equipment; vacuum tubes; incandescent lights; lubricants; dusting agents; exterior paint filler; roofing and insulation materials; wallboard/wallpaper cement). Also, mica is reportedly used in cosmetics, drilling muds, and rubber products.

Comments/Recommendations

Hercules reported that the company is re-analyzing the air in the affected employee's work area and will forward the results to the Agency.

It is not completely clear that the information provided by Hercules is of the type required for submission to the Agency under Section 8(e), the substantial risk information reporting provision of TSCA. It is quite probable, on the other hand, that the subject information is of the type required to be maintained by the company under Section 8(c), the 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 involving significant adverse reactions in workers be maintained for 30 years and that other recordable allegations be kept for 5 years. It should be noted that EPA is empowered to both inspect and require submission of Section 8(c) records and has done so on a number of occasions to date.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask Hercules to ensure that the Agency is apprised of any further developments concerning the reported adverse effects.

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

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: OCT 3 1986

SUBJECT: Status Report* 8EHQ-0986-0633 S Approved: James F. Darr for Frank D. Kover 10/3/86

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

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 the submitter to substantiate this TSCA CBI claim. In its submission, Du Pont reported non-confidentially that 1) the tested chemical is a haloalkyl substituted cyclic ether, and 2) the chemical was the subject of a Premanufacture Notification (PMN 85-367) submitted to EPA under Section 5 of TSCA. According to EPA's public file for PMN 85-367, the Agency has issued a TSCA Section 5(e) "Consent Order" for the haloalkyl substituted cyclic ethers cited in PMN 85-367, PMN 85-368 and PMN 85-369.

Submission Description

Under TSCA Section 8(e), E. I. Du Pont de Nemours & Company, Inc. provided the following information with regard to the conduct and preliminary results from a 2-week inhalation study of a haloalkyl substituted cyclic ether in male rats:

> "Groups of 25 male rats were exposed by inhalation to concentrations of the haloalkyl substituted cyclic ether of 0, 10, 50 or 250 ppm for six hours a day, five days a week. The concentrations selected for this repeated exposure study were lower than those that would have been selected normally for a material with a 4-hour lethal concentration of 4300 ppm because preliminary work indicated that the rats would probably not survive repeated exposure to higher concentrations. The planned exposure period was two weeks followed by a 14-day recovery period. In each exposure group [(25 rats/group)], 10 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.

per group were designated for toxicological assessment; the other 15 rats were used to assess effects on motor activity. Following six exposures to 250 ppm, severe losses in body weight, clinical signs of toxicity and mortality were observed and exposures at this level were discontinued. Rats exposed to 50 and 250 ppm had significantly depressed testes weights immediately following the last exposure and at the end of the recovery period. Microscopic examination revealed degeneration of the germinal cells in the testes and epididymides in rats from all exposure groups. The incidence and severity of the lesions were dose-dependent. These lesions were still present after the 14-day recovery period, although some evidence of regeneration was observed. No significant effects on motor activity were observed except for reduced activity noted on the day after termination of exposures in rats exposed to 250 ppm."

In its Section 8(e) submission, Du Pont reported also that 1) "an additional . . . inhalation study will be conducted using male and female rats to better define the toxic effects on the reproductive system" and 2) "exposure concentrations will overlap the 10 ppm level used in the present [2-week inhalation] study."

Submission Evaluation

In view of the fact that the Agency issued a TSCA Section 5(e) Consent Order covering the tested chemical, copies of this TSCA Section 8(e) notice were immediately delivered by the Chemical Screening Branch/ECAD/OTS to the Premanufacture Notice Management Branch/CCD/OTS for review and disposition.

Current Production and Use

According to the public file copy of PMN 85-367, this haloalkyl substituted cyclic ether is used as an intermediate and a solvent. In its Section 8(e) submission, Du Pont stated that the chemical "is currently employed as a research and development material and is used captively within Du Pont, thus there are few employees working with this material." In addition, Du Pont provided the following information regarding the potential for worker exposure to this haloalkyl substituted cyclic ether:

"The haloalkyl substituted cyclic ether has been treated by Du Pont as a no-contact chemical and therefore respiratory protection and other protective equipment is employed in all manufacturing operations where there is a potential for exposure. Industrial hygiene data [that have been] obtained at the facility where this chemical is made indicate that in most operations sampled, the chemical is non-detectable (detection limit of 0.5 ppm) but occasional peaks of 2-3 ppm have been observed. Workers have not been exposed to these concentrations since they wear airline respirators in the area where

these concentrations have been measured. Du Pont plans to continue its practice of treating this chemical as a non-contact chemical until more definitive toxicologic information is available."

Comments/Recommendations

In its Section 8(e) submission, Du Pont stated that the company plans to notify all employees who work with the tested chemical substance about the reported toxicologic findings. In addition, Du Pont stated that copies of the final report from the current 2-week study, as well as the interim and final reports from the planned follow-up studies, would be sent to EPA as soon as the reports become available.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask Du Pont to ensure that EPA receives complete copies of the final reports (including the actual experimental protocols, results of gross and histopathologic examinations, results of statistical analyses, etc.) from the current 2-week study and the planned follow-up studies on this haloalkyl substituted cyclic ether.

   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 Du Pont to describe the nature and results, if available, of all studies (other than those studies submitted already to EPA) 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 this haloalkyl substituted cyclic ether.

b) As in the case of the initial Section 8(e) notice, the Chemical Screening Branch will immediately send all of the reported information to the Premanufacture Notice Management Branch/CCD for review and disposition.

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 PNMB/CCD/OTS. In addition, copies of this status report will be provided to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: OCT 14 1986

SUBJECT: Status Report* 8EHQ-0986-0634
8EHQ-1086-0634 SUPP.

Approved: 10/16/86

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 Hoechst Corporation submitted an English translation of a letter (received recently by the company from Hoechst AG in Germany) regarding new epidemiological findings of bladder cancer among workers exposed chronically to 4-chloro-2-methyl aniline (CAS No. 95-69-2). The following excerpts are from the submitted translation of the letter received by American Hoechst:

> "During the last year, [Hoechst AG] had undertaken and published a retrospective mortality study as to the potential causation of cancer of the bladder by 4-chloro-2-methyl aniline. Within the framework of this study, which had a data collection closing date of December 31, 1982, there was no indication of respective malignant neoplastic activity. However, after the closing date, [Hoechst AG] learned of five cases of bladder cancer within the [epidemiologic] study cohort. One person of the five affected has died in the meantime.
>
> "In consideration of the cause/effect relationship in the above mentioned cases, [Hoechst AG] cannot any more exclude the possibility that 4-chloro-2-methyl aniline has contributed to the above findings."

In its Section 8(e) submission, American Hoechst also provided a copy of the company's 4-chloro-2-methyl aniline Material Safety Data Sheet (MSDS) as well as additional information regarding the importation volumes and uses of the chemical.

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Submission Evaluation

An EPA evaluation of the overall significance of the reported epidemiologic findings should be possible upon EPA's receipt of more in-depth information regarding the conduct and results of the performed study.

It is important to note that in 1978, the International Agency for Research on Cancer (IARC) published a review of available data on 4-chloro-2-methyl aniline (IARC Monograph; Volume 16; pages 277-285). In this 1978 review, IARC stated that the only data available to the workgroup at that time was from a 1972 abstract of results of a lifetime feeding study of of 4-chloro-2-methyl aniline hydrochloride in male and female mice. According to IARC, although this particular abstract stated that 4-chloro-2-methyl aniline hydrochloride induced 40 haemangiosarcomas in various organs in 82 mice (no tumors were reportedly found in control mice), the summary nature of the abstract (no further information concerning the study was available to IARC at that time) did not allow for an evaluation of the carcinogenicity of the chemical. IARC stated further in its 1978 Monograph on 4-chloro-2-methyl aniline hydrochloride that insufficient human data were available at that time to allow the IARC workgroup to evaluate the potential carcinogenicity of the chemical. In 1983, however, IARC published (IARC Monograph; Volume 30; pages 61-72) its review of available data on the pesticide, chlordimeform. In that 1983 Monograph, IARC noted that 4-chloro-2-methyl aniline is an intermediate in the production of, an impurity (as the hydrochloride salt) in, and a metabolite of chlordimeform, which is an insecticide, acaricide and ovicide. IARC reported also that the results of chronic feeding studies in mice and rats conducted at the National Cancer Institute (NCI) showed that 4-chloro-2-methyl aniline hydrochloride induced haemangiosarcomas in two strains of mice; the NCI feeding studies conducted in two strains of rats were negative although IARC did note certain limitations in the design of those studies. In the 1983 Monograph on chlordimeform, IARC stated further that the ability of 4-chloro-2-methyl aniline to cause urinary tract injury in humans was known and pointed to the results of a 1933 study of 4-chloro-2-methyl aniline-exposed workers in an English chemical factory. With regard to this 1933 study, IARC stated that the investigator had detected 11 workers with urinary tract problems and that the follow-up examination (3 years later) of 3 of the affected workers showed that 1 of those 3 workers had developed a bladder carcinoma.

Current Production and Use

A review of the production range (includes importation volumes) statistics for 4-chloro-2-methyl aniline (CAS No. 95-69-2), which is listed in the initial TSCA Chemical Substance Inventory, shows that 10,000 to 100,000 pounds of this chemical 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) who reported 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 TSCA Inventory Reporting Regulations (40 CFR 710).

In its submission, the American Hoechst Corporation stated that it imports 4-chloro-2-methyl aniline from Hoechst AG and resells approximately 15,000 to 30,000 pounds/year for use in pigment manufacture. As stated previously, 4-chloro-2-methyl aniline is used also in the production of the pesticide, chlordimeform.

With regard to product handling, American Hoechst reported that 4-chloro-2-methyl aniline is imported in 55 gallon drums with bungs and because of the chemical's low melting point (26.8°C), filling and emptying of the drums is performed above the melting point with the product in liquid form.

Comments/Recommendations

It should be noted that American Hoechst has updated the "Health Information" section of the company's 4-chloro-2-methyl aniline MSDS to include the following information:

> "Based on data from a recent Hoechst AG epidemiological study, newly discovered cases of human bladder cancer may be linked to chronic exposure to 4-chloro-2-methyl aniline."

It should be noted also that based on the new epidemiological findings, Hoechst AG has 1) decided to immediately cease all 4-chloro-2-methyl aniline production, shipping and marketing, and 2) communicated the new findings to several European commissions.

In a letter dated September 29, 1986 (8EHQ-1086-0634 Supplement), American Hoechst provided a copy of a letter by which the company informed its customers about the new epidemiological findings. In that letter, American Hoechst also told its customers that due to the Hoechst AG decision to cease the production, marketing and shipping of 4-chloro-2-methyl aniline, American Hoechst would no longer be able to supply the chemical.

a) The Chemical Screening Branch will ask American Hoechst to ensure that EPA receives full copies of all documents (including correspondence, reports, transcripts, etc.) in the company's possession now or that the company obtains in the future that relate to the epidemiologic findings cited in the company's Section 8(e) submission.

   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, American Hoechst will be asked to describe the nature and results, if available, from all studies (other than those published in the open

scientific literature or submitted already to EPA) about which American Hoechst is aware or that the company has conducted, is conducting, or is planning to conduct to determine the toxicity of or the exposure to 4-chloro-2-methyl aniline. American Hoechst will be asked also to describe the actions that the company has taken or plans to take 1) to notify its own workers about the reported epidemiological findings, and 2) to reduce or eliminate exposure to 4-chloro-2-methyl aniline that remains in the company's current inventory.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of 4-chloro-2-methyl aniline.

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. Copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: NOV 7 1986

SUBJECT: Status Report* 8EHQ-1086-0635 Approved: 11/7/86

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) notice, the Union Carbide Corporation stated that "UCON 50-HB Polyethers are homologous members of a series of butanol-initiated co-polymers of 50% ethylene oxide and 50% propylene oxide . . .[and] differ only in degrees of polymerization as indicated by the final numbers which reference their viscosities in SUS (Saybolt Universal Seconds)."

Submission Description

The Union Carbide Corporation submitted the following summarized information concerning the conduct and preliminary results of a 14-week aerosol inhalation study of UCON Lubricant 50-HB-5100 (CAS No. 9038-95-3) in rats:

> "The effects of inhalation of aerosols of UCON Lubricant 50-HB-5100 were investigated in Fischer 344 rats. Four groups of 30 animals of each sex were exposed to aerosol concentrations of 0, 0.3, 1.1 or 5.2 mg/m^3 of the test material. The aerosols were generated from dilute (5%) water solutions of the UCON fluid, and the particle sizes were in the respirable range (1.6 microns with a geometric standard deviation of 1.6 microns). Animals were exposed for 6 hours a day, 5 days a week for 14 weeks. At the end of this exposure regimen, animals in each group were sacrificed and examined to determine potential toxic effects of the exposure. Additional animals in each group were maintained without further exposure for an additional 5 week recovery interval after which they were sacrificed and examined.

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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 principle and essentially only effects noted were on the lungs of the [UCON Lubricant 50-HB-5100-]exposed animals. The findings included increased lung weights in the 1.1 and 5.2 mg/m^3 exposure groups, grey and tan foci on the surface of lungs from animals of all exposure groups, and microscopic evidence of lung tissue injury in all exposure groups, described as hemorrhage, alveolar histiocytosis, interstitial pneumonia and focal or multifocal fibrosis of the pulmonary interstitium.

"Both absolute and relative (lung weight as a percent of body weight) lung weights were increased in male and female rats exposed to 5.2 mg/m^3 and in females exposed to 1.1 mg/m^3, while relative lung weight was increased in males exposed to 1.1 mg/m^3. There was a slight, but not statistically significant, increase in lung weights of males and females exposed to 0.3 mg/m^3. The incidence of the macroscopic lesions in the lungs increased with increasing exposure concentrations as did the incidence and severity of the histopathological lesions.

"The lung weights of male and female rats in the 5.2 mg/m^3 recovery group and males in the 1.1 mg/m^3 recovery group remained statistically significantly heavier than those of control recovery animals. In addition, mean lung weights of the 0.3 mg/m^3 recovery group, and those of females in the 1.1 mg/m^3 recovery group were slightly but not significantly greater than those of the control group. The magnitude of increased lung weight in the recovery animals was less than that seen in animals sacrificed immediately after the 14 weeks of [inhalation] exposure, demonstrating a degree of recovery possibly from associated pulmonary edema. There was some evidence for repair of the lung injury upon recovery, particularly with respect to alveolar histiocytosis and hemorrhage. Generally, the pulmonary fibrosis seen upon microscopic examination of lung tissue in this study is considered to be a permanent type of injury.

"The injury to lung tissue observed in this 14-week subchronic study is believed to be a natural progression of the injury noted in two short-term repeated (9 exposures in 11 days) studies which have been previously submitted to the Agency. [These short-term inhalation studies were provided to EPA on "For Your Information" (FYI) basis, FYI-OTS-0784-0335 et seq.] The injury observed in the present [14-week inhalation] study was of a slight, to at most, moderate degree of severity, even at the highest exposure concentration employed, 5 mg/m^3. The impairment of pulmonary function from this degree of injury would likely be minimal if detectable at all. Although the test data showed minimal injury, continued exposure beyond 14 weeks might lead to impairment of pulmonary function."

In a supplemental FYI submission (FYI-OTS-1084-0335 Supplement Seq. C), the Union Carbide Corporation reported that "extensive testing by other routes of exposure (swallowing, skin absorption, etc.) have demonstrated [that] these copolymeric materials do not constitute a health hazard by these routes of exposure." In addition, Union Carbide stated that no adverse human health effects have been observed during manufacture or use of these copolymers.

Submission Evaluation

In order for EPA to evaluate the overall significance of the observed lung toxicity, Union Carbide should be asked to ensure that the Agency receives a complete copy of the final report (including the actual experimental protocol, results of gross and histopathologic examinations, results of statistical analyses, etc.) from the 14-week inhalation 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 CAS No. 9038-95-3, which is listed on the initial TSCA Chemical Substance Inventory, has shown that 2 million to 20 million pounds 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 persons reporting for the 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 E. I. Du Pont de Nemours & Company, Inc. (the submitter of the initial FYI notice (FYI-OTS-0784-0335 Seq. A) on UCON Lubricant 50-HB-5100), this chemical is a component in a textile finish formulation.

Comments/Recommendations

In its Section 8(e) notice, Union Carbide stated that the company is 1) notifying its employees and customers about the reported findings, and 2) revising the UCON Lubricant 50-HB-5100 label and Material Safety Data Sheet to reflect the reported findings.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the Union Carbide Corporation to ensure that the Agency 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 the 14-week inhalation 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, Union Carbide will be requested to describe nature and results, if available, of all studies (other than those published 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 or the exposure to UCON Lubricant 50-HB-5100.

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

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. Copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: NOV 7 1986

SUBJECT: Status Report* 8EHQ-1086-0636 S Approved: 11/7/86

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

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

Note

PPG Industries, Inc. claimed the exact identities of the tested chemical substances to be TSCA Confidential Business Information (TSCA CBI). In the non-CBI version of the submission, PPG provided the following generic names for the chemicals: 1) chloride capped alcohol ethoxylates (BSF-02), and 2) quaternary ammonium chloride (BSC-57). Staff of the Information Management Division (IMD/OTS) will ask PPG to substantiate the company's CBI claims.

Submission Description

PPG Industries, Inc. submitted summarized preliminary findings from acute eye irritation studies of two research and development (R&D) chemicals (BSF-02 and BSC-57 (see Note above)) in rabbits. According to PPG, these R&D materials were found to be severe eye irritants. In addition, PPG reported that BSF-02 and BSC-57 produced corneal opacity in 1/6 and 6/6 rabbits, respectively, at day 21 following eye application.

Submission Evaluation

In order for the Agency to evaluate the overall significance of the reported eye toxicity, PPG should be asked to submit complete copies of the final reports from the acute eye irritation studies cited in the company's Section 8(e) notice.

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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 PPG's TSCA CBI claims, no information concerning the TSCA Chemical Substance Inventory status of the tested materials will appear in this report.

In its submission, PPG provided the following information with regard to the potential for exposure to the chemicals:

> "The extent of risk was and is currently limited by the fact that only developmental amounts . . . are available and the synthesis has been performed on site of the submitter by technically qualified staff. The evaluation of the materials has been conducted by a limited number of personnel outside of PPG who are normally involved in R&D evaluation. Personnel with potential for exposure are protected by use of protective facilities, equipment and clothing, e.g., laboratory hoods, impervious gloves, coveralls or lab coats, and eye protective equipment. The most likely route of exposure would be dermal. . ., with inhalation a less likely route because of the physical properties of the materials, particularly . . . [the] low vapor pressure."

Comments/Recommendations

In its Section 8(e) submission, PPG reported that the company's "safety procedures call for establishing and updating whatever guidelines for safe handling are appropriate as data on the potential toxicity of new materials are received." In addition, PPG stated that "all personnel with potential exposure to the materials will be informed of the findings and guidelines for handling." Finally, PPG reported that "the Experimental Product Data Sheets will be modified to include a statement about the severe eye irritation."

Based on EPA's initial evaluation of the summarized information presented in PPG's submission, it is not entirely clear that the provided information is of the type required for reporting to EPA under Section 8(e), the "substantial risk" information reporting provision of TSCA. As further information is received from PPG concerning the performed studies, PPG's rationale for submitting the findings to EPA under Section 8(e) may become more apparent.

a) The Chemical Screening Branch (CSB/ECAD) will ask PPG to submit complete copies of the final reports (including the actual experimental protocols, results of gross and histopathological examinations, results of statistical analyses, etc.) from the acute eye irritation 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, PPG will be requested to describe the nature and results, if available, from all studies (other than those published in the scientific literature or those submitted already to EPA) 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 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 tested chemicals.

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: NOV 14 1986

SUBJECT: Status Report* 8EHQ-1086-0637 Approved: 11/17/86

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 Chevron Chemical Company submitted the following information concerning the conduct and preliminary findings from a 28-day dermal application study of trans-1-chloro-3-oxyaminopropene hydrochloride (CAS No. 82244-86-8) in rats:

> "Preliminary evaluation of the data from a 28-day dermal toxicity study of this substance in male and female rats indicates that this substance produced methemoglobinemia, macrocytic anemia (characterized by decreased erythrocyte count, hemoglobin, and mean cell hemoglobin concentration and increased reticulocyte count, mean cell hemoglobin and mean cell volume) and histopathological changes in the spleen (described as dilated sinusoidal spaces packed with erythrocytes) in a dose-related pattern in both sexes. . . . . Animals were treated dermally six hours per day, seven days per week, for four weeks with a 1.0 ml/kg solution of 5.0 mg/kg, 20.0 mg/kg or 80.0 mg/kg of . . .an aqueous solution containing 47.4% trans-1-chloro-3-oxyaminopropene hydrochloride. Compound related effects were noted at all dose levels."

In its submission, Chevron stated that trans-1-chloro-3-oxyaminopropene hydrochloride is a research and development compound that is an isolated intermediate used in the manufacture of a candidate pesticide. Chevron stated also that the manufacture of the candidate pesticide involves reacting the isolated intermediate with the trione that was the subject of a previous Section 8(e) submission (8EHQ-0186-0584 et seq.).

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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

Notwithstanding the brief and preliminary nature of the reported findings, the observed adverse effects do appear to be related to dermal application of the test material. The observed adverse effects with the most serious toxicological consequences are the formation of methemoglobinemia and macrocytic anemia.

The formation of methemoglobinemia should be viewed in light of the fact that the test material is a derivative of hydroxylamine, a chemical substance known to induce methemoglobinemia in animals and man. It is important to note that sufficient amounts of the test chemical were absorbed through the skin to produce a dose-related and statistically significant methemoglobinemia response. In addition, it should be noted that humans have lower levels of the enzyme (methemoglobin reductase) that reduces methemoglobin. It is likely, therefore, that humans would be more susceptible than rats to methemoglobinemia induced by the test material. Further, the adverse effects on the spleen (i.e., sinusoidal dilatation and increase in absolute and relative spleen weight) are most likely secondary to methemoglobinemia and due to the sequestration of methemoglobin-containing red blood cells in the spleen. Finally, if exposure to the test material had been continued for a longer period of time or if higher doses were used, both major structural/functional spleen damage might occur.

Another adverse effect of concern is the induction of macrocytic anemia, especially in combination with methemoglobinemia. In the absence of detailed information on histopathology, particularly on the bone marrow and liver, an explanation of this effect is speculative. If the test compound causes liver damage, the red cell membrane may take up excess cholesterol to increase the membrane surface area and may "spread out" upon smearing to form what appears to be a thin macrocyte; it was not clear from the submitted information whether or not serum cholesterol levels were determined.

Current Production and Use

According to Chevron, the company's "current development plans call for the submission of a [TSCA Section 5] premanufacturing notification and subsequent importation of . . . [trans-1-chloro-3-oxyaminopropene hydrochloride] and the trione as well during 1987 for pilot plant manufacture of the pesticide." In addition, Chevron reported that "it is known that if . . . [trans-1-chloro-3-oxyaminopropene hydrochloride] appears in the final product at all, it will be at less than 0.1% (w/w)."

Comments/Recommendations

Chevron reported that the Material Safety Data Sheet for trans-1-chloro-3-oxyaminopropene hydrochloride was revised to reflect the reported effects and sent to Chevron employees and potential toll producers.

a) The Chemical Screening Branch will ask Chevron 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 28-day skin application 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 information, Chevron will be asked to describe the nature and results, if available, of all other studies that Chevron has conducted, is conducting, or is planning to conduct to determine the toxicity of or the exposure to trans-1-chloro-3-oxyaminopropene hydrochloride.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment of trans-1-chloro-3-oxyaminopropene hydrochloride at the present time.

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; copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: NOV 13 1986

SUBJECT: Status Report* 8EHQ-1086-0638 Approved: 11/13/86

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 AZS Corporation submitted final reports from several acute in vivo studies of Coronate EH (hexamethylene diisocyanate trimer; CAS No. 28182-81-2). According to the submitted information, the chemical is moderately irritating to rabbit skin and eyes, is not corrosive to rabbit skin, has an oral LD50 in excess of 5.0 g/kg in rats, has a 1-hour median lethal inhalation concentration of approximately 18.5 mg/l in rats, and has a dermal LD50 greater than 2.0 g/kg in rats.

Submission Evaluation

Immediately upon receipt of this Section 8(e) submission, the Chemical Screening Branch (CSB/ECAD/OTS) delivered copies of the notice to the Risk Analysis Branch (RAB/ECAD/OTS) for inclusion in the ongoing review of available data on diisocyanates.

Current Production and Use

A review of the production range (includes importation volumes) statistics for CAS No. 28182-81-2, which is listed in the initial TSCA Inventory, has shown that no 1977 manufacture or importation was reported or that all manufacture/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 data submitted for the TSCA Inventory, including the production range data, are subject to the limitations contained in the TSCA Inventory Reporting Regulations (40 CFR 710).

AZS did not submit any information regarding current production, importation, or use(s) of Coronate EH, nor was such information located in the secondary literature sources consulted by EPA.

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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

It has been EPA's longstanding position that certain types of acute animal toxicity data may not warrant submission to EPA under Section 8(e), the substantial risk information reporting provision of TSCA. The basis for EPA's position in this matter is as follows:

> 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 [human] health or the environment is a risk of considerable concern because of (a) the seriousness of the [adverse] effect . . . and (b) the fact or probability of its [(i.e., the effect's)] occurrence."
>
> With regard to the seriousness of the effect, Part V of the Section 8(e) policy statement explains that EPA considers the 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 [tested] chemical substance or mixture can produce cancer, mutation, birth defects, or toxic effects resulting in death, or serious or prolonged incapacitation." Information with respect to these types of effects can be obtained directly or inferred from studies of a designed or undesigned nature (see Part VI of the TSCA Section 8(e) policy statement).
>
> With regard to the criterion concerning the "fact or probability" of the occurrence of such serious effects, Part V as well as other portions of the Section 8(e) policy statement explain that certain types of health effects are so serious that relatively little or, in some cases, no weight should be given to the subject chemical's exposure in determining whether a risk is substantial. In the case of cancer, for example, the mere fact that the implicated chemical or mixture is in commerce would constitute sufficient evidence that there is potential exposure to the substance(s).
>
> EPA's response to Comment 14 in Appendix B of the TSCA Section 8(e) policy statement provides guidance with regard to the 8(e)-reportability of results obtained from acute in vivo toxicity range finding studies (e.g., LD50 determinations, skin/eye irritation studies, etc.). In its response, EPA stated that unknown effects that occur and are observed/determined during such routine tests may have to be reported under Section 8(e) if the effects are serious and meet the reporting criteria set forth in Part V of the Section 8(e) policy statement. Thus, when evaluating the results of acute animal tests for possible submission to EPA under Section 8(e), EPA

believes that a subject company should consider such factors as lethal dose, pH of the test material, the route(s) of administration, occurrence of unexpected serious effects (which could be determined via "cage-side" observation or during necropsy), and the extent and pattern of the actual or potential exposure to the tested material(s). In general, when evaluating such information for 8(e) reporting, the following factors should be kept in mind: the greater the acute toxicity, the less heavily one should weigh the actual/potential exposure to the test material(s) and vice versa.

In light of the preceding discussion, it does not appear that the acute toxicity information, as presented in the AZS Corporation's submission, warranted reporting under Section 8(e) of TSCA. In making this initial determination on Section 8(e)-reportability, however, it must be understood that the Agency is not aware of any additional pertinent information that was available to and/or considered by AZS in deciding to report under Section 8(e).

a) In view of the Agency's initial position with regard to TSCA Section 8(e)-reportability, the Chemical Screening Branch will request the AZS Corporation to provide its rationale (in light of the discussion at the beginning of the Comments/Recommendations section of this status report) as to why the the submitted information was believed to have warranted reporting under Section 8(e).

   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 AZS Corporation 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 Coronate EH. In addition, AZS will be requested to describe the nature and results, if available, from all studies (other than those reported 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 or the exposure to Coronate EH.

b) As in the case of the initial TSCA Section 8(e) notice, the Chemical Screening Branch will transmit copies of all further information received on Coronate EH to the Risk Analysis Branch/ECAD for inclusion in the ongoing review of diisocyanates.

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 RAB/ECAD/OTS; copies of this report will be sent also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: NOV 17 1986

SUBJECT: Status Report* 8EHQ-1086-0639 S Approved: 11/17/86

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

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

Note

PPG Industries, Inc. has claimed the exact identity and use of the tested chemical substance to be TSCA Confidential Business Information (TSCA CBI); the Information Management Division (IMD/OTS) will request the submitting company to substantiate these TSCA CBI claims. In the non-confidential version of the submission, PPG reported that the chemical is a chlorinated acid.

Submission Description

PPG Industries, Inc. submitted preliminary results of several acute in vivo toxicity studies of a chlorinated acid. According to PPG, although this chlorinated acid was found to have an oral LD50 of approximately 1 g/kg (male/female rats), the chemical was found to be corrosive to rabbit skin and to have a 4-hour inhalation LC50 of .39 mg/l (male/female rats) and a 1-hour inhalation LC50 of approximately 1 mg/l (male/female rats). In addition, it should be noted that this chlorinated acid was reported in PPG's Section 8(e) submission to be similar in structure to a chemical substance found to cause cancer in laboratory animals.

Submission Evaluation

In order for EPA to evaluate the overall significance of the reported toxicologic findings, PPG should be asked to provide to EPA full copies of the final reports from all studies 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 PPG's TSCA CBI claims, no information concerning the TSCA Chemical Substance Inventory status or use(s) of the tested chemical will appear in this report.

In the non-confidential version of PPG's submission, the company stated that 1) this chlorinated acid has a vapor pressure of 11.2 mm Hg at 20°C, and 2) the following production procedures for the chemical are in place at the present time:

> "NIOSH approved category 19C air supplied positive pressure respirator[s are] required for persons who might be exposed to this product during manufacturing, processing and use.
>
> "Any person who may be reasonably expected to be exposed dermally to this product are required to wear a) impervious gloves [and] b) protective clothing.
>
> "The product is labeled: **Warning - avoid all contact. A chemical similar in structure has been found to cause cancer in laboratory animals. The required use of respirators, protective clothing and impervious gloves will help protect you.**
>
> "All persons who work with this product are properly trained. Persons with possible exposure to this material are PPG employees engaged in manufacture and employees of the contract manufacturer.
>
> "Distribution of the product is limited to the contract manufacturer."

Comments/Recommendations

In its Section 8(e) submission, PPG reported that the company's "safety procedures call for establishing and updating guidelines for safe handling as appropriate based on the new data." In addition, PPG stated that the company will 1) notify all persons potentially exposed to the tested chemical about the submitted findings, 2) update the product label and Material Safety Data Sheet (MSDS) to reflect the reported toxicologic findings, and 3) ensure that all shipping containers comply with U.S. Department of Transportation (DOT) requirements.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask PPG to submit to EPA full copies of the final reports, including the actual experimental protocols, results of gross and histopathologic examinations, results of any statistical analyses, 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 information, PPG will be requested to describe the nature and results, if available, from all studies (other than those reported already to the Agency or those published in the open scientific literature) about which PPG is aware or that PPG has conducted, is conducting, or is planning to conduct to determine the toxicity of or the exposure to this chlorinated acid.

b) The Chemical Screening Branch will ensure that all of the reported information is forwarded immediately to appropriate offices within OTS to determine the need for further assessment of this chlorinated acid.

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. Copies of this report will be provided also to the TSCA Assistance Office (TAO/OTS/OPTS) for further distribution.

DATE: NOV 19 1986

SUBJECT: Status Report* 8EHQ-1086-0640 S Approved: 11/19/86

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 as TSCA Confidential Business Information (CBI). The Information Management Division will request the submitting company to substantiate this claim.

Submission Description

In its TSCA Section 8(e) submission, the company reported that "diethylethoxymethyleneoxalacetate, when placed in one eye of each of three rabbits at a dose of 0.1 cc, caused persistent severe corneal opacity, severe iritis, and severe conjunctivitis." In addition, the submitting company reported that the tested material was a mixture of two isomeric forms with the following CAS Registry Numbers: 55130-49-9 and 55130-39-7. According to the company, CAS Number 52942-64-0 has been "assigned to this compound without reference to isomeric form." Finally, the submitter reported that "the proportions of the two isomers in the mixture have not been determined."

Submission Evaluation

In order for EPA to evaluate the overall significance of the reported findings, the submitting company should be requested to provide complete copies of the final report from the cited rabbit eye irritation study.

Current Production and Use

None of the CAS Numbers provided by the submitting company were located in the computerized version of the non-confidential TSCA Chemical Substance Inventory. According to the submitting company, the tested material is a "non-isolated intermediate in the manufacture of a pesticide that is in the research and development stage." The submitting company reported also that "less than 750 kilograms of the intermediate have been manufactured."

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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 submitting company stated that company personnel who may work with this chemical mixture have been notified about the reported toxicologic findings. In addition, the submitter stated that the reported findings will be reflected in the product manufacturing instructions. Finally, the submitting company stated that "eye protection will be provided to workers, if it becomes necessary to isolate any more . . . [diethylethoxymethyleneoxalacetate]."

Based on a preliminary review of the provided information, it is not clear that the information warranted submission to EPA under Section 8(e), the "substantial risk" information reporting provision of TSCA. The submitting company's rationale for reporting the information under Section 8(e) may become apparent upon EPA's receipt of a complete copy of the final report from the performed study.

a) The Chemical Screening Branch will ask the submitting company to provide to EPA a complete copy of the final report (including the actual experimental protocol, results of gross/histopathological examinations, pH of the tested material (if known), etc.) from the acute eye irritation study that was cited in the company's TSCA Section 8(e) notification.

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

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. Copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: DEC 3 1986

SUBJECT: Status Report* 8EHQ-1086-0641 Approved: 12/4/86
8EHQ-1186-0641 SUPP.

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

In its initial TSCA Section 8(e) submission, the Union Carbide Corporation provided a copy of an abstract entitled "The Neurological Manifestations of Chronic Ethylene Oxide Exposure" that had appeared in the July 1986 issue of the Annals of Neurology (Vol. 20, No. 1, pg. 136, Abstract No. P51). The following excerpt is from the submitted abstract:

> ". . .[The investigators, G. Ristow and D. Cornelius of Michigan State University, studied] 14 persons chronically exposed to . . .[ethylene oxide (EO)] over a period of 18 months. Sensory symptoms were present in 93% (13 of 14), motor symptoms were present in 79% (11 of 14), and in addition, disturbances in cognitive function were present in 79% (11 of 14). The cognitive defects included memory disturbance, mood change, and language and speech disturbance. Additional symptoms . . . [reported] included seizures (29%, 4 of 14) and headache (43%, 6 of 14) . . . .[The performed study included] 9 women and 5 men with ages ranging from 18 to 55 years. Follow-up after 12 to 18 months revealed marked improvement in motor function and sensory symptoms and significant improvement in mood and memory, although some patients continue to complain of cognitive problems and paresthesias. . . .[The investigators believe] there is significant risk for the development of neurological symptoms associated with both intimate and prolonged casual contact with EO."

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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 supplemental notice, Union Carbide reported that the results of the study were "presented by the authors as a Poster Presentation at a recent meeting of the American Neurologic Association." In the supplemental submission, Union Carbide provided a copy of the manuscript which (according to Union Carbide) contains the text of the authors' presentation. The submitted manuscript contains the following background information:

> "At a small town bulk medical supply sterilization plant, two large industrial sterilizers for hospital material were in frequent use during the period in which several workers were exposed. At this plant, the sterilant used was 12% [ethylene oxide (ETO)] mixed with 88% fluorocarbon (FREON) and the sterilizers operated at about 300,000 parts per million [(ppm)] during sterilization. At the time employees became symptomatic, there was no dedicated external exhaust equipment for the sterilizers. The sterilizer exhaust fumes had to pass into plant air and the fumes were ventilated through adjacent preparation and sewing areas where non-sterilizer workers were stationed. In addition, the standard three air-wash procedure after sterilization had often been reduced to two or one air-washes and the sterilization equipment was frequently in operation day and night. Material to be sterilized was loaded and unloaded into the sterilizers on wooden pallets which were later stacked and stored in the shipping area, presumably saturated with ETO residue. The sterilizer operators did not wear protective clothing or equipment (e.g., masks, gloves, or self-contained ventilation equipment) and were not cautioned about potential hazards of the gas.
>
> "Persons loading and unloading the sterilizers frequently reported smelling the characteristic odor of the gas, indicating a level of above 700 ppm and could at all times feel a slippery, oily residue on handled materials which had been sterilized. Packers in the preparation area at times had to repack items for resterilization and reported occasional odor and feeling of residue. In mid-1984, the plant resumed the three air-wash procedure, installed a dedicated ventilation system at the sterilizers and instructed sterilizer operators not to enter the chambers for loading and unloading. Other additional safety precautions were instituted at this time.
>
> "[The study involved] nine males and five females who were exposed and symptomatic. The age range was 18 to 55 years. None had a history of alcohol abuse or diabetes. None were taking prescription medications and none were exposed to other toxins. During the time of their employment, none of them described any episodes of <u>acute</u> ETO intoxication. The range of employment time from hiring to the development of the first symptom was 0.4 to 8.0 years with an average in this series of 3.9 years.

"Fifteen workers were exposed to increased ambient concentrations of ETO during 1983 and early 1984. Fourteen of the 15 became symptomatic. Several of these workers had intimate contact with the gas and sterilization equipment while others worked at some distance from the sterilizers. Those in close contact included persons who loaded and unloaded the sterilizers and emptied and stacked the wooden pallets used to hold large quantities of material during sterilization. Those working at a further distance from the sterilization equipment included persons stacking and packing material to be sterilized as well as unwrapping and repacking items which required re-sterilization.

"Eleven persons who became symptomatic noticed a gradual and insidious progression of various mood change, memory and speech disturbance. Thirteen patients noted acral numbness, paresthesias and dysesthesias. Distal weakness was noted in 11 patients. In 7 patients, the symptoms led to domestic difficulties including impotence in all 5 males. A peculiar feeling of persistent fatigue occurred in 12 patients. Muscle cramps and spasms were noted in 10 patients and new and persistent headaches occurred in 6 patients. Seven patients complained of chest pain or discomfort. Four patients noted tachycardia and 6 noted visual disturbance (blurred or double vision).

"Six patients had an electroencephalogram [(EEG)] during their course of exposure, 3 of these were abnormal with the presence of nonfocal sharp activity or increased generalized slow activity. Three patients had a seizure during the period of exposure although 1 of the 3 had a history of seizures in childhood. The EEG was abnormal in 2 of these patients and normal in 1.

"Ten patients described a speech disturbance during the course of [the] symptoms, described variously as slurred or mushy speech, slow speech, problems with word substitution or word finding difficulty.

"The first patient seeking medical attention did so because of progressive difficulty with coordination of the feet. The majority of patients who were bothered by disturbances in higher cortical and cognitive function indicated that these symptoms did not diminish or change significantly over weekends, holidays or vacations and only diminished when the persons were removed from the workplace or after the sterilization procedure had been changed. Most patients were not aware that the ethylene oxide exposure might account for their symptoms of mood change, behavior change and cognitive difficulties.

"In a one year follow-up, some patients continued to complain of persistent but mild cognitive problems

including decreased concentration, poor memory, episodic blurring of vision and slurred speech. One patient continues having headaches and several of the patients most severely affected with the polyneuropathy continue to complain of pain, dysesthesias and paresthesias although the distal weakness has resolved. As of mid 1986, 10 of the patients continue to work at the same facility."

Submission Evaluation

The submitted information has been forwarded for inclusion in the Chemical Screening Branch's ongoing review of ethylene oxide. The purpose of this review is to determine the need for further OTS assessment of ethylene oxide and/or transmittal of the submitted information to other EPA Offices and/or other appropriate Federal agencies for consideration in any ongoing assessments of the potential risks posed by exposure to ethylene oxide.

Immediately upon receipt of the Union Carbide Corporation's initial and supplemental TSCA Section 8(e) notices on ethylene oxide, the Chemical Screening Branch sent copies of the notices to the Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH), the Food and Drug Administration (FDA) and to EPA's Office of Pesticide Programs. It should be noted that on June 22, 1984, OSHA promulgated (49 FR 25734) a final standard for occupational exposure to ethylene oxide. OSHA's Permissible Exposure Level (PEL) for occupational exposure to ethylene oxide was set at 1 ppm as an 8-hour Time Weighted Average (TWA).

It should be noted that the Office of Toxic Substances (OTS) has received a number of TSCA Section 8(e) and "For Your Information" notices on ethylene oxide. In addition, the Chemical Screening Branch prepared (in 1982) a Chemical Hazard Information Profile (CHIP) on ethylene oxide. EPA has also promulgated TSCA Section 8(a) and 8(d) information gathering rules on ethylene oxide.

Current Production and Use

According to Chemical & Engineering News (July 9, 1986 issue), 5.7 billion and 5.8 billion pounds of ethylene oxide were manufactured in the United States in 1984 and 1985, respectively.

Ethylene oxide is used mainly as a chemical intermediate (e.g., in the production of ethylene glycol) and as a chemosterilant/fumigant (e.g., for medical and surgical equipment and devices, packaging materials, dried foods). According to EPA's Office of Pesticide Programs (OPP/OPTS) ethylene oxide is present as the active ingredient in 38 pesticide products registered under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

Comments/Recommendations

It should be noted that a search of several publicly available computerized data bases (including those listed in 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)) did not reveal any references to the submitted study. It appears, therefore, that Union Carbide was correct (in the strictest interpretation of EPA's Section 8(e) policy statement) in submitting the information to the Agency pursuant to Section 8(e) of TSCA.

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

DATE: NOV 19 1986

SUBJECT: Status Report* 8EHQ-1086-0642 Approved: 11/19/86

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 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) submitted the following information regarding the conduct and preliminary results of a two-year inhalation study of vinyl acetate (CAS No. 108-05-4) 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 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."

In submitting these findings on behalf of the above mentioned companies (who are the primary co-sponsors of the cited chronic inhalation study), SPI stated that the provided information is "preliminary and not all tissues from all the mice in the control or the treatment groups have been reviewed." SPI stated also that the conducting laboratory, which is located in the United Kingdom, expects to complete the pathology by the end of 1986.

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Submission Evaluation

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

It should be noted that 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 in 1984, the Chemical Screening Branch prepared a Chemical Hazard Information Profile (CHIP) on vinyl acetate.

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

Thus far, 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.

a) The Chemical Screening Branch will ask SPI to ensure that copies of the status report EPA has prepared for the present TSCA Section 8(e) notice are distributed to the U.S. co-sponsors of the cited two-year inhalation study of vinyl acetate in mice. In addition, SPI will be requested to ensure that EPA receives full copies of all future interim reports as well as the final report from this chronic vinyl acetate inhalation study.

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

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.

DATE: DEC 5 1986

SUBJECT: Status Report* 8EHQ-1186-0643 Approved: 12/8/86

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 Dow Corning Corporation reported that the company recently discovered that low molecular weight nitrosamines (see TABLE 1. below) are produced and liberated during the foaming of 2 (two) Dow Corning silicone elastomer foams (Silastic® Q4-4682 Silicone Rubber and Silastic® Q4-4683 Silicone Rubber) used in applications such as foam rubber gaskets. In its Section 8(e) notice, Dow Corning stated that the company assumes that the nitrosamines form as the result of thermal decomposition of the blowing agent (Nitropore® ATA, a product of the Olin Corporation). Dow Corning also submitted a copy of the Nitropore® ATA Material Safety Data Sheet (MSDS) that states that Nitropore® ATA is a proprietary mixture identified simply as an "azotetramine derivative."

TABLE 1.	NITROSAMINES IDENTIFIED	CAS Number
	N-Nitrosodimethylamine (NDMA)	62-75-9
	N-Nitrosodiethylamine (NDEA)	55-18-5
	N-Nitrosodibutylamine (NDBA)	924-16-3
	N-Nitrosomorpholine (NMOR)	59-89-2

Dow Corning reported that its testing procedures were based on actual fabrication conditions used by a Dow Corning customer. According to Dow Corning, this customer uses curing times of 10 to 20 minutes at temperatures ranging from 275°F to 325°F. Dow Corning reported also that certain articles are cured at 392°F for 4 hours. Dow Corning reported further that the analyses involved volatiles (collected during curing) and extractables (collected via solvent extraction of cured foam). The results of Dow Corning's analyses are shown in TABLE 2. on the next page.

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TABLE 2. "RESULTS [1]

SAMPLE	CURE TEMP./TIME	VOLATILE NITROSOAMINES	EXTRACTED NITROSOAMINES
Q4-4682	275°F/10 min.	61 ng* (NDMA) 29 ng (NDEA) 12 ng (NMOR)	450 ppb** (NDMA) 85 ppb (NMOR)
Q4-4682	325°F/20 min.	3600 ng (NDMA) 790 ng (NDBA)	720 ppb (NDMA) 48 ppb (NDBA)
Q4-4682 & Flame Retardant	275°F/10 min.	32 ng (NDMA)	1100 ppb (NDMA) 110 ppb (NDBA)
Q4-4682 & Flame Retardant	325°F/10 min.	5200 ng (NDMA) 800 ng (NDBA)	450 ppb (NDMA) 46 ppb (NDBA)
Q4-4682	392°F/4 hrs.	17,600 ng (NDMA) 350 ng (NDBA)	80 ppb (NDMA)
Q4-4683	325°F/20 min.	4200 ng (NDMA) 460 ng (NDBA)	327 ppb (NDMA) 24 ppb (NMOR) 24 ppb (NDBA)
Q4-4683	392°F/4 hrs.	60,200 ng (NDMA) 1500 ng (NDMA)	18 ppb (NDMA)

*Nanograms
**Parts per billion

[1]Method of Analysis - GC-TEA (Gas Chromatography - Thermal Energy Analyzer)
- HPLC-TEA (High Pressure Liquid Chromatography - Thermal Energy Analyzer) "

Submission Evaluation

EPA's concern about human exposure to nitrosamines is well known and is based mainly on a large number of animal studies in which nitrosamine exposure by a variety of routes resulted in cancer.

It should be noted that EPA's Office of Toxic Substances (OTS) has received a number of Section 8(e) and "For Your Information" submissions on nitrosamines. In addition, the Chemical Screening Branch (CSB/ECAD/OTS) has prepared Chemical Hazard Information Profiles (CHIPs) on several nitrosamines.

Immediately upon receipt of this TSCA Section 8(e) submission, the Chemical Screening Branch provided copies of the notice to the Risk Analysis Branch (RAB/ECAD/OTS) and the Existing Chemical Control Branch (ECCB/CCD/OTS) for inclusion in the OTS evaluation of available toxicologic and exposure data on nitrosamines. It should be noted also that in September 1984, EPA published two "Chemical Advisories" that outline the Agency's concerns about nitrosamines in metalworking fluids. Copies of these advisories may be obtained by calling (202)-554-1404, or by writing to:

Ed Klein, Director
TSCA Assistance Office (TS-799)
Office of Toxic Substances (OTS)
Environmental Protection Agency
401 "M" Street, S.W.
Washington, D.C. 20460

Comments/Recommendations

Dow Corning stated that the company "has temporarily suspended the manufacture of silicone elastomer products." In addition, Dow Corning stated that the submitted findings were communicated to Dow Corning personnel as well as Dow Corning's customer who has also suspended the manufacture of foamed elastomer. Dow Corning stated also that the reported findings have been sent to the "Olin Corporation and Kenrich Petrochemicals Inc., a contract formulator." Finally, Dow Corning reported that the company is still investigating this matter and will inform the Agency about any further pertinent findings.

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, RAB/ECAD/OTS and ECCB/CCD/OTS. Copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS/OPTS) for further distibution.

DATE: DEC 5 1986

SUBJECT: Status Report* 8EHQ-1186-0644 Approved: 12/8/86

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 Dow Corning Corporation reported that the company discovered recently that 3,3,3-trifluoropropionaldehyde (CAS No. 460-40-2) "is produced when fluorosilicone fluids and greases are held at elevated temperatures for extended periods of time." According to Dow Corning, the company "exposed fluorosilicone fluids, greases and elastomers [(listed below)] to elevated temperatures and analyzed the chemical substances produced." Dow Corning reported that "trace quantities of trifluoropropionaldehyde were detected [by Fourier Transform Infra-Red (FTIR) spectroscopy] when fluorosilicone fluids and greases were heated at temperatures of 400°F - 500°F in air for several hours." The company also reported, however, that "trifluoropropionaldehyde was not produced when the fluorosilicone elastomer was exposed to these same conditions." The company noted also that "in certain applications, fluorosilicone fluids and greases may reach these temperatures."

Dow Corning Materials Analyzed

DOW CORNING® FS-1265 Fluid (300 CS)
DOW CORNING® FS-1265 Fluid (1,000 CS)
DOW CORNING® FS-1265 Fluid (10,000 CS)
MOLYKOTE® FS-3451 Grease
MOLYKOTE® FS-3452 Valve Lubricant
SILASTIC® LS-2860 Fluorosilicone Rubber

In its submission, Dow Corning reported that all of the products listed above "are based on polymers that contain trifluoropropyl substitution."

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Dow Corning stated that because the company could not locate any toxicologic information on trifluoropropionaldehyde and was not able to find a commercial supplier for the chemical, Dow Corning synthesized a small amount of trifluoropropionaldehyde to verify chemical structure and to conduct toxicologic testing. According to Dow Corning, "an initial rangefinding acute oral toxicity study with rats was conducted . . . and indicates the material to be highly toxic, [with an] ALD50 < 25 mg/Kg body weight."

Submission Evaluation

In order for EPA to evaluate the overall significance of the reported information, Dow Corning should be asked to submit a full copy of the final report from the acute oral toxicity test cited in the company's TSCA Section 8(e) notice. In addition, Dow Corning should be asked to report the levels of trifluoropropionaldehyde detected by the company.

Current Production and Use

3,3,3-Trifluoropropionaldehyde (CAS No. 460-40-2) was not located during a search of the non-confidential computerized version of the initial TSCA Chemical Substance Inventory.

Comments/Recommendations

In its TSCA Section 8(e) submission, the Dow Corning Corporation reported that the company has 1) revised Material Safety Data Sheets (MSDSs), labels, and literature to reflect the reported data; 2) notified affected Dow Corning personnel and customers; and 3) notified the General Electric Company (a U.S. producer of fluorosilicone materials) as well as "other global fluorosilicone producers." Dow Corning reported also that the company will continue to investigate the matter and will report to the Agency any further pertinent information obtained by the company.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the Dow Corning Corporation to submit a complete copy of the final report (including the actual experimental protocol, results of gross/histopathological examinations, results of statistical analyses (if performed), etc.) from the acute rat oral 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 chemical toxicity or exposure data, Dow Corning will be requested to describe the nature and results, if available, of all studies that Dow Corning has conducted, is conducting or is planning to conduct to determine the toxicity of or the exposure to trifluoropropionaldehyde.

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

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. Copies of this status report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: DEC 11 1986

SUBJECT: Status Report* 8EHQ-1286-0645 Approved: 12/11/86

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 Lever Brothers Company provided summarized results of an Ames test of C.I. (Color Index) Direct Yellow 28 (CAS No. 8005-72-9). According to the submission, C.I. Direct Yellow 28 was found to induce a "weak" mutagenic effect when tested with and without exogenous metabolic activation in two strains (TA 98 and TA 1538) of Salmonella typhimurium (bacteria).

Submission Evaluation

In order for the Agency to evaluate the overall significance of the reported genotoxicologic findings, Lever Brothers should be asked to submit a complete copy of the final report from the Ames test 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 C.I. Direct Yellow 28 (CAS No. 8005-72-9), which is listed in EPA's initial TSCA Chemical Substance Inventory, showed that between 12 thousand and 120 thousand pounds of this chemical were reported as manufactured/imported in 1977. This production range information does not include any information claimed to be 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 Chemical Substance 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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According to secondary literature sources, C.I. Direct Yellow 28 is a thiazole derivative used to dye/stain a variety of natural and synthetic materials. In its TSCA Section 8(e) submission, Lever Brothers reported that this dye "is not being used in any Lever Brothers' products but was being investigated for possible use." (Lever Brothers did not disclose, however, the nature of the company's possible use of this dye.)

Comments/Recommendations

In its Section 8(e) notice, Lever Brothers stated that a company "decision to conduct additional mutagenicity testing will be made after further discussions with . . . [Tricon Colors Incorporated (the supplier of C.I. Direct Yellow 28)] and after assessment of Lever's continued interest in this material."

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 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 a single positive genotoxicity finding is of value in assessing the possible risk(s) posed by exposure to the tested chemical or mixture. In addition, EPA believes that a positive genotoxicity result, 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 to determine better the toxicity of or the exposure to that chemical or mixture. The results of such additional testing should be considered also for submission to EPA under Section 8(e) of TSCA.

a) The Chemical Screening Branch (CSB/ECAD/OTS) will ask the Lever Brothers Company to submit to EPA a full copy of the final report (including the actual experimental protocol, data, results of statistical analyses (if performed), etc.) from the Ames test cited in the company's TSCA Section 8(e) submission.

   In addition, the Chemical Screening Branch will ask Tricon Colors Incorporated to provide to EPA the exact chemical identity of C.I. Direct Yellow 28, a dye that is supplied by Tricon as Yellow Shade 18569.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, Lever Brothers and Tricon will be asked to describe the actions the companies have taken or plan to take 1) to notify workers/others about the reported findings, and 2) to reduce or eliminate exposure to C.I. Direct Yellow 28. In addition, Tricon and Lever Brothers will be asked to describe the nature

and results, if available, from all studies (other than those that have been published in the open scientific literature or those that have been submitted already to EPA) 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 C.I. Direct Yellow 28.

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, NTP, FDA, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. Copies of this report will be provided also to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: DEC 12 1986

SUBJECT: Status Report* 8EHQ-1186-0646 S Approved: 12/12/86

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 identities and use(s) of the tested material and its components to be TSCA Confidential Business Information (TSCA CBI). The Information Management Division (IMD/OTS) will be reviewing the adequacy of the submitter's substantiation of these CBI claims. In the non-confidential version of this TSCA Section 8(e) notice, the tested material was identified as an acrylate mixture.

Submission Description

The submitting company provided summarized preliminary results from a number of in vitro and in vivo genotoxicty studies of an acrylate mixture. According to the submitted information, this acrylate mixture was found to be:

- negative at all dose levels tested with and without exogenous metabolic activation in a "modified" Ames Salmonella typhimurium (bacteria) assay;
- positive at all dose levels tested in the absence of exogenous metabolic activation in an in vitro Chinese hamster ovary (CHO) cell Sister Chromatid Exchange (SCE) assay (a positive response was reportedly observed only at the highest dose tested in the presence of metabolic activation);
- positive (in a dose-related manner) in a micronucleus assay conducted in vivo using Swiss CD-1 mice;
- negative at all dose levels tested in an Unscheduled DNA Synthesis (UDS) assay in cultured rat hepatocytes; and

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° negative at all dose levels tested in the presence of exogenous metabolic activation in an in vitro CHO cell mutagenicity assay (an increase in mutation frequency was reportedly observed only at the highest dose level tested in the absence of metabolic activation.)

Submission Evaluation

In order for EPA to evaluate the overall significance of the reported genotoxicologic findings, the submitting company should be asked to ensure that EPA receives complete copies of the final reports from all studies cited in the company's submission.

Current Production and Use

In light of the submitter's TSCA CBI claims, no information concerning the use(s) or TSCA Inventory status of the subject mixture or its components will appear in this report.

Comments

EPA's Office of Toxic Substances (OTS) has received a number of TSCA Section 8(e), TSCA Section 5 and "For Your Information" submissions on acrylates. In addition, the Chemical Screening Branch (CSB/ECAD/OTS) has prepared Chemical Hazard Information Profiles (CHIPs) on several acrylates. Further, OTS is assessing available toxicologic and exposure data on acrylates as a class. Finally, the reader's attention is directed to a notice in 51 FR 43785 (December 4, 1986) which announces a public meeting to held at EPA Headquarters in Washington, D.C. on February 3, 1987 from 9:00 AM to 5:30 PM. The focus of this public meeting will be to identify and discuss the potential health risk issues associated with chemicals in the acrylate category.

a) The Chemical Screening Branch will ask the submitter to ensure that EPA receives a full copy of the final report (including the actual experimental protocol(s), data, results of statistical analyses (if performed), etc.) from each assay cited in the company's submission. In addition, the submitter will be requested to report the amount of each component in the tested mixture.

   In view of EPA's general interest in corporate actions taken on a voluntary basis in response to chemical toxicity or exposure data, the submitting company will be asked to describe the actions the company has taken or plans to take 1) to reduce or eliminate exposure to the

tested mixture and/or its components, and 2) to notify workers and others about the reported genotoxicologic findings. In addition, the submitting company 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 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 acrylate mixture and/or its components.

b) The Chemical Screening Branch will review the reported information in order to determine the need for separate OTS assessment of the subject acrylate mixture (or its components) and/or referral of the data for inclusion in the ongoing OTS assessment of acrylates as a class.

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, RAB/ECAD/OTS and ECCB/CCD/OTS. 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: JAN 12 1987

SUBJECT: Status Report* 8EHQ-1186-0647 Approved: 1/12/87

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

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

Submission Description

Allied-Signal Inc. provided summarized results from a series of acute in vivo and in vitro studies of a tetraoximinosilane (TOS) and methyloximinosilane (MOS) mixture. Allied-Signal stated non-confidentially by phone on January 6, 1987 that the composition of the mixture was 15% TOS (CAS No. 34206-40-1) and 85% MOS (CAS No. 22984-54-9). According to the submitted information, the TOS/MOS mixture was found to be a severe irritant in a primary dermal irritancy test in rabbits. Based on these results, Allied-Signal stated that the TOS/MOS mixture was not tested in an acute rabbit eye irritancy study, although the material was expected to be severely irritating to the eyes. Allied-Signal stated further that the TOS/MOS mixture was found to be an extreme skin sensitizer in guinea pigs. In addition, Allied-Signal reported that although no deaths occurred among rats dosed once orally with the mixture at levels of 0.1, 0.75 or 2.0 ml/kg, "reversible neurological effects (narcosis) were apparent at all dose levels." Allied-Signal also provided the following information regarding the findings from an acute rabbit dermal toxicity study in which the TOS/MOS mixture was applied to the skin (5 male and 5 female rabbits/group) for 24 hours at doses of 0.05, 1.0 or 2.0 ml/kg:

> "The test substance caused 9 deaths at the 2.0 ml/kg level and 1 death at the 1.0 ml/kg level. The mortalities were associated with either severe methemoglobinemia or erythrolysis and resultant hemoglobinuria. Both hepatic and renal lesions appeared to have occurred secondarily to hypoxia associated with the erythrocytic toxicity induced by the test substance. Eight/nine surviving rabbits at the 1.0 ml/kg level had increased hemosiderin pigment of the spleen indicating a sublethal

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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.

test substance effect had occurred in these animals. A microscopic no effect level occurred in rabbits dosed at the 0.05 ml/kg level."

With regard to in vitro genotoxicity, Allied-Signal reported that the TOS/MOS mixture was negative with and without exogenous metabolic activation in 1) an Ames Salmonella typhimurium (bacteria) assay, and 2) cultured mammalian cell mutation and chromosomal aberration assays. In addition, Allied-Signal reported that an in vitro mammalian cell Sister Chromatid Exchange assay was negative with activation, and, without activation, "the highest dose level was significantly elevated, causing a positive trend test."

Finally, Allied-Signal's submission contained a memorandum in which the findings from acute rat oral toxicity studies of the TOS/MOS mixture and MOS alone were compared. According to this memorandum, the TOS/MOS mixture "produces nearly the same qualitative and quantitative effects" as MOS. The memorandum states further that "based on mortality patterns, the presence of TOS in the mixture . . . seems to have had a diluent effect and produced less acute lethality for similar dose levels." In addition, the memorandum states that effects other than lethality were similar for both the TOS/MOS mixture and MOS alone.

Submission Evaluation

The submitted information has been provided to the Risk Analysis Branch (RAB/ECAD/OTS) for inclusion in their recently initiated review of organosilanes.

Current Production and Use

A review of the production range (includes importation volumes) statistics for MOS (CAS No. 22984-54-7), which is listed in the initial TSCA Chemical Substance Inventory, has shown that no 1977 manufacture/importation was reported or that all of the reported data was claimed as TSCA Confidential Business Information (CBI) by the person(s) reporting for the TSCA Inventory and cannot be disclosed (see Section 14(a) of TSCA; U.S.C. 2613(a)). 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).

Tetraoximinosilane (TOS; CAS No. 34206-40-1) was not found in the current non-confidential versions of either the printed or computerized TSCA Inventory. According to staff of the Information Management Division (IMD/OTS), however, this chemical substance is included in the non-confidential TSCA Inventory.

Allied-Signal did not submit any information with regard to the actual/planned use(s) of TOS and/or MOS nor was such information located in the secondary literature sources consulted by EPA.

Comments/Recommendations

EPA's Office of Toxic Substances (OTS) has received a number of TSCA Section 5 and 8(e) submissions as well as several "For Your Information" (FYI) submissions on organosilanes. The Chemical Screening Branch recently prepared a Chemical Hazard Information Profile (CHIP) on organosilanes and did prepare (in 1982) a CHIP on 3,4-epoxycyclohexylethyltrimethoxysilane (TMOHS). As stated previously, staff of the Risk Analysis Branch/ECAD/OTS recently initiated a review of organosilanes.

a) The Chemical Screening Branch will request Allied-Signal to provide full copies of the final reports (including the actual experimental protocols, results of gross and histopathologic examinations, results of any statistical analyses, etc.) from all 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, Allied-Signal will be asked 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 the exposure to TOS and/or MOS. In addition, Allied-Signal will be requested 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 Allied-Signal is aware or that the company has conducted, is conducting, or plans to conduct to determine the toxicity of or the exposure to TOS and/or MOS.

b) The Chemical Screening Branch will transmit all of the reported information immediately to the Risk Analysis Branch/ECAD/OTS for inclusion in their ongoing review of organosilanes.

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, RAB/ECAD/OTS and CCD/OTS. In addition, copies of this status report will be provided to the TSCA Assistance Office (TAO/OTS) for further distribution.

DATE: JAN 16 1987

SUBJECT: Status Report* 8EHQ-1286-0648 Approved: 1/16/87

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 Ethyl Corporation provided summarized findings from a sub-chronic feeding study of diethyltoluenediamine (DETDA; CAS No. 68479-98-1) in rats. According to the submission, DETDA (which is a mixture comprised mainly of 3,5-diethyltoluene-2,4-diamine (CAS No. 2095-02-5) and 3,5-diethyltoluene-2,6-diamine (CAS No. 2095-01-4)) was incorporated into the diet and fed ad libitum to 4 groups (20 males and 20 females per group) of Sprague-Dawley rats at dose levels of 0, 50, 125 or 320 parts per million (ppm) per day for 90 days. The Conclusions section of the submitted pathology report presented the following information regarding the results of this sub-chronic feeding study:

> "Administration of diethyltoluenediamine (DETDA) to rats by repeated oral exposure for a period of ninety days at levels of 50, 125, and 320 ppm resulted in a high mortality rate in the high dose animals. Treatment-related microscopic changes were present in all of the male and female rats receiving 320 ppm. In these high dose rats, there was a high incidence of bilateral cataractous change in the eyes, diffuse atrophy of the acinar cells of the pancreas, bone marrow depletion, tubular vacuolation (hydropic change) of the kidneys and vacuolation of the islet cells of the pancreas, atrophy of many organs [including the genital organs of both sexes], lymphoid depletion of the spleen, thymus and mesenteric lymph nodes, and [an] increased pigmentation of the liver and spleen. A minimal to moderate multifocal degeneration of the acinar cells of the pancreas and increased splenic pigmentation in the females were present in the tissues examined from the rats receiving 50 and 125 ppm DETDA in the diet."

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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, the Ethyl Corporation stated that the doses used in the 90-day study were expected to cause toxic effects in order to set the dose levels for a 2-year bioassay of DETDA. In addition, Ethyl reported non-confidentially by phone on December 31, 1986 that DETDA has the following composition:

74% to 80% of 3,5-diethyltoluene-2,4-diamine;
18% to 24% of 3,5-diethyltoluene-2,6-diamine;
a maximum of 1% 2,4,6-triethylbenzene-1,3-diamine; and
0 to 4% of other polyalkylated m-phenylenediamines.

Submission Evaluation

The draft summary report from this 90-day feeding study of DETDA in rats indicates that the highest dietary DETDA dose (320 ppm) produced a high rate of mortality (27 deaths/40 exposed rats) and severe toxic manifestations in both sexes. The observed adverse effects included: bilateral degenerative changes in the lens of the eye; diffuse atrophy of the pancreatic acinar cells, vacuolation and reduction in the quantity of pancreatic islet cells; bone marrow hypocellularity; hydropic changes in the kidney; lymphoid depletion in the thymus, spleen and mesenteric lymph nodes; thymic involution; atrophy of the salivary gland, thymus, stomach, and reproductive organs; and increased pigmentation in the liver and spleen which, in combination with the decreased hemoglobin content in the blood, is undoubtedly hemosiderosis. A considerable number of these serious toxic effects were noted in male and female rats at the mid-dose level (125 ppm). In view of the fact that 1) the low-dose (50 ppm) females demonstrated a moderately severe splenic pigmentation in 8/20 rats as compared to 0/20 control rats, and 2) the low-dose (50 ppm) males were found to have varying degrees of pancreatic acinar cell degeneration in 12/20 rats as compared to 5/20 control rats with less severe degeneration, a "no-observed-adverse-effect-level" (NOAEL) was not determined in this 90-day DETDA feeding study.

Current Production and Use

A review of the production range (includes importation volumes) statistics for diethyltoluenediamine (CAS No. 68479-98-1), 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 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 (TSCA Section 14(a), 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 TSCA Inventory Reporting Regulations (40 CFR 710).

According to secondary literature sources, DETDA is used as an extender/curing agent for polyurethane, as a curing agent for epoxy resins, and as a chemical intermediate.

With regard to worker exposure to DETDA, the Ethyl Corporation stated that "industrial hygiene monitoring [(minimum detection limit of 50 parts per billion)] of Ethyl employees engaged in the manufacture of DETDA has shown no detectable airborne DETDA in the workplace." Ethyl reported also that "DETDA has a very low vapor pressure and is handled in a closed system." In addition, Ethyl stated that its "workers wear full body protective clothing to prevent skin contact [with DETDA]."

Comments/Recommendations

In its TSCA Section 8(e) submission, the Ethyl Corporation stated that the company is notifying its workers and customers about the reported toxicologic findings. In addition, Ethyl stated that a copy of the final report from the 90-day DETDA feeding study will be sent to EPA as soon as that report is received by the company. Finally, Ethyl reported that the company plans to conduct further studies (in addition to the 2-year bioassay) in an attempt to "elucidate the mechanism of DETDA's toxic effect in the pancreas and determine if this effect is species specific or reversible."

It should be noted that EPA's Office of Toxic Substances (OTS) received previously a Section 8(e) submission (8EHQ-0883-0489 et seq.) in which Lonza Inc. reported that DETDA caused a dose-dependent mutagenic response in the presence of metabolic activation in an Ames Salmonella typhimurium (bacteria) assay.

a) The Chemical Screening Branch will request the Ethyl Corporation to ensure that the Agency 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 company's 90-day DETDA feeding study.

   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 the Ethyl Corporation to describe the nature and results, if available, from 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 is planning to conduct to determine the toxicity of DETDA or its constituents.

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

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 report will be transmitted to the TSCA Assistance Office (TAO/OTS) for further distribution.

APPENDIX A

THURSDAY, MARCH 16, 1978
PART V

federal register

ENVIRONMENTAL PROTECTION AGENCY

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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 responsiblity 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: (1) 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.

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_{∞}'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]

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 55-18-5 CHEMICAL NAME: ETHANAMINE, N-ETHYL-N-NITROSO-
SUBMISSION #: 8EHQ-1186-0643

CAS NUMBER: 55-18-5 CHEMICAL NAME: N-NITROSODIETHYLAMINE
SUBMISSION #: 8EHQ-1186-0643

CAS NUMBER: 59-89-2 CHEMICAL NAME: MORPHOLINE, N-NITROSO-
SUBMISSION #: 8EHQ-0885-0564 S 8EHQ-1186-0643

CAS NUMBER: 59-89-2 CHEMICAL NAME: N-NITROSOMORPHOLINE
SUBMISSION #: 8EHQ-0885-0564 S 8EHQ-1186-0643

CAS NUMBER: 60-01-5 CHEMICAL NAME: BUTANOIC ACID, 1,2,3-PROPANETRIYL ESTER
SUBMISSION #: 8EHQ-0486-0600

CAS NUMBER: 60-12-8 CHEMICAL NAME: BENZENEETHANOL
SUBMISSION #: 8EHQ-0186-0587

CAS NUMBER: 62-75-9 CHEMICAL NAME: METHANAMINE, N-METHYL-N-NITROSO-
SUBMISSION #: 8EHQ-0885-0564 S 8EHQ-1186-0643

CAS NUMBER: 62-75-9 CHEMICAL NAME: N-NITROSODIMETHYLAMINE
SUBMISSION #: 8EHQ-0885-0564 S 8EHQ-1186-0643

CAS NUMBER: 64-17-5 CHEMICAL NAME: ETHANOL
SUBMISSION #: 8EHQ-0786-0617

CAS NUMBER: 64-19-7 CHEMICAL NAME: ACETIC ACID
SUBMISSION #: 8EHQ-0486-0600

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 64-67-5 CHEMICAL NAME: SULFURIC ACID, DIETHYL ESTER
SUBMISSION #: 8EHQ-0585-0554 S

CAS NUMBER: 67-63-0 CHEMICAL NAME: 2-PROPANOL
SUBMISSION #: 8EHQ-0985-0566

CAS NUMBER: 68-12-2 CHEMICAL NAME: FORMAMIDE, N,N-DIMETHYL-
SUBMISSION #: 8EHQ-0486-0598

CAS NUMBER: 75-01-4 CHEMICAL NAME: ETHENE, CHLORO-
SUBMISSION #: 8EHQ-0986-0629

CAS NUMBER: 75-01-4 CHEMICAL NAME: VINYL CHLORIDE
SUBMISSION #: 8EHQ-0986-0629

CAS NUMBER: 75-21-8 CHEMICAL NAME: ETHYLENE OXIDE
SUBMISSION #: 8EHQ-0786-0611 8EHQ-1086-0641

CAS NUMBER: 75-21-8 CHEMICAL NAME: OXIRANE
SUBMISSION #: 8EHQ-0786-0611 8EHQ-1086-0641

CAS NUMBER: 76-13-1 CHEMICAL NAME: ETHANE, 1,1,2-TRICHLORO-1,2,2-TRIFLUORO-
SUBMISSION #: 8EHQ-0986-0631 S

CAS NUMBER: 79-06-1 CHEMICAL NAME: ACRYLAMIDE
SUBMISSION #: 8EHQ-0785-0560

CAS NUMBER: 79-06-1 CHEMICAL NAME: 2-PROPENAMIDE
SUBMISSION #: 8EHQ-0785-0560

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 79-09-4 CHEMICAL NAME: PROPANOIC ACID
SUBMISSION #: 8EHQ-0486-0600

CAS NUMBER: 79-10-7 CHEMICAL NAME: ACRYLIC ACID
SUBMISSION #: 8EHQ-0386-0592

CAS NUMBER: 79-10-7 CHEMICAL NAME: 2-PROPENOIC ACID
SUBMISSION #: 8EHQ-0386-0592

CAS NUMBER: 84-74-2 CHEMICAL NAME: 1,2-BENZENEDICARBOXYLIC ACID, DIBUTYL ESTER
SUBMISSION #: 8EHQ-0886-0620

CAS NUMBER: 88-12-0 CHEMICAL NAME: PYROL
SUBMISSION #: 8EHQ-0785-0561 S

CAS NUMBER: 88-12-0 CHEMICAL NAME: 2-PYRROLIDINONE, 1-ETHENYL-
SUBMISSION #: 8EHQ-0785-0561 S

CAS NUMBER: 95-69-2 CHEMICAL NAME: BENZENAMINE, 4-CHLORO-2-METHYL-
SUBMISSION #: 8EHQ-0986-0634

CAS NUMBER: 97-00-7 CHEMICAL NAME: BENZENE, 1-CHLORO-2,4-DINITRO-
SUBMISSION #: 8EHQ-0485-0552

CAS NUMBER: 101-77-9 CHEMICAL NAME: BENZENAMINE, 4,4'-METHYLENEBIS-
SUBMISSION #: 8EHQ-1285-0577

CAS NUMBER: 106-99-0 CHEMICAL NAME: 1,3-BUTADIENE
SUBMISSION #: 8EHQ-0786-0615

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 107-13-1 CHEMICAL NAME: ACRYLONITRILE
SUBMISSION #: 8EHQ-0486-0598

CAS NUMBER: 107-13-1 CHEMICAL NAME: 2-PROPENENITRILE
SUBMISSION #: 8EHQ-0486-0598

CAS NUMBER: 107-21-1 CHEMICAL NAME: 1,2-ETHANEDIOL
SUBMISSION #: 8EHQ-0485-0552

CAS NUMBER: 107-92-6 CHEMICAL NAME: BUTANOIC ACID
SUBMISSION #: 8EHQ-0486-0600

CAS NUMBER: 108-05-4 CHEMICAL NAME: ACETIC ACID ETHENYL ESTER
SUBMISSION #: 8EHQ-0185-0543 8EHQ-1086-0642

CAS NUMBER: 108-05-4 CHEMICAL NAME: VINYL ACETATE
SUBMISSION #: 8EHQ-0185-0543 8EHQ-1086-0642

CAS NUMBER: 108-30-5 CHEMICAL NAME: 2,5-FURANDIONE, DIHYDRO-
SUBMISSION #: 8EHQ-0885-0565 S

CAS NUMBER: 108-30-5 CHEMICAL NAME: SUCCINIC ANHYDRIDE
SUBMISSION #: 8EHQ-0885-0565 S

CAS NUMBER: 108-45-2 CHEMICAL NAME: 1,3-BENZENEDIAMINE
SUBMISSION #: 8EHQ-1285-0577

CAS NUMBER: 108-65-6 CHEMICAL NAME: 2-PROPANOL, 1-METHOXY-, ACETATE
SUBMISSION #: 8EHQ-0585-0572

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 109-52-4 CHEMICAL NAME: PENTANOIC ACID
SUBMISSION #: 8EHQ-0486-0600

CAS NUMBER: 110-69-0 CHEMICAL NAME: BUTANAL, OXIME
SUBMISSION #: 8EHQ-1185-0573

CAS NUMBER: 110-69-0 CHEMICAL NAME: EXKIN NO. 1 ANTI-SKINNING AGENT
SUBMISSION #: 8EHQ-1185-0573

CAS NUMBER: 110-69-0 CHEMICAL NAME: EXKIN 1
SUBMISSION #: 8EHQ-1185-0573

CAS NUMBER: 111-15-9 CHEMICAL NAME: ETHANOL, 2-ETHOXY-, ACETATE
SUBMISSION #: 8EHQ-0386-0593

CAS NUMBER: 111-86-4 CHEMICAL NAME: 1-OCTANAMINE
SUBMISSION #: 8EHQ-1085-0569

CAS NUMBER: 115-07-1 CHEMICAL NAME: 1-PROPENE
SUBMISSION #: 8EHQ-0985-0566

CAS NUMBER: 115-07-1 CHEMICAL NAME: PROPYLENE
SUBMISSION #: 8EHQ-0985-0566

CAS NUMBER: 123-38-6 CHEMICAL NAME: PROPANAL
SUBMISSION #: 8EHQ-0985-0566

CAS NUMBER: 123-38-6 CHEMICAL NAME: PROPIONALDEHYDE
SUBMISSION #: 8EHQ-0985-0566

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 123-54-6 CHEMICAL NAME: 2,4-PENTANEDIONE
SUBMISSION #: 8EHQ-0386-0595

CAS NUMBER: 123-72-8 CHEMICAL NAME: BUTANAL
SUBMISSION #: 8EHQ-0786-0617

CAS NUMBER: 128-85-8 CHEMICAL NAME: 9,10-ANTHRACENEDIONE, 1-(METHYLAMINO)-4-[(4-METHYLPHENYL)AMINO]-
SUBMISSION #: 8EHQ-1285-0580

CAS NUMBER: 128-85-8 CHEMICAL NAME: C. I. SOLVENT BLUE 11
SUBMISSION #: 8EHQ-1285-0580

CAS NUMBER: 128-85-8 CHEMICAL NAME: SUDAN BLUE GA
SUBMISSION #: 8EHQ-1285-0580

CAS NUMBER: 131-11-3 CHEMICAL NAME: 1,2-BENZENEDICARBOXYLIC ACID, DIMETHYL ESTER
SUBMISSION #: 8EHQ-0886-0620

CAS NUMBER: 137-29-1 CHEMICAL NAME: COPPER, BIS(DIMETHYLCARBAMODITHIOATO-S,S')-, (SP-4-1)-
SUBMISSION #: 8EHQ-0786-0616

CAS NUMBER: 137-40-6 CHEMICAL NAME: PROPANOIC ACID, SODIUM SALT
SUBMISSION #: 8EHQ-0486-0600

CAS NUMBER: 142-62-1 CHEMICAL NAME: HEXANOIC ACID
SUBMISSION #: 8EHQ-0486-0600

CAS NUMBER: 409-21-2 CHEMICAL NAME: SILICON CARBIDE FIBERS
SUBMISSION #: 8EHQ-1185-0574

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 409-21-2 CHEMICAL NAME: SILICON CARBIDE, (SIC)
SUBMISSION #: 8EHQ-1185-0574

CAS NUMBER: 460-40-2 CHEMICAL NAME: PROPANAL, 3,3,3-TRIFLUORO-
SUBMISSION #: 8EHQ-1186-0644

CAS NUMBER: 460-40-2 CHEMICAL NAME: PROPIONALDEHYDE, 3,3,3-TRIFLUORO-
SUBMISSION #: 8EHQ-1186-0644

CAS NUMBER: 598-62-9 CHEMICAL NAME: CARBONIC ACID, MANGANESE(2+) SALT (1:1)
SUBMISSION #: 8EHQ-0286-0588 *

CAS NUMBER: 681-84-5 CHEMICAL NAME: SILICIC ACID, (H4SIO4), TETRAMETHYL ESTER
SUBMISSION #: 8EHQ-0785-0563

CAS NUMBER: 756-80-9 CHEMICAL NAME: PHOSPHORODITHIOIC ACID, O,O-DIMETHYL ESTER
SUBMISSION #: 8EHQ-0385-0547

CAS NUMBER: 764-41-0 CHEMICAL NAME: 2-BUTENE, 1,4-DICHLORO-
SUBMISSION #: 8EHQ-0985-0567

CAS NUMBER: 924-16-3 CHEMICAL NAME: 1-BUTANAMINE, N-BUTYL-N-NITROSO-
SUBMISSION #: 8EHQ-1186-0643

CAS NUMBER: 924-16-3 CHEMICAL NAME: N-NITROSODIBUTYLAMINE
SUBMISSION #: 8EHQ-1186-0643

CAS NUMBER: 999-21-3 CHEMICAL NAME: 2-BUTENEDIOIC ACID (Z)-, DI-2-PROPENYL ESTER
SUBMISSION #: 8EHQ-0786-0612

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 1116-54-7 CHEMICAL NAME: ETHANOL, 2,2'-(NITROSOIMINO)BIS-
SUBMISSION #: 8EHQ-0185-0542 S 8EHQ-0885-0564 S

CAS NUMBER: 1116-54-7 CHEMICAL NAME: N-NITROSODIETHANOLAMINE
SUBMISSION #: 8EHQ-0185-0542 S 8EHQ-0885-0564 S

CAS NUMBER: 1271-55-2 CHEMICAL NAME: FERROCENE, ACETYL-
SUBMISSION #: 8EHQ-1285-0578

CAS NUMBER: 1306-19-0 CHEMICAL NAME: CADMIUM OXIDE (CDO)
SUBMISSION #: 8EHQ-0886-0618 S

CAS NUMBER: 1306-23-6 CHEMICAL NAME: CADMIUM SULFIDE, (CDS)
SUBMISSION #: 8EHQ-0886-0618 S

CAS NUMBER: 1310-73-2 CHEMICAL NAME: SODIUM HYDROXIDE, (NA(OH))
SUBMISSION #: 8EHQ-0485-0552

CAS NUMBER: 1313-13-9 CHEMICAL NAME: MANGANESE OXIDE, (MNO2)
SUBMISSION #: 8EHQ-0286-0588 *

CAS NUMBER: 1332-21-4 CHEMICAL NAME: ASBESTOS
SUBMISSION #: 8EHQ-0586-0601

CAS NUMBER: 1569-01-3 CHEMICAL NAME: 2-PROPANOL, 1-PROPOXY-
SUBMISSION #: 8EHQ-0686-0603

CAS NUMBER: 1569-01-3 CHEMICAL NAME: PROPASOL SOLVENT P
SUBMISSION #: 8EHQ-0686-0603

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 1825-62-3 CHEMICAL NAME: SILANE, ETHOXYTRIMETHYL-
SUBMISSION #: 8EHQ-0985-0568 S

CAS NUMBER: 2095-01-4 CHEMICAL NAME: 1,3-BENZENEDIAMINE, 4,6-DIETHYL-2-METHYL-
SUBMISSION #: 8EHQ-1286-0648

CAS NUMBER: 2095-02-5 CHEMICAL NAME: 1,3-BENZENEDIAMINE, 2,4-DIETHYL-6-METHYL-
SUBMISSION #: 8EHQ-1286-0648

CAS NUMBER: 2386-90-5 CHEMICAL NAME: ERR 4205
SUBMISSION #: 8EHQ-1285-0577

CAS NUMBER: 2386-90-5 CHEMICAL NAME: 6-OXABICYCLO[3.1.0]HEXANE, 2,2'-OXYBIS-
SUBMISSION #: 8EHQ-1285-0577

CAS NUMBER: 2564-83-2 CHEMICAL NAME: 1-PIPERIDINYLOXY, 2,2,6,6-TETRAMETHYL-
SUBMISSION #: 8EHQ-0786-0607 S

CAS NUMBER: 2628-17-3 CHEMICAL NAME: PHENOL, 4-ETHENYL-
SUBMISSION #: 8EHQ-1285-0579 S

CAS NUMBER: 2831-60-9 CHEMICAL NAME: ETHANOL, 2-(2,4-DINITROPHENOXY)-
SUBMISSION #: 8EHQ-0485-0552

CAS NUMBER: 3091-25-6 CHEMICAL NAME: STANNANE, TRICHLOROOCTYL-
SUBMISSION #: 8EHQ-0786-0614 S

CAS NUMBER: 3542-36-7 CHEMICAL NAME: STANNANE, DICHLORODIOCTYL-
SUBMISSION #: 8EHQ-0786-0614 S

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 3734-48-3 CHEMICAL NAME: CHLORDENE

SUBMISSION #: 8EHQ-1085-0570

CAS NUMBER: 3734-48-3 CHEMICAL NAME: 4,7-METHANO-1H-INDENE, 4,5,6,7,8,8-HEXACHLORO-3A,4,7,7A-TETRAHYDRO-

SUBMISSION #: 8EHQ-1085-0570

CAS NUMBER: 3852-09-3 CHEMICAL NAME: PROPANOIC ACID, 3-METHOXY-, METHYL ESTER

SUBMISSION #: 8EHQ-0486-0599

CAS NUMBER: 4075-81-4 CHEMICAL NAME: PROPANOIC ACID, CALCIUM SALT

SUBMISSION #: 8EHQ-0486-0600

CAS NUMBER: 5538-94-3 CHEMICAL NAME: 1-OCTANAMINIUM, N,N-DIMETHYL-N-OCTYL-, CHLORIDE

SUBMISSION #: 8EHQ-0386-0591

CAS NUMBER: 6320-14-5 CHEMICAL NAME: C. I. BASIC RED 12

SUBMISSION #: 8EHQ-1285-0581

CAS NUMBER: 6320-14-5 CHEMICAL NAME: CALCOZINE RED BG

SUBMISSION #: 8EHQ-1285-0581

CAS NUMBER: 6320-14-5 CHEMICAL NAME: 3H-INDOLIUM, 2-[3-(1,3-DIHYDRO-1,3,3-TRIMETHYL-2H-INDOL-2-YLIDENE)-1-PROPENYL]-1,3,3-TRIMETHYL-, CHLORIDE

SUBMISSION #: 8EHQ-1285-0581

CAS NUMBER: 7439-92-1 CHEMICAL NAME: LEAD

SUBMISSION #: 8EHQ-0285-0546 8EHQ-0286-0588 * 8EHQ-0586-0601

CAS NUMBER: 7439-96-5 CHEMICAL NAME: MANGANESE

SUBMISSION #: 8EHQ-0286-0588 *

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 7439-97-6 CHEMICAL NAME: MERCURY

SUBMISSION #: 8EHQ-0286-0588 * 8EHQ-0586-0601

CAS NUMBER: 7440-02-0 CHEMICAL NAME: NICKEL

SUBMISSION #: 8EHQ-0586-0601

CAS NUMBER: 7440-38-2 CHEMICAL NAME: ARSENIC

SUBMISSION #: 8EHQ-0586-0601

CAS NUMBER: 7440-43-9 CHEMICAL NAME: CADMIUM

SUBMISSION #: 8EHQ-0286-0588 * 8EHQ-0586-0601

CAS NUMBER: 7440-50-8 CHEMICAL NAME: COPPER

SUBMISSION #: 8EHQ-0586-0601

CAS NUMBER: 7440-66-6 CHEMICAL NAME: ZINC

SUBMISSION #: 8EHQ-0286-0588 * 8EHQ-0586-0601

CAS NUMBER: 7446-09-5 CHEMICAL NAME: SULFUR DIOXIDE

SUBMISSION #: 8EHQ-0586-0601

CAS NUMBER: 7664-93-9 CHEMICAL NAME: SULFURIC ACID

SUBMISSION #: 8EHQ-0985-0566

CAS NUMBER: 7785-87-7 CHEMICAL NAME: SULFURIC ACID, MANGANESE(2+) SALT (1:1)

SUBMISSION #: 8EHQ-0286-0588 *

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-1286-0645

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 8005-72-9 CHEMICAL NAME: C.I. DIRECT YELLOW 28
SUBMISSION #: 8EHQ-1286-0645

CAS NUMBER: 8005-72-9 CHEMICAL NAME: YELLOW SHADE 18569
SUBMISSION #: 8EHQ-1286-0645

CAS NUMBER: 9003-13-8 CHEMICAL NAME: POLY[OXY(METHYL-1,2-ETHANEDIYL)], .ALPHA.-BUTYL-.OMEGA.-HYDROXY-
SUBMISSION #: 8EHQ-0985-0566

CAS NUMBER: 9003-13-8 CHEMICAL NAME: UCON LUBRICANT LB-250
SUBMISSION #: 8EHQ-0985-0566

CAS NUMBER: 9038-95-3 CHEMICAL NAME: OXIRANE, METHYL-, POLYMER WITH OXIRANE, MONOBUTYL ETHER
SUBMISSION #: 8EHQ-1086-0635

CAS NUMBER: 9038-95-3 CHEMICAL NAME: UCON LUBRICANT 50-HB-5100
SUBMISSION #: 8EHQ-1086-0635

CAS NUMBER: 9046-10-0 CHEMICAL NAME: JEFFAMINE D-2000
SUBMISSION #: 8EHQ-0885-0565 S

CAS NUMBER: 9046-10-0 CHEMICAL NAME: POLY[OXY(METHYL-1,2-ETHANEDIYL)], .ALPHA.-(2-AMINOMETHYLETHYL)-.OMEGA.-(2-AMINOMETHYLETHOXY)-
SUBMISSION #: 8EHQ-0885-0565 S

CAS NUMBER: 9080-79-9 CHEMICAL NAME: BENZENESULFONIC ACID, ETHENYL-, HOMOPOLYMER, SODIUM SALT
SUBMISSION #: 8EHQ-0485-0549 S

CAS NUMBER: 9080-79-9 CHEMICAL NAME: VERSA-TL 600
SUBMISSION #: 8EHQ-0485-0549 S

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 10024-97-2 CHEMICAL NAME: NITROGEN OXIDE (N2O)
SUBMISSION #: 8EHQ-0886-0628

CAS NUMBER: 10024-97-2 CHEMICAL NAME: NITROUS OXIDE
SUBMISSION #: 8EHQ-0886-0628

CAS NUMBER: 10124-36-4 CHEMICAL NAME: SULFURIC ACID, CADMIUM SALT (1:1)
SUBMISSION #: 8EHQ-0886-0618 S

CAS NUMBER: 10606-42-5 CHEMICAL NAME: PROPANOIC ACID, 3-METHOXY-, ETHYL ESTER
SUBMISSION #: 8EHQ-0486-0599

CAS NUMBER: 12001-26-2 CHEMICAL NAME: MICA (DUST), SILICEOUS MUSCOVITE
SUBMISSION #: 8EHQ-0986-0632

CAS NUMBER: 12001-26-2 CHEMICAL NAME: SILICATE, MICA
SUBMISSION #: 8EHQ-0986-0632

CAS NUMBER: 12225-84-2 CHEMICAL NAME: C. I. REACTIVE ORANGE 12
SUBMISSION #: 8EHQ-0386-0589 S

CAS NUMBER: 15112-89-7 CHEMICAL NAME: SILANETRIAMINE, N,N,N',N',N'',N''-HEXAMETHYL-
SUBMISSION #: 8EHQ-0685-0559 S

CAS NUMBER: 15571-58-1 CHEMICAL NAME: 8-OXA-3,5-DITHIA-4-STANNATETRADECANOIC ACID, 10-ETHYL-4,4-DI OCTYL-7-OXO-, 2-ETHYLHEXYL ESTER
SUBMISSION #: 8EHQ-0386-0594 S

CAS NUMBER: 21297-72-3 CHEMICAL NAME: 1-SILA-2-AZACYCLOPENTANE, 1,1-DIETHOXY-2-TRIMETHYLSILYL-
SUBMISSION #: 8EHQ-0985-0568 S

CAS NUMBER: 22984-54-9 CHEMICAL NAME: 2-BUTANONE, O,O',O''-(METHYLSILYLIDYNE)TRIOXIME

SUBMISSION #: 8EHQ-1186-0647

CAS NUMBER: 22984-54-9 CHEMICAL NAME: SILANE, METHYLOXIMINO-

SUBMISSION #: 8EHQ-1186-0647

CAS NUMBER: 23209-59-8 CHEMICAL NAME: METAPHOSPHORIC ACID, (HPO3), CALCIUM SODIUM SALT

SUBMISSION #: 8EHQ-0386-0619

CAS NUMBER: 23676-09-7 CHEMICAL NAME: BENZOIC ACID, 4-ETHOXY-, ETHYL ESTER

SUBMISSION #: 8EHQ-0585-0554 S

CAS NUMBER: 25068-38-6 CHEMICAL NAME: ARALDITE 6010

SUBMISSION #: 8EHQ-1285-0577

CAS NUMBER: 25068-38-6 CHEMICAL NAME: PHENOL, 4,4'-(1-METHYLETHYLIDENE)BIS-, POLYMER WITH (CHLOROM ETHYL)OXIRANE

SUBMISSION #: 8EHQ-1285-0577

CAS NUMBER: 25646-77-9 CHEMICAL NAME: ETHANOL, 2-[(4-AMINO-3-METHYLPHENYL)ETHYLAMINO]-, SULFATE (1 :1) (SALT)

SUBMISSION #: 8EHQ-1185-0575

CAS NUMBER: 25646-77-9 CHEMICAL NAME: KODAK COLOR DEVELOPING AGENT (CD-4)

SUBMISSION #: 8EHQ-1185-0575

CAS NUMBER: 26538-44-3 CHEMICAL NAME: 1H-2-BENZOXACYCLOTETRADECIN-1-ONE, 3,4,5,6,7,8,9,10,11,12-DE CAHYDRO-7,14,16-TRIHYDROXY-3-METHYL-, [3S-(3R*,7S*)]-

SUBMISSION #: 8EHQ-0485-0551 *

CAS NUMBER: 26538-44-3 CHEMICAL NAME: ZERANOL

SUBMISSION #: 8EHQ-0485-0551 *

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 28182-81-2 CHEMICAL NAME: CORONATE EH
SUBMISSION #: 8EHQ-1086-0638 *

CAS NUMBER: 28182-81-2 CHEMICAL NAME: HEXANE, 1,6-DIISOCYANATO-, HOMOPOLYMER
SUBMISSION #: 8EHQ-1086-0638 *

CAS NUMBER: 32536-52-0 CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, OCTABROMO DERIV.
SUBMISSION #: 8EHQ-0585-0555

CAS NUMBER: 34206-40-1 CHEMICAL NAME: 2-BUTANONE, O,O',O'',O'''-SILANETETRAYLTETRAOXIME
SUBMISSION #: 8EHQ-1186-0647

CAS NUMBER: 34206-40-1 CHEMICAL NAME: SILANE, TETRAOXIMINO-
SUBMISSION #: 8EHQ-1186-0647

CAS NUMBER: 36483-60-0 CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, HEXABROMO DERIV.
SUBMISSION #: 8EHQ-0585-0555

CAS NUMBER: 52942-64-0 CHEMICAL NAME: BUTANEDIOIC ACID, (ETHOXYMETHYLENE)OXO-, DIETHYL ESTER
SUBMISSION #: 8EHQ-1086-0640 S *

CAS NUMBER: 55130-39-7 CHEMICAL NAME: BUTANEDIOIC ACID, (ETHOXYMETHYLENE)OXO-, DIETHYL ESTER, (E)-
SUBMISSION #: 8EHQ-1086-0640 S *

CAS NUMBER: 55130-49-9 CHEMICAL NAME: BUTANEDIOIC ACID, (ETHOXYMETHYLENE)OXO-, DIETHYL ESTER, (Z)-
SUBMISSION #: 8EHQ-1086-0640 S *

CAS NUMBER: 57116-45-7 CHEMICAL NAME: 1-AZIRIDINEPROPANOIC ACID, 2-[[3-(1-AZIRIDINYL)-1-OXOPROPOXY]METHYL]-2-(HYDROXYMETHYL)-1,3-PROPANEDIYL ESTER
SUBMISSION #: 8EHQ-0986-0630

CAS NUMBER: 63843-89-0 CHEMICAL NAME: PROPANEDIOIC ACID, [[3,5-BIS(1,1-DIMETHYLETHYL)-4-HYDROXYPHENYL]METHYL]BUTYL-, BIS(1,2,2,6,6-PENTAMETHYL-4-PIPERIDINYL) ESTER

SUBMISSION #: 8EHQ-0186-0585 S

CAS NUMBER: 63843-89-0 CHEMICAL NAME: TINUVIN 144

SUBMISSION #: 8EHQ-0186-0585 S

CAS NUMBER: 63936-56-1 CHEMICAL NAME: BENZENE, PENTABROMO(TETRABROMOPHENOXY)-

SUBMISSION #: 8EHQ-0585-0555

CAS NUMBER: 63936-56-1 CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, NONABROMO DERIV.

SUBMISSION #: 8EHQ-0585-0555

CAS NUMBER: 64741-62-4 CHEMICAL NAME: CLARIFIED OILS (PETROLEUM), CATALYTIC CRACKED

SUBMISSION #: 8EHQ-1185-0576

CAS NUMBER: 64741-62-4 CHEMICAL NAME: OIL (PETROLEUM), CLARIFIED SLURRY

SUBMISSION #: 8EHQ-1185-0576

CAS NUMBER: 64742-80-9 CHEMICAL NAME: DISTILLATES (PETROLEUM), HYDRODESULFURIZED MIDDLE

SUBMISSION #: 8EHQ-0786-0610

CAS NUMBER: 64742-80-9 CHEMICAL NAME: OIL (PETROLEUM), MINERAL SEAL

SUBMISSION #: 8EHQ-0786-0610

CAS NUMBER: 64742-94-5 CHEMICAL NAME: SOLVENT NAPHTHA (PETROLEUM), HEAVY AROM.

SUBMISSION #: 8EHQ-0686-0604

CAS NUMBER: 68479-98-1 CHEMICAL NAME: BENZENEDIAMINE, AR,AR-DIETHYL-AR-METHYL-

SUBMISSION #: 8EHQ-1286-0648

APPENDIX B: STATUS REPORTS BY CAS NUMBER

CAS NUMBER: 68928-80-3 CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, HEPTABROMO DERIV.

SUBMISSION #: 8EHQ-0585-0555

CAS NUMBER: 70657-70-4 CHEMICAL NAME: 1-PROPANOL, 2-METHOXY-, ACETATE

SUBMISSION #: 8EHQ-0585-0572

CAS NUMBER: 76714-88-0 CHEMICAL NAME: 1-PENTEN-3-OL, (E)-1-(2,4-DICHLOROPHENYL)-4,4-DIMETHYL-2-(1, 2,4-TRIAZOL-1-YL)-

SUBMISSION #: 8EHQ-0485-0548

CAS NUMBER: 80387-97-9 CHEMICAL NAME: ACETIC ACID, [[[3,5-BIS(1,1-DIMETHYLETHYL)-4-HYDROXYPHENYL]M ETHYL]THIO]-, 2-ETHYLHEXYL ESTER

SUBMISSION #: 8EHQ-0285-0544

CAS NUMBER: 80387-97-9 CHEMICAL NAME: IRGANOX 1192

SUBMISSION #: 8EHQ-0285-0544

CAS NUMBER: 82244-86-8 CHEMICAL NAME: HYDROXYLAMINE, O-(3-CHLORO-2-PROPENYL)-, HYDROCHLORIDE

SUBMISSION #: 8EHQ-1086-0637

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-0186-0586 S
CHEMICAL NAME: ACETAMIDE, 2-CHLORO-N-METHYL-N-SUBSTITUTED

CAS NUMBER: 64-19-7
SUBMISSION #: 8EHQ-0486-0600
CHEMICAL NAME: ACETIC ACID

CAS NUMBER: 108-05-4
SUBMISSION #: 8EHQ-0185-0543
CHEMICAL NAME: ACETIC ACID ETHENYL ESTER
8EHQ-1086-0642

CAS NUMBER: 80387-97-9
SUBMISSION #: 8EHQ-0285-0544
CHEMICAL NAME: ACETIC ACID, [[[3,5-BIS(1,1-DIMETHYLETHYL)-4-HYDROXYPHENYL]METHYL]THIO]-, 2-ETHYLHEXYL ESTER

CAS NUMBER: 79-06-1
SUBMISSION #: 8EHQ-0785-0560
CHEMICAL NAME: ACRYLAMIDE

CAS NUMBER: 79-10-7
SUBMISSION #: 8EHQ-0386-0592
CHEMICAL NAME: ACRYLIC ACID

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-0586-0602 S
CHEMICAL NAME: ACRYLIC ACID DERIVATIVES
8EHQ-1186-0646 S

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-0585-0556 S
CHEMICAL NAME: ACRYLIC ACID, 2-METHYL-, (COMPLEX MONOMER MIXTURE)

CAS NUMBER: 107-13-1
SUBMISSION #: 8EHQ-0486-0598
CHEMICAL NAME: ACRYLONITRILE

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-1086-0636 S
CHEMICAL NAME: ALCOHOL ETHOXYLATES, CHLORIDE CAPPED

CAS NUMBER: NONE
CHEMICAL NAME: ALUMINOSILICATE FIBERS
SUBMISSION #: 8EHQ-0485-0553

CAS NUMBER: 128-85-8
CHEMICAL NAME: 9,10-ANTHRACENEDIONE, 1-(METHYLAMINO)-4-[(4-METHYLPHENYL)AMINO]-
SUBMISSION #: 8EHQ-1285-0580

CAS NUMBER: 25068-38-6
CHEMICAL NAME: ARALDITE 6010
SUBMISSION #: 8EHQ-1285-0577

CAS NUMBER: 7440-38-2
CHEMICAL NAME: ARSENIC
SUBMISSION #: 8EHQ-0586-0601

CAS NUMBER: 1332-21-4
CHEMICAL NAME: ASBESTOS
SUBMISSION #: 8EHQ-0586-0601

CAS NUMBER: NONE
CHEMICAL NAME: AUTOMOTIVE COOLANTS
SUBMISSION #: 8EHQ-0885-0564 S

CAS NUMBER: 57116-45-7
CHEMICAL NAME: 1-AZIRIDINEPROPANOIC ACID, 2-[[3-(1-AZIRIDINYL)-1-OXOPROPOXY]METHYL]-2-(HYDROXYMETHYL)-1,3-PROPANEDIYL ESTER
SUBMISSION #: 8EHQ-0986-0630

CAS NUMBER: 6320-14-5
CHEMICAL NAME: C. I. BASIC RED 12
SUBMISSION #: 8EHQ-1285-0581

CAS NUMBER: CONFIDENT
CHEMICAL NAME: BENZENAMINE, ALKYLATED
SUBMISSION #: 8EHQ-0886-0621 S

CAS NUMBER: 95-69-2
CHEMICAL NAME: BENZENAMINE, 4-CHLORO-2-METHYL-
SUBMISSION #: 8EHQ-0986-0634

CAS NUMBER: 101-77-9 CHEMICAL NAME: BENZENAMINE, 4,4'-METHYLENEBIS-
SUBMISSION #: 8EHQ-1285-0577

CAS NUMBER: 108-45-2 CHEMICAL NAME: 1,3-BENZENEDIAMINE
SUBMISSION #: 8EHQ-1285-0577

CAS NUMBER: 68479-98-1 CHEMICAL NAME: BENZENEDIAMINE, AR,AR-DIETHYL-AR-METHYL-
SUBMISSION #: 8EHQ-1286-0648

CAS NUMBER: 2095-02-5 CHEMICAL NAME: 1,3-BENZENEDIAMINE, 2,4-DIETHYL-6-METHYL-
SUBMISSION #: 8EHQ-1286-0648

CAS NUMBER: 2095-01-4 CHEMICAL NAME: 1,3-BENZENEDIAMINE, 4,6-DIETHYL-2-METHYL-
SUBMISSION #: 8EHQ-1286-0648

CAS NUMBER: 84-74-2 CHEMICAL NAME: 1,2-BENZENEDICARBOXYLIC ACID, DIBUTYL ESTER
SUBMISSION #: 8EHQ-0886-0620

CAS NUMBER: 131-11-3 CHEMICAL NAME: 1,2-BENZENEDICARBOXYLIC ACID, DIMETHYL ESTER
SUBMISSION #: 8EHQ-0886-0620

CAS NUMBER: 60-12-8 CHEMICAL NAME: BENZENEETHANOL
SUBMISSION #: 8EHQ-0186-0587

CAS NUMBER: 63936-56-1 CHEMICAL NAME: BENZENE, PENTABROMO(TETRABROMOPHENOXY)-
SUBMISSION #: 8EHQ-0585-0555

CAS NUMBER: 9080-79-9 CHEMICAL NAME: BENZENESULFONIC ACID, ETHENYL-, HOMOPOLYMER, SODIUM SALT
SUBMISSION #: 8EHQ-0485-0549 S

CAS NUMBER: 97-00-7 CHEMICAL NAME: BENZENE, 1-CHLORO-2,4-DINITRO-

SUBMISSION #: 8EHQ-0485-0552

CAS NUMBER: NONE CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, BROMINATED DERIV.

SUBMISSION #: 8EHQ-0585-0555

CAS NUMBER: 68928-80-3 CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, HEPTABROMO DERIV.

SUBMISSION #: 8EHQ-0585-0555

CAS NUMBER: 36483-60-0 CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, HEXABROMO DERIV.

SUBMISSION #: 8EHQ-0585-0555

CAS NUMBER: 63936-56-1 CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, NONABROMO DERIV.

SUBMISSION #: 8EHQ-0585-0555

CAS NUMBER: 32536-52-0 CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, OCTABROMO DERIV.

SUBMISSION #: 8EHQ-0585-0555

CAS NUMBER: 23676-09-7 CHEMICAL NAME: BENZOIC ACID, 4-ETHOXY-, ETHYL ESTER

SUBMISSION #: 8EHQ-0585-0554 S

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-1286-0645

CAS NUMBER: CONFIDENT CHEMICAL NAME: BENZOTRIAZOLE-2-YL SUBSTITUTED HYDROXYPHENYLPROPIONATE ESTER

SUBMISSION #: 8EHQ-0486-0597 S

CAS NUMBER: 26538-44-3 CHEMICAL NAME: 1H-2-BENZOXACYCLOTETRADECIN-1-ONE, 3,4,5,6,7,8,9,10,11,12-DECAHYDRO-7,14,16-TRIHYDROXY-3-METHYL-, [3S-(3R*,7S*)]-

SUBMISSION #: 8EHQ-0485-0551 *

CAS NUMBER: 106-99-0 CHEMICAL NAME: 1,3-BUTADIENE
SUBMISSION #: 8EHQ-0786-0615

CAS NUMBER: 123-72-8 CHEMICAL NAME: BUTANAL
SUBMISSION #: 8EHQ-0786-0617

CAS NUMBER: 110-69-0 CHEMICAL NAME: BUTANAL, OXIME
SUBMISSION #: 8EHQ-1185-0573

CAS NUMBER: 924-16-3 CHEMICAL NAME: 1-BUTANAMINE, N-BUTYL-N-NITROSO-
SUBMISSION #: 8EHQ-1186-0643

CAS NUMBER: 52942-64-0 CHEMICAL NAME: BUTANEDIOIC ACID, (ETHOXYMETHYLENE)OXO-, DIETHYL ESTER
SUBMISSION #: 8EHQ-1086-0640 S *

CAS NUMBER: 55130-39-7 CHEMICAL NAME: BUTANEDIOIC ACID, (ETHOXYMETHYLENE)OXO-, DIETHYL ESTER, (E)-
SUBMISSION #: 8EHQ-1086-0640 S *

CAS NUMBER: 55130-49-9 CHEMICAL NAME: BUTANEDIOIC ACID, (ETHOXYMETHYLENE)OXO-, DIETHYL ESTER, (Z)-
SUBMISSION #: 8EHQ-1086-0640 S *

CAS NUMBER: 107-92-6 CHEMICAL NAME: BUTANOIC ACID
SUBMISSION #: 8EHQ-0486-0600

CAS NUMBER: 60-01-5 CHEMICAL NAME: BUTANOIC ACID, 1,2,3-PROPANETRIYL ESTER
SUBMISSION #: 8EHQ-0486-0600

CAS NUMBER: 22984-54-9 CHEMICAL NAME: 2-BUTANONE, O,O',O''-(METHYLSILYLIDYNE)TRIOXIME
SUBMISSION #: 8EHQ-1186-0647

CAS NUMBER: 34206-40-1 CHEMICAL NAME: 2-BUTANONE, O,O',O'',O'''-SILANETETRAYLTETRAOXIME
SUBMISSION #: 8EHQ-1186-0647

CAS NUMBER: 999-21-3 CHEMICAL NAME: 2-BUTENEDIOIC ACID (Z)-, DI-2-PROPENYL ESTER
SUBMISSION #: 8EHQ-0786-0612

CAS NUMBER: 764-41-0 CHEMICAL NAME: 2-BUTENE, 1,4-DICHLORO-
SUBMISSION #: 8EHQ-0985-0567

CAS NUMBER: 7440-43-9 CHEMICAL NAME: CADMIUM
SUBMISSION #: 8EHQ-0286-0588 * 8EHQ-0586-0601

CAS NUMBER: 1306-19-0 CHEMICAL NAME: CADMIUM OXIDE (CDO)
SUBMISSION #: 8EHQ-0886-0618 S

CAS NUMBER: 1306-23-6 CHEMICAL NAME: CADMIUM SULFIDE, (CDS)
SUBMISSION #: 8EHQ-0886-0618 S

CAS NUMBER: 6320-14-5 CHEMICAL NAME: CALCOZINE RED BG
SUBMISSION #: 8EHQ-1285-0581

CAS NUMBER: NONE CHEMICAL NAME: CARBAZOLES
SUBMISSION #: 8EHQ-1185-0576

CAS NUMBER: 598-62-9 CHEMICAL NAME: CARBONIC ACID, MANGANESE(2+) SALT (1:1)
SUBMISSION #: 8EHQ-0286-0588 *

CAS NUMBER: CONFIDENT CHEMICAL NAME: CARBOXANILIDE, HALOGENATED ALIPHATIC
SUBMISSION #: 8EHQ-0486-0596 S

CAS NUMBER: CONFIDENT CHEMICAL NAME: CGA-143686
SUBMISSION #: 8EHQ-0685-0583 S

CAS NUMBER: CONFIDENT CHEMICAL NAME: CGA-149071
SUBMISSION #: 8EHQ-0285-0545 S

CAS NUMBER: UNKNOWN CHEMICAL NAME: CGA-18809
SUBMISSION #: 8EHQ-0786-0613

CAS NUMBER: 3734-48-3 CHEMICAL NAME: CHLORDENE
SUBMISSION #: 8EHQ-1085-0570

CAS NUMBER: CONFIDENT CHEMICAL NAME: CHLORINATED ACID
SUBMISSION #: 8EHQ-1086-0639 S

CAS NUMBER: CONFIDENT CHEMICAL NAME: CHLOROBENZENE, SUBSTITUTED
SUBMISSION #: 8EHQ-0986-0625 S

CAS NUMBER: NONE CHEMICAL NAME: CIBACRON BLACK GR-D
SUBMISSION #: 8EHQ-0386-0589 S

CAS NUMBER: NONE CHEMICAL NAME: CIBACRON BLACK GR LQ 40
SUBMISSION #: 8EHQ-0386-0589 S

CAS NUMBER: NONE CHEMICAL NAME: CIBACRON GOLDEN YELLOW 2R
SUBMISSION #: 8EHQ-0386-0589 S

CAS NUMBER: NONE CHEMICAL NAME: CIBACRON GOLDEN YELLOW 2R-A
SUBMISSION #: 8EHQ-0386-0589 S

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-0386-0589 S
CHEMICAL NAME: CIBACRON GOLDEN YELLOW 2R LQ 25

CAS NUMBER: 64741-62-4
SUBMISSION #: 8EHQ-1185-0576
CHEMICAL NAME: CLARIFIED OILS (PETROLEUM), CATALYTIC CRACKED

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-0586-0601
CHEMICAL NAME: COAL DUST

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-0585-0554 S
8EHQ-1186-0646 S
CHEMICAL NAME: CONFIDENTIAL
8EHQ-0386-0594 S
8EHQ-0586-0602 S

CAS NUMBER: 7440-50-8
SUBMISSION #: 8EHQ-0586-0601
CHEMICAL NAME: COPPER

CAS NUMBER: 137-29-1
SUBMISSION #: 8EHQ-0786-0616
CHEMICAL NAME: COPPER, BIS(DIMETHYLCARBAMODITHIOATO-S,S')-, (SP-4-1)-

CAS NUMBER: 28182-81-2
SUBMISSION #: 8EHQ-1086-0638 *
CHEMICAL NAME: CORONATE EH

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-0185-0542 S
CHEMICAL NAME: CUTTING FLUID

CAS NUMBER: 99422-01-2
SUBMISSION #: 8EHQ-0186-0584
CHEMICAL NAME: 1,3-CYCLOHEXANEDIONE, 5-[2-(ETHYLTHIO)PROPYL]-2-(1-OXOPROPYL)-

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-1085-0571 S
CHEMICAL NAME: DIAMINE, AROMATIC

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-0785-0562 S
CHEMICAL NAME: DICHLOROPHENYLALKOXYALKYLOXOHETEROMONOCYCLE

CAS NUMBER: UNKNOWN
SUBMISSION #: 8EHQ-0786-0613
CHEMICAL NAME: O,O-DIMETHYL-S-(6-CHLOR-OXAZOLO(4,5,B)PYRIDIN-2(3H)-ON-3-YL-METHYL)-THIOPHOSPHATE

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-0986-0623 S
CHEMICAL NAME: DIPHENYL ETHER, SUBSTITUTED

CAS NUMBER: 8005-72-9
SUBMISSION #: 8EHQ-1286-0645
CHEMICAL NAME: C.I. DIRECT YELLOW 28

CAS NUMBER: 64742-80-9
SUBMISSION #: 8EHQ-0786-0610
CHEMICAL NAME: DISTILLATES (PETROLEUM), HYDRODESULFURIZED MIDDLE

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-0585-0557
CHEMICAL NAME: DISTILLATES (PETROLEUM), REFINERY STREAMS

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-1186-0644
CHEMICAL NAME: DOW CORNING FS-1265 FLUID (1,000 CS)

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-1186-0644
CHEMICAL NAME: DOW CORNING FS-1265 FLUID (10,000 CS)

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-1186-0644
CHEMICAL NAME: DOW CORNING FS-1265 FLUID (300 CS)

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-0586-0601
CHEMICAL NAME: DUST, COAL

CAS NUMBER: NONE CHEMICAL NAME: EPOXY RESINS
SUBMISSION #: 8EHQ-1285-0577

CAS NUMBER: NONE CHEMICAL NAME: ERL-2258
SUBMISSION #: 8EHQ-1285-0577

CAS NUMBER: 2386-90-5 CHEMICAL NAME: ERR 4205
SUBMISSION #: 8EHQ-1285-0577

CAS NUMBER: 55-18-5 CHEMICAL NAME: ETHANAMINE, N-ETHYL-N-NITROSO-
SUBMISSION #: 8EHQ-1186-0643

CAS NUMBER: 107-21-1 CHEMICAL NAME: 1,2-ETHANEDIOL
SUBMISSION #: 8EHQ-0485-0552

CAS NUMBER: 76-13-1 CHEMICAL NAME: ETHANE, 1,1,2-TRICHLORO-1,2,2-TRIFLUORO-
SUBMISSION #: 8EHQ-0986-0631 S

CAS NUMBER: 64-17-5 CHEMICAL NAME: ETHANOL
SUBMISSION #: 8EHQ-0786-0617

CAS NUMBER: 111-15-9 CHEMICAL NAME: ETHANOL, 2-ETHOXY-, ACETATE
SUBMISSION #: 8EHQ-0386-0593

CAS NUMBER: 1116-54-7 CHEMICAL NAME: ETHANOL, 2,2'-(NITROSOIMINO)BIS-
SUBMISSION #: 8EHQ-0185-0542 S 8EHQ-0885-0564 S

CAS NUMBER: 2831-60-9 CHEMICAL NAME: ETHANOL, 2-(2,4-DINITROPHENOXY)-
SUBMISSION #: 8EHQ-0485-0552

CAS NUMBER: 25646-77-9 CHEMICAL NAME: ETHANOL, 2-[(4-AMINO-3-METHYLPHENYL)ETHYLAMINO]-, SULFATE (1 :1) (SALT)

SUBMISSION #: 8EHQ-1185-0575

CAS NUMBER: 75-01-4 CHEMICAL NAME: ETHENE, CHLORO-

SUBMISSION #: 8EHQ-0986-0629

CAS NUMBER: CONFIDENT CHEMICAL NAME: ETHER (CYCLIC), HALOALKYL SUBSTITUTED

SUBMISSION #: 8EHQ-0986-0633 S

CAS NUMBER: 75-21-8 CHEMICAL NAME: ETHYLENE OXIDE

SUBMISSION #: 8EHQ-0786-0611 8EHQ-1086-0641

CAS NUMBER: 110-69-0 CHEMICAL NAME: EXKIN NO. 1 ANTI-SKINNING AGENT

SUBMISSION #: 8EHQ-1185-0573

CAS NUMBER: 110-69-0 CHEMICAL NAME: EXKIN 1

SUBMISSION #: 8EHQ-1185-0573

CAS NUMBER: 1271-55-2 CHEMICAL NAME: FERROCENE, ACETYL-

SUBMISSION #: 8EHQ-1285-0578

CAS NUMBER: NONE CHEMICAL NAME: FIBERFRAX

SUBMISSION #: 8EHQ-0485-0553

CAS NUMBER: 68-12-2 CHEMICAL NAME: FORMAMIDE, N,N-DIMETHYL-

SUBMISSION #: 8EHQ-0486-0598

CAS NUMBER: 108-30-5 CHEMICAL NAME: 2,5-FURANDIONE, DIHYDRO-

SUBMISSION #: 8EHQ-0885-0565 S

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-0786-0609 S
CHEMICAL NAME: HETEROCYCLIC DERIVATIVE

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-0186-0582 S
CHEMICAL NAME: HETEROMONOCYCLIC HETEROMONOCYCLE, CHLOROPHENOXY CHLOROPHENYL ALKYL SUBSTITUTED

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-0285-0545 S
CHEMICAL NAME: HETEROMONOCYCLIC HETEROMONOCYCLE, HALOPHENOXY HALOPHENYL SUBSTITUTED

CAS NUMBER: 28182-81-2
SUBMISSION #: 8EHQ-1086-0638 *
CHEMICAL NAME: HEXANE, 1,6-DIISOCYANATO-, HOMOPOLYMER

CAS NUMBER: 142-62-1
SUBMISSION #: 8EHQ-0486-0600
CHEMICAL NAME: HEXANOIC ACID

CAS NUMBER: 82244-86-8
SUBMISSION #: 8EHQ-1086-0637
CHEMICAL NAME: HYDROXYLAMINE, O-(3-CHLORO-2-PROPENYL)-, HYDROCHLORIDE

CAS NUMBER: 6320-14-5
SUBMISSION #: 8EHQ-1285-0581
CHEMICAL NAME: 3H-INDOLIUM, 2-[3-(1,3-DIHYDRO-1,3,3-TRIMETHYL-2H-INDOL-2-YLIDENE)-1-PROPENYL]-1,3,3-TRIMETHYL-, CHLORIDE

CAS NUMBER: 80387-97-9
SUBMISSION #: 8EHQ-0285-0544
CHEMICAL NAME: IRGANOX 1192

CAS NUMBER: 9046-10-0
SUBMISSION #: 8EHQ-0885-0565 S
CHEMICAL NAME: JEFFAMINE D-2000

CAS NUMBER: UNKNOWN
SUBMISSION #: 8EHQ-0485-0550
CHEMICAL NAME: KEVLAR

CAS NUMBER: 25646-77-9 CHEMICAL NAME: KODAK COLOR DEVELOPING AGENT (CD-4)
SUBMISSION #: 8EHQ-1185-0575

CAS NUMBER: 7439-92-1 CHEMICAL NAME: LEAD
SUBMISSION #: 8EHQ-0285-0546 8EHQ-0286-0588 * 8EHQ-0586-0601

CAS NUMBER: 7439-96-5 CHEMICAL NAME: MANGANESE
SUBMISSION #: 8EHQ-0286-0588 *

CAS NUMBER: 1313-13-9 CHEMICAL NAME: MANGANESE OXIDE, (MNO2)
SUBMISSION #: 8EHQ-0286-0588 *

CAS NUMBER: 7439-97-6 CHEMICAL NAME: MERCURY
SUBMISSION #: 8EHQ-0286-0588 * 8EHQ-0586-0601

CAS NUMBER: NONE CHEMICAL NAME: MERCURY/ZINC ALMALGAM
SUBMISSION #: 8EHQ-0286-0588 *

CAS NUMBER: 23209-59-8 CHEMICAL NAME: METAPHOSPHORIC ACID, (HPO3), CALCIUM SODIUM SALT
SUBMISSION #: 8EHQ-0386-0619

CAS NUMBER: 62-75-9 CHEMICAL NAME: METHANAMINE, N-METHYL-N-NITROSO-
SUBMISSION #: 8EHQ-0885-0564 S 8EHQ-1186-0643

CAS NUMBER: 3734-48-3 CHEMICAL NAME: 4,7-METHANO-1H-INDENE, 4,5,6,7,8,8-HEXACHLORO-3A,4,7,7A-TETR AHYDRO-
SUBMISSION #: 8EHQ-1085-0570

CAS NUMBER: 12001-26-2 CHEMICAL NAME: MICA (DUST), SILICEOUS MUSCOVITE
SUBMISSION #: 8EHQ-0986-0632

CAS NUMBER: UNKNOWN
CHEMICAL NAME: MINERAL SPIRITS
SUBMISSION #: 8EHQ-0986-0631 S

CAS NUMBER: NONE
CHEMICAL NAME: MISC. CHEMICALS
SUBMISSION #: 8EHQ-0985-0566

CAS NUMBER: NONE
CHEMICAL NAME: MOLYKOTE FS-3451 GREASE
SUBMISSION #: 8EHQ-1186-0644

CAS NUMBER: NONE
CHEMICAL NAME: MOLYKOTE FS-3452 VALVE LUBRICANT
SUBMISSION #: 8EHQ-1186-0644

CAS NUMBER: NONE
CHEMICAL NAME: MONOMER PCM-200
SUBMISSION #: 8EHQ-0585-0556 S

CAS NUMBER: NONE
CHEMICAL NAME: MONOMER PCM-400
SUBMISSION #: 8EHQ-0585-0556 S

CAS NUMBER: NONE
CHEMICAL NAME: MONOMER QM-867
SUBMISSION #: 8EHQ-0585-0556 S

CAS NUMBER: NONE
CHEMICAL NAME: MONOMER QM-928
SUBMISSION #: 8EHQ-0585-0556 S

CAS NUMBER: 59-89-2
CHEMICAL NAME: MORPHOLINE, N-NITROSO-
SUBMISSION #: 8EHQ-0885-0564 S
8EHQ-1186-0643

CAS NUMBER: 7440-02-0
CHEMICAL NAME: NICKEL
SUBMISSION #: 8EHQ-0586-0601

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-0986-0624 S
CHEMICAL NAME: NITROBENZENE, SUBSTITUTED

CAS NUMBER: 10024-97-2
SUBMISSION #: 8EHQ-0886-0628
CHEMICAL NAME: NITROGEN OXIDE (N2O)

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-1186-0643
CHEMICAL NAME: NITROPORE ATA

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-0185-0542 S
CHEMICAL NAME: NITROSAMINES
8EHQ-0885-0564 S
8EHQ-1186-0643

CAS NUMBER: 924-16-3
SUBMISSION #: 8EHQ-1186-0643
CHEMICAL NAME: N-NITROSODIBUTYLAMINE

CAS NUMBER: 1116-54-7
SUBMISSION #: 8EHQ-0185-0542 S
CHEMICAL NAME: N-NITROSODIETHANOLAMINE
8EHQ-0885-0564 S

CAS NUMBER: 55-18-5
SUBMISSION #: 8EHQ-1186-0643
CHEMICAL NAME: N-NITROSODIETHYLAMINE

CAS NUMBER: 62-75-9
SUBMISSION #: 8EHQ-0885-0564 S
CHEMICAL NAME: N-NITROSODIMETHYLAMINE
8EHQ-1186-0643

CAS NUMBER: 59-89-2
SUBMISSION #: 8EHQ-0885-0564 S
CHEMICAL NAME: N-NITROSOMORPHOLINE
8EHQ-1186-0643

CAS NUMBER: 10024-97-2
SUBMISSION #: 8EHQ-0886-0628
CHEMICAL NAME: NITROUS OXIDE

CAS NUMBER: 111-86-4 CHEMICAL NAME: 1-OCTANAMINE
SUBMISSION #: 8EHQ-1085-0569

CAS NUMBER: 5538-94-3 CHEMICAL NAME: 1-OCTANAMINIUM, N,N-DIMETHYL-N-OCTYL-, CHLORIDE
SUBMISSION #: 8EHQ-0386-0591

CAS NUMBER: 64741-62-4 CHEMICAL NAME: OIL (PETROLEUM), CLARIFIED SLURRY
SUBMISSION #: 8EHQ-1185-0576

CAS NUMBER: 64742-80-9 CHEMICAL NAME: OIL (PETROLEUM), MINERAL SEAL
SUBMISSION #: 8EHQ-0786-0610

CAS NUMBER: NONE CHEMICAL NAME: OIL (PETROLEUM), REFINERY STREAMS
SUBMISSION #: 8EHQ-0585-0557

CAS NUMBER: 2386-90-5 CHEMICAL NAME: 6-OXABICYCLO[3.1.0]HEXANE, 2,2'-OXYBIS-
SUBMISSION #: 8EHQ-1285-0577

CAS NUMBER: 15571-58-1 CHEMICAL NAME: 8-OXA-3,5-DITHIA-4-STANNATETRADECANOIC ACID, 10-ETHYL-4,4-DI OCTYL-7-OXO-, 2-ETHYLHEXYL ESTER
SUBMISSION #: 8EHQ-0386-0594 S

CAS NUMBER: CONFIDENT CHEMICAL NAME: OXIMIDOALKANE, SUBSTITUTED
SUBMISSION #: 8EHQ-0685-0558 S

CAS NUMBER: 75-21-8 CHEMICAL NAME: OXIRANE
SUBMISSION #: 8EHQ-0786-0611 8EHQ-1086-0641

CAS NUMBER: 9038-95-3 CHEMICAL NAME: OXIRANE, METHYL-, POLYMER WITH OXIRANE, MONOBUTYL ETHER
SUBMISSION #: 8EHQ-1086-0635

CAS NUMBER: 123-54-6 CHEMICAL NAME: 2,4-PENTANEDIONE
SUBMISSION #: 8EHQ-0386-0595

CAS NUMBER: 109-52-4 CHEMICAL NAME: PENTANOIC ACID
SUBMISSION #: 8EHQ-0486-0600

CAS NUMBER: 76714-88-0 CHEMICAL NAME: 1-PENTEN-3-OL, (E)-1-(2,4-DICHLOROPHENYL)-4,4-DIMETHYL-2-(1, 2,4-TRIAZOL-1-YL)-
SUBMISSION #: 8EHQ-0485-0548

CAS NUMBER: NONE CHEMICAL NAME: PERFLUOROALKYL COMPOUNDS
SUBMISSION #: 8EHQ-0986-0631 S

CAS NUMBER: CONFIDENT CHEMICAL NAME: PERFLUOROALKYL RESIN
SUBMISSION #: 8EHQ-0986-0631 S

CAS NUMBER: 2628-17-3 CHEMICAL NAME: PHENOL, 4-ETHENYL-
SUBMISSION #: 8EHQ-1285-0579 S

CAS NUMBER: 25068-38-6 CHEMICAL NAME: PHENOL, 4,4'-(1-METHYLETHYLIDENE)BIS-, POLYMER WITH (CHLOROM ETHYL)OXIRANE
SUBMISSION #: 8EHQ-1285-0577

CAS NUMBER: NONE CHEMICAL NAME: PHOSPHATE FIBERS
SUBMISSION #: 8EHQ-0386-0619

CAS NUMBER: CONFIDENT CHEMICAL NAME: PHOSPHINE, ALKYL ARYL
SUBMISSION #: 8EHQ-0386-0590 S

CAS NUMBER: CONFIDENT CHEMICAL NAME: PHOSPHORIC ACID ESTER, METAL SALT
SUBMISSION #: 8EHQ-0786-0608 S

CAS NUMBER: 756-80-9 CHEMICAL NAME: PHOSPHORODITHIOIC ACID, O,O-DIMETHYL ESTER

SUBMISSION #: 8EHQ-0385-0547

CAS NUMBER: 2564-83-2 CHEMICAL NAME: 1-PIPERIDINYLOXY, 2,2,6,6-TETRAMETHYL-

SUBMISSION #: 8EHQ-0786-0607 S

CAS NUMBER: NONE CHEMICAL NAME: PM ACETATE

SUBMISSION #: 8EHQ-0585-0572

CAS NUMBER: 9003-13-8 CHEMICAL NAME: POLY[OXY(METHYL-1,2-ETHANEDIYL)], .ALPHA.-BUTYL-.OMEGA.-HYDROXY-

SUBMISSION #: 8EHQ-0985-0566

CAS NUMBER: 9046-10-0 CHEMICAL NAME: POLY[OXY(METHYL-1,2-ETHANEDIYL)], .ALPHA.-(2-AMINOMETHYLETHYL)-.OMEGA.-(2-AMINOMETHYLETHOXY)-

SUBMISSION #: 8EHQ-0885-0565 S

CAS NUMBER: UNKNOWN CHEMICAL NAME: POLY P-PHENYLENE TEREPHTHALAMIDE ARAMID FIBER

SUBMISSION #: 8EHQ-0485-0550

CAS NUMBER: UNKNOWN CHEMICAL NAME: PPD-T ARAMID FIBER

SUBMISSION #: 8EHQ-0485-0550

CAS NUMBER: 123-38-6 CHEMICAL NAME: PROPANAL

SUBMISSION #: 8EHQ-0985-0566

CAS NUMBER: 460-40-2 CHEMICAL NAME: PROPANAL, 3,3,3-TRIFLUORO-

SUBMISSION #: 8EHQ-1186-0644

CAS NUMBER: 63843-89-0 CHEMICAL NAME: PROPANEDIOIC ACID, [[3,5-BIS(1,1-DIMETHYLETHYL)-4-HYDROXYPHENYL]METHYL]BUTYL-, BIS(1,2,2,6,6-PENTAMETHYL-4-PIPERIDINYL) ESTER

SUBMISSION #: 8EHQ-0186-0585 S

CAS NUMBER: 79-09-4 CHEMICAL NAME: PROPANOIC ACID
SUBMISSION #: 8EHQ-0486-0600

CAS NUMBER: 4075-81-4 CHEMICAL NAME: PROPANOIC ACID, CALCIUM SALT
SUBMISSION #: 8EHQ-0486-0600

CAS NUMBER: 137-40-6 CHEMICAL NAME: PROPANOIC ACID, SODIUM SALT
SUBMISSION #: 8EHQ-0486-0600

CAS NUMBER: 10606-42-5 CHEMICAL NAME: PROPANOIC ACID, 3-METHOXY-, ETHYL ESTER
SUBMISSION #: 8EHQ-0486-0599

CAS NUMBER: 3852-09-3 CHEMICAL NAME: PROPANOIC ACID, 3-METHOXY-, METHYL ESTER
SUBMISSION #: 8EHQ-0486-0599

CAS NUMBER: 67-63-0 CHEMICAL NAME: 2-PROPANOL
SUBMISSION #: 8EHQ-0985-0566

CAS NUMBER: 108-65-6 CHEMICAL NAME: 2-PROPANOL, 1-METHOXY-, ACETATE
SUBMISSION #: 8EHQ-0585-0572

CAS NUMBER: 1569-01-3 CHEMICAL NAME: 2-PROPANOL, 1-PROPOXY-
SUBMISSION #: 8EHQ-0686-0603

CAS NUMBER: 70657-70-4 CHEMICAL NAME: 1-PROPANOL, 2-METHOXY-, ACETATE
SUBMISSION #: 8EHQ-0585-0572

CAS NUMBER: 1569-01-3 CHEMICAL NAME: PROPASOL SOLVENT P
SUBMISSION #: 8EHQ-0686-0603

CAS NUMBER: 79-06-1 CHEMICAL NAME: 2-PROPENAMIDE
SUBMISSION #: 8EHQ-0785-0560

CAS NUMBER: 115-07-1 CHEMICAL NAME: 1-PROPENE
SUBMISSION #: 8EHQ-0985-0566

CAS NUMBER: 107-13-1 CHEMICAL NAME: 2-PROPENENITRILE
SUBMISSION #: 8EHQ-0486-0598

CAS NUMBER: 79-10-7 CHEMICAL NAME: 2-PROPENOIC ACID
SUBMISSION #: 8EHQ-0386-0592

CAS NUMBER: CONFIDENT CHEMICAL NAME: 2-PROPENOIC ACID DERIVATIVES
SUBMISSION #: 8EHQ-0586-0602 S 8EHQ-1186-0646 S

CAS NUMBER: NONE CHEMICAL NAME: 2-PROPENOIC ACID, 2-METHYL-, (COMPLEX MONOMER MIXTURE)
SUBMISSION #: 8EHQ-0585-0556 S

CAS NUMBER: 123-38-6 CHEMICAL NAME: PROPIONALDEHYDE
SUBMISSION #: 8EHQ-0985-0566

CAS NUMBER: 460-40-2 CHEMICAL NAME: PROPIONALDEHYDE, 3,3,3-TRIFLUORO-
SUBMISSION #: 8EHQ-1186-0644

CAS NUMBER: 115-07-1 CHEMICAL NAME: PROPYLENE
SUBMISSION #: 8EHQ-0985-0566

CAS NUMBER: CONFIDENT CHEMICAL NAME: PYRIDINE, HALOGENATED
SUBMISSION #: 8EHQ-0986-0626 S

CAS NUMBER: 88-12-0 CHEMICAL NAME: PYROL
SUBMISSION #: 8EHQ-0785-0561 S

CAS NUMBER: 88-12-0 CHEMICAL NAME: 2-PYRROLIDINONE, 1-ETHENYL-
SUBMISSION #: 8EHQ-0785-0561 S

CAS NUMBER: CONFIDENT CHEMICAL NAME: QUATERNARY AMMONIUM CHLORIDE
SUBMISSION #: 8EHQ-1086-0636 S

CAS NUMBER: NONE CHEMICAL NAME: RALGRO
SUBMISSION #: 8EHQ-0485-0551 *

CAS NUMBER: UNKNOWN CHEMICAL NAME: REACTION PRODUCT OF BETA-[3-(2H-BENZOTRIAZOL-2-YL)-4-HYDROXY -5-TERT-BUTYLPHENYL]PROPIONIC ACID, METHYL ESTER AND POLYETH YLENE GLYCOL 300
SUBMISSION #: 8EHQ-0986-0627

CAS NUMBER: CONFIDENT CHEMICAL NAME: C. I. REACTIVE ORANGE 12
SUBMISSION #: 8EHQ-0386-0589 S

CAS NUMBER: 12225-84-2 CHEMICAL NAME: C. I. REACTIVE ORANGE 12
SUBMISSION #: 8EHQ-0386-0589 S

CAS NUMBER: NONE CHEMICAL NAME: REFRACTORY CERAMIC FIBERS
SUBMISSION #: 8EHQ-0485-0553

CAS NUMBER: NONE CHEMICAL NAME: SAYTEX 111
SUBMISSION #: 8EHQ-0585-0555

CAS NUMBER: 1825-62-3 CHEMICAL NAME: SILANE, ETHOXYTRIMETHYL-
SUBMISSION #: 8EHQ-0985-0568 S

CAS NUMBER: 22984-54-9
SUBMISSION #: 8EHQ-1186-0647
CHEMICAL NAME: SILANE, METHYLOXIMINO-

CAS NUMBER: CONFIDENT
SUBMISSION #: 8EHQ-0686-0605 S
CHEMICAL NAME: SILANE (ORGANO) OLIGOMER

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-0686-0605 S
CHEMICAL NAME: SILANE (ORGANO) OLIGOMERS, MIXTURE OF COMPLEX

CAS NUMBER: 34206-40-1
SUBMISSION #: 8EHQ-1186-0647
CHEMICAL NAME: SILANE, TETRAOXIMINO-

CAS NUMBER: 15112-89-7
SUBMISSION #: 8EHQ-0685-0559 S
CHEMICAL NAME: SILANETRIAMINE, N,N,N',N',N'',N''-HEXAMETHYL-

CAS NUMBER: NONE
SUBMISSION #: 8EHQ-1186-0644
CHEMICAL NAME: SILASTIC LS-2860 FLUOROSILICONE RUBBER

CAS NUMBER: UNKNOWN
SUBMISSION #: 8EHQ-1186-0643
CHEMICAL NAME: SILASTIC Q4-4682 SILICONE RUBBER

CAS NUMBER: UNKNOWN
SUBMISSION #: 8EHQ-1186-0643
CHEMICAL NAME: SILASTIC Q4-4683 SILICONE RUBBER

CAS NUMBER: 21297-72-3
SUBMISSION #: 8EHQ-0985-0568 S
CHEMICAL NAME: 1-SILA-2-AZACYCLOPENTANE, 1,1-DIETHOXY-2-TRIMETHYLSILYL-

CAS NUMBER: UNKNOWN
SUBMISSION #: 8EHQ-0985-0568 S
CHEMICAL NAME: 1-SILA-2-AZACYCLOPENTANE, 1,1-DIETHOXY-2-TRIMETHYLSILYL-, DIMER

CAS NUMBER: 12001-26-2 CHEMICAL NAME: SILICATE, MICA
SUBMISSION #: 8EHQ-0986-0632

CAS NUMBER: 681-84-5 CHEMICAL NAME: SILICIC ACID, (H4SIO4), TETRAMETHYL ESTER
SUBMISSION #: 8EHQ-0785-0563

CAS NUMBER: 409-21-2 CHEMICAL NAME: SILICON CARBIDE FIBERS
SUBMISSION #: 8EHQ-1185-0574

CAS NUMBER: 409-21-2 CHEMICAL NAME: SILICON CARBIDE, (SIC)
SUBMISSION #: 8EHQ-1185-0574

CAS NUMBER: 1310-73-2 CHEMICAL NAME: SODIUM HYDROXIDE, (NA(OH))
SUBMISSION #: 8EHQ-0485-0552

CAS NUMBER: 128-85-8 CHEMICAL NAME: C. I. SOLVENT BLUE 11
SUBMISSION #: 8EHQ-1285-0580

CAS NUMBER: 64742-94-5 CHEMICAL NAME: SOLVENT NAPHTHA (PETROLEUM), HEAVY AROM.
SUBMISSION #: 8EHQ-0686-0604

CAS NUMBER: 3542-36-7 CHEMICAL NAME: STANNANE, DICHLORODIOCTYL-
SUBMISSION #: 8EHQ-0786-0614 S

CAS NUMBER: 3091-25-6 CHEMICAL NAME: STANNANE, TRICHLOROOCTYL-
SUBMISSION #: 8EHQ-0786-0614 S

CAS NUMBER: 108-30-5 CHEMICAL NAME: SUCCINIC ANHYDRIDE
SUBMISSION #: 8EHQ-0885-0565 S

CAS NUMBER: 128-85-8 CHEMICAL NAME: SUDAN BLUE GA
SUBMISSION #: 8EHQ-1285-0580

CAS NUMBER: 7446-09-5 CHEMICAL NAME: SULFUR DIOXIDE
SUBMISSION #: 8EHQ-0586-0601

CAS NUMBER: 7664-93-9 CHEMICAL NAME: SULFURIC ACID
SUBMISSION #: 8EHQ-0985-0566

CAS NUMBER: 10124-36-4 CHEMICAL NAME: SULFURIC ACID, CADMIUM SALT (1:1)
SUBMISSION #: 8EHQ-0886-0618 S

CAS NUMBER: 64-67-5 CHEMICAL NAME: SULFURIC ACID, DIETHYL ESTER
SUBMISSION #: 8EHQ-0585-0554 S

CAS NUMBER: 7785-87-7 CHEMICAL NAME: SULFURIC ACID, MANGANESE(2+) SALT (1:1)
SUBMISSION #: 8EHQ-0286-0588 *

CAS NUMBER: UNKNOWN CHEMICAL NAME: TINUVIN 1130
SUBMISSION #: 8EHQ-0986-0627

CAS NUMBER: 63843-89-0 CHEMICAL NAME: TINUVIN 144
SUBMISSION #: 8EHQ-0186-0585 S

CAS NUMBER: 9003-13-8 CHEMICAL NAME: UCON LUBRICANT LB-250
SUBMISSION #: 8EHQ-0985-0566

CAS NUMBER: 9038-95-3 CHEMICAL NAME: UCON LUBRICANT 50-HB-5100
SUBMISSION #: 8EHQ-1086-0635

CAS NUMBER: NONE — CHEMICAL NAME: UNKNOWN CHEMICAL(S)
SUBMISSION #: 8EHQ-0886-0622 S

CAS NUMBER: CONFIDENT — CHEMICAL NAME: UREA, HETEROMONOCYCLIC CARBOMONOCYCLIC
SUBMISSION #: 8EHQ-0786-0606 S

CAS NUMBER: 9080-79-9 — CHEMICAL NAME: VERSA-TL 600
SUBMISSION #: 8EHQ-0485-0549 S

CAS NUMBER: 108-05-4 — CHEMICAL NAME: VINYL ACETATE
SUBMISSION #: 8EHQ-0185-0543 8EHQ-1086-0642

CAS NUMBER: 75-01-4 — CHEMICAL NAME: VINYL CHLORIDE
SUBMISSION #: 8EHQ-0986-0629

CAS NUMBER: 8005-72-9 — CHEMICAL NAME: YELLOW SHADE 18569
SUBMISSION #: 8EHQ-1286-0645

CAS NUMBER: 26538-44-3 — CHEMICAL NAME: ZERANOL
SUBMISSION #: 8EHQ-0485-0551 *

CAS NUMBER: 7440-66-6 — CHEMICAL NAME: ZINC
SUBMISSION #: 8EHQ-0286-0588 * 8EHQ-0586-0601

CAS NUMBER: NONE — CHEMICAL NAME: ZINC/MERCURY ALMALGAM
SUBMISSION #: 8EHQ-0286-0588 *

APPENDIX D : STATUS REPORTS BY INFORMATION TYPE

ACUTE TOXICITY (ANIMAL)

SUBMISSION #:	8EHQ-0485-0548	8EHQ-0485-0549 S	8EHQ-0485-0550
	8EHQ-0585-0556 S	8EHQ-0685-0559 S	8EHQ-0785-0563
	8EHQ-0885-0565 S	8EHQ-0985-0568 S	8EHQ-1085-0569
	8EHQ-1085-0571 S	8EHQ-1185-0573	8EHQ-1185-0575
	8EHQ-1285-0578	8EHQ-1285-0579 S	8EHQ-1285-0580
	8EHQ-1285-0581	8EHQ-0186-0584	8EHQ-0186-0585 S
	8EHQ-0386-0589 S	8EHQ-0486-0596 S	8EHQ-0486-0597 S
	8EHQ-0486-0599	8EHQ-0786-0607 S	8EHQ-0786-0609 S
	8EHQ-0786-0616	8EHQ-0886-0621 S	8EHQ-0986-0631 S
	8EHQ-1086-0636 S	8EHQ-1086-0638 *	8EHQ-1086-0639 S
	8EHQ-1086-0640 S *	8EHQ-1186-0644	8EHQ-1186-0647

ACUTE TOXICITY (HUMAN)

SUBMISSION #:	8EHQ-0485-0552	8EHQ-0985-0566	8EHQ-0186-0585 S
	8EHQ-0886-0622 S	8EHQ-0986-0632	

ALLERGENICITY (ANIMAL)

SUBMISSION #:	8EHQ-0485-0550	8EHQ-1285-0580	8EHQ-0186-0585 S
	8EHQ-0386-0589 S	8EHQ-0486-0597 S	8EHQ-1186-0647

ALLERGENICITY (HUMAN)

SUBMISSION #:	8EHQ-0485-0550	8EHQ-0186-0585 S	8EHQ-0386-0589 S
	8EHQ-0786-0612	8EHQ-0886-0622 S	

CELL TRANSFORMATION (IN VITRO)

SUBMISSION #:	8EHQ-0685-0558 S	8EHQ-0785-0561 S	8EHQ-0786-0610

APPENDIX D : STATUS REPORTS BY INFORMATION TYPE

CELL TRANSFORMATION (IN VITRO)

SUBMISSION #:	8EHQ-0786-0613	8EHQ-0886-0620	8EHQ-0886-0621 S
	8EHQ-0986-0630		

CHEMICAL/PHYSICAL PROPERTIES

SUBMISSION #:	8EHQ-0185-0542 S	8EHQ-0285-0544	8EHQ-0485-0548
	8EHQ-0485-0549 S	8EHQ-0485-0550	8EHQ-0485-0553
	8EHQ-0585-0554 S	8EHQ-0585-0555	8EHQ-0585-0556 S
	8EHQ-0685-0559 S	8EHQ-0885-0564 S	8EHQ-0985-0568 S
	8EHQ-1085-0569	8EHQ-1085-0571 S	8EHQ-1185-0574
	8EHQ-1185-0576	8EHQ-1285-0577	8EHQ-1285-0579 S
	8EHQ-0186-0584	8EHQ-0186-0585 S	8EHQ-0386-0589 S
	8EHQ-0486-0597 S	8EHQ-0786-0609 S	8EHQ-0786-0610
	8EHQ-0786-0614 S	8EHQ-0786-0616	8EHQ-0386-0619
	8EHQ-0986-0627	8EHQ-0986-0632	8EHQ-0986-0634
	8EHQ-1086-0635	8EHQ-1086-0636 S	8EHQ-1086-0639 S
	8EHQ-1186-0643	8EHQ-1186-0644	8EHQ-1286-0648

CHRONIC TOXICITY (ANIMAL)

SUBMISSION #:	8EHQ-0285-0545 S	8EHQ-0485-0550	8EHQ-0485-0553
	8EHQ-0785-0562 S	8EHQ-0985-0567	8EHQ-0685-0583 S
	8EHQ-0386-0592	8EHQ-0486-0600	8EHQ-0686-0604
	8EHQ-0786-0606 S	8EHQ-0786-0614 S	8EHQ-0886-0618 S
	8EHQ-0386-0619	8EHQ-0986-0624 S	8EHQ-0986-0625 S
	8EHQ-1086-0642		

APPENDIX D : STATUS REPORTS BY INFORMATION TYPE

CHRONIC TOXICITY (HUMAN)

SUBMISSION #:	8EHQ-0285-0546	8EHQ-0585-0557	8EHQ-0486-0598
	8EHQ-0586-0601	8EHQ-0786-0615	8EHQ-0986-0629
	8EHQ-0986-0634		

CLASTOGENICITY (ANIMAL)

SUBMISSION #:	8EHQ-0486-0597 S	8EHQ-0586-0602 S	8EHQ-0786-0613
	8EHQ-0986-0627	8EHQ-1186-0646 S	

CLASTOGENICITY (IN VITRO)

SUBMISSION #:	8EHQ-0685-0558 S	8EHQ-1285-0580	8EHQ-0386-0595
	8EHQ-0586-0602 S	8EHQ-0786-0608 S	8EHQ-0786-0610
	8EHQ-0886-0621 S	8EHQ-0986-0630	8EHQ-1186-0646 S
	8EHQ-1186-0647		

DNA ADDUCT (IN VITRO)

SUBMISSION #: 8EHQ-0386-0592

DNA DAMAGE/REPAIR

SUBMISSION #:	8EHQ-0785-0561 S	8EHQ-0586-0602 S	8EHQ-0786-0613
	8EHQ-0886-0621 S	8EHQ-1186-0646 S	

ECOTOXICITY/AQUATIC TOXICITY

SUBMISSION #: 8EHQ-0486-0597 S

EMERGENCY INCIDENT OF ENV. CONTAMINATION

SUBMISSION #:	8EHQ-0985-0566	8EHQ-0386-0593	8EHQ-0786-0617

APPENDIX D : STATUS REPORTS BY INFORMATION TYPE

ENV. OCCURRENCE/RELEASE/FATE

SUBMISSION #:	8EHQ-0985-0566		8EHQ-0386-0593		8EHQ-0486-0597 S
	8EHQ-0786-0617				

EPIDEMIOLOGY/CLINICAL

SUBMISSION #:	8EHQ-0285-0546		8EHQ-0485-0551	*	8EHQ-0485-0552
	8EHQ-0585-0557		8EHQ-0985-0567		8EHQ-0186-0585 S
	8EHQ-0286-0588	*	8EHQ-0386-0589 S		8EHQ-0486-0598
	8EHQ-0586-0601		8EHQ-0786-0611		8EHQ-0786-0612
	8EHQ-0786-0615		8EHQ-0986-0629		8EHQ-0986-0632
	8EHQ-0986-0634		8EHQ-1086-0641		

HUMAN EXPOSURE (ACCIDENTAL)

SUBMISSION #:	8EHQ-0985-0566	8EHQ-0786-0617	

HUMAN EXPOSURE (MONITORING)

SUBMISSION #:	8EHQ-0185-0542 S		8EHQ-0285-0546		8EHQ-0385-0547
	8EHQ-0485-0550		8EHQ-0485-0551	*	8EHQ-0485-0553
	8EHQ-0585-0554 S		8EHQ-0985-0566		8EHQ-0286-0588 *
	8EHQ-0586-0601		8EHQ-0986-0633 S		8EHQ-1286-0648

HUMAN EXPOSURE (PRODUCT CONTAMINATION)

SUBMISSION #:	8EHQ-0185-0542 S	8EHQ-0585-0554 S	8EHQ-0885-0564 S
	8EHQ-1186-0643	8EHQ-1186-0644	

APPENDIX D : STATUS REPORTS BY INFORMATION TYPE

IMMUNOTOXICITY (ANIMAL)

SUBMISSION #:	8EHQ-0186-0585 S	8EHQ-0386-0594 S	

METABOLISM/PHARMACOKINETICS (ANIMAL)

SUBMISSION #:	8EHQ-0585-0572	8EHQ-1185-0576	8EHQ-0186-0587
	8EHQ-0386-0591	8EHQ-0486-0600	8EHQ-0386-0619

METABOLISM/PHARMACOKINETICS (HUMAN)

SUBMISSION #:	8EHQ-0285-0546	8EHQ-0485-0551 *	8EHQ-0486-0600

MUTAGENICITY (IN VITRO)

SUBMISSION #:	8EHQ-0685-0558 S	8EHQ-0785-0561 S	8EHQ-1085-0571 S
	8EHQ-1285-0579 S	8EHQ-1285-0580	8EHQ-0186-0584
	8EHQ-0186-0585 S	8EHQ-0486-0597 S	8EHQ-0586-0602 S
	8EHQ-0786-0606 S	8EHQ-0786-0608 S	8EHQ-0786-0610
	8EHQ-0786-0613	8EHQ-0886-0620	8EHQ-0886-0621 S
	8EHQ-0986-0627	8EHQ-1286-0645	8EHQ-1186-0646 S
	8EHQ-1186-0647		

MUTAGENICITY (IN VIVO)

SUBMISSION #:	8EHQ-0785-0560	8EHQ-1285-0577	8EHQ-0786-0613

NEUROTOXICITY (ANIMAL)

SUBMISSION #:	8EHQ-0585-0556 S	8EHQ-1085-0571 S	8EHQ-0186-0584
	8EHQ-0386-0590 S	8EHQ-0486-0599	8EHQ-0886-0628

APPENDIX D : STATUS REPORTS BY INFORMATION TYPE

NEUROTOXICITY (HUMAN)

SUBMISSION #: 8EHQ-0786-0611	8EHQ-1086-0641	

ONCOGENICITY (ANIMAL)

SUBMISSION #: 8EHQ-0485-0550	8EHQ-0485-0553	8EHQ-0785-0561 S
8EHQ-0785-0562 S	8EHQ-0985-0567	8EHQ-0685-0583 S
8EHQ-0386-0592	8EHQ-0486-0600	8EHQ-0686-0604
8EHQ-0786-0606 S	8EHQ-0786-0614 S	8EHQ-0886-0618 S
8EHQ-0386-0619	8EHQ-1086-0642	

ONCOGENICITY (HUMAN)

SUBMISSION #: 8EHQ-0285-0546	8EHQ-0585-0557	8EHQ-0486-0598
8EHQ-0586-0601	8EHQ-0786-0615	8EHQ-0986-0629
8EHQ-0986-0634		

PRODUCT COMPOSITION/CHEMICAL IDENTITY

SUBMISSION #: 8EHQ-0185-0542 S	8EHQ-0285-0545 S	8EHQ-0485-0548
8EHQ-0485-0551 *	8EHQ-0485-0553	8EHQ-0585-0554 S
8EHQ-0585-0555	8EHQ-0585-0556 S	8EHQ-0785-0562 S
8EHQ-0885-0564 S	8EHQ-0985-0568 S	8EHQ-1085-0571 S
8EHQ-0585-0572	8EHQ-1185-0576	8EHQ-1285-0577
8EHQ-0186-0582 S	8EHQ-0685-0583 S	8EHQ-0386-0589 S
8EHQ-0386-0594 S	8EHQ-0486-0596 S	8EHQ-0486-0597 S
8EHQ-0586-0602 S	8EHQ-0686-0605 S	8EHQ-0786-0606 S
8EHQ-0786-0608 S	8EHQ-0786-0609 S	8EHQ-0786-0610
8EHQ-0786-0614 S	8EHQ-0886-0621 S	8EHQ-0986-0623 S

APPENDIX D : STATUS REPORTS BY INFORMATION TYPE

PRODUCT COMPOSITION/CHEMICAL IDENTITY

SUBMISSION #:	8EHQ-0986-0624 S	8EHQ-0986-0625 S	8EHQ-0986-0626 S
	8EHQ-0986-0627	8EHQ-0986-0631 S	8EHQ-0986-0632
	8EHQ-0986-0633 S	8EHQ-1086-0636 S	8EHQ-1086-0637
	8EHQ-1086-0639 S	8EHQ-1086-0640 S *	8EHQ-1186-0643
	8EHQ-1186-0644	8EHQ-1186-0646 S	

PRODUCTION/USE/PROCESS

SUBMISSION #:	8EHQ-0185-0542 S	8EHQ-0285-0544	8EHQ-0285-0545 S
	8EHQ-0285-0546	8EHQ-0385-0547	8EHQ-0485-0548
	8EHQ-0485-0549 S	8EHQ-0485-0550	8EHQ-0485-0551 *
	8EHQ-0485-0552	8EHQ-0485-0553	8EHQ-0585-0554 S
	8EHQ-0585-0555	8EHQ-0585-0556 S	8EHQ-0585-0557
	8EHQ-0685-0558 S	8EHQ-0685-0559 S	8EHQ-0785-0561 S
	8EHQ-0785-0562 S	8EHQ-0785-0563	8EHQ-0885-0564 S
	8EHQ-0885-0565 S	8EHQ-0985-0566	8EHQ-0985-0568 S
	8EHQ-1085-0569	8EHQ-1085-0570	8EHQ-1085-0571 S
	8EHQ-0585-0572	8EHQ-1185-0573	8EHQ-1185-0574
	8EHQ-1185-0575	8EHQ-1185-0576	8EHQ-1285-0577
	8EHQ-1285-0578	8EHQ-1285-0579 S	8EHQ-1285-0580
	8EHQ-1285-0581	8EHQ-0186-0582 S	8EHQ-0685-0583 S
	8EHQ-0186-0584	8EHQ-0186-0585 S	8EHQ-0186-0586 S
	8EHQ-0286-0588 *	8EHQ-0386-0589 S	8EHQ-0386-0591
	8EHQ-0386-0594 S	8EHQ-0486-0596 S	8EHQ-0486-0597 S
	8EHQ-0486-0599	8EHQ-0486-0600	8EHQ-0586-0601
	8EHQ-0586-0602 S	8EHQ-0686-0603	8EHQ-0786-0606 S

APPENDIX D : STATUS REPORTS BY INFORMATION TYPE

PRODUCTION/USE/PROCESS

SUBMISSION #:	8EHQ-0786-0607 S	8EHQ-0786-0608 S	8EHQ-0786-0609 S
	8EHQ-0786-0613	8EHQ-0786-0614 S	8EHQ-0786-0615
	8EHQ-0786-0616	8EHQ-0886-0622 S	8EHQ-0986-0623 S
	8EHQ-0986-0624 S	8EHQ-0986-0625 S	8EHQ-0986-0627
	8EHQ-0986-0629	8EHQ-0986-0630	8EHQ-0986-0631 S
	8EHQ-0986-0633 S	8EHQ-0986-0634	8EHQ-1086-0635
	8EHQ-1086-0636 S	8EHQ-1086-0637	8EHQ-1086-0639 S
	8EHQ-1086-0640 S *	8EHQ-1086-0641	8EHQ-1086-0642
	8EHQ-1186-0643	8EHQ-1186-0644	8EHQ-1286-0645
	8EHQ-1286-0648		

REPRODUCTIVE TOXICITY/TERATO. (ANIMAL)

SUBMISSION #:	8EHQ-0185-0543	8EHQ-0285-0544	8EHQ-0385-0547
	8EHQ-0485-0548	8EHQ-0585-0555	8EHQ-0785-0560
	8EHQ-0785-0562 S	8EHQ-1085-0570	8EHQ-0585-0572
	8EHQ-1285-0577	8EHQ-0186-0587	8EHQ-0986-0623 S
	8EHQ-0986-0626 S	8EHQ-0886-0628	8EHQ-0986-0633 S

REPRODUCTIVE TOXICITY/TERATO. (HUMAN)

SUBMISSION #:	8EHQ-0286-0588 *	

SUBACUTE TOXICITY (ANIMAL)

SUBMISSION #:	8EHQ-0385-0547	8EHQ-0485-0549 S	8EHQ-0485-0550
	8EHQ-0585-0556 S	8EHQ-0785-0561 S	8EHQ-0785-0562 S
	8EHQ-1085-0571 S	8EHQ-0186-0585 S	8EHQ-0386-0590 S

APPENDIX D : STATUS REPORTS BY INFORMATION TYPE

SUBACUTE TOXICITY (ANIMAL)

SUBMISSION #:	8EHQ-0386-0591	8EHQ-0486-0597 S	8EHQ-0686-0603
	8EHQ-0686-0605 S	8EHQ-0786-0608 S	8EHQ-0986-0627
	8EHQ-0986-0633 S	8EHQ-1086-0637	

SUBCHRONIC TOXICITY (ANIMAL)

SUBMISSION #:	8EHQ-0785-0561 S	8EHQ-0785-0562 S	8EHQ-1185-0574
	8EHQ-1185-0576	8EHQ-0186-0582 S	8EHQ-0186-0586 S
	8EHQ-0386-0594 S	8EHQ-0486-0600	8EHQ-1086-0635
	8EHQ-1286-0648		

TSCA 8(C) ALLEGATION

SUBMISSION #:	8EHQ-0386-0589 S	8EHQ-0786-0612	8EHQ-0886-0622 S
	8EHQ-0986-0632		

8EHQ-0185-0542 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : NONE CHEMICAL NAME: CUTTING FLUID

CAS NUMBER : NONE CHEMICAL NAME: NITROSAMINES

CAS NUMBER : 1116-54-7 CHEMICAL NAME: ETHANOL, 2,2'-(NITROSOIMINO)BIS-

CAS NUMBER : 1116-54-7 CHEMICAL NAME: N-NITROSODIETHANOLAMINE

8EHQ-0185-0543 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-0285-0544 SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : 80387-97-9 CHEMICAL NAME: ACETIC ACID, [[[3,5-BIS(1,1-DIMETHYLETHYL)-4-HYDROXYPHENYL]METHYL]THIO]-, 2-ETHYLHEXYL ESTER

CAS NUMBER : 80387-97-9 CHEMICAL NAME: IRGANOX 1192

8EHQ-0285-0545 S SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : CONFIDENT CHEMICAL NAME: CGA-149071

CAS NUMBER : CONFIDENT CHEMICAL NAME: HETEROMONOCYCLIC HETEROMONOCYCLE, HALOPHENOXY HALOPHENYL SUBSTITUTED

8EHQ-0285-0546 SUBMITTER: INTERNATIONAL LEAD ZINC RESEARCH ORGANIZATION INC.

CAS NUMBER : 7439-92-1 CHEMICAL NAME: LEAD

8EHQ-0385-0547 SUBMITTER: MONSANTO COMPANY

CAS NUMBER : 756-80-9 CHEMICAL NAME: PHOSPHORODITHIOIC ACID, O,O-DIMETHYL ESTER

8EHQ-0485-0548 SUBMITTER: CHEVRON CHEMICAL COMPANY

CAS NUMBER : 76714-88-0 CHEMICAL NAME: 1-PENTEN-3-OL, (E)-1-(2,4-DICHLOROPHENYL)-4,4-DIMETHYL-2-(1,2,4-TRIAZOL-1-YL)-

8EHQ-0485-0549 S SUBMITTER: NATIONAL STARCH AND CHEMICAL CORPORATION

CAS NUMBER : 9080-79-9 CHEMICAL NAME: BENZENESULFONIC ACID, ETHENYL-, HOMOPOLYMER, SODIUM SALT

8EHQ-0485-0549 S SUBMITTER: NATIONAL STARCH AND CHEMICAL CORPORATION

CAS NUMBER : 9080-79-9 CHEMICAL NAME: VERSA-TL 600

8EHQ-0485-0550 SUBMITTER: E. I. DUPONT DE NEMOURS & COMPANY, INC.

CAS NUMBER : UNKNOWN CHEMICAL NAME: KEVLAR

CAS NUMBER : UNKNOWN CHEMICAL NAME: POLY P-PHENYLENE TEREPHTHALAMIDE ARAMID FIBER

CAS NUMBER : UNKNOWN CHEMICAL NAME: PPD-T ARAMID FIBER

8EHQ-0485-0551 * SUBMITTER: INTERNATIONAL MINERALS & CHEMICAL CORPORATION

CAS NUMBER : NONE CHEMICAL NAME: RALGRO

CAS NUMBER : 26538-44-3 CHEMICAL NAME: 1H-2-BENZOXACYCLOTETRADECIN-1-ONE, 3,4,5,6,7,8,9,10,11,12-DECAHYDRO-7,14,16-TRIHYDROXY-3-METHYL-, [3S-(3R*,7S*)]-

CAS NUMBER : 26538-44-3 CHEMICAL NAME: ZERANOL

8EHQ-0485-0552 SUBMITTER: OLIN CORPORATION

CAS NUMBER : 97-00-7 CHEMICAL NAME: BENZENE, 1-CHLORO-2,4-DINITRO-

CAS NUMBER : 107-21-1 CHEMICAL NAME: 1,2-ETHANEDIOL

CAS NUMBER : 1310-73-2 CHEMICAL NAME: SODIUM HYDROXIDE, (NA(OH))

CAS NUMBER : 2831-60-9 CHEMICAL NAME: ETHANOL, 2-(2,4-DINITROPHENOXY)-

8EHQ-0485-0553 SUBMITTER: SOHIO ENGINEERED MATERIALS COMPANY

CAS NUMBER : NONE CHEMICAL NAME: ALUMINOSILICATE FIBERS

CAS NUMBER : NONE CHEMICAL NAME: FIBERFRAX

CAS NUMBER : NONE CHEMICAL NAME: REFRACTORY CERAMIC FIBERS

8EHQ-0585-0554 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: CONFIDENTIAL

CAS NUMBER : 64-67-5 CHEMICAL NAME: SULFURIC ACID, DIETHYL ESTER

CAS NUMBER : 23676-09-7 CHEMICAL NAME: BENZOIC ACID, 4-ETHOXY-, ETHYL ESTER

8EHQ-0585-0555 SUBMITTER: ETHYL CORPORATION

CAS NUMBER : NONE	CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, BROMINATED DERIV.
CAS NUMBER : NONE	CHEMICAL NAME: SAYTEX 111
CAS NUMBER : 32536-52-0	CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, OCTABROMO DERIV.
CAS NUMBER : 36483-60-0	CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, HEXABROMO DERIV.
CAS NUMBER : 63936-56-1	CHEMICAL NAME: BENZENE, PENTABROMO(TETRABROMOPHENOXY)-
CAS NUMBER : 63936-56-1	CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, NONABROMO DERIV.
CAS NUMBER : 68928-80-3	CHEMICAL NAME: BENZENE, 1,1'-OXYBIS-, HEPTABROMO DERIV.

8EHQ-0585-0556 S SUBMITTER: ROHM AND HAAS COMPANY

CAS NUMBER : NONE	CHEMICAL NAME: ACRYLIC ACID, 2-METHYL-, (COMPLEX MONOMER MIXTURE)
CAS NUMBER : NONE	CHEMICAL NAME: MONOMER PCM-200
CAS NUMBER : NONE	CHEMICAL NAME: MONOMER PCM-400
CAS NUMBER : NONE	CHEMICAL NAME: MONOMER QM-867
CAS NUMBER : NONE	CHEMICAL NAME: MONOMER QM-928
CAS NUMBER : NONE	CHEMICAL NAME: 2-PROPENOIC ACID, 2-METHYL-, (COMPLEX MONOMER MIXTURE)

8EHQ-0585-0557 SUBMITTER: AMOCO CORPORATION

CAS NUMBER : NONE	CHEMICAL NAME: DISTILLATES (PETROLEUM), REFINERY STREAMS
CAS NUMBER : NONE	CHEMICAL NAME: OIL (PETROLEUM), REFINERY STREAMS

8EHQ-0685-0558 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT	CHEMICAL NAME: OXIMIDOALKANE, SUBSTITUTED

8EHQ-0685-0559 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : 15112-89-7	CHEMICAL NAME: SILANETRIAMINE, N,N,N',N',N'',N''-HEXAMETHYL-

8EHQ-0785-0560 SUBMITTER: NALCO CHEMICAL COMPANY

CAS NUMBER : 79-06-1	CHEMICAL NAME: ACRYLAMIDE

8EHQ-0785-0560 SUBMITTER: NALCO CHEMICAL COMPANY

CAS NUMBER : 79-06-1 CHEMICAL NAME: 2-PROPENAMIDE

8EHQ-0785-0561 S SUBMITTER: BASF WYANDOTTE CORPORATION

CAS NUMBER : 88-12-0 CHEMICAL NAME: PYROL

CAS NUMBER : 88-12-0 CHEMICAL NAME: 2-PYRROLIDINONE, 1-ETHENYL-

8EHQ-0785-0562 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: DICHLOROPHENYLALKOXYALKYLOXOHETEROMONOCYCLE

8EHQ-0785-0563 SUBMITTER: DOW CORNING CORPORATION

CAS NUMBER : 681-84-5 CHEMICAL NAME: SILICIC ACID, (H4SIO4), TETRAMETHYL ESTER

8EHQ-0885-0564 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : NONE CHEMICAL NAME: AUTOMOTIVE COOLANTS

CAS NUMBER : NONE CHEMICAL NAME: NITROSAMINES

CAS NUMBER : 59-89-2 CHEMICAL NAME: MORPHOLINE, N-NITROSO-

CAS NUMBER : 59-89-2 CHEMICAL NAME: N-NITROSOMORPHOLINE

CAS NUMBER : 62-75-9 CHEMICAL NAME: METHANAMINE, N-METHYL-N-NITROSO-

CAS NUMBER : 62-75-9 CHEMICAL NAME: N-NITROSODIMETHYLAMINE

CAS NUMBER : 1116-54-7 CHEMICAL NAME: ETHANOL, 2,2'-(NITROSOIMINO)BIS-

CAS NUMBER : 1116-54-7 CHEMICAL NAME: N-NITROSODIETHANOLAMINE

8EHQ-0885-0565 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : 108-30-5 CHEMICAL NAME: 2,5-FURANDIONE, DIHYDRO-

CAS NUMBER : 108-30-5 CHEMICAL NAME: SUCCINIC ANHYDRIDE

CAS NUMBER : 9046-10-0 CHEMICAL NAME: JEFFAMINE D-2000

CAS NUMBER : 9046-10-0 CHEMICAL NAME: POLY[OXY(METHYL-1,2-ETHANEDIYL)], .ALPHA.-(2-AMINOMETHYLETHYL)-.OMEGA.-(2-AMINOMETHYLETHOXY)-

8EHQ-0985-0566 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : NONE	CHEMICAL NAME: MISC. CHEMICALS
CAS NUMBER : 67-63-0	CHEMICAL NAME: 2-PROPANOL
CAS NUMBER : 115-07-1	CHEMICAL NAME: 1-PROPENE
CAS NUMBER : 115-07-1	CHEMICAL NAME: PROPYLENE
CAS NUMBER : 123-38-6	CHEMICAL NAME: PROPANAL
CAS NUMBER : 123-38-6	CHEMICAL NAME: PROPIONALDEHYDE
CAS NUMBER : 7664-93-9	CHEMICAL NAME: SULFURIC ACID
CAS NUMBER : 9003-13-8	CHEMICAL NAME: POLY[OXY(METHYL-1,2-ETHANEDIYL)], .ALPHA.-BUTYL-.OMEGA.-HYDROXY-
CAS NUMBER : 9003-13-8	CHEMICAL NAME: UCON LUBRICANT LB-250

8EHQ-0985-0567 SUBMITTER: E. I. DUPONT DE NEMOURS & COMPANY, INC.

CAS NUMBER : 764-41-0	CHEMICAL NAME: 2-BUTENE, 1,4-DICHLORO-

8EHQ-0985-0568 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : UNKNOWN	CHEMICAL NAME: 1-SILA-2-AZACYCLOPENTANE, 1,1-DIETHOXY-2-TRIMETHYLSILYL-, DIMER
CAS NUMBER : 1825-62-3	CHEMICAL NAME: SILANE, ETHOXYTRIMETHYL-
CAS NUMBER : 21297-72-3	CHEMICAL NAME: 1-SILA-2-AZACYCLOPENTANE, 1,1-DIETHOXY-2-TRIMETHYLSILYL-

8EHQ-1085-0569 SUBMITTER: CELANESE CORPORATION

CAS NUMBER : 111-86-4	CHEMICAL NAME: 1-OCTANAMINE

8EHQ-1085-0570 SUBMITTER: VELSICOL CHEMICAL CORPORATION

CAS NUMBER : 3734-48-3	CHEMICAL NAME: CHLORDENE
CAS NUMBER : 3734-48-3	CHEMICAL NAME: 4,7-METHANO-1H-INDENE, 4,5,6,7,8,8-HEXACHLORO-3A,4,7,7A-TETRAHYDRO-

8EHQ-1085-0571 S SUBMITTER: E. I. DUPONT DE NEMOURS & COMPANY, INC.

CAS NUMBER : CONFIDENT	CHEMICAL NAME: DIAMINE, AROMATIC

8EHQ-1085-0571 S SUBMITTER: E. I. DUPONT DE NEMOURS & COMPANY, INC.

8EHQ-0585-0572 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : NONE	CHEMICAL NAME: PM ACETATE
CAS NUMBER : 108-65-6	CHEMICAL NAME: 2-PROPANOL, 1-METHOXY-, ACETATE
CAS NUMBER : 70657-70-4	CHEMICAL NAME: 1-PROPANOL, 2-METHOXY-, ACETATE

8EHQ-1185-0573 SUBMITTER: NUODEX INC.

CAS NUMBER : 110-69-0	CHEMICAL NAME: BUTANAL, OXIME
CAS NUMBER : 110-69-0	CHEMICAL NAME: EXKIN NO. 1 ANTI-SKINNING AGENT
CAS NUMBER : 110-69-0	CHEMICAL NAME: EXKIN 1

8EHQ-1185-0574 SUBMITTER: ATLANTIC RICHFIELD COMPANY

CAS NUMBER : 409-21-2	CHEMICAL NAME: SILICON CARBIDE FIBERS
CAS NUMBER : 409-21-2	CHEMICAL NAME: SILICON CARBIDE, (SIC)

8EHQ-1185-0575 SUBMITTER: EASTMAN KODAK COMPANY

CAS NUMBER : 25646-77-9	CHEMICAL NAME: ETHANOL, 2-[(4-AMINO-3-METHYLPHENYL)ETHYLAMINO]-, SULFATE (1 :1) (SALT)
CAS NUMBER : 25646-77-9	CHEMICAL NAME: KODAK COLOR DEVELOPING AGENT (CD-4)

8EHQ-1185-0576 SUBMITTER: MOBIL RESEARCH AND DEVELOPMENT CORPORATION

CAS NUMBER : NONE	CHEMICAL NAME: CARBAZOLES
CAS NUMBER : 64741-62-4	CHEMICAL NAME: CLARIFIED OILS, (PETROLEUM), CATALYTIC CRACKED
CAS NUMBER : 64741-62-4	CHEMICAL NAME: OIL (PETROLEUM), CLARIFIED SLURRY

8EHQ-1285-0577 SUBMITTER: U. S. DEPARTMENT OF ENERGY

CAS NUMBER : NONE	CHEMICAL NAME: EPOXY RESINS
CAS NUMBER : NONE	CHEMICAL NAME: ERL-2258
CAS NUMBER : NONE	CHEMICAL NAME: ZZL-0820

8EHQ-1285-0577 SUBMITTER: U. S. DEPARTMENT OF ENERGY

CAS NUMBER : 101-77-9	CHEMICAL NAME:	BENZENAMINE, 4,4'-METHYLENEBIS-
CAS NUMBER : 108-45-2	CHEMICAL NAME:	1,3-BENZENEDIAMINE
CAS NUMBER : 2386-90-5	CHEMICAL NAME:	ERR-4205
CAS NUMBER : 2386-90-5	CHEMICAL NAME:	6-OXABICYCLO[3.1.0]HEXANE, 2,2'-OXYBIS-
CAS NUMBER : 25068-38-6	CHEMICAL NAME:	ARALDITE 6010
CAS NUMBER : 25068-38-6	CHEMICAL NAME:	PHENOL, 4,4'-(1-METHYLETHYLIDENE)BIS-, POLYMER WITH (CHLOROMETHYL)OXIRANE

8EHQ-1285-0578 SUBMITTER: SYNTEX (U.S.A.) INC.

CAS NUMBER : 1271-55-2	CHEMICAL NAME:	FERROCENE, ACETYL-

8EHQ-1285-0579 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : 2628-17-3	CHEMICAL NAME:	PHENOL, 4-ETHENYL-

8EHQ-1285-0580 SUBMITTER: IBM CORPORATION

CAS NUMBER : 128-85-8	CHEMICAL NAME:	9,10-ANTHRACENEDIONE, 1-(METHYLAMINO)-4-[(4-METHYLPHENYL)AMINO]-
CAS NUMBER : 128-85-8	CHEMICAL NAME:	C. I. SOLVENT BLUE 11
CAS NUMBER : 128-85-8	CHEMICAL NAME:	SUDAN BLUE GA

8EHQ-1285-0581 SUBMITTER: AMERICAN CYANAMID COMPANY

CAS NUMBER : 6320-14-5	CHEMICAL NAME:	C. I. BASIC RED 12
CAS NUMBER : 6320-14-5	CHEMICAL NAME:	CALCOZINE RED BG
CAS NUMBER : 6320-14-5	CHEMICAL NAME:	3H-INDOLIUM, 2-[3-(1,3-DIHYDRO-1,3,3-TRIMETHYL-2H-INDOL-2-YLIDENE)-1-PROPENYL]-1,3,3-TRIMETHYL-, CHLORIDE

8EHQ-0186-0582 S SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : CONFIDENT	CHEMICAL NAME:	HETEROMONOCYCLIC HETEROMONOCYCLE, CHLOROPHENOXY CHLOROPHENYL ALKYL SUBSTITUTED

8EHQ-0685-0583 S SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : CONFIDENT CHEMICAL NAME: CGA-143686

8EHQ-0685-0583 S SUBMITTER: CIBA-GEIGY CORPORATION

8EHQ-0186-0584 SUBMITTER: CHEVRON CHEMICAL COMPANY

CAS NUMBER : 99422-01-2 CHEMICAL NAME: 1,3-CYCLOHEXANEDIONE, 5-[2-(ETHYLTHIO)PROPYL]-2-(1-OXOPROPYL)-

8EHQ-0186-0585 S SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : 63843-89-0 CHEMICAL NAME: PROPANEDIOIC ACID, [[3,5-BIS(1,1-DIMETHYLETHYL)-4-HYDROXYPHENYL]METHYL]BUTYL-, BIS(1,2,2,6,6-PENTAMETHYL-4-PIPERIDINYL) ESTER

CAS NUMBER : 63843-89-0 CHEMICAL NAME: TINUVIN 144

8EHQ-0186-0586 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: ACETAMIDE, 2-CHLORO-N-METHYL-N-SUBSTITUTED

8EHQ-0186-0587 SUBMITTER: FRAGRANCE MATERIALS ASSOCIATION (U.S.)

CAS NUMBER : 60-12-8 CHEMICAL NAME: BENZENEETHANOL

8EHQ-0286-0588 * SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : NONE CHEMICAL NAME: MERCURY/ZINC ALMALGAM

CAS NUMBER : NONE CHEMICAL NAME: ZINC/MERCURY ALMALGAM

CAS NUMBER : 598-62-9 CHEMICAL NAME: CARBONIC ACID, MANGANESE(2+) SALT (1:1)

CAS NUMBER : 1313-13-9 CHEMICAL NAME: MANGANESE OXIDE, (MNO2)

CAS NUMBER : 7439-92-1 CHEMICAL NAME: LEAD

CAS NUMBER : 7439-96-5 CHEMICAL NAME: MANGANESE

CAS NUMBER : 7439-97-6 CHEMICAL NAME: MERCURY

CAS NUMBER : 7440-43-9 CHEMICAL NAME: CADMIUM

CAS NUMBER : 7440-66-6 CHEMICAL NAME: ZINC

CAS NUMBER : 7785-87-7 CHEMICAL NAME: SULFURIC ACID, MANGANESE(2+) SALT (1:1)

8EHQ-0386-0589 S SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : CONFIDENT CHEMICAL NAME: C. I. REACTIVE ORANGE 12

8EHQ-0386-0589 S SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : NONE CHEMICAL NAME: CIBACRON BLACK GR-D

CAS NUMBER : NONE CHEMICAL NAME: CIBACRON BLACK GR LQ 40

CAS NUMBER : NONE CHEMICAL NAME: CIBACRON GOLDEN YELLOW 2R

CAS NUMBER : NONE CHEMICAL NAME: CIBACRON GOLDEN YELLOW 2R-A

CAS NUMBER : NONE CHEMICAL NAME: CIBACRON GOLDEN YELLOW 2R LQ 25

CAS NUMBER : 12225-84-2 CHEMICAL NAME: C. I. REACTIVE ORANGE 12

8EHQ-0386-0590 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: PHOSPHINE, ALKYL ARYL

8EHQ-0386-0591 SUBMITTER: PROCTER & GAMBLE COMPANY

CAS NUMBER : 5538-94-3 CHEMICAL NAME: 1-OCTANAMINIUM, N,N-DIMETHYL-N-OCTYL-, CHLORIDE

8EHQ-0386-0592 SUBMITTER: CELANESE CORPORATION

CAS NUMBER : 79-10-7 CHEMICAL NAME: ACRYLIC ACID

CAS NUMBER : 79-10-7 CHEMICAL NAME: 2-PROPENOIC ACID

8EHQ-0386-0593 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : 111-15-9 CHEMICAL NAME: ETHANOL, 2-ETHOXY-, ACETATE

8EHQ-0386-0594 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: CONFIDENTIAL

CAS NUMBER : 15571-58-1 CHEMICAL NAME: 8-OXA-3,5-DITHIA-4-STANNATETRADECANOIC ACID, 10-ETHYL-4,4-DI OCTYL-7-OXO-, 2-ETHYLHEXYL ESTER

8EHQ-0386-0595 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : 123-54-6 CHEMICAL NAME: 2,4-PENTANEDIONE

8EHQ-0486-0596 S SUBMITTER: ELI LILLY AND COMPANY

CAS NUMBER : CONFIDENT CHEMICAL NAME: CARBOXANILIDE, HALOGENATED ALIPHATIC

8EHQ-0486-0596 S SUBMITTER: ELI LILLY AND COMPANY

8EHQ-0486-0597 S SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : CONFIDENT CHEMICAL NAME: BENZOTRIAZOLE-2-YL SUBSTITUTED HYDROXYPHENYLPROPIONATE ESTER

8EHQ-0486-0598 SUBMITTER: E. I. DUPONT DE NEMOURS & COMPANY, INC.

CAS NUMBER : 68-12-2 CHEMICAL NAME: FORMAMIDE, N,N-DIMETHYL-

CAS NUMBER : 107-13-1 CHEMICAL NAME: ACRYLONITRILE

CAS NUMBER : 107-13-1 CHEMICAL NAME: 2-PROPENENITRILE

8EHQ-0486-0599 SUBMITTER: EASTMAN KODAK COMPANY

CAS NUMBER : 3852-09-3 CHEMICAL NAME: PROPANOIC ACID, 3-METHOXY-, METHYL ESTER

CAS NUMBER : 10606-42-5 CHEMICAL NAME: PROPANOIC ACID, 3-METHOXY-, ETHYL ESTER

8EHQ-0486-0600 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : 60-01-5 CHEMICAL NAME: BUTANOIC ACID, 1,2,3-PROPANETRIYL ESTER

CAS NUMBER : 64-19-7 CHEMICAL NAME: ACETIC ACID

CAS NUMBER : 79-09-4 CHEMICAL NAME: PROPANOIC ACID

CAS NUMBER : 107-92-6 CHEMICAL NAME: BUTANOIC ACID

CAS NUMBER : 109-52-4 CHEMICAL NAME: PENTANOIC ACID

CAS NUMBER : 137-40-6 CHEMICAL NAME: PROPANOIC ACID, SODIUM SALT

CAS NUMBER : 142-62-1 CHEMICAL NAME: HEXANOIC ACID

CAS NUMBER : 4075-81-4 CHEMICAL NAME: PROPANOIC ACID, CALCIUM SALT

8EHQ-0586-0601 SUBMITTER: SMELTER ENVIRONMENTAL RESEARCH ASSOCIATION

CAS NUMBER : NONE CHEMICAL NAME: COAL DUST

CAS NUMBER : NONE CHEMICAL NAME: DUST, COAL

CAS NUMBER : 1332-21-4 CHEMICAL NAME: ASBESTOS

CAS NUMBER : 7439-92-1 CHEMICAL NAME: LEAD

8EHQ-0586-0601 SUBMITTER: SMELTER ENVIRONMENTAL RESEARCH ASSOCIATION

CAS NUMBER : 7439-97-6	CHEMICAL NAME: MERCURY
CAS NUMBER : 7440-02-0	CHEMICAL NAME: NICKEL
CAS NUMBER : 7440-38-2	CHEMICAL NAME: ARSENIC
CAS NUMBER : 7440-43-9	CHEMICAL NAME: CADMIUM
CAS NUMBER : 7440-50-8	CHEMICAL NAME: COPPER
CAS NUMBER : 7440-66-6	CHEMICAL NAME: ZINC
CAS NUMBER : 7446-09-5	CHEMICAL NAME: SULFUR DIOXIDE

8EHQ-0586-0602 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT	CHEMICAL NAME: ACRYLIC ACID DERIVATIVES
CAS NUMBER : CONFIDENT	CHEMICAL NAME: CONFIDENTIAL
CAS NUMBER : CONFIDENT	CHEMICAL NAME: 2-PROPENOIC ACID DERIVATIVES

8EHQ-0686-0603 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : 1569-01-3	CHEMICAL NAME: 2-PROPANOL, 1-PROPOXY-
CAS NUMBER : 1569-01-3	CHEMICAL NAME: PROPASOL SOLVENT P

8EHQ-0686-0604 SUBMITTER: AMOCO CORPORATION

CAS NUMBER : 64742-94-5	CHEMICAL NAME: SOLVENT NAPHTHA, (PETROLEUM), HEAVY AROM.

8EHQ-0686-0605 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT	CHEMICAL NAME: SILANE (ORGANO) OLIGOMER
CAS NUMBER : CONFIDENT	CHEMICAL NAME: SILANE (ORGANO) OLIGOMER
CAS NUMBER : NONE	CHEMICAL NAME: SILANE (ORGANO) OLIGOMERS, MIXTURE OF COMPLEX

8EHQ-0786-0606 S SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : CONFIDENT	CHEMICAL NAME: UREA, HETEROMONOCYCLIC CARBOMONOCYCLIC

8EHQ-0786-0607 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : 2564-83-2	CHEMICAL NAME: 1-PIPERIDINYLOXY, 2,2,6,6-TETRAMETHYL-

8EHQ-0786-0607 S SUBMITTER: CONFIDENTIAL

8EHQ-0786-0608 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: PHOSPHORIC ACID ESTER, METAL SALT

8EHQ-0786-0609 S SUBMITTER: R. T. VANDERBILT COMPANY, INC.

CAS NUMBER : CONFIDENT CHEMICAL NAME: HETEROCYCLIC DERIVATIVE

8EHQ-0786-0610 SUBMITTER: TOTAL PETROLEUM, INC.

CAS NUMBER : 64742-80-9 CHEMICAL NAME: DISTILLATES, (PETROLEUM), HYDRODESULFURIZED MIDDLE

CAS NUMBER : 64742-80-9 CHEMICAL NAME: OIL (PETROLEUM), MINERAL SEAL

8EHQ-0786-0611 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : 75-21-8 CHEMICAL NAME: ETHYLENE OXIDE

CAS NUMBER : 75-21-8 CHEMICAL NAME: OXIRANE

8EHQ-0786-0612 SUBMITTER: ALCOLAC

CAS NUMBER : 999-21-3 CHEMICAL NAME: 2-BUTENEDIOIC ACID (Z)-, DI-2-PROPENYL ESTER

8EHQ-0786-0613 SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : UNKNOWN CHEMICAL NAME: CGA-18809

CAS NUMBER : UNKNOWN CHEMICAL NAME: O,O-DIMETHYL-S-(6-CHLOR-OXAZOLO(4,5,B)PYRIDIN-2(3H)-ON-3-YL-METHYL)-THIOPHOSPHATE

8EHQ-0786-0614 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : 3091-25-6 CHEMICAL NAME: STANNANE, TRICHLOROOCTYL-

CAS NUMBER : 3542-36-7 CHEMICAL NAME: STANNANE, DICHLORODIOCTYL-

8EHQ-0786-0615 SUBMITTER: TEXACO INC.

CAS NUMBER : 106-99-0 CHEMICAL NAME: 1,3-BUTADIENE

8EHQ-0786-0616 SUBMITTER: R. T. VANDERBILT COMPANY, INC.

CAS NUMBER : 137-29-1 CHEMICAL NAME: COPPER, BIS(DIMETHYLCARBAMODITHIOATO-S,S')-, (SP-4-1)-

8EHQ-0786-0616 SUBMITTER: R. T. VANDERBILT COMPANY, INC.

8EHQ-0786-0617 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : 64-17-5 CHEMICAL NAME: ETHANOL

CAS NUMBER : 123-72-8 CHEMICAL NAME: BUTANAL

8EHQ-0886-0618 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : 1306-19-0 CHEMICAL NAME: CADMIUM OXIDE, (CDO)

CAS NUMBER : 1306-23-6 CHEMICAL NAME: CADMIUM SULFIDE, (CDS)

CAS NUMBER : 10124-36-4 CHEMICAL NAME: SULFURIC ACID, CADMIUM SALT (1:1)

8EHQ-0386-0619 SUBMITTER: MONSANTO COMPANY

CAS NUMBER : NONE CHEMICAL NAME: PHOSPHATE FIBERS

CAS NUMBER : 23209-59-8 CHEMICAL NAME: METAPHOSPHORIC ACID, (HPO3), CALCIUM SODIUM SALT

8EHQ-0886-0620 SUBMITTER: CHEMICAL MANUFACTURERS ASSOCIATION

CAS NUMBER : 84-74-2 CHEMICAL NAME: 1,2-BENZENEDICARBOXYLIC ACID, DIBUTYL ESTER

CAS NUMBER : 131-11-3 CHEMICAL NAME: 1,2-BENZENEDICARBOXYLIC ACID, DIMETHYL ESTER

8EHQ-0886-0621 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: BENZENAMINE, ALKYLATED

8EHQ-0886-0622 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : NONE CHEMICAL NAME: UNKNOWN CHEMICAL(S)

8EHQ-0986-0623 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: DIPHENYL ETHER, SUBSTITUTED

8EHQ-0986-0624 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: NITROBENZENE, SUBSTITUTED

8EHQ-0986-0625 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: CHLOROBENZENE, SUBSTITUTED

8EHQ-0986-0626 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: PYRIDINE, HALOGENATED

8EHQ-0986-0627 SUBMITTER: CIBA-GEIGY CORPORATION

CAS NUMBER : UNKNOWN CHEMICAL NAME: REACTION PRODUCT OF BETA-[3-(2H-BENZOTRIAZOL-2-YL)-4-HYDROXY-5-TERT-BUTYLPHENYL]PROPIONIC ACID, METHYL ESTER AND POLYETHYLENE GLYCOL 300

CAS NUMBER : UNKNOWN CHEMICAL NAME: TINUVIN 1130

8EHQ-0886-0628 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : 10024-97-2 CHEMICAL NAME: NITROGEN OXIDE, (N2O)

CAS NUMBER : 10024-97-2 CHEMICAL NAME: NITROUS OXIDE

8EHQ-0986-0629 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : 75-01-4 CHEMICAL NAME: ETHENE, CHLORO-

CAS NUMBER : 75-01-4 CHEMICAL NAME: VINYL CHLORIDE

8EHQ-0986-0630 SUBMITTER: CELANESE CORPORATION

CAS NUMBER : 57116-45-7 CHEMICAL NAME: 1-AZIRIDINEPROPANOIC ACID, 2-[[3-(1-AZIRIDINYL)-1-OXOPROPOXY]METHYL]-2-(HYDROXYMETHYL)-1,3-PROPANEDIYL ESTER

8EHQ-0986-0631 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT CHEMICAL NAME: PERFLUOROALKYL RESIN

CAS NUMBER : CONFIDENT CHEMICAL NAME: PERFLUOROALKYL RESIN

CAS NUMBER : NONE CHEMICAL NAME: PERFLUOROALKYL COMPOUNDS

CAS NUMBER : UNKNOWN CHEMICAL NAME: MINERAL SPIRITS

CAS NUMBER : 76-13-1 CHEMICAL NAME: ETHANE, 1,1,2-TRICHLORO-1,2,2-TRIFLUORO-

8EHQ-0986-0632 SUBMITTER: HERCULES INCORPORATED

CAS NUMBER : 12001-26-2 CHEMICAL NAME: MICA (DUST), SILICEOUS MUSCOVITE

8EHQ-0986-0632 SUBMITTER: HERCULES INCORPORATED

CAS NUMBER : 12001-26-2 CHEMICAL NAME: SILICATE, MICA

8EHQ-0986-0633 S SUBMITTER: E. I. DUPONT DE NEMOURS & COMPANY, INC.

CAS NUMBER : CONFIDENT CHEMICAL NAME: ETHER (CYCLIC), HALOALKYL SUBSTITUTED

8EHQ-0986-0634 SUBMITTER: AMERICAN HOECHST CORPORATION

CAS NUMBER : 95-69-2 CHEMICAL NAME: BENZENAMINE, 4-CHLORO-2-METHYL-

8EHQ-1086-0635 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : 9038-95-3 CHEMICAL NAME: OXIRANE, METHYL-, POLYMER WITH OXIRANE, MONOBUTYL ETHER

CAS NUMBER : 9038-95-3 CHEMICAL NAME: UCON LUBRICANT 50-HB-5100

8EHQ-1086-0636 S SUBMITTER: PPG INDUSTRIES, INC.

CAS NUMBER : CONFIDENT CHEMICAL NAME: ALCOHOL ETHOXYLATES, CHLORIDE CAPPED

CAS NUMBER : CONFIDENT CHEMICAL NAME: QUATERNARY AMMONIUM CHLORIDE

8EHQ-1086-0637 SUBMITTER: CHEVRON CHEMICAL COMPANY

CAS NUMBER : 82244-86-8 CHEMICAL NAME: HYDROXYLAMINE, O-(3-CHLORO-2-PROPENYL)-, HYDROCHLORIDE

8EHQ-1086-0638 * SUBMITTER: AZS CORPORATION

CAS NUMBER : 28182-81-2 CHEMICAL NAME: CORONATE EH

CAS NUMBER : 28182-81-2 CHEMICAL NAME: HEXANE, 1,6-DIISOCYANATO-, HOMOPOLYMER

8EHQ-1086-0639 S SUBMITTER: PPG INDUSTRIES, INC.

CAS NUMBER : CONFIDENT CHEMICAL NAME: CHLORINATED ACID

8EHQ-1086-0640 S * SUBMITTER: CONFIDENTIAL

CAS NUMBER : 52942-64-0 CHEMICAL NAME: BUTANEDIOIC ACID, (ETHOXYMETHYLENE)OXO-, DIETHYL ESTER

CAS NUMBER : 55130-39-7 CHEMICAL NAME: BUTANEDIOIC ACID, (ETHOXYMETHYLENE)OXO-, DIETHYL ESTER, (E)-

CAS NUMBER : 55130-49-9 CHEMICAL NAME: BUTANEDIOIC ACID, (ETHOXYMETHYLENE)OXO-, DIETHYL ESTER, (Z)-

8EHQ-1086-0640 S * SUBMITTER: CONFIDENTIAL

8EHQ-1086-0641 SUBMITTER: UNION CARBIDE CORPORATION

CAS NUMBER : 75-21-8 CHEMICAL NAME: ETHYLENE OXIDE

CAS NUMBER : 75-21-8 CHEMICAL NAME: OXIRANE

8EHQ-1086-0642 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-1186-0643 SUBMITTER: DOW CORNING CORPORATION

CAS NUMBER : NONE CHEMICAL NAME: NITROPORE ATA

CAS NUMBER : NONE CHEMICAL NAME: NITROSAMINES

CAS NUMBER : UNKNOWN CHEMICAL NAME: SILASTIC Q4-4682 SILICONE RUBBER

CAS NUMBER : UNKNOWN CHEMICAL NAME: SILASTIC Q4-4683 SILICONE RUBBER

CAS NUMBER : 55-18-5 CHEMICAL NAME: ETHANAMINE, N-ETHYL-N-NITROSO-

CAS NUMBER : 55-18-5 CHEMICAL NAME: N-NITROSODIETHYLAMINE

CAS NUMBER : 59-89-2 CHEMICAL NAME: MORPHOLINE, N-NITROSO-

CAS NUMBER : 59-89-2 CHEMICAL NAME: N-NITROSOMORPHOLINE

CAS NUMBER : 62-75-9 CHEMICAL NAME: METHANAMINE, N-METHYL-N-NITROSO-

CAS NUMBER : 62-75-9 CHEMICAL NAME: N-NITROSODIMETHYLAMINE

CAS NUMBER : 924-16-3 CHEMICAL NAME: 1-BUTANAMINE, N-BUTYL-N-NITROSO-

CAS NUMBER : 924-16-3 CHEMICAL NAME: N-NITROSODIBUTYLAMINE

8EHQ-1186-0644 SUBMITTER: DOW CORNING CORPORATION

CAS NUMBER : NONE CHEMICAL NAME: DOW CORNING FS-1265 FLUID (1,000 CS)

CAS NUMBER : NONE CHEMICAL NAME: DOW CORNING FS-1265 FLUID (10,000 CS)

CAS NUMBER : NONE CHEMICAL NAME: DOW CORNING FS-1265 FLUID (300 CS)

CAS NUMBER : NONE CHEMICAL NAME: MOLYKOTE FS-3451 GREASE

8EHQ-1186-0644 SUBMITTER: DOW CORNING CORPORATION

CAS NUMBER : NONE	CHEMICAL NAME: MOLYKOTE FS-3452 VALVE LUBRICANT
CAS NUMBER : NONE	CHEMICAL NAME: SILASTIC LS-2860 FLUOROSILICONE RUBBER
CAS NUMBER : 460-40-2	CHEMICAL NAME: PROPANAL, 3,3,3-TRIFLUORO-
CAS NUMBER : 460-40-2	CHEMICAL NAME: PROPIONALDEHYDE, 3,3,3-TRIFLUORO-

8EHQ-1286-0645 SUBMITTER: LEVER BROTHERS COMPANY (INCORPORATED)

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: YELLOW SHADE 18569

8EHQ-1186-0646 S SUBMITTER: CONFIDENTIAL

CAS NUMBER : CONFIDENT	CHEMICAL NAME: ACRYLIC ACID DERIVATIVES
CAS NUMBER : CONFIDENT	CHEMICAL NAME: CONFIDENTIAL
CAS NUMBER : CONFIDENT	CHEMICAL NAME: 2-PROPENOIC ACID DERIVATIVES

8EHQ-1186-0647 SUBMITTER: ALLIED-SIGNAL INC.

CAS NUMBER : 22984-54-9	CHEMICAL NAME: 2-BUTANONE, O,O',O''-(METHYLSILYLIDYNE)TRIOXIME
CAS NUMBER : 22984-54-9	CHEMICAL NAME: SILANE, METHYLOXIMINO-
CAS NUMBER : 34206-40-1	CHEMICAL NAME: 2-BUTANONE, O,O',O'',O'''-SILANETETRAYLTETRAOXIME
CAS NUMBER : 34206-40-1	CHEMICAL NAME: SILANE, TETRAOXIMINO-

8EHQ-1286-0648 SUBMITTER: ETHYL CORPORATION

CAS NUMBER : 2095-01-4	CHEMICAL NAME: 1,3-BENZENEDIAMINE, 4,6-DIETHYL-2-METHYL-
CAS NUMBER : 2095-02-5	CHEMICAL NAME: 1,3-BENZENEDIAMINE, 2,4-DIETHYL-6-METHYL-
CAS NUMBER : 68479-98-1	CHEMICAL NAME: BENZENEDIAMINE, AR,AR-DIETHYL-AR-METHYL-

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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 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, 1985 to December 31, 1986 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 the Agency 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 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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