EPA/600/8-86/032a
March 1987

Integrated Risk Information System
Supportive Documentation
Volume I

Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC 20460

U.S. Environmental Protection Agency

DISCLAIMER

This document has been reviewed in accordance with United States Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

CONTENTS

INTRODUCTION TO IRIS

OVERVIEW

IRIS is a computer-housed, electronically communicated catalogue of Agency risk assessment and risk management information for chemical substances. This system is designed especially for federal, state, and local environmental health agencies as a source of the latest information about Agency health assessments and regulatory decisions for specific chemicals.

The development of IRIS is a response to repeated requests for Agency risk assessment information to deal with various environmental issues and a response to the need for consistency and quality in EPA risk assessment and risk management decisions. IRIS is intended to introduce the user to Agency information which may be useful for building the database necessary to make a risk assessment.

IRIS is not a primary toxicologic data base or a conclusive risk resource; rather, it is an introduction to EPA's risk information, and should be used with an understanding of its capabilities as well as its limitations and constraints (see background documents in Service Code 4). Supportive documentation included in the system provides instruction and explanation for the risk information presented. The information contained in IRIS is intended for users without extensive training in toxicology, but with some knowledge of health science.

The risk assessment information contained in IRIS, except as specifically noted, has been reviewed and agreed upon by intra-agency review groups, representing an Agency consensus. An intra-agency work group has been responsible for the development of IRIS.

As intra-agency review groups continue to review and verify risk assessment values, additional chemicals and data components will be added to IRIS. Although IRIS is available in hardcopy, it is also available through Dialcom, Inc.'s Electronic Mail, the computer-based electronic communications system to which the EPA subscribes. Designed as an electronic loose-leaf notebook, IRIS provides users with the ability to access, copy, and print information from the data base. IRIS hardcopy, which will be available in the future through the National Technical Information Service (NTIS), is provided initially to help users get started. This material can then be expanded and updated by users through electronic retrieval of new and revised data.

SYSTEM STRUCTURE

The information contained within IRIS is divided into two major components: the chemical files, which form the heart of the system, and the supportive documentation, which provides instruction and explanation in support of the system and the chemical files. This information is distributed among six Service Codes, with the chemical files (the functional files in IRIS) contained in one Service Code and the supporting documentation contained in the remaining five. The Service Codes and their functions are as follows:

Service Code 1 — *Chemical Files*: This is the heart of the system. It is within this file that the actual chemical-specific data have been compiled. A detailed presentation of the content and format of this Service Code will be provided later in this Introduction and in the Chemical File Structure description in Service Code 4.

Service Code 2 — *List of Chemicals on IRIS*: A simple alphabetical and Chemical Abstract System (CAS) number listing of all the chemicals contained in IRIS.

Chemical File Update Information: The chemical files which have been recently updated are listed here. Chemical name, CAS No. and date of revision are given.

Service Code 3 — *Chemical File Revision History*: This Service Code contains a running record of specific revisions to each chemical file. The information is more specific than that found in Service Code 2, which is just a list of updated files. The specific file sections that have been changed or modified are given and the type of change is indicated (e.g., "Oral RfD: UF text modified", "Risk Estimates for Carcinogens: slope factor corrected", "Risk Management Section added", etc.). The date of the change is also given.

Service Code 4 — *Introduction to IRIS (this document)*: a brief overview of IRIS.

Chemical File Structure: General background information is provided on each of the data elements contained in the chemical files. This section is intended to help the user understand the information contained in the chemical files. In addition, there is some discussion of the general limitations, restrictions, and qualifications placed on the EPA data so as to minimize misinterpretation of the data presented.

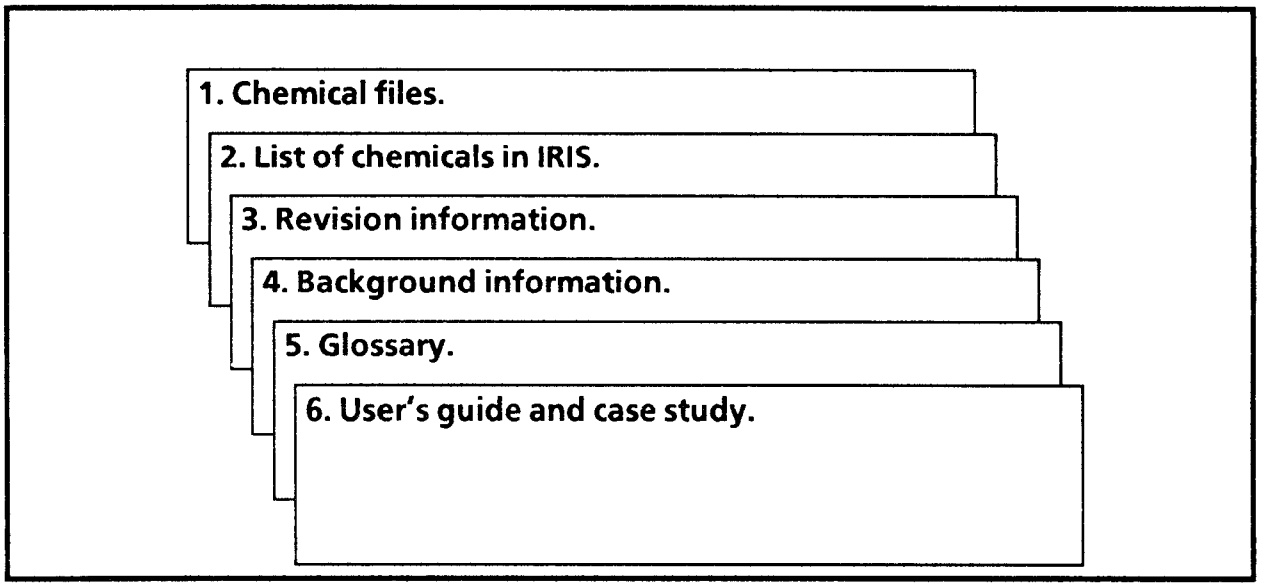
Background Documents (Appendices): Concept papers are provided for the categories of information contained in the chemical files (oral RfD, carcinogenicity assessment, risk management actions, and supplementary data). As background documents are prepared for other information categories, such as inhalation RfDs or Drinking Water Health Advisories, they will be added to the system.

EPA Chemical Profile Database References: List of references cited in the Supplementary Data section of the chemical files is provided at the end of the background document for that section.

Service Code 5 — *Glossary*: A glossary of terms and abbreviations used in the chemical files and supportive documentation is provided for user reference.

Service Code 6 — *User's Guide*: An operations manual is provided which describes how to use the system and lists commands, procedures, helpful hints, and a series of examples for illustration.

Case Study: A case study is included to provide an example of a situation to which IRIS can be applied and how the information it contains might be used.



Service Codes in IRIS

CHEMICAL FILE FORMAT

The chemical files are intended to assist the user in developing risk assessments which can be used in making management decisions for specific situations. For reference, agency risk management information is also included. One is cautioned, however, that the EPA risk management data have been developed for conditions and with constraints which may have little applicability to a given user's specific situation.

Each chemical file begins with a short introductory paragraph followed by a status table indicating the availability of various components of the chemical file. The information contained within the chemical file includes risk assessment and risk management information. The specific chemical file content is outlined below:

IRIS CHEMICAL FILE STRUCTURE

INTRODUCTION AND STATUS

I. CHRONIC SYSTEMIC TOXICITY (NON-CARCINOGENIC HEALTH EFFECTS)

A. REFERENCE DOSE (RfD) FOR ORAL EXPOSURE

1. REFERENCE DOSE SUMMARY TABLE
2. PRINCIPAL AND SUPPORTING STUDIES
3. UNCERTAINTY AND MODIFYING FACTORS
4. ADDITIONAL COMMENTS
5. CONFIDENCE IN THE RfD
6. DOCUMENTATION AND REVIEW
7. U.S. EPA CONTACTS

B. REFERENCE DOSE (RfD) FOR INHALATION EXPOSURE

(same format as for oral exposure)

II. RISK ESTIMATES FOR CARCINOGENS

A. U.S. EPA CLASSIFICATION AND BASIS

1. HUMAN DATA
2. ANIMAL DATA
3. SUPPORTING DATA

B. ORAL QUANTITATIVE ESTIMATE

1. UNIT RISK SUMMARY TABLE
2. DOSE RESPONSE DATA
3. ADDITIONAL COMMENTS
4. STATEMENT OF CONFIDENCE

C. INHALATION QUANTITATIVE ESTIMATE

1. UNIT RISK SUMMARY TABLE
2. DOSE RESPONSE DATA
3. ADDITIONAL COMMENTS
4. STATEMENT OF CONFIDENCE

D. DOCUMENTATION AND REVIEW

1. REFERENCES
2. REVIEW
3. U.S. EPA CONTACTS

III. DRINKING WATER HEALTH ADVISORIES

(format in preparation)

IV. RISK MANAGEMENT SUMMARIES

A. RISK MANAGEMENT ACTIONS

B. RISK MANAGEMENT RATIONALE

V. SUPPLEMENTARY DATA

A. ACUTE HEALTH HAZARD INFORMATION

B. PHYSICAL-CHEMICAL PROPERTIES

SYNONYMS

Each section consists of a data and rationale summary of two or three pages in length. In addition, EPA contacts who are familiar with the chemical are provided in each section (except for the Supplementary Information section).

Unavailability of data for a section will be indicated, and, if known, other information pertaining to the status of the data will be provided. A more detailed description of each of these sections is provided in the Chemical File Structure document following this Introduction.

ELECTRONIC REPRESENTATION OF SPECIAL CHARACTERS

The use of a computerized telecommunication system for IRIS imposes limits on the number and types of nonalphanumeric characters that can be represented. Special characters such as degree symbols or Greek letters, and print codes such as superscripts and subscripts cannot be reproduced on most display terminals. Therefore, very small numbers are given in scientific notation using the "E" format. That is, a number such as 0.0006 is expressed as 6E-4, which is equivalent to saying "6 times 10 to the power of -4." Large numbers are given in "E" format in some instances, for consistency (for example, 2E2 for the number, 200). Some other substitutions for notations generally represented by superscripts or subscripts are: "cu. m" for cubic meter, "**" for exponentiation in formulas (for example, "Y = X**2" represents "Y equals X squared"), and Ca(CN)2 for the chemical formula of calcium cyanide (chemical formula subscripts are subscripted one full line in other instances). Upper case "L" is occasionally used as the abbreviation for liter in those cases where the lower case "l" may be misinterpreted as the number, one.

IRIS CHEMICAL FILE STRUCTURE

PREFACE

The user is directed to Service Code 6 for instructions on how to call up information on specific chemicals. The discussion below supplements the introduction under Service Code 4 by describing in detail the information displayed in each of the chemical-specific files. The Appendices are background documents which provide more detailed information on risk assessments and risk management concepts and terms.

When one calls up a chemical, sections of information are displayed in the following order: INTRODUCTION & STATUS, CHRONIC SYSTEMIC TOXICITY: NONCARCINOGENIC HEALTH EFFECTS, RISK ESTIMATES FOR CARCINOGENS, DRINKING WATER HEALTH ADVISORIES, RISK MANAGEMENT SUMMARIES, SUPPLEMENTARY DATA, and SYNONYMS. Each numbered section (all sections except the Introduction and Synonyms) begin with a heading with the following information:

Chemical: The chemical name of the agent is given, with the common name in parentheses where appropriate.

CAS No.: The Chemical Abstract Service number unique to the compound.

Preparation date: The date of the most recent revision of the summary sheet.

The subsections and data entries found in each of the sections are discussed below.

INTRODUCTION AND STATUS

The chemical name and Chemical Abstracts Service (CAS) number which uniquely identifies this substance is given, along with the latest revision date for the chemical file. An introductory statement is included in each file, followed by a status table indicating the availability of each section. A status of "review pending" means that a chemical is currently under review, or is scheduled for review by an EPA work group.

I. CHRONIC SYSTEMIC TOXICITY: NON-CARCINOGENIC HEALTH EFFECTS

Risk assessors are often faced with the task of interpreting the significance of long-term exposure to chemicals which might produce toxic effects other than cancer. These effects are sometimes referred to as the "systemic toxicity" of the compound. Traditionally, these effects have been assessed by identifying the lowest No Observed Effect Level (NOEL) and reducing this amount by some factor (Safety Factor or Uncertainty Factor) to estimate a level which is judged to be without significant toxicologic concern to humans.

The CHRONIC SYSTEMIC TOXICITY section contains chemical-specific information couched in terms of a Reference Dose (RfD), a concept which is discussed in greater detail in Appendix A. The RfD is related to a formerly used notion of "acceptable daily intake (ADI)" but has been tailored to the risk assessment/risk management approach used at EPA.

A. REFERENCE DOSE (RfD) FOR ORAL EXPOSURE

Chemical name, CAS No., and preparation date are given.

1. REFERENCE DOSE SUMMARY TABLE

This table summarizes the data used in the derivation of the reference dose.

Critical Effect

This first column lists the critical effect, the species and type of study, and the reference.

Experimental Doses

The second column is a summary of the information on the highest level at which no adverse effects were found (i.e., the No Observed Adverse Effect Level [NOAEL]) and/or

the lowest level tested at which adverse effects were found (i.e., the Lowest Observed Adverse Effect Level [LOAEL]). The dose levels are usually given in the units presented in the original study and in units of milligrams per kilogram body weight per day (mg/kg/day or mg/kg-day).

UF

The Uncertainty Factor which contributes as a divisor to the NOAEL (or LOAEL) in calculating the Reference Dose is given. In most instances, these uncertainty factors are standardized, based on the particular data set available. See the paper on the Reference Dose in Appendix A for a more complete description.

MF

The Modifying Factor which also contributes as a divisor to the NOAEL in calculating the Reference Dose is given. In most cases, this factor is 1; however, in certain instances, the review group uses its collective professional judgment to adjust the RfD through the use of a Modifying Factor. In such cases, explanations are provided in the text following the table.

RfD

The RfD is an estimate (uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a liftime. The RfD is expressed in units of milligrams per kilogram body weight per day (mg/kg/day or mg/kg-day). See Appendix A for a full discussion of the concept and its use in risk assessment and risk management.

Dose Conversion Factors And Assumptions

The factors used to convert the dose to mg/kg-day are listed, as well as any assumptions made. These factors include food and water consumption, and, in some cases, inhalation-to-oral conversion factors.

2. PRINCIPAL AND SUPPORTING STUDIES

An elaboration of the material in the summary table immediately above is presented, providing descriptions of the critical study and other germane studies.

3. UNCERTAINTY AND MODIFYING FACTORS

An explicit presentation of the individual Uncertainty Factors contributing to the overall Uncertainty Factor is given. The UFs are:

10-fold factor for extrapolation from animal to human (10a)
10-fold factor for variability in the human population (10h)
10-fold factor for use of a less-than-chronic study (10s)
1 to 10-fold factor for extrapolation from a LOAEL (1 --> 10e)

See Appendix A for a more complete discussion.

An explicit explanation of the selection of any Modifying Factor is also presented.

4. ADDITIONAL COMMENTS

Ancillary information is given which may be of use or interest, e.g., other approaches taken to establishing an RfD and why EPA prefers its approach.

5. CONFIDENCE IN THE RfD

This entry provides a qualitative estimate, expressed in both summary and narrative form, of the confidence that the EPA review group had in the quality of the critical study, the supporting data base, and the RfD. A "Low" designation for the RfD suggests that the value is likely to change as new data are generated.

6. DOCUMENTATION AND REVIEW

The EPA document(s) in which the RfD (ADI) was originally derived, and the level of review of that document, are given. The dates of the RfD work group meetings at which the chemical was discussed are also given.

7. U.S. EPA CONTACTS

Persons to contact for additional details on the technical issues associated with the RfD of this chemical are listed.

B. REFERENCE DOSE (RfD) FOR INHALATION EXPOSURE

Inhalation RfD methods are under development.

II. RISK ESTIMATES FOR CARCINOGENS

A. U.S. EPA CLASSIFICATION AND BASIS

Classification

The EPA weight-of-evidence classification of the agent, as described in the Hazard Identification section (IIA) of appendix B.

1. HUMAN DATA

A description of the human evidence leading to the classification. Difficulties in determining the final classification are also given where necessary.

2. ANIMAL DATA

A description of the experimental animal evidence leading to the classification. Difficulties in determining the final classification are given where necessary.

3. SUPPORTING DATA

A description of data lending support to the classification, such as genotoxicity.

B. ORAL QUANTITATIVE ESTIMATE

Slope Factor

The upper-bound incremental lifetime cancer risk estimated to result from a continuous orally absorbed dose of 1 mg per kg body weight per day. Since the oral absorption fraction is usually assumed to be 100%, the same oral slope factor is used for continuous oral intake.

1. UNIT RISK SUMMARY TABLE

Water concentration producing risk levels of E-4, E-5, E-6

The concentration of the agent (micrograms per liter) in drinking water estimated to result in upper-bound incremental lifetime cancer risk of E-4, E-5, E-6, if 2 liters of water which is contaminated with the agent were ingested per day continuously for a lifetime.

Unit Risk

The upper-bound incremental lifetime cancer risk estimated to result from ingestion of 2 liters of water per day of drinking water contaminated with the agent at a concentration of one microgram per liter.

Model

The abbreviation for the dose extrapolation model used to estimate cancer risk at low doses from experimental observations at higher doses. M is the multistage procedure, W is Weibull, P is probit, LO is logit, OH is one-hit, GM is gamma multi-hit.

2. DOSE-RESPONSE DATA

This table shows the animal data set from which the risk parameters were estimated. The table shows the species and strain of the animals used, the tumor type or types used for the estimate, the dose administered in the experiment, the lifetime tumor incidence observed, a code for the literature citation of the report where the data was published, and the route of administration used in the experiment. The table is modified when human data are used for the estimation of risk parameters.

3. ADDITIONAL COMMENTS

An explanation of the assumptions used in deriving the risk estimate. For each agent the following information is presented:

method of selecting the data set,

animal-to-human equivalent dose assumption,

statement of whether the administered animal dose or a pharmaco-kinetically-derived effective metabolized dose was used, and

relevant non-cancer toxicity.

Other comments describing the estimation procedure for the agent are included. A statement is also made that the risk estimate should not be used if the water concentration is larger than x µg/l and the air concentration is larger than y µg/cu.m. In this statement the values of x and y are the concentrations above which the risk exceeds 1.0%.

4. STATEMENT OF CONFIDENCE

A high, medium, or low rating based on the factors enumerated in section II of appendix B. A description of the main factors leading to this rating is included.

C. INHALATION QUANTITATIVE ESTIMATE

The entries in this subsection are analogous to those in the Oral Quantitative Estimate subsection above.

D. DOCUMENTATION REVIEW

1. REFERENCES

Literature citations for the major papers used in the classification of the agent and in quantitative estimates.

2. REVIEW

Description of the review procedure received by the EPA evaluation document which is summarized by these sheets:

Agency CRAVE Work Group Review

Dates on which the Agency review committee met to review data on the agent.

Verification Date

Date on which the Agency review committee agreed that the information is accurate.

3. U.S. EPA CONTACTS

The person or persons at EPA who can explain the origin of the items on the summary sheet.

III. DRINKING WATER HEALTH ADVISORIES

Health advisories are still under development.

IV. RISK MANAGEMENT SUMMARIES

INTERPRETATION OF RISK MANAGEMENT DATA

A cautionary statement is presented concerning the interpretation of the data.

A. RISK MANAGEMENT ACTIONS

A table summarizing the risk management actions taken by the U.S. EPA is given. This table includes the following categories:

Risk Management Action

The type of action (i.e., official name)

Status

Current status of this action

Date

Date of the action

Risk Management Value

The numeric risk management value. Some values are specific for duration of exposure, and are so indicated. Values that vary according to a given set of conditions (e.g., site-specific values) will not be listed here. Call the EPA Contact for specific information.

Considers Econ/Tech Feasibility

Indicates whether or not the economical or technical feasibility of the risk management action has been considered prior to setting the value.

Reference

The document in which the value was published.

B. RISK MANAGEMENT RATIONALE

The chemical-specific information underlying each of the risk management actions is described. U.S. EPA contacts are also given.

V. SUPPLEMENTARY DATA

A. ACUTE HEALTH HAZARD INFORMATION

In response to concerns raised following the tragic release of toxic substances from a chemical plant in Bhopal, India in 1985, EPA has generated a list of chemicals which could conceivably pose acute hazards to people living in the neighborhood of production or storage facilities. The list includes a range of chemical-specific information which would be useful in assessing the significance of levels determined in the environment.

B. PHYSICAL-CHEMICAL PROPERTIES

The chemical and physical properties of the compound are listed and other properties of the substance are presented.

SYNONYMS

A listing of synonyms for the chemical as extracted from a number of sources is given.

IRIS USER'S GUIDE

INTRODUCTION

This guide describes how to use IRIS on the U. S. Environmental Protection Agency (EPA) electronic mail (EMail) system. Printed copies of this guide will be distributed to IRIS users; this guide is also available electronically on IRIS for those who do not have immediate access to a printed copy.

IRIS consists of a set of electronic documents filed in Electronic Publishing (EPUB) computer software under EPA's EMail system. The EPUB makes it easy for users to search for and read documents from their computer terminal. With appropriate equipment, users can also print copies of electronic IRIS documents for further review in paper form. IRIS can be accessed by most computer terminals, personal computers, and word processors with proper communications capabilities. The summary of access requirements, which appears at the end of this document, provides detailed information regarding required technical features.

IRIS is divided into various "service codes," with each service code identified by a service code number. A service code is like an electronic file drawer. Each service code contains one or more IRIS documents which belong in that service code "drawer." When you use IRIS, you can only work with one service code at a time. Within a service code, you can search for documents containing specific words, scan the titles of documents, and read individual documents. In order to work with a different service code, you must tell IRIS that you want to "stop" the current service code and get a chance to enter a new service code.

Here are the services and their codes:

Code	Service
1	Chemical Files
2	Lists of Chemicals in IRIS
3	Chemical File Revision History
4	Background Information
5	Glossary
6	User's Guide and Case Study

The remainder of this guide provides more detailed instructions for using IRIS. Any technical questions or problems should be referred to the EPA Electronic Mail User Support Group by telephoning FTS 382-5639, area code (202) 382-5639, or an electronic mail message can be sent to the USER.SUPPORT mailbox on the EMail system.

Questions or comments on the overall structure and content of IRIS should be referred to the IRIS support office which is being established. Messages will be posted on IRIS to inform users when this is accomplished.

Questions concerning specific information in IRIS chemical files should be directed to the U.S. EPA contact(s) listed in these files.

PROCEDURES FOR USING IRIS

General

IRIS can be used by people who have a user account on the Dialcom EMail system and who have been authorized by EPA to access IRIS. EPA employees who wish to get a user account, also called a "mailbox," on the EMail system should contact EPA electronic mail user support at FTS 382-5639, area code (202) 382-5639. Other interested parties should contact Dialcom directly at the contact point listed in Section VI. The EPA Electronic Mail Service User Guide provides general information about how to log onto EMail which will not be repeated here. If you need help and do not have a copy of the EMail User Guide, contact the EMail User Support group at the telephone number listed above. The User Support group can also be reached at mailbox USER.SUPPORT.

Using IRIS

When you are logged onto EMail, the system will indicate that it is waiting for you to issue a command by typing a "prompt" consisting of the greater-than sign, ">". The ">" is the prompt for the EMail system; as you will see later, a double-dash symbol is the prompt from IRIS. When you see the greater-than sign, you are talking to EMail and not to IRIS; when you see the double dashes, you are talking to IRIS. Now, to go into IRIS, type "IRIS" and press RETURN.

Once you have issued the IRIS command, you will receive a greeting similar to the following:

```
************************************************************
*                                                          *
*        Welcome to EPA's Integrated Risk Information System       *
*                                                          *
************************************************************
Code          Service

 *1           Chemical Files
 *2           Lists of Chemicals in IRIS
 *3           Chemical File Revision History
 *4           Background Information
 *5           Glossary
 *6           User's Guide and Case Study
Enter a service code
--
```

Whenever IRIS expects a response, you will see the double-dash prompt: "--". IRIS will wait for you to type a service code number, followed by RETURN. (Note: As in many other computer systems, you must press the key labeled RETURN after the line of IRIS commands that you type. On IBM personal computers (PCs), press the key labeled ENTER.) Once you have opened a service code "file drawer," you then can scan the titles of documents in the service code, search for documents containing a keyword or keywords, and read specific documents. The next section provides examples of the use of IRIS to retrieve chemical information.

EXAMPLES OF THE USE OF IRIS TO RETRIEVE CHEMICAL INFORMATION

Search for a Chemical File

Suppose you wish to read the chemical file for dimethoate. First, enter the chemical file service code by typing the appropriate number -- 1. In response to the "Read, Scan or Search --" prompt, type SEARCH and press the RETURN or ENTER key twice. IRIS will respond with "Enter keywords or Read or Scan or Mail --". Now, you type in the name of the chemical -- dimethoate. It doesn't matter whether you use upper- or lower-case letters. IRIS will respond: "Searching -- Please wait..." and there will be a short delay as the search is conducted. IRIS will then tell you how many chemical files contained the word "dimethoate"; for example, you may see the following:

```
3 Occurrences
Enter keywords or Read or Scan or Mail
--
```

"3 Occurrences" means that three different files each contained at least one occurrence of the word "dimethoate" within their texts. At this point, you should always type "SCAN" so you can look at the heading of each file and pick the file you want. Because the keyword search will find any file that contains the keyword, and because many files contain cross-references to other chemicals, you will often find that a chemical name has multiple occurrences. By following a SEARCH with a SCAN, you can see which files met the search criteria and pick only the file(s) you want to read. When you SCAN following a SEARCH, each file name has an index number on the left. Use that index number to indicate which file(s) you want to read. For example, if you want to read the third file, type: READ 3 following the prompt of "Enter keywords or Read or Scan or Mail --". Here's an example of searching

for and reading the document for dimethoate. In this example, the user typed everything on the line after the double dashes.

Enter a service code

-- 1

Read, Scan or Search

-- SEARCH

Enter keywords or Read or Scan or Mail

-- DIMETHOATE

Searching - Please wait...
3 Occurrences...
Enter keywords or Read or Scan or Mail

-- SCAN

1 Dinitrochickenwire...
2 Dimethyldoorknob...
3 Dimethoate...

Enter keywords or Read or Scan or Mail

-- READ 3

[The dimethoate document now appears on the screen]

In this example, the reason "dinitrochickenwire" and "dimethyldoorknob" appear when you search for dimethoate is because the other two documents refer to dimethoate somewhere within their texts.

An Example of "Wild Card" Searching

Sometimes you may want to search for documents containing a word that begins with a particular sequence. For example, suppose you are looking for chemicals that start with the sequence "2,4,5-T". When you are keyword searching, IRIS allows you to "wild card" the remainder of a word that starts with two or more characters. For example, after you have told IRIS to SEARCH and received the "Enter keywords or Read or Scan or Mail --" prompt, type the opening characters followed by a question mark or an asterisk:

Enter keywords or Read or Scan or Mail

-- 2,4,5-T?

Searching - Please wait...
3 Occurrences...

In this example, IRIS found three files containing a word beginning with "2,4,5-T". You can then SCAN the files and read any which are of interest.

Combination (Boolean) Searching

IRIS also permits simple combination, or "boolean" searching. Suppose you are looking for files which contain a word starting with "2,4,5-T" or a word starting with "furan". You can enter the keywords:

-- 2,4,5-T? or furan?

and IRIS will show you how many occurrences contained one term or the other (or both). You can also use the word "and" to look for files which contain one term AND another term:

-- furan? AND 2,4,5-T?

Remember that IRIS doesn't care whether you use upper- or lower-case letters. Available combination terms are "and," "or," and "and not."

Backing Up

Suppose you have used IRIS to search for and read one or more chemical file documents. IRIS will be prompting you: "Enter keywords or Read or Scan or Mail --". To back up to the "Read, Scan or Search --" prompt, type "BACK". If you wish to exit the current service code completely so that you can go into a new service code, type "STOP".

Leaving IRIS

When you are ready to leave IRIS, type QUIT at the IRIS prompt. If you have become stuck, use the Control-P command to bring on the next IRIS prompt. Typing "OFF" tells the system to leave IRIS and immediately log off EMail as well. The OFF command works at each prompt except the "More?" prompt.

SUPPRESSING THE "MORE?" PROMPT TO DOWNLOAD IRIS DOCUMENTS FOR LOCAL PRINTING

If you wish to capture information from IRIS for local reference and printing, you will want to suppress the "More?" prompt which normally occurs every 23 lines. The recommended procedure is as follows:

Determine what IRIS material you wish to capture. QUIT out of IRIS. At the "system prompt" of a greater-than sign -- > -- type "TERM TYPE HARDCOPY". Then reenter IRIS, open your capture file, and read your material. The "More?" prompt will no longer appear. If you want to freeze the screen, use Control-S (and Control-Q to unfreeze). If you wish to restore the "More?" prompt later, QUIT out of IRIS, type "TERM TYPE CRT", and reenter IRIS.

DESCRIPTION OF IRIS COMMANDS

Note that IRIS commands, with the exception of the "control" commands, must always be completed by pressing the RETURN key or the ENTER key on a PC. To use a control command, hold down the CONTROL key (which is usually labeled "Ctrl") and press the appropriate letter key. For example, to issue the CONTROL-P command, hold down the Ctrl key and press the letter P. You do not need to press the RETURN key when you issue a control command. The CONTROL key works in a similar way as the shift key, except that the letter typed while you hold down the CONTROL key will not be visible on your screen. Note that quotation marks used in the following examples should NOT be typed into the computer.

Below, the valid responses to IRIS prompts are summarized; then the IRIS commands are listed and described.

Responses to IRIS Prompts

Responses to the "Enter a service code --" prompt:

> Press the number of the service code you want to work with, or HELP to see the list of service codes, or QUIT, or OFF.

Responses to the "Read, Scan or Search --" prompt:

> You may type in READ, SCAN, SEARCH, HELP, QUIT, or OFF.

Responses to the "More?...(Yes or No) --" prompt:

> When you are reading an IRIS document, the system will usually display 23 lines at a time, and then give you the prompt of "More?...(Yes or No) --". If you type RETURN or "y", IRIS will display the next 23 lines. If you type "n", IRIS will stop with the current document. If you are reading following a scan following a search, IRIS may continue with the start of the next document. Use Control-P to completely stop a read operation in this case. You may also type QUIT or OFF at the "More?" prompt. NO OTHER COMMANDS WORK AT THE "MORE?" PROMPT!

IRIS Commands

READ

If you type READ by itself, you will begin to read every document in the service code, one at a time, or every document in the service code which met your keyword search. If you only want to read a specific document or documents (the recommended approach), type READ followed by the index numbers of the documents you wish to read. Separate index numbers by spaces. Example: "READ 1 4 7". Use SCAN before the READ to see the documents and their index numbers.

SCAN

The SCAN command is used to scan the titles of the documents currently available in the service code. The use of SCAN is NOT recommended when in the service code containing chemical files, because it takes a long time to scan through all the titles. The use of SCAN is strongly recommended following a search, to see the titles of the documents which met the search criteria.

SEARCH

The SEARCH command is used to search for a word or phrase within the documents in tbe service code. For SEARCH to work, the search word must be at least two letters long.

Keyword searching techniques:

Every word in an IRIS file is indexed as a "keyword" which can be searched. When IRIS says: "Enter keyword..." you can type in any word(s) for which you wish to search. Search words must be at least two characters long.

Wild cards:

Sometimes you may want to know which files contain a word that begins with a particular sequence of characters. To do so, type in the opening sequence, followed by a question mark or asterisk; for example DIMETH? or DIMETH*. The system will tell you how many files in the service code contain at least one word which begins with "dimeth...". This type of search is sometimes called a "wild card" search.

Simple Combination or "Boolean" searches:

You can search for files which contain one word OR another, or both one word AND another. Simply use the connector words "or" or "and". You may also use the "and not" connector.

STOP

This important command, which can be issued at the "Read, Scan or Search" prompt or at the "Enter keywords or Read or Scan or Mail" prompt, is the way you tell IRIS that you want to STOP using the current service code. By saying STOP, you will once again see the "Enter a service code" prompt.

BACK

The BACK command, which can be issued at every prompt except the "More?" prompt, sends you back one step in the series of prompts which you have seen. In fact, if you type BACK at the "Enter a service code" prompt, you will go back to where you were before you entered IRIS, namely the "system level" of electronic mail, with the ">" prompt.

HELP

The HELP command may be entered at any prompt except the "More?" prompt to get a brief "help" message which may help to remind you of what to do next.

INFO MORE

If you type INFO MORE in response to the "Enter a service code" prompt, you will see a message providing more information about IRIS.

QUIT

The QUIT command is used to leave IRIS -- "quit" using the IRIS system. The QUIT command also may be used at any point except for the "More?" prompt.

OFF

The OFF command is used to leave IRIS and immediately log off of the electronic mail system. It is the fastest way to completely stop an IRIS session and logoff. The OFF command may be issued at any point except for the "More?" prompt.

CONTROL-S

The Control-S command "freezes" the screen as lines of information scroll by during a display from a SCAN or a READ. Control-Q unfreezes the display. CAUTION: After you type Control-S, your keyboard will not seem to work until you type Control-Q!

CONTROL-Q

This command "unfreezes" the screen and keyboard following a Control-S.

CONTROL-P

This convenient command (the same as a BREAK command) tells IRIS to interrupt what it was doing and give you a chance to move on. For example, if you have issued a SCAN command or a READ command and no longer want to keep looking at the information scrolling on the screen, Control-P will interrupt the process and bring you to the prompt which would have appeared at the end of the process. For example, if you interrupt a SCAN with Control-P, IRIS will prompt with "Read, or Mail which ones?"

Summary of IRIS Commands

READ - Read all documents, or those specific documents whose index numbers follow after "READ".

SCAN - Scan the titles of all current documents and display index numbers.

SEARCH - Search the documents for a specific word or words.

STOP - Stop working with the current service code.

BACK - Go back to the next-to-the-last prompt message.

HELP - Provides help information or a list of service codes.

QUIT - Leave the IRIS system.

OFF - Leave IRIS and logoff EMail.

INFO MORE - List system information.

Control-P - Interrupt the current process and go to the next prompt.

Control-S - "Freeze" the screen and keyboard.

Control-Q - Unfreeze the screen and keyboard.

NOTES:

The ONLY commands which work at the "More?" prompt are the responses of RETURN, "y" or "n", QUIT, or Control-P.

The only commands which work at the "Enter a service code --" prompt are INFO MORE, QUIT, OFF, HELP, or a valid service code number.

As a rule, if you become "stuck" or "lost," try Control-P. And remember that you must use the STOP command to change service codes.

SUMMARY OF ACCESS HARDWARE/SOFTWARE REQUIREMENTS FOR IRIS

Terminal requirements

Typical "ASCII" device; for example, a DEC VT100 terminal, a Televideo 925 terminal, a Prime PT200 terminal, a Lexitron word processor with communications, or an IBM PC with communications software such as Crosstalk.

Modem

Preferred 1200-baud Bell 212A-compatible.

Cables

Appropriate cables are needed to connect the terminal to the modem and the modem to a telephone line.

Settings

1. Full duplex or echoplex.
2. 8 bits, no parity, 1 stop bit.
3. 1200 baud preferred, 330 baud supported by some access lines.

Access Telephone Numbers

See the EPA Electronic Mail Service User Guide.

Special Notes

The Crosstalk XVI communications software package is recommended for PC users. Lexitron users should set their screens to 10 pitch and their margins to the far left and far right of the screen. IRIS material can be printed by users who have a local printer and refer to their printer and terminal manuals for instructions regarding capturing and printing material from a remote source. The EPA Electronic Mail Service User Guide explains how to store material on a Lexitron disk for later reading or printing.

USER SUPPORT SERVICES

Users who are having difficulty in using IRIS should telephone EPA EMail User Support at FTS 382-5639, area code (202) 382-5639. Alternatively, an EMail message may be sent to the USER.SUPPORT mailbox.

ELECTRONIC MAIL ACCOUNT INFORMATION
Dialcom, Inc.
Mike McLaughlin
600 Maryland Avenue, S.W.
Washington, DC 20024
(202) 488-0550

IRIS EXERCISE

IRIS is designed primarily to make EPA risk assessment (RA) and risk management (RM) numbers available to users in the Regions and the States. The information may be useful for a wide range of purposes, one of the most important being that of contributing to risk management (RM) decisions at the local level. IRIS is not intended to provide pre-packaged RM decisions, but is intended to provide some of the data necessary for local decision-making.

The following exercise presents a hypothetical situation which might confront a local decisionmaker and shows one way in which IRIS might be of assistance in resolving the problem. There are many different ways in which a risk management decision can be made; therefore, this exercise is meant to be merely illustrative, not prescriptive.

THE PROBLEM

On Monday morning, the Troubled Times newspaper in the capital of the State of Ecstasy broke a story on the likely contamination of the city's water supply. The paper alleges to have in its possession a preliminary report from the Regional EPA office which purportedly shows the presence of dinitrochickenwire and dimethyldoorknob at concentrations of 500 µg/L (500 ppb) and 200 µg/L (200 ppb), respectively.

Sensationalizing the story a bit by suggesting the possible involvement of agents from the People's Bureau of the State of Despair, the Troubled Times has raised the specter of imminent death to thousands of people over the short term and irreversible death to thousands more over the long term, if water use is not terminated immediately.

The Governor of Ecstasy is returning from a brief vacation in the State of Reality to personally take charge of the crisis. His plane is due to land within the next two hours. Consequently, reasoned decisions must be made quickly.

["Thank heavens, we have IRIS!", a small boy was heard to murmur.]

THE TOXICITY AND EXPOSURE CONSIDERATIONS

Given: A rumored report of unknown quality which alleges the presence of DiNitroChickenWire (DNCW) and DiMethylDoorKnob (DMDK) at levels of 500 µg/L (500 ppb) and 200 µg/L (200 ppb), respectively. While there are many paths one could take in traveling from data to a RM decision, for purposes of this exercise, we will begin by following the steps in conducting a risk assessment:

A. Hazard identification
B. Dose-response assessment
C. Exposure assessment
D. Risk characterization.

This risk assessment will then be coupled with non-risk factors, such as economic considerations, technological feasibility, and control options, in order to construct some risk management options.

Hazard Identification and Dose-Response Information Gleaned from IRIS

DNCW *Service Code 1: Non-Carcinogenicity.* NOAEL of 3 mg/kg-day and UF x MF of 100 leads to RfD of .03 mg/kg-day; liver and kidney effects. Confidence: High.

Service Code 1: Carcinogenicity. No information available.

Service Code 1: Supplementary Data. Information on air concentrations may not be particularly relevant in this case since direct air contamination is not a major exposure route of concern. However, note that DNCW may aggravate liver and kidney diseases. Also, one might want to consider the impact of the release of DNCW from heated cooking water or during bathing and showering. The DNCW concentration in this case (500 µg/L) is about 3% of the limit of solubility of the compound (.002 g/100 mL = 20 mg/L = 20,000 µg/L).

DMDK *Service Code 1: Non-carcinogenicity.* NOAEL of 19.4 mg/kg-day and UF x MF of 1000 leads to RfD of .02 mg/kg-day; kidney and liver changes. Confidence: Medium, due to limited number of animals and the conversion from an inhalation to an oral route of exposure.

Service Code 1: Carcinogenicity. B2: probable human carcinogen, based on sufficient animal data and inadequate human data.

Potency q_1^* = 5.1 E-2 $(mg/kg\text{-}day)^{-1}$
Air unit risk = 4.8 E-7 $(\mu g/m^3)^{-1}$
Water unit risk = 1.5 E-6 $(\mu g/L)^{-1}$

Service Code 1: Supplementary Data. None available at this time.

Exposure Assessment

It is unclear that there is any exposure. There is only a rumor of an alleged exposure. Therefore, we need to verify this information by contacting the Regional EPA lab to determine the veracity of the Troubled Times report.

We would like to know things such as the following:

(1) The sampling design
(2) The sampling procedure
(3) The chain of custody of the samples
(4) The analytical method used
(5) The quality assurance program conducted as a part of the study
(6) The percentage of positive values found
(7) The limits of detection used in the study
(8) The average value found
(9) The range of values found

...and so on.

In addition, we would like to know something about the type and size of the population served by the water supply. Also, are there special segments of the population involved, such as a pediatric hospital specializing in treatment of kidney and liver dysfunction?

For its general purposes, the Agency assumes that an average child weighs 10 kg and drinks about 1 L of water per day and that an average adult weighs 70 kg and drinks 2 L of water per day. Further, it is assumed that a person lives to be 70 years old. Therefore, the following estimated doses can be calculated from the drinking water route of exposure:

DNCW

Child (10 kg): 500 µg/L x 1 L/day / 10 kg = 50 µg/kg-day = .05 mg/kg-day
or 500 µg/day (.5 mg/day) for 10 kg-child

Adult (70 kg): 500 µg/L x 2 L/day / 70 kg = 14 µg/kg-day = .014 mg/kg-day
or 1000 µg/d (1 mg/d) for 70-kg adult

DMDK

Child (10 kg): 200 µg/L x 1 L/day / 10 kg = 20 µg/kg-day = .02 mg/kg-day
or 200 µg/day (.2 mg/day) for 10-kg child

Adult (70 kg): 200 µg/L x 2 L/day / 70 kg = 6 µg/kg-day = .006 mg/kg-day
or 400 µg/day (.4 mg/day) for 70-kg adult

Some question remains about dermal exposure, although that is likely to pale in comparison to the drinking water ingestion. Another route of exposure which has not been directly addressed is food chain contamination.

Additional work would have to be done to determine the source of the contamination. Some sources could lead to bioaccumulation in the food chain (e.g., fish and dairy produce), which has not been directly addressed.

Similarly, additional data gathering should be done to determine the environmental fate and effects of these compounds; e.g., how long is the problem likely to persist, once a source has been identified and its flow stopped.

Risk Characterization

Non-Cancer Effects

The RfDs and the estimated drinking water (DW) exposures are summarized below.

DNCW

RfD = .03 mg/kg day — Child DW exposure = .05 mg/kg-day; Adult DW exposure = .01 mg/kg-day

DMDK

RfD = .02 mg/kg-day — Child DW exposure = .02 mg/kg-day; Adult DW exposure = .006 mg/kg-day

Although the DNCW exposure level calculated for children is above the RfD, keep in mind that the RfD is likely to be without adverse effects when it is the level of exposure encountered over a lifetime. Further, the RfD estimate is uncertain to an order of magnitude; that is, it is a very broad estimate. Therefore, unless the RfD is based on effects to children, no great concern should be associated with this excursion above the RfDs. The oral RfDs for both compounds are based on long-term effects.

Cancer Effects

We can calculate the upper bound of the excess lifetime cancer risk which would be associated with lifetime exposure to such DMDK-contaminated water:

Upper bound on the excess lifetime cancer risk associated with DMDK is

= water unit risk x water concentration
= 1.5 E-6 $(\mu g/L)^{-1}$ x 200 ug/L
= 3 E-4 for this B2 carcinogen.

If this exposure continued for only 1 year, a crude approximation to the upper limit of the 1-year risk could be calculated by dividing the lifetime risk by the assumed length of life; i.e., 70 years:

3.0 E-4/70 = 4 E-6 (rounded) for this B2 carcinogen.

RISK MANAGEMENT CONSIDERATIONS

In a given situation, the risk considerations above must be combined with non-risk considerations of the following types:

(1) What can be done about the problem?
What can be done to find the source(s)?
What can be done to "fix" the source(s)?
What can be done to clean up the situation?

(2) Alternative sources of water
Is it conceivable that the population could be supplied by alternative sources?
What is known about the hazards associated with alternatives?
What about the logistics involved, including the time to set up and the resources to fund the operation?

The Agency has reached some general (i.e., not tailored to this specific case) risk management positions. These are found in Service Code 1, under Risk Management Summaries. The following information can be obtained from that section and the Drinking Water Health Advisories.

DNCW
Reportable Quantity -- 10 lbs.

Water Quality Criteria (based on water and aquatic organisms)

1.01 mg/L = 1010 µg/L = 1010 ppb

Drinking Water Health Advisories

1-day	(10 kg child): 1000 µg/L = 1000 ppb
10-day	(10 kg child): 300 µg/L = 300 ppb
Longer term	(10 kg child): 300 µg/L = 300 ppb
Longer term	(70 kg adult): 1050 µg/L = 1050 ppb
Lifetime	(70 kg adult): 210 µg/L = 1050 ppb

The last four Health Advisory (HA) numbers can be derived from the RfD as follows:

For a 10-kg child ingesting 1 L of water per day:

Longer term HA = RfD x body weight / water consumption
= .03 mg/kg-day x 10 kg / 1 liter/day
= .3 mg/L = 300 µg/L = 300 ppb

Since the 1-day child exposure of 1000 ppb is 3.3 times greater than the 300 ppb level just examined, it must correspond to a daily exposure of 3.3 x .03 mg/kg-day = .1 mg/kg-day

For a 70-kg adult ingesting 2 L of water per day:

Longer term or Lifetime HA = RfD x body weight / water consumption
= .03 mg/kg-day x 70 kg / 1 L/day = 1.05 mg/L
= 1050 µg/L = 1050 ppb

The contact person and/or the cited references should be consulted for the underlying rationale for all of the Health Advisory numbers to determine their applicability to a specific situation.

DMDK
Reportable quantity -- 1 lb.

Water Quality Criteria

The 1E-7 to 1E-5 range of the upper limit of risk is associated with the following water concentrations:

Drinking water and aquatic organisms	.08 - 8 µg/L (ppb)
Aquatic organisms only	.9 - 90 µg/L (ppb)

Drinking Water Health Advisories

10-day (10 kg child): 34,000 µg/L = 34,000 ppb
[Exposure = 34000 µg/L x 1 L/day / 10 kg = 3400 µg/mg-day = 3.4 mg/kg-day]

Longer term (10 kg child): 1940 µg/liter = 1940 ppb
[Exposure = 1940 µg/L x 1 L/day / 10 kg = 194 µg/kg-day = .2 mg/kg-day]

Longer term (70 kg adult): 6800 µg/L = 6800 ppb
[Exposure = 6800 µg/L x 2 L/day / 70 kg = 194 µg/kg-day = .2 mg/kg-day]

Reference concentration (concentration in drinking water corresponding to an upper limit of lifetime cancer risk of 1E-7 to 1E-5):

.07 - 7 ug/L = .07 - 7 ppb
[Exposure = .07 µg/L x 2 L/day / 70 kg = .0194 µg/kg-day = .00002 mg/kg-day]

Therefore, lifetime exposures of .00002 - .002 mg/kg-day are associated with upper limits of excess cancer risk of 1E-7 - 1E-5.

These Risk Management numbers are not direct carryovers from the risk assessment numbers. Therefore, the user should telephone the contact person to determine the underlying assumptions and rationale.

INTERIM SUMMARY

There are several types of information which we have not been able to explore:

(1) The veracity of the analytical reports
(2) Possible sources of the contamination (and appropriate corrective measures)
(3) Possible alternative sources of water
(4) The basis for the HAs for DMDK
(5) The non-drinking water exposures

The information we have gathered, however, can be summarized as follows:

DNCW (Roughly Linear Scale)

HA (Child: 1-day)	.1 mg/kg-day
Estimated maximum child exposure (Probably short term)	.05 mg/kg-day
RfD (Lifetime exposure)	.03 mg/kg-day
HA (Child: 10-day or longer term)	.03 mg/kg-day
HA (Adult: longer term and lifetime)	1 mg/kg-day
Estimated maximum adult exposure (Probably short term)	.01 mg/kg-day

DMDK (Roughly logarithmic scale)

HA (Child: 1-day)	3 mg/kg-day
HA (Child and adult: longer term)	.2 mg/kg-day
RfD (Lifetime exposure)	.02 mg/kg-day
Estimated maximum child exposure (Probably short term)	.02 mg/kg-day
Estimated maximum adult exposure (Probably short term)	.006 mg/kg-day
1E-5 upper limit of lifetime cancer	.002 mg/kg-day
1E-6 upper limit of lifetime cancer	.0002 mg/kg-day

POSSIBLE INTERIM RM DECISION AND RATIONALE

Note the limitations on the data and the extent of exploration of the data mentioned above. Within those caveats, since none of the estimated maximum exposures for either chemical is vastly in excess of the RfD (which assumes a lifetime exposure) and all are less than the 1-day Health Advisory for a child, there is no apparent short-term health threat posed by the alleged conditions, with the possible exceptions of those individuals who are compromised by pre-existing liver and/or kidney conditions.

Further, if the conditions were to persist for a lifetime, the risk of greatest concern might be the cancer threat posed by DMDK. However, for a 1-year exposure, it would appear that even that cancer risk may not be excessive.

This conclusion is tempered by the lack of information on the carcinogenicity of DNCW and is based upon a foundation of data in which we have only medium confidence.

Therefore, given this risk picture and the logistical and resource difficulties likely to be posed by alternative measures, it appears that no emergency action is needed at this time. As a precaution, however, it might be good to advise the public that people with liver or kidney dysfunction would be at somewhat higher risk, if the allegations of contamination prove to be true.

Specific action should be taken to rigorously check the validity of the data (and perhaps initiate additional monitoring) and to systematically check for, identify, and correct the source(s) of the contamination.

In our view, this plan would constitute responsible, prudent action and should serve to reassure the concerned public.

GLOSSARY OF ACRONYMS AND ABBREVIATIONS

ACGIH	American Conference of Government and Industrial Hygienists
ADI	Acceptable Daily Intake
AIHA	American Industrial Health Association
ASCII	American Standard Code for Information Exchange
AUR	Air Unit Risk
BHP	biodegradation, hydrolysis, and photolysis
bw	body weight
CAG	Carcinogen Assessment Group, U.S. EPA
CAS	Chemical Abstracts Service
CC	closed cup
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act of 1980
CFR	Code of Federal Regulations
CNS	central nervous system
CRAVE	Carcinogen Risk Assessment Verification Endeavor
cu. m	cubic meter
CWA	Clean Water Act
DOT	U.S. Department of Transportation
DW	drinking water
E	exponent, base 10 (e.g., 1.5 E-6 = 1.5 x 10 to the power of -6)
EED	Estimated Exposure Dose
EEG	electroencephalogram
EKG	electrocardiogram
EMail	electronic mail
EPA	U.S. Environmental Protection Agency
EPUB	Electronic Publishing computer system (part of EPA's E-mail system)
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register
FTS	Federal Telecommunications System
GM	gamma multi-hit dose extrapolation model
HA	Health Advisory
HAPPS	Hazardous Air Pollution Prioritization System
HAS	Health Assessment Summary
HSDB	Hazardous Substance Data Base
IARC	International Agency for Research on Cancer
i.m.	intramuscularly
i.p.	intraperitoneally

IRIS	Integrated Risk Information System
kg	kilogram
L	liter
LCLO	Lethal Concentration Low; the lowest concentration at which death occurred
LC50	Lethal Concentration 50; the concentration at which 50% of the animals died; a calculated value
LDLO	Lethal Dose Low; the lowest dose at which death occurred
LD50	Lethal Dose 50; the dose at which 50% of the animals died; a calculated value
LEL	lowest effect level (same as LOAEL)
LM	linearized multistage procedure
LO	logit dose extrapolation model
LOAEL	Lowest Observed Adverse Effect Level
m	meter
M	multistage dose extrapolation model
MF	Modifying Factor
mg	milligram
mg/kg	milligrams per kilogram
mg/l	milligrams per liter
mmHg	millimeters of mercury; a measure of pressure
MOE	Margin of Exposure
MOS	Margin of Safety
NAAQS	National Ambient Air Quality Standards
NESHAPs	National Emission Standards for Hazardous Air Pollutants
NFPA	National Fire Prevention Association
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
n.a.	not available
n.o.s.	not otherwise specified
NRC	National Research Council, National Academy of Sciences
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
OAQPS	Office of Air Quality Planning and Standards, U.S. EPA
OAR	Office of Air and Radiation, U.S. EPA
OARM	Office of Administration and Resources Management, U.S. EPA
OC	open cup

ODW	Office of Drinking Water, U.S. EPA
OH	one-hit dose extrapolation model
OHEA	Office of Health and Environmental Assessment, U.S. EPA
OPP	Office of Pesticides Programs, U.S. EPA
OPPE	Office of Policy Planning and Evaluation, U.S. EPA
OPTS	Office of Pesticides and Toxic Substances, U.S. EPA
ORD	Office of Research and Development, U.S. EPA
OSHA	U.S. Occupational Safety and Health Administration
OSWER	Office of Solid Waste and Emergency Response, U.S. EPA
OTS	Office of Toxic Substances, U.S. EPA
OWRS	Office of Water Regulations and Standards, U.S. EPA
P	probit dose extrapolation model
PD	Position Document
PEL	Permissible Exposure Limit
p. o..	per os (by mouth)
ppb	parts per billion
ppm	parts per million
RA	Risk Assessment
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RfD	Reference Dose
RgD	Regulatory Dose
RM	Risk Management
RQ	Reportable Quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SAB	Science Advisory Board
S. C.	subcutaneous
SDWA	Safe Drinking Water Act
SF	Safety Factor
SMR	Standardized Mortality Ratio
STEL	short-term exposure limit
TCC	Tagliabue Closed Cup, a standard method of determining flash point
TDB	Toxicology Data Base
TOC	Tagliabue Open Cup, a standard method of determining flash point
TLV	Threshold Limit Value
TSCA	Toxic Substances Control Act
TWA	Time-Weighted Average
UEL	Upper Explosive Limit

UF	Uncertainty Factor
µg	microgram
µg/cu. m	microgram per cubic meter
µg/l	microgram per liter
VOC	volatile organic compound
W	Weibull dose extrapolation model
WQC	Water Quality Criteria
WUR	Water Unit Risk
--	not applicable

GLOSSARY OF TERMS

Acaricide -- An agent that destroys mites.

Acceptable Daily Intake -- An estimate of the daily exposure dose that is likely to be without deleterious effect even if continued exposure occurs over a lifetime.

Acidosis -- A pathologic condition resulting from accumulation of acid in, or loss of base from, the blood or body tissues.

Acneform -- Resembling acne.

Acute Exposure -- A one-time or short-term exposure (usually high-level) that may or may not cause a health problem.

Acute Hazard or Toxicity -- see Health Hazard.

Added Risk -- The difference between the cancer incidence in the treated group of animals or the exposed humans and the control group of animals or the spontaneous incidence in humans.

Algicide -- A chemical that controls or destroys the growth of algae.

Ambient Air -- Any unconfined portion of the atmosphere; open air.

Albuminuria -- Presence of serum albumin in the urine.

Alopecia -- Baldness; absence of hair from skin areas where it is usually present.

Amorphous -- Without definite form; not crystallized.

Anaphylactoid -- Resembling an unusual or exaggerated allergic reaction to foreign protein or other substances.

Anorexia -- Lack or loss of appetite for food.

Anoxia -- Absence or lack of oxygen; reduction of oxygen in the body tissues below physiologic levels.

Anthelmintic -- An agent that is destructive to worms, especially of the intestines.

Anticoagulant-- An agent that prevents blood clotting.

Antimetabolite -- A substance that interferes with utilization of an essential metabolite.

Antipyretic -- An agent that relieves or reduces fever.

Aphasia -- Defect or loss of power of expression by or comprehension of speech, writing, or signs.

Aplasia -- Lack of development of an organ or tissue, or the cellular products from an organ or tissue; germinal aplasia -- complete failure of gonad development.

Argyrosis -- Poisoning by silver or a silver salt, evidenced by ashen-gray discoloration of skin.

Arrhythmia -- Any variation from the normal rhythm of the heartbeat.

Arteriosclerosis -- Hardening and thickening of the walls of the smaller arteries.

Asthenia -- Lack or loss of strength; weakness.

Astringent -- Causing contraction, usually locally after surface application.

Ataxia -- Failure of muscular coordination; irregularity of muscular action.

Avicide -- An agent that kills birds.

Benign -- Not malignant; remaining localized.

Bilirubin -- A red pigment that occurs in soluble form in bile and in insoluble form in gallstones.

Bioaccumulation -- Increased concentrations of a chemical in an organism compared to the surrounding envrironment.

Bioavailability -- The physiological availability of a given amount of a substance, as distinct from its chemical potency.

Bradycardia -- Slowness of the heartbeat, as evidenced by slowing of pulse rate to less than 60.

Bronchoconstriction -- Narrowing of the air passages of the lungs.

Calcification -- Process by which organic tissue becomes hardened by a deposit of calcium salts within its substance.

Carcinogen -- An agent capable of inducing a cancer response.

Carcinogenic -- Producing or inciting cancer.

Carcinogens, classification of -- Group A: human carcinogen (sufficient evidence from epidemiologic studies); Group B: probable human carcinogen (subgroup B1: limited evidence from epidemiologic studies; subgroup B2: sufficient evidence from animal studies and inadequate evidence or no data from epidemiologic studies); Group C: possible human carcinogen (limited evidence from animal studies and no data from epidemiologic studies), from *Guidelines for Carcinogen Risk Assessment* (51 FR 33992-34003, September 24, 1986).

Cathartic -- Causing evacuation of the bowels; laxative.

Cheyne-Stokes respiration -- Respiratory distress related to posture (especially reclining at night) that occurs in association with heart disease.

Chloracne -- Acne-like eruption caused by exposure to chlorine compounds.

Cholinesterase -- An enzyme which hydrolyzes acetylcholine into choline and acetic acid and is important in the functioning of the nervous system.

Chronic effect -- A biological change produced by an alteration in the environment and persisting over a major portion of lifetime.

Chronic exposure -- Exposure (usually low-level) during a major portion of lifetime to an environmental alteration that may or may not cause a health problem.

Chronic hazard or toxicity -- see Health hazard.

Chronic study -- An experiment in which certain biological parameters are measured during and/or after exposure to an altered environment during a major portion of lifetime.

Clonic -- Pertaining to alternate muscular contraction and relaxation in rapid succession.

Cohort study -- A study of a group of persons who share a common experience within a defined time period.

Conjunctivitis -- Inflammation of the lining of the eyelids.

Contraindication -- Any condition which renders some particular line of treatment improper or undesirable.

Cryogenic -- Pertaining to or causing the production of low temperatures.

Cyanosis -- Bluish discoloration, especially of the skin and mucous membranes and fingernail beds.

Decoction -- Substance prepared by boiling.

Decomposition -- Separation into basic component parts.

Dehydrogenase -- Any of a class of enzymes which induce oxidation in a number of compounds by removing hydrogen.

Demulcent -- Soothing.

Dermal -- Pertaining to the skin.

Dermatitis -- Inflammation of the skin.

Desiccant -- A drying agent.

Desquamation -- Shedding of an outer layer in scales or shreds.

Diluent -- A diluting agent.

Diuresis -- Increased secretion of urine.

Diuretic -- Agent that increases urine production.

Dose-response -- A relationship between the amount of an agent either administered, absorbed, or believed to be effective and the response of the biological system to that agent.

DS2 -- Standard decontaminant for chemical agents; highly corrosive and highly toxic.

Ductile -- Capable of being drawn out or hammered thin.

Dysfunction -- Abnormal, impaired, or incomplete functioning.

Dyspnea -- Difficult or labored breathing.

Ectoparasiticide -- An agent that kills parasites living on the exterior of its host.

Edema -- Presence of abnormally large amounts of fluid in intercellular spaces of body tissues.

Emesis -- Vomiting.

End point -- The final result of a series of changes or processes.

Enteritis -- Inflammation of the intestine.

Epigastric -- Pertaining to the upper-middle region of the abdomen.

Epileptiform -- Occurring in severe or sudden spasms.

Epithelium -- Cells covering the internal and external surfaces of the body.

Erythema -- Redness of the skin produced by congestion of the capillaries.

Estimated exposure dose -- The estimated or calculated dose to which humans are likely to be exposed.

Exothermic -- Denoting a chemical reaction characterized by the development or liberation of heat.

Explosive -- Characterized by or relating to blowing up or bursting with sudden violence and noise; relating to a rapid chemical reaction with production of noise, heat, and violent expansion of gases.

Extra risk -- The probability that the agent produced an observed response, as distinguished from the probability that the response was caused by a spontaneous event unrelated to the agent.

Extrapolation -- An estimation of the numerical value of an empirical function at a point outside the range of data that established the function.

Fetotoxic -- Toxic to fetuses.

Flammable -- Capable of being easily ignited and supporting combustion.

Flash point -- The lowest temperature at which the vapor of a volatile oil will ignite with a flash.

Fumigant -- A pesticide that is vaporized to kill pests.

Fungicide -- A substance that kills fungi or checks the growth of spores.

Gamma multi-hit model -- A dose-response model of the form

$$P(d) = \int_0^d [a^k s^{k-1} exp(-as)/G(k)]\, ds$$

$$where \quad G(u) = \int_0^\infty s^{u-1} exp(-s)\, ds$$

where P(d) is the probability of cancer death from a dose d, k is the number of hits necessary to induce the tumor and a is a constant.

Gastrointestinal -- Pertaining to the stomach and intestine.

Glomerular -- Pertaining to a tuft or cluster, as of blood vessels or nerve fibers.

Guidelines for Carcinogen Risk Assessment -- Agency guidelines intended to guide Agency evaluation of suspect carcinogens in line with the policies and procedures established in the statutes administered by the EPA. See 51 FR 33992-34003, September 24, 1986.

Guidelines for Exposure Assessment -- Agency guidelines intended to guide Agency analysis of exposure assessment data in line with the policies and procedures established in the statutes administered by the EPA. See 51 FR 34042-34054, September 24, 1986.

Guidelines for the Health Assessment of Suspect Developmental Toxicants -- Agency guidelines intended to guide Agency analysis of developmental toxicity data in line with the policy and procedures established in the statutes administered by the EPA. See 51 FR 34028-34040, September 24, 1986.

Guidelines for the Health Risk Assessment of Chemical Mixtures -- Agency guidelines intended to guide Agency analysis of information relating to health effects data on chemical mixtures in line with the policy and procedures established in the statutes administered by the EPA. See 51 FR 34014-34025, September 24, 1986.

Guidelines for Mutagenicity Risk Assessment -- Agency guidelines intended to guide Agency analysis of mutagenicity data in line with the policy and procedures established in the statutes administered by the EPA. See 51 FR 34006-34012, September 24, 1986.

Half-life -- The time in which the concentration of a substance will be reduced by half.

Halogen -- Any of the five nonmetallic chemical elements--fluorine, chlorine, bromine, astatine, and iodine.

Halon -- Halogenated hydrocarbon (e.g., carbon tetrachloride).

Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable Federal standard, but serves as technical guidance to assist federal, state, and local officials.

Health hazard --

Acute -- Immediate toxic effects.

Chronic -- Persistent or prolonged injury.

Delayed -- Toxic effect occurring after a lapse of time.

Hematoma -- Localized collection of blood, usually clotted, in an organ, space, or tissue, due to a break in the wall of the blood vessel.

Hematuria -- Blood in the urine.

Hemoglobinuria -- Presence of free hemoglobin in the urine.

Hemolysis -- Separation of hemoglobin from red blood cells, and its appearance in the plasma.

Hemolytic -- Pertaining to or characterized by hemolysis.

Hepatic -- Pertaining to the liver.

Herbicide -- A substance that controls or destroys undesirable plants.

Histogenic origin -- The germ cell layer of the embryo from which the adult tissue developed.

Human equivalent dose -- The human dose of an agent which is believed to induce the same magnitude of toxic effect that the known animal dose has induced.

Humectant -- Moistening or diluent substance.

Homeostasis -- Maintenance of normal, internal stability in an organism by coordinated responses of the organ systems that automatically compensate for environmental changes.

Hydrolysis -- Double decomposition reaction involving the splitting of water into its ions and the formation of a weak acid and/or a weak base.

Hygroscopic -- Readily taking up and retaining moisture (water).

Hyperactivity -- Abnormally increased activity.

Hyperalimentation -- Ingestion or administration of a greater-than-optimal amount of nutrients.

Hyperbilirubinemia -- An excess of bilirubin in the blood.

Hypercalcemia -- An excess of calcium in the blood.

Hyperparathyroidism -- Abnormally increased activity of the parathyroid glands which affects and is affected by serum calcium levels.

Hyperpyrexia -- A highly elevated body temperature.

Hyperreflexia -- Exaggeration of reflexes.

Hypersalivation -- Excessive secretion of saliva.

Hypertension -- Persistently high arterial blood pressure.

Hypervitaminosis -- Condition due to ingestion of an excess of one or more vitamins.

Hypobilirubinemia -- Abnormally low levels of bilirubin in the blood.

Hypocalcemia -- Abnormal reduction of blood calcium levels.

Hypovolemic -- Pertaining to an abnormally decreased volume of circulating fluid (plasma) in the body.

Hypoxemia -- Deficient oxygenation of the blood.

Hypoxia -- Low oxygen content or tension; deficiency of oxygen in the inspired air.

Inadequate evidence -- According to the EPA carcinogen risk assessment guidelines, inadequate evidence is a collection of facts and accepted scientific inferences which is not definitive enough to allow conclusions to be drawn.

Incidence -- The number of new cases of a disease within a specified period of time.

Individual risk -- The probability that an individual person will experience an adverse effect.

Initiation -- The ability of an agent to induce a change in a tissue which leads to the induction of tumors after a second agent, called a promoter, is administered to the tissue repeatedly.

Interstitial pneumonia -- A chronic form of pneumonia involving increase of the interstitial tissue and decrease of the lung tissue.

in vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

in vivo -- Occurring within the living organism.

Isotonic -- A solution having the same effective osmotic pressure as the body fluid to which it is compared.

Jaundice -- Syndrome characterized by hyperbilirubinemia and deposition of bile pigment in the skin, resulting in yellow appearance of the patient.

Lachrymator (or lacrimator) -- A substance which increases the flow of tears.

Lacrimation -- Secretion and discharge of tears.

Laryngospasm -- Spasmodic closure of the larynx.

Larynx -- The muscular and cartilage structure situated at the top of the trachea (windpipe) and below the root of the tongue, functioning as sphincter into the trachea and as the organ of voice.

Lassitude -- Weakness; exhaustion.

Latency -- A state of seeming inactivity.

Lesion -- A pathologic or traumatic discontinuity of tissue or loss of function of a part.

Lethal -- Deadly; fatal.

Leukopenia -- Reduction in the number of leukocytes in the blood.

Lewisite -- A lethal war gas which is a vesicant, lacrimator, and lung irritant.

Limited evidence -- According to the EPA carcinogen risk assessment guidelines, limited evidence is a collection of facts and accepted scientific inferences which suggests that the agent may be causing an effect but the suggestion is not strong enough to be an established fact.

Linearized multistage procedure -- A sequence of steps in which a) the multistage model is fitted to the tumor incidence data; b) the maximum linear term consistent with the data is calculated; c) the low-dose slope of the dose-response function is equated to the coefficient of the maximum linear term; and d) the resulting slope is then equated to the upper bound of potency.

Logit model -- A dose-response model of the form

$$P(d) = 1/[1 + exp\ (-a - log\ d)]$$

where P(d) is the probability of cancer death from a continuous dose rate, d, and a and b are constants.

Lowest observed adverse effect level -- The lowest dose in an experimental study at which a statistically or biologically significant adverse effect was observed.

Malaise -- A vague feeling of bodily discomfort.

Malignant -- Tending to become progressively worse and to result in death. Having the properties of anaplasia, invasion, and metastasis.

Mania -- A phase of mental disorder characterized by an expansive emotional state, elation, overtalkativeness, and increased motor activity.

Margin of exposure -- The ratio of the NOAEL and the EED, which, in the case of a regulatory decision, is the RgD; i.e., MOE = NOAEL/RgD.

Margin of safety -- The term formerly applied to the Margin of Exposure concept.

Metastatic -- Pertaining to the transfer of disease from one organ or part to another not directly connected with it.

Methemoglobinemia -- Presence of methemoglobin (oxidized hemoglobin) in the blood.

Miosis (or myosis) -- Contraction of the pupil.

Miscible -- Capable of mixing in any ratio without separation of two phases, refers to liquid mixtures.

Model -- A mathematical function with parameters which can be adjusted so that the function closely describes a set of empirical data.

Modifying factor -- An uncertainty factor, greater than zero and less than or equal to 10; its magnitude reflects professional judgment regarding aspects of the data used for the assessment; e.g., the completeness of the overall data base and the number of animals tested.

Mordant -- A chemical that fixes a dye in or on a substance by combining with the dye to form an insoluble compound.

Multistage model -- A dose-response model of the form

$$P(d) = 1 - exp[-(q_0 + q_1 d + q_2 d^2 + ...)]$$

where P(d) is the probability of cancer death from a continuous dose rate, d, and the q's are constants.

Mutagenic -- Inducing genetic mutation.

Mydriasis -- Extreme dilation of the pupil.

Myelosuppression -- Suppression of the formation of bone marrow.

Narcotic -- An agent that produces insensibility or stupor.

Necrosis -- Death of tissue, usually as individual cells, as groups of cells, or in localized areas.

Nephritis -- Inflammation of the kidney.

Neural -- Pertaining to a nerve or to the nerves.

Neuropathy -- Functional disturbances and/or pathological changes in the peripheral nervous system.

Neurotoxicity -- Exerting a destructive or poisonous effect on nerve tissue.

Nocturia -- Excessive urination at night.

No data -- According to the EPA carcinogen risk assessment guidelines, no data is a category of both human and animal evidence in which no studies are available from which to draw conclusions.

No observed adverse effect level -- The highest experimental dose at which there was no statistically significant increase in a toxicologically significant end point.

No observed effect level -- The highest experimental dose at which there was no statistically significant increase in any monitored end point.

Ocular -- Pertaining to or affecting the eye.

Oliguria -- Secretion of a diminished amount of urine in relation to fluid intake.

One-hit model -- A dose-response model of the form

$$P(d) = 1 - exp(-b\ d)$$

where P(d) is the probability of cancer death from a continuous dose rate, d, and b is a constant.

Ophthalmic -- Pertaining to the eye.

Organoleptic -- Affecting or involving an organ, especially a sense organ as of taste, smell, or sight.

Osteosclerosis -- Hardening or abnormal density of bone.

Oxidizer -- A substance that unites with oxygen, as in burning or rusting.

Palpitation -- Unduly rapid heartbeat which is noted by the patient; it may be regular or irregular.

Parameter -- A quantity which is constant under a given set of conditions, but may be different under other conditions.

Parasympathomimetic -- Relating to drugs or chemicals having an action resembling that caused by stimulation of the parasympathetic nervous system; also called cholinomimetic.

Parenteral -- introduced other than by way of the intestines, (e.g., subcutaneous, intramuscular, intravenous, etc.)

Paresthesia -- An abnormal sensation, as burning or prickling.

Perfusion -- Liquid poured over or through an organ or tissue.

Pharmacokinetics -- Movements of chemicals within biological systems, as affected by uptake, distribution, elimination, and biotransformation.

Pharynx -- The muscular membrane sac between the mouth and nostrils and the esophagus.

Photophobia -- Abnormal visual intolerance of light.

Photosensitize -- To induce a state of abnormal responsiveness to the influence of light.

Phytotoxic -- Poisonous to plants; inhibiting plant growth.

Polydipsia -- Excessive thirst persisting for long periods of time.

Polymerization -- The process of joining two or more like molecules to form a more complex molecule.

Population risk -- The number of cases occurring in a group of people.

Potency slope -- Synonomous with slope factor.

Precordial -- Pertaining to the region over the heart and lower part of the thorax.

Probit model -- A dose-response model of the form

$$P(d) = 0.4 \int_{-\infty}^{[log(d-u)]/s} [exp(-y^2/2)]\, dy$$

where P(d) is the probability of cancer death from a continuous dose rate d, and u and s are constants.

Proteinuria -- An excess of serum proteins in the urine; also called albuminuria.

Psychosis -- Any major mental disorder characterized by derangement of the personality and loss of contact with reality.

Psychotropic -- Exerting an effect upon the mind; capable of modifying mental activity.

q_1^* -- The upper-bound slope parameter as determined by the multistage procedure.

Pulmonary -- Pertaining to the lungs.

Radionuclide -- A radioactive atom.

Rales -- Abnormal respiratory sound heard when listening for sounds within the body.

Reactivity -- Tendency of a substance to undergo chemical change.

Recumbent -- Lying down.

Reference dose -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effect during a lifetime. The RfD is expressed in units of mg/kg-b.w./day.

Registration (of a pesticide) -- Under FIFRA and its amendments, new pesticide products cannot be sold unless they are registered with EPA. Registration involves a comprehensive evaluation of risks and benefits based on all relevant data.

Regulatory dose -- The dose reflected in the final risk management decision.

Renal -- Pertaining to the kidney.

Reportable quantity -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) one pound, or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Risk -- The difference between the cancer incidence in the treated group of animals or the exposed humans and the control group of animals or the spontaneous incidence in humans.

Risk Assessment -- The scientific activity of evaluating the toxic properties of a chemical and the conditions of human exposure to it in order both to ascertain the likelihood that exposed humans will be adversely affected, and to characterize the nature of the effects they may experience.

Safety factor -- The term formerly applied to the uncertainty factor concept.

Scotoma -- An area of depressed vision within the visual field, surrounded by an area of less depressed or normal vision.

Serum -- The clear, watery fluid that moistens the surface of internal membranes; the watery portion of blood which remains after the blood clots.

Slimicide -- A chemical that prevents the growth of slime in paper stock.

Slope factor -- The slope of the upper-bound dose extrapolation model at doses approaching zero.

Specific gravity -- The ratio of the density of a material to the density of some standard material; also known as relative density.

Standardized mortality ratio -- The ratio of the number of deaths observed in the study group to the number of deaths "expected" in the study group under the set of rates for the control population.

Subchronic effect -- A biological change resulting from an environmental alteration lasting about 10% of lifetime.

Subchronic exposure -- An environmental alteration occurring over about 10% of lifetime.

Subchronic study -- An experiment in which certain biological parameters are measured during and/or after exposure to an altered environment during about 10% of lifetime.

Sufficient evidence -- According to the EPA carcinogen risk assessment guidelines, sufficient evidence is a collection of facts and accepted scientific inferences which is definitive enough to establish that the observed effect is caused by the agent in question.

Summary sheet -- The two-to-four page summary of risk assessments conducted by EPA.

Superfund -- Federal authority, established by the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) in 1980, to respond directly to releases or threatened releases of hazardous substances that may endanger health or welfare.

Supertropical bleach -- Bleaching agent containing calcium hypochlorite (a powerful oxidizer) and calcium oxide (a corrosive material).

Systemic -- Pertaining to or affecting the body or organism as a whole.

Systemic Effects -- Systemic effects are those that require absorption and distribution of the toxicant to a site distant from its entry point at which point effects are produced. Most chemicals that produce systemic toxicity do not cause a similar degree of toxicity in all organs but usually demonstrate major toxicity to one or two organs. These are referred to as the target organs of toxicity for that chemical. *Toxicology: The Basic Science of Poisons*, Casarett and Doull, Second Edition, MacMillan Publishing Co., Incv., 1980. (Operationally EPA does not include carcinogens in this category).

Systemic Toxicity -- See Systemic Effects.

Systemic Toxicants -- See Systemic Effects.

Tachycardia -- Excessively rapid heartbeat.

Target Organ of Toxicity -- See Systemic Effects.

Tepid -- Moderately warm; lukewarm.

Teratogenic -- Tending to produce anomalies of formation or development.

Tetanic -- Pertaining to or of the nature of tetanus, a disease characterized by muscle spasm.

Threshold -- A dose at which an effect occurs.

Thrombocytopenia -- Decrease in the number of blood platelets.

Tidal volume -- Amount of gas that is inhaled and exhaled during one respiratory cycle.

Tinnitus -- A noise in the ears, such as ringing, buzzing, roaring, or clicking.

Toxic -- Pertaining to, due to, or of the nature of a poison.

Triglyceridemia -- Excess of triglycerides in the blood.

Tumor progression -- The sequence of changes in which a tumor develops from a microscopic lesion to a malignant stage.

Uncertainty factor -- Factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population; (2) the uncertainty in extrapolating animal data to the case of humans; (3) the uncertainty in extrapolating from data obtained in a study that is of less-than-lifetime exposure; and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors are set equal to 10.

Unit risk -- The incremental upper-bound lifetime risk estimated to result from lifetime exposure to an agent if it is in the air at a concentration of 1 microgram per cubic meter or in the water at a concentration of 1 microgram per liter.

Urticaria -- A vascular reaction of the skin marked by the transient appearance of smooth, slightly elevated patches (wheals) which are redder or paler than the surrounding skin and often attended by severe itching.

Vacuole -- A membrane-bound cavity within a cell.

Vasodilation -- Dilation (expansion) of a blood vessel, leading to increased blood flow.

Ventricular fibrillation -- Irregular heartbeat characterized by uncoordinated contractions of the ventricle.

Vertigo -- Dizziness; an illusion of movement as if the external world were revolving around an individual or as if the individual were revolving in space.

Vesicant -- Causing blisters.

Volatile -- Readily vaporizable at a relatively low temperature.

Weibull model -- A dose-response model of the form

$$P(d) = 1 - exp\,(-b\ d^m)$$

where P(d) is the probability of cancer death due to a continuous dose rate, d, and b and m are constants.

Weight-of-evidence for carcinogenicity -- The end result of process in which all relevant factors affecting the likelihood that the agent is a human carcinogen are evaluated.

APPENDIX A

REFERENCE DOSE (RfD): DESCRIPTION AND USE IN HEALTH RISK ASSESSMENTS

PRINCIPAL AUTHOR:

Donald Barnes, Ph.D. (OPTS)

RfD WORK GROUP:

Donald Barnes, Ph.D. (OPTS)
Judith Bellin, Ph.D. (OSWER)
Christopher DeRosa, Ph.D. (ORD)
Michael Dourson, Ph.D. (ORD)*
Reto Engler, Ph.D. (OPTS)
Linda Erdreich, Ph.D (ORD)
Theodore Farber, Ph.D. (OPTS)
Penny Fenner-Crisp, Ph.D. (ODW)
Elaine Francis, Ph.D. (OPTS)
George Ghali, Ph.D. (OPTS)
Richard Hill, M.D., Ph.D. (OPTS)
Stephanie Irene, Ph.D (OPTS)
William Marcus, Ph.D. (OW)
David Patrick, P.E., B.S. (OAR)
Susan Perlin, Ph.D. (OPPE)
Peter Preuss, Ph.D. (ORD)*
Aggie Revesz, B.S. (OPTS)
Reva Rubenstein, Ph.D. (OSWER)
Jerry Stara, D.V.M., Ph. D (ORD)
Jeanette Wiltse, Ph.D. (OPTS)
Larry Zaragosa, Ph.D. (OAR)

*Co-Chair

CONTENTS

I. INTRODUCTION

This concept paper describes the U.S. Environmental Protection Agency's principal approach to and rationale for assessing risks for health effects other than cancer and gene mutations from chronic chemical exposure. By outlining principles and concepts that guide EPA risk assessment for such systemic* effects, the report complements the new risk assessment guidelines, which describe the Agency's approach to risk assessment in other areas (carcinogenicity, mutagenicity, developmental toxicity, exposure, and chemical mixtures.) See the IRIS glossary for a description and citation of each guideline.

A. Background

Chemicals that give rise to toxic end points other than cancer and gene mutations are often referred to as "systemic toxicants" because of their effects on the function of various organ systems. It should be noted, however, that chemicals which cause cancer and gene mutations also commonly evoke other toxic effects (systemic toxicity). Generally, based on our understanding of homeostatic and adaptive mechanisms, systemic toxicity is treated as if there is an identifiable exposure threshold (both for the individual and for the population) below which effects are not observable. This characteristic distinguishes systemic end points from carcinogenic and mutagenic end points, which are often treated as nonthreshold processes.

Systemic effects have traditionally been evaluated in terms of concepts such as "acceptable daily intake" and "margin of safety." The scientific community has identified certain limits on some of these approaches, and these limits have been borne out in EPA's experience. Nonetheless, EPA is called upon to apply these concepts in making and explaining decisions about the significance for human health of certain chemicals in the environment.

To meet these needs, the RfD Work Group has drawn on traditional concepts, as well as on recommendations in the 1983 National Academy of Sciences (NAS) report on risk assessment, to more fully articulate the use of noncancer, nonmutagenic experimental data in reaching decisions on the significance of exposures to chemicals. In the process, the Agency has coined new terminology to clarify and distinguish between aspects of risk assessment and risk management. EPA has tested and implemented these innovations in developing consistent information for several recent regulatory needs, for instance under RCRA.

B. Overview

This Appendix consists of four parts in addition to this introduction. In Section II, much of the traditional information on assessing risks of systemic toxicity is presented, with the focus on the concepts of "acceptable daily intake (ADI)" and "safety factor (SF)." Issues associated with these approaches are identified and discussed.

In Section III, the Agency's approach to assessing the risks of systemic toxicity is presented in the context of the NAS scheme of risk assessment and risk management in regulatory decision-making. This approach includes recasting earlier ADI and SF concepts into the less value-laden terms "reference dose (RfD)" and "uncertainty factor (UF)." A new term, "margin of exposure,"** as utilized in the EPA regulatory context, is introduced to avoid some of the issues associated with the traditional approach.

Section IV examines how these new concepts can be applied in reaching risk management decisions, while Section V briefly mentions some of the additional approaches the Agency is using and exploring to address this issue. Section VI provides a sample RfD calculation.

---

*In this document the term "systemic" refers to an effect other than carcinogenicity or mutagenicity induced by a toxic chemical

**In this Appendix, the ratio of the NOAEL to the estimated exposure (often referred to as "margin of safety") is referred to as the "margin of exposure (MOE)" in order to avoid confusion with the original use of the term "margin of safety" in pharmacology (i e , the ratio of the toxic dose to the theraputic dose) and to avoid the use of the value-laden term "safety."

II. TRADITIONAL APPROACH TO ASSESSING SYSTEMIC (NONCARCINOGENIC) TOXICITY

The Agency's approach to assessing the risks associated with systemic toxicity is different from that for the risks associated with carcinogenicity. This is because different mechanisms of action are thought to be involved in the two cases. In the case of carcinogens, the Agency assumes that a small number of molecular events can evoke changes in a single cell that can lead to uncontrolled cellular proliferation. This mechanism for carcinogenesis is referred to as "nonthreshold," since there is essentially no level of exposure for such a chemical that does not pose a small, but finite, probability of generating a carcinogenic response. In the case of systemic toxicity, organic homeostatic, compensating, and adaptive mechanisms exist that must be overcome before the toxic end point is manifested. For example, there could be a large number of cells performing the same or similar function whose population must be significantly depleted before the effect is seen.

The threshold concept is important in the regulatory context. The individual threshold hypothesis holds that a range of exposures from zero to some finite value can be tolerated by the organism with essentially no chance of expression of the toxic effect. Further, it is often prudent to focus on the most sensitive members of the population; therefore, regulatory efforts are generally made to keep exposures below the population threshold, which is defined as the lowest of the thresholds of the individuals within a population.

A. The Traditional Approach

In many cases, risk decisions on systemic toxicity have been made by the Agency using the concept of the "acceptable daily intake (ADI)." This quantity is derived by dividing the appropriate "no-observed-adverse-effect level (NOAEL)" by a "safety factor (SF)" as follows:*

$$\text{ADI (human dose)} = \text{NOAEL (experimental dose)} / \text{SF} \qquad (1)$$

The ADI is often viewed as the amount of a chemical to which one can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. Often, the ADI has been used as a tool in reaching risk management decisions; e.g., establishing allowable levels of contaminants in foodstuffs and water.

Once the critical study demonstrating the toxic effect of concern has been identified, the selection of the NOAEL derives from an essentially objective, scientific examination of the data available on the chemical in question.

Generally, the SF consists of multiples of 10, each factor representing a specific area of uncertainty inherent in the available data. For example, an SF may be developed by taking into account the expected differences in responsiveness between humans and animals in prolonged exposure studies; i.e., a 10- fold factor. In addition, a second factor of 10 may be introduced to account for variability among individuals within the human population. For many chemicals, the resultant SF of 100 has been judged to be appropriate. For other chemicals, with a less complete data base (e.g., those for which only the results of subchronic studies are available), an additional factor of 10 (leading to an SF of 1,000) might be judged to be more appropriate. On the other hand, for some chemicals, based on well-characterized responses in sensitive humans (e.g., effect of fluoride on human teeth), an SF as small as 1 might be selected.

---

*A NOAEL is an experimentally determined dose at which there was no statistically or biologically significant indication of the toxic effect of concern. In an experiment with several NOAELs, the regulatory focus is normally on the highest one, leading to the common usage of the term NOAEL as the highest experimentally determined dose without statistical or adverse biological effect. In some treatments, the NOAEL for the critical toxic effect is simply referred to as the NOEL. This latter term, however, invites ambiguity in that there may be observable effects which are not of toxicologic significance; i e , they are not "adverse." In order to be explicit, this Appendix uses the term NOAEL and it refers to the highest NOAEL in an experiment Further, in cases in which a NOAEL has not been demonstrated experimentally, the formulation calls for use of the "lowest-observed-adverse-effect level (LOAEL)." In order to focus on the major concepts, however, we will use NOAEL as a general example

While the original selection of SFs appears to have been rather arbitrary (Lehman and Fitzhugh, 1954)*, subsequent analysis of data as reviewed by Dourson and Stara (1983) lends theoretical (and in some instances experimental) support for their selection. Further, some scientists, but not all, within the EPA interpret the absence of widespread effects in the exposed human populations as evidence of the adequacy of the SFs traditionally employed.

B. Some Difficulties in Utilizing the Traditional Approach

1. Scientific Issues

While the traditional approach has performed well over the years and the Agency has sought to be consistent in its application, observers have identified scientific shortcomings of the approach. Examples include the following:

- By focusing on the NOAEL, information on the shape of the dose-response curve is ignored. Such data could be important in estimating levels of concern for public safety.
- As scientific knowledge is increased and the correlation of precursor effects (e.g., enzyme induction) with frank toxicity becomes known, questions about the selection of the appropriate "adverse effect" arise.
- Guidelines have not been developed to take into account the fact that some studies have used larger numbers of animals and, hence, are generally more reliable than other studies.

These and other "generic issues" are not susceptible to immediate resolution, because the data base needed is not yet sufficiently developed or analyzed. Therefore, these issues are beyond the scope of this Appendix. However, the Agency has established a work group to consider them.

2. Management-related Issues

a. The use of the term "safety factor"

The term "safety factor" suggests, perhaps inadvertently, the notion of absolute safety, i.e., absence of risk. While there is a conceptual basis for believing in the existence of a threshold and "absolute safety" associated with certain chemicals, in the majority of cases a firm experimental basis for this notion does not exist.

b. The implication that any exposure in excess of the ADI is "unacceptable" and that any exposure less than the ADI is "acceptable" or "safe"

In practice, the ADI is viewed by many as an "acceptable" level of exposure, and, by inference, any exposure greater than the ADI is seen as "unacceptable." This strict demarcation between what is "acceptable" and what is "unacceptable" is contrary to the views of most toxicologists, who typically interpret the ADI as a relatively crude estimate of a level of chronic exposure not likely to result in adverse effects to humans. The ADI is generally viewed as a "soft" estimate, whose bounds of uncertainty can span an order of magnitude. That is, within reasonable limits, while exposures somewhat higher than the ADI are associated with increased probability of adverse effects, that probability is not a certainty. Similarly, while the ADI is seen as a level at which the probability of adverse effects is low, the absence of risk to all people cannot be assured at this level.

c. Possible limitations imposed on risk management decisions

Awareness of the "softness" of the ADI estimate (see b. above) argues for careful case-by-case consideration of the implications of the toxicological analysis as it applies to any particular situation. To the degree that ADIs generated by the traditional approach are the determining factors in risk

*Lehman, A.J. and Fitzhugh, O.G (1954). Association of Food Drug Officials. USQ Bulletin 18:33-35.

management decisions, they can take on a significance beyond that intended by the toxicologist or merited by the underlying scientific support.

Further, in administering risk/benefit or cost/benefit statutes, the risk manager is required to consider factors other than risk (e.g., estimated exposures compared to the ADI) in reaching a decision. The ADI is only one factor in a management decision and should not prevent the risk manager from weighing the full range of factors.

d. Development of different ADIs by different programs

In addition to occasionally selecting different critical toxic effects, Agency scientists have reflected their best scientific judgments in the final ADI by adopting factors different from the standard factors listed in Table A-1. For example, if the toxic end point for a chemical in experimental animals is the same as that which has been established for a related chemical in humans at similar doses, one could argue for an SF of less than the traditional 100. On the other hand, if the total toxicologic data base is incomplete, one could argue that an additional SF should be included, both as a matter of prudent public policy and as an incentive to others to generate the appropriate data.

Such practices, as employed by a number of scientists in different programs, exercising their best scientific judgment, have in many cases resulted in different ADIs for the same chemical. The fact that different ADIs were generated (e.g., by adopting different SFs) can be a source of considerable confusion when the ADIs are applied in risk management decisionmaking (see c. above). For example, although they generally agree on the experimental data base for 2,3,7,8-TCDD, regulatory agencies within the United States and around the world have generated different ADIs by selecting different "safety factors"; specifically, 1000, 500, 250, and 100. These different ADIs have been used to justify different regulatory decisions. The existence of different ADIs need not imply that any of them is more "wrong"--or "right"--than the rest. It is more nearly a reflection of the honest difference in scientific judgment.

These differences, which may reflect differences in the interpretation of the scientific data, can also be characterized as differences in the management of the risk. As a result, scientists may be inappropriately impugned,and/or perfectly justifiable risk management decisions may be tainted by charges of "tampering with the science." This unfortunate state of affairs arises, at least in part, from treating the ADI as an absolute measure of safety.

III. EPA ASSESSMENT OF RISKS ASSOCIATED WITH SYSTEMIC TOXICITY

In 1983, the National Academy of Sciences published a report* which discusses the conceptual framework within which regulatory decisions on toxic chemicals are made; see Figure A-1. The determination of the presence of risk and its potential magnitude is made during the risk assessment process, which consists of hazard identification, dose-response assessment, exposure assessment, and risk characterization. Having been apprised by the risk assessor that a potential risk exists, the risk manager answers the question: "What, if anything, are we going to do about it?"

A. Hazard Identification

1. Evidence

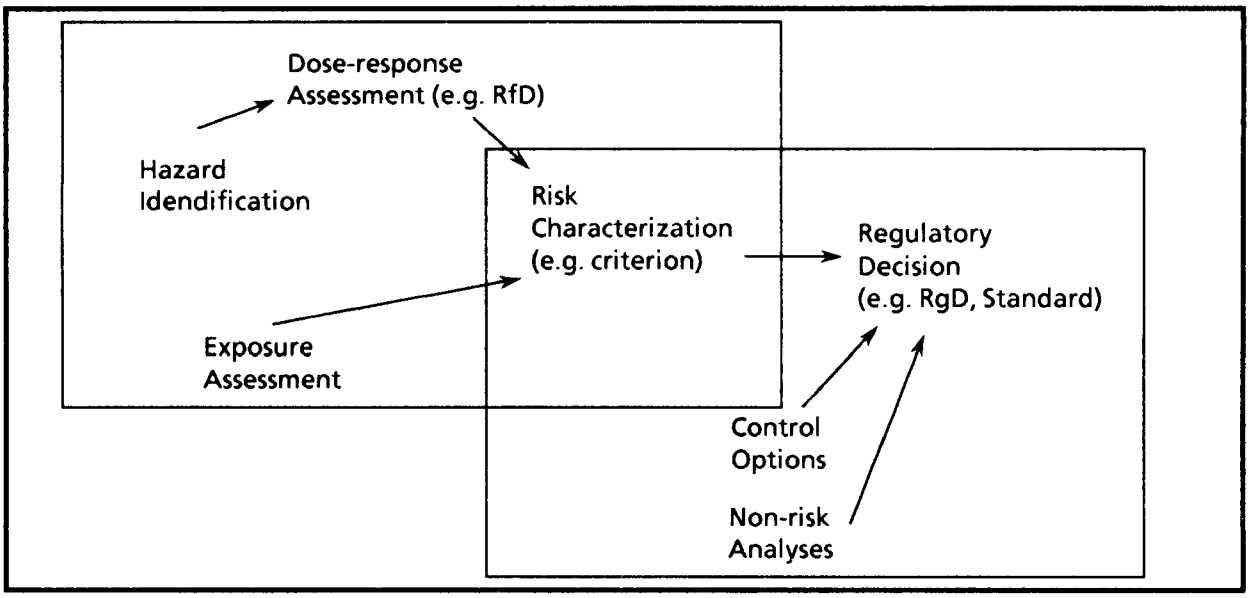
a. Type of effect

Exposure to a given chemical, depending on the dose employed, may result in a variety of toxic effects. These may range from gross effects, such as death, to more subtle biochemical, physiologic, or pathologic changes. The risk assessor considers each of the toxic end points from all studies evaluated in assessing the risk posed by a chemical, although primary attention usually is given to the effect exhibiting the lowest NOAEL, often referred to as the critical effect. For chemicals with a limited data base, there may be a need for more toxicity testing.

---

*NAS *Risk Assessment in the Federal Government. Managing the Process* (NAS Press, 1983)

FIGURE A-1



b. Principal studies

Principal studies are those that contribute most significantly to the qualitative assessment of whether or not a particular chemical is potentially a systemic toxicant in humans. In addition, they may be used in the quantitative dose-response assessment phase of the risk assessment. These studies are of two types:

(1) Human studies

Human data are often useful in qualitatively establishing the presence of an adverse effect in exposed human populations. Further, when there is information on the exposure level associated with an appropriate end point, epidemiologic studies can also provide the basis for a quantitative dose-response assessment. Use of these latter data avoids the necessity of extrapolating from animals to humans, and therefore, human studies, when available, are given first priority, with animal toxicity studies serving to complement them.

In epidemiologic studies, confounding factors that are recognized can be controlled and measured, within limits. Case reports and acute exposures resulting in severe effects provide support for the choice of critical toxic effect, but they are often of limited utility in establishing a quantitative relationship between environmental exposures and anticipated effects. Available human studies on ingestion are usually of this nature. Cohort studies and clinical studies may contain exposure-response information that can be used in estimating effect levels, but the method of establishing exposure must be evaluated for validity and applicability.

(2) Animal studies

Usually, the data base on a given chemical lacks appropriate information on effects in humans. In such cases, the principal studies are drawn from experiments conducted on non-human mammals, most often the rat, mouse, rabbit, guinea pig, hamster, dog, or monkey.

c. Supporting studies

Supporting studies include information from a wide variety of sources. For example, metabolic and other pharmacokinetic studies can provide insights into the mechanism of action of a particular compound. By comparing the metabolism of the compound exhibiting the toxic effect in the animal

with the metabolism found in humans, some light may be cast on the potential for the toxic manifestation in humans or for estimating the equitoxic dose in humans.

Similarly, *in vitro* studies can provide insights into the compound's potential for biological activity, although a definite connection to the human experience cannot be drawn. Under certain circumstances, consideration of structure-activity relationships between the chemical under test and the effects of structurally related agents can provide a clue to the biological activity of the former.

At the present time, these data are supportive, not definitive, in assessing risk. However, there is focused activity aimed at developing more reliable *in vitro* tests to minimize the need for live-animal testing. Similarly, there is increased emphasis on generating mechanism-of-action and pharmacokinetic information as a means of increasing the fundamental understanding of toxic processes in humans and nonhumans. It is expected that in the future these considerations will play a larger role in our determination of toxicity of chemicals.

d. Route of exposure

The Agency often approaches the investigation of a chemical with a particular route of exposure in mind; e.g., an oral exposure for a drinking water contaminant or a residue in food. Although the route of exposure is oral in both cases, specific considerations may differ. For example, the bioavailability of the chemical administered in food may differ from that when administered in water or inhaled. Usually, the toxicologic data base on the compound does not include detailed testing on all possible routes of administration.

In general, it is the Agency's view that the potential for toxicity manifested by one route of exposure is relevant to any other route of exposure, unless convincing evidence exists to the contrary. Consideration is always given to potential differences in absorption or metabolism resulting from different routes of exposure, and whenever appropriate data (e.g., comparative metabolism studies) are available, the quantitative impacts of these differences on the risk assessment are fully delineated.

e. Length of exposure

The Agency is concerned about the potential toxic effects in humans associated with all possible exposures to chemicals. The magnitude, frequency, and duration of exposure may vary considerably in different situations. Animal studies are conducted using a variety of exposure durations (e.g., acute, subchronic, and chronic) and schedules (e.g., single, intermittent, or continuous dosing). Information from all of these studies is useful in the hazard identification phase of risk assessment. For example, overt neurological problems identified in high-dose acute studies tend to reinforce the observation of subtle neurological changes seen in a low-dose chronic study. Special concern exists for low-dose, chronic exposures, however, since such exposures can elicit effects absent in higher-dose, shorter exposures, through mechanisms such as accumulation of toxicants in the organisms.

f. Quality of the study

Evaluation of individual studies in humans and animals requires the consideration of several factors associated with a study's hypothesis, design, execution, and interpretation. An ideal study addresses a clearly delineated hypothesis, follows a carefully prescribed protocol, and includes sufficient subsequent analysis to support its conclusions convincingly.

In evaluating the results from such studies, consideration is given to many other factors, including chemical characterization of the compound(s) under study, the type of test species, similarities and differences between the test species and humans (e.g., chemical absorption and metabolism), the number of individuals in the study groups, the number of study groups, the spacing and choice of dose levels tested, the types of observations and methods of analysis, the nature of pathologic changes, the alteration in metabolic responses, the sex and age of test animals, and the route and duration of exposure.

2. Weight-of-Evidence Determination

As the culmination of the hazard identification step, a discussion of the weight-of-evidence summarizes the highlights of the information gleaned from the entire range of principal and

supporting studies. Emphasis in the analysis is given to examining the results from different studies to determine the extent to which a consistent, plausible picture of toxicity emerges. For example, the following factors add to the weight of the evidence that the chemical poses a hazard to humans: similar results in replicated animal studies by different investigators; similar effects across sex, strain, species, and route of exposure; clear evidence of a dose-response relationship; a plausible relation between data on metabolism, postulated mechanism-of-action, and the effect of concern; similar toxicity exhibited by structurally related compounds; and some link between the chemical and evidence of the effect of concern in humans. The greater the weight-of-evidence, the greater one's confidence in the conclusions drawn.

B. Dose-Response Assessment

1. Concepts and Problems

Empirical observation generally reveals that as the dosage of a toxicant is increased, the toxic response (in terms of severity and/or incidence of effect) also increases. This dose-response relationship is well-founded in the theory and practice of toxicology and pharmacology. Such behavior is observed in the following instances: in quantal responses, in which the proportion of responding individuals in a population increases with dose; in graded responses, in which the severity of the toxic response within an individual increases with dose; and in continuous responses, in which changes in a biological parameter (e.g., body or organ weight) vary with dose.

However, in evaluating a dose-response relationship, certain difficulties arise. For example, one must decide on the critical end point to measure as the "response." One must also decide on the correct measure of "dose." In addition to the interspecies extrapolation aspects of the question of the appropriate units for dose, the more fundamental question of administered dose versus absorbed dose versus target organ dose should be considered. These questions are the subject of much current research.

2. Selection of the Critical Data

a. Critical study

Often animal data are selected as the governing information for quantitative risk assessments, since available human data are generally insufficient for this purpose. These animal studies typically reflect situations in which exposure to the toxicant has been carefully controlled and the problems of heterogeneity of the exposed population and concurrent exposures to other toxicants have been minimized. In evaluating animal data, a series of professional judgments are made that involve, among others, consideration of the scientific quality of the studies. Presented with data from several animal studies, the risk assessor first seeks to identify the animal model that is most relevant to humans, based on the most defensible biological rationale, for instance using comparative pharmacokinetic data. In the absence of a clearly most relevant species, however, the most sensitive species (i.e., the species showing a toxic effect at the lowest admininistered dose) is adopted as a matter of scientific policy at EPA, since no assurance exists that humans are not innately more sensitive than any species tested. This selection process is made more difficult if animal tests have been conducted using different routes of exposure, particularly if the routes are different from those involved in the human situation under investigation.

In any event, the use of data from carefully controlled studies of genetically homogeneous animals inescapably confronts the risk assessor with the problems of extrapolating between species and the need to account for human heterogeneity and concurrent human exposures to other chemicals, which may modify the human risk.

While there is usually a lack of well-controlled cohort studies that investigate non-cancer end points and human exposure to chemicals of interest, in some cases human data may be selected as the critical data (e.g., in cases of cholinesterase inhibition). Risk assessments based on human data have the advantage of avoiding the problems inherent in interspecies extrapolation. In many instances, use of such studies, as is the case with the animal investigations, involves extrapolation from relatively high doses (such as those found in occupational settings) to the low doses found in the environmental situations to which the general population is more likely to be exposed. In some

cases, a well-designed and well-conducted epidemiologic study that shows no association between known exposures and toxicity can be used to directly project an RfD (as has been done in the case of fluoride).

b. Critical data

In the simplest terms, an experimental exposure level is selected from the critical study that represents the highest level tested in which "no adverse effect" was demonstrated. This "no-observed-adverse-effect level" (NOAEL) is the key datum gleaned from the study of the dose-response relationship and, traditionally, is the primary basis for the scientific evaluation of the risk posed to humans by systemic toxicants. This approach is based on the assumption that if the critical toxic effect is prevented, then all toxic effects are prevented.

More formally, the NOAEL is defined in this discussion as the highest experimental dose of a chemical at which there is no statistically or biologically significant increase in frequency or severity of an adverse effect between individuals in an exposed group and those in its appropriate control. (See also discussion in the footnote on page A-4). As noted above, there may be sound professional differences of opinion in judging whether or not a particular response is adverse. In addition, the NOAEL is a function of the size of the population under study. Studies with a small number of subjects are less likely to detect low-dose effects than studies using larger numbers of subjects. Also, if the interval between doses in an experiment is large, it is possible that the experimentally determined NOAEL is lower than that which would be observed in a study using intervening doses.

c. Critical end point

A chemical may elicit more than one toxic effect (end point), even in one test animal, or in tests of the same or different duration (acute, subchronic, and chronic exposure studies). In general, NOAELs for these effects will differ. The critical end point used in the dose-response assessment is the one at the lowest NOAEL.

3. Reference Dose (RfD)

In response to many of the problems associated with ADIs and SFs, which were outlined in Section II, the concept of the "reference dose (RfD)" and "uncertainty factor (UF)" is recommended. The RfD is a benchmark dose operationally derived from the NOAEL by consistent application of generally order of magnitude uncertainty factors (UFs) that reflect various types of data used to estimate RfDs (for example, a valid chronic human NOAEL normally is divided by an UF of 10) and an additional modifying factor (MF), which is based on a professional judgment of the entire data base of the chemical.* See Table A-1.

The RfD is determined by use of the following equation:

$$RfD = NOAEL/(UF \times MF) \qquad (2)$$

which is the functional equivalent of Eq. (1). In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is appropriately expressed in units of mg/kg-bw/day.

The RfD is useful as a reference point for gauging the potential effects of other doses. Usually, doses that are less than the RfD are not likely to be associated with any health risks, and are therefore less likely to be of regulatory concern. However, as the frequency of exposures exceeding the RfD increases, and as the size of the excess increases, the probability increases that adverse effects may be observed in a human population. Nonetheless, a clear conclusion cannot be categorically drawn that all doses below the RfD are "acceptable" and that all doses in excess of the RfD are "unacceptable."

---

*"Uncertainty factor" is the new description applied to the term "safety factor" (see Page A-4) This new name is more descriptive in that these factors represent scientific uncertainties, and avoids the risk management connotation of "safety " The "modifying factor" can range from greater than zero to 10, and reflects qualitative professional judgements regarding scientific uncertainties not covered under the standard UF, such as the completeness of the overall data base and the number of animals in the study.

TABLE A-1.
GUIDELINES FOR THE USE OF UNCERTAINTY FACTORS IN DERIVING REFERENCE DOSE (RfD)

Standard Uncertainty Factors (UFs)

Use a 10-fold factor when extrapolating from valid experimental results from studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population. [10H]

Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to the case of humans. [10A]

Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there are no useful long-term human data. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs. [10S]

Use an additional 10-fold factor when deriving a RfD from a LOAEL, instead of a NOAEL. This factor is intended to account for the uncertainty in extrapolating from LOAELs to NOAELs. [10L]

Modifying Factor (MF)

Use professional judgment to determine another uncertainty factor (MF) which is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and database not explicitly treated above; e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

SOURCE: Adapted from Dourson, M.L.; and Stara, J.F. (1983) Regulatory Toxicology and Pharmacology 3:224-238.

(This is a consequence of the inability of either the traditional or the RfD approach to completely address the question of dose-response extrapolation.)

The Agency is attempting to standardize its approach to determining RfDs. The RfD Work Group has developed a systematic approach to summarizing its evaluations, conclusions, and reservations regarding RfDs in a "cover sheet" of a few pages in length. The cover sheet includes a statement on the confidence the evaluators have in the stability of the RfD: high, medium, or low. High confidence indicates that the RfD is unlikely to change in the future because there is consistency among the toxic responses observed in different sexes, species, study designs, or in dose-response relationships, or the reasons for differences, if any, are well understood. Often, high confidence is given to RfDs that are based on human data for the exposure route of concern, because in such cases the problems of interspecies extrapolation are avoided. Low confidence indicates that the RfD may be especially vulnerable to change if additional chronic toxicity data are published on the chemical, because the data supporting the estimation of the RfD are of limited quality and/or quantity.

C. Exposure Assessment

The third step in the risk assessment process focuses on exposure issues. For a full discussion of exposure assessment, the reader is referred to EPA's recently published guidelines on the subject (51 *Federal Register* 34042-34054, Sept. 24, 1986). There is no substantive difference in the conceptual approach to exposure assessment in the case of systemic toxicants and of carcinogens.

In brief, the exposure assessment includes consideration of the populations exposed and the magnitude, frequency, duration and routes of exposure, as well as evaluation of the nature of the exposed populations.

D. Risk Characterization

Risk characterization is the final step in the risk assessment process and the first step in the risk management process. Its purpose is to present to the risk manager a synopsis and synthesis of all the data that contribute to a conclusion on the risk, including:

- The qualitative ("weight-of-evidence") conclusions about the likelihood that the chemical may pose a hazard to human health.
- A discussion of dose-response and how this information, through the use of particular uncertainty and modifying factors, was used to determine the RfD.
- Data such as the shapes and slopes of the dose-response curves for the various toxic end points, toxicodynamics (absorption and metabolism), structure-activity correlations, and the nature and severity of the observed effect. These data should be clearly discussed by the risk assessor, since they may influence the final decision of the risk manager (see below).
- The estimates of exposure, the nature of the exposure, and the number and types of people exposed, together with a discussion of the uncertainties involved.
- A discussion of the sources of uncertainty, major assumptions, areas of scientific judgment, and, to the extent possible, estimates of the uncertainties embodied in the assessment.

In the risk characterization process, comparison is made between the RfD and the estimated (calculated or measured) exposure dose (EED), which should consider exposure by all sources and routes of exposure. The risk assessment should contain a discussion of the assumptions underlying the estimation of the RfD (nature of the critical end point, nature of other toxic end points, degree of confidence in the data base, etc.), and the degree of conservatism in its derivation. The assumptions used to derive the EED should also be discussed. If the EED is less than the RfD, the need for regulatory concern is likely to be small.

An alternative measure that may be useful to some risk managers is the "margin of exposure (MOE)" (see footnote on p. A-3), which is the magnitude by which the NOAEL of the critical toxic effect exceeds the estimated exposure dose (EED), where both are expressed in the same units:

$$\text{MOE} = \text{NOAEL (experimental dose)} / \text{EED (human dose)} \qquad (3)$$

In parallel to the statements above on EED and RfD, the risk assessment should contain a discussion of the assumptions underlying the estimates of the RfD and the degree of possible conservatism of the UF and MF. It can be noted that when the MOE is equal to or greater than UF x MF, the need for regulatory concern is likely to be small.

Section VI contains an example of the use of the concepts of NOAEL, UF, MF, RfD, and MOE.

IV. APPLICATION IN RISK MANAGEMENT

Once the risk characterization is completed, the focus turns to risk management. In reaching decisions, the risk manager must consider a number of risk factors, nonrisk factors, and regulatory options that influence the final judgment. It is generally useful to the risk manager to have information regarding the contribution to the RfD from various environmental media. Such information can provide insights that are helpful in choosing among available control options. However, in cases in which site-specific criteria are being considered, local exposures through various media can often be determined more accurately than exposure estimates based upon generic approaches. In such cases, the exposure assessor's role is particularly important. For instance, at a given site, consumption of fish may clearly dominate the local exposure routes, while, on a national basis, fish consumption may play a minor role compared to ingestion of treated crops.

RfDs should be apportioned by route of exposure. Where specific exposure analysis can be made, such apportionment is readily performed. If exposure information is not available, assumptions must be made concerning the relative contributions from different routes of exposure. At present, different EPA offices use assumptions that differ to some degree. These assumptions are being reviewed by an Agency risk assessment group.

As illustrated in Figure A-1, the risk manager utilizes the results of risk characterization, other technological factors, and nontechnical social and economic considerations in reaching a regulatory decision. Some of these factors include efficiency, timeliness, equity, administrative simplicity, consistency, public acceptability, technological feasibility, and legislative mandate.

Because of the way these risk management factors may impact different cases, consistent--but not necessarily identical--risk management decisions must be made on a case-by-case basis. For example, the Clean Water Act calls for decisions with "an ample margin of safety"; the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) calls for "an ample margin of safety," taking benefits into account; and the Safe Drinking Water Act (SDWA) calls for standards that protect the public "to the extent feasible." Consequently, it is entirely possible and appropriate that a chemical with a specific RfD may be regulated under different statutes and situations through the use of different "regulatory doses (RgDs)".

Expressed in general terms, after carefully considering the various risk and nonrisk factors, regulatory options, and statutory mandates in a given case (i), the risk manager decides upon the appropriate statutory alternatives to arrive at an "ample" or "adequate" margin of exposure [MOE(i)], thereby establishing the regulatory dose, RgD(i) (e.g., a tolerance under FIFRA or a maximum contaminant level under SDWA), applicable to that case:

$$RgD(i) = NOAEL / MOE(i) \qquad (4)$$

Note that, for the same chemical (with a single RfD), the risk manager(s) can develop different regulatory doses for different situations that may involve different exposures, available control options, alternative chemicals, benefits, and statutory mandates. Also note that comparing the RfD to a particular RgD(i) is equivalent to comparing the MOE(i) with the UF x MF:

$$RfD/RgD(i) = MOE(i)/UF \times MF \qquad (5)$$

In assessing the significance of a case in which the RgD is greater (or less) than the RfD, the risk manager should carefully consider the case-specific data laid out by the risk assessors, as discussed in in Section III. D. 4. In some cases this may require additional explanation and insight from the risk assessor. In any event, the risk manager has the responsibility to clearly articulate the reasoning leading to the final RgD decision.

V. OTHER DIRECTIONS

While the Agency is in the process of systematizing the approach outlined in this Appendix, risk assessment research for systemic toxicity is also being conducted along entirely separate lines. For example, the Office of Air Quality Planning and Standards is using probabilistic risk assessment procedures for criteria pollutants. This procedure characterizes the population at risk, and the likelihood of various effects occurring, through the use of available scientific literature and elicitation of expert judgment concerning dose-response relationships. The dose-response information is combined with exposure analysis modeling to generate population risk estimates for alternative standards. These procedures present the decisionmaker with ranges of risk estimates, and explicitly consider the uncertainties associated with both the toxicity and exposure information. The Office of Policy, Planning, and Evaluation is investigating similar procedures in order to balance health risk and cost. In addition, scientists in the Office of Research and Development have initiated a series of studies that should lead to future improvements in risk estimation. First, they are investigating the use of extrapolation models as well as the statistical variability of the NOAEL and underlying UFs as means of estimating RfDs. Second, they are exploring procedures for less-than-lifetime health risk assessment. Finally, they are working on ranking the severity of toxic effects as a way to further refine EPA's health risk assessments. While these procedures are promising, they cannot be expected at this time to serve as a foundation of a generalized health risk assessment for systemic toxicity in the Agency.

VI. HYPOTHETICAL, SIMPLIFIED EXAMPLE OF DETERMINING AND USING RfD

Suppose the Agency had a sound 90-day subchronic gavage study in rats with the following data:

A. Experimental Results

Dose (mg/kg-day)	Observation	Effect Level
0	Control - no adverse effects observed	--
1	No statistical or biological significant differences between treated and control animals	NOEL
5	2% decrease* in body weight gain (not considered to be of biological significance)	NOAEL
	Increased ratio of liver weight to body weight	
	Histopathology indistinguishable from controls	
	Elevated liver enzyme levels	
25	20% decrease* in body weight gain	LOAEL
	Increased* ratio of liver weight to body weight	
	Enlarged, fatty liver with vacuole formation	
	Increased* liver enzyme levels	

* = Statistically significant compared to controls.

B. Analysis

1. Determination of the Reference Dose (RfD)

a. From the NOAEL

UF = 10H x 10A x 10S = 1000

MF = 0.8, a subjective adjustment based on the fact that the experiment involved an astonishing 250 animals per dose group.

Therefore UF x MF = 800, so that

RfD = NOAEL/(UF x MF) = 5 mg/kg-day / 800 = 0.006 mg/kg-day

b. From the LOAEL (i.e., if a NOAEL is not available)

If 25 mg/kg-day had been the lowest dose tested,

UF = 10H x 10A x 10S x 10L = 10,000

MF = 0.8

Therefore UF x MF = 8,000, so that

RfD = LOAEL/(UF x MF) = 25 (mg/kg-day) / 8000 = .003 mg/kg-day)

2. Risk Characterization Considerations

Suppose the estimated exposure dose (EED) for humans exposed to the chemical under the proposed use pattern were .01 mg/kg-day; i.e.,

EED > RfD

Viewed alternatively, the MOE is:

MOE = NOAEL/EED = 5 mg/kg-day / 0.01 mg/kg-day = 500

Because the EED exceeds the RfD (and the MOE is less than the UF x MF), the risk manager will need to look carefully at the data set, the assumptions for both the RfD and the exposure estimates, and the comments of the risk assessors. In addition, the risk manager will need to weigh the benefits associated with the case, and other nonrisk factors, in reaching a decision on the regulatory dose (RgD).

APPENDIX B

EPA APPROACH FOR ASSESSING THE RISK ASSOCIATED WITH EXPOSURE TO ENVIRONMENTAL CARCINOGENS

PRINCIPAL AUTHOR:

Robert E. McGaughy, Ph.D. (ORD)

CARCINOGEN RISK ASSESSMENT VERIFICATION ENDEAVOR (CRAVE) WORK GROUP:

Larry D. Anderson, Ph.D. (OW)
Diane D. Beal, Ph.D. (OPTS)
Judith Bellin, Ph.D. (ORD)
Chao W. Chen, Ph.D. (ORD)*
Ila Coty, Ph.D. (ORD)
Theodore Farber, Ph.D (OPTS)
William Farland, Ph.D. (ORD)
Herman J. Gibb, B.S., M.P.H. (ORD)
Richard Hill, M.D., Ph.D (OPTS)
Elizabeth H. Margosches, Ph.D (OPTS)
Robert E. McGaughy, Ph.D. (ORD)
Stephen Nesnow, Ph.D. (ORD)
Peter Preuss, Ph.D. (ORD)*
John A. Quest, Ph.D. (OPPE)
Reva Rubenstein, Ph.D. (OSWER)
Rita Schoeny, Ph.D. (ORD)*
Dorothy G. Wellington, Ph. D (OPPE)

*Co-Chair

I. INTRODUCTION

In the analysis of data regarding the potential human carcinogenicity of chemicals, the Agency uses the approach described in the document entitled *Guidelines for Carcinogen Risk Assessment* (51 FR 33992-34003, Sept. 24, 1986). This approach had its origins in the 1976 Interim Guidelines for Health Risk and Economic Impact Assessments of Suspected Carcinogens (41 FR 21402-21405), which describes the conceptual basis of carcinogen risk assessment. The approach is consistent with the broad scientific principles of carcinogen risk assessment developed by the Office of Science and Technology Policy (OSTP) (50 FR 10372-10442), and the EPA guidelines quote the OSTP principles extensively. Detailed applications of the procedures currently used by the Agency are described in two documents: (1) *Health Assessment Document for Epichlorohydrin*, p. 7-32 to 7-48 (EPA 600/8-83-032F, December, 1984); and (2) *OTS Assessment of Health Risk of Garment Workers and Certain Home Residents from Exposure to Formaldehyde*, Appendix 4 (April, 1986).

The Agency approach follows the general format of the National Academy of Sciences (NAS) description of the risk assessment process (see *Risk Assessment in the Federal Government: Managing the Process* [NAS Press, 1983]). In that report, the four elements of the risk assessment process are defined as follows:

(1) Hazard identification, in which a determination is made of whether human exposure to the agent in question has the potential to increase the incidence of cancer.

(2) Dose-response assessment, in which a quantitative relationship is derived between the dose, or more generally the human exposure, and the probability of induction of a carcinogenic effect.

(3) Exposure assessment, in which an evaluation is made of of the human exposure to the agent. Exposure assessments identify the exposed population, describe its composition and size, and present the type, magnitude, frequency, and duration of exposure.

(4) Risk characterization, in which the exposure and dose-response assessments are combined to produce a quantitative risk estimate, and in which the strengths and weaknesses, major assumptions, judgments, and estimates of uncertainties are discussed.

The carcinogen summary sheets included in the IRIS system are designed to supply concise information about the hazard identification and dose-response assessment steps in this overall process. In order to use this information, individuals who wish to estimate geographic site-specific risks must be able to do an exposure evaluation based on the information available, and must be able to combine the first three elements into a comprehensive risk characterization which can support regulatory decision. The risk assessment process is an activity independent of the process of formulating regulatory control options being considered and independent of economic and political factors influencing the regulatory process. The Agency recognizes the distinction between these regulatory concerns (referred to as "risk management considerations" in the 1983 NAS report) and the risk assessment process.

II. ELEMENTS OF CARCINOGEN RISK ASSESSMENT

A. Hazard Identification

The purpose of this evaluation is to arrive at some conclusions as to whether or not the agent poses a carcinogenic hazard in exposed populations. The main types of evidence bearing on this question are: (1) human studies of the association between cancer incidence and exposure; and (2) long-term animal studies under controlled laboratory conditions. Other evidence, such as short-term tests for genotoxicity, metabolic and pharmacokinetic properties, toxicological effects other than cancer, structure-activity relationships, and physical/chemical properties of the agent, is ancillary to the primary evidence.

The question of the likelihood that the agent is a human carcinogen is answered by considering all of the available information relevant to carcinogenicity, by judging the quality of the studies available, by attempting to reconcile any differences found between studies and coming to an overall evaluation. This process is termed the weight-of-evidence approach, and the results are expressed in terms of an EPA stratification system for the weight of this evidence. The system, which is a

modification of the approach taken by the International Agency for Research on Cancer (IARC),* classifies the likelihood that the agent is a human carcinogen into the following five categories:

Group	Description
A	Human Carcinogen
B1 or B2	Probable Human Carcinogen
	B1 indicates that limited human data are available
	B2 indicates sufficient evidence in animals and inadequate or no evidence in humans
C	Possible Human Carcinogen
D	Not Classifiable as to human carcinogenicity
E	Evidence of Non-Carcinogenicity for Humans

In making this classification for an agent, a two-stage procedure is followed. In the first stage, a provisional classification is made based on the degree of human and animal evidence. The degree of evidence is characterized separately for both human studies and animal studies as sufficient, limited, inadequate, no data, or evidence of no effect. The guidelines broadly define the meaning of these terms, which are basically the same as the IARC definitions. In the second stage, EPA scientists adjust these provisional classifications upwards or downwards, based on the supporting evidence of carcinogenicity described earlier, using judgments about the degree of adjustment warranted in each case. For further description of the role of supporting evidence, see the EPA Guidelines.

B. Dose-Response

The purpose of the dose-response assessment is to define the relationship between the dose of an agent and the likelihood of a carcinogenic effect, on the assumption that the agent is a human carcinogen. After the dose-response assessment is made, it is combined with the exposure evaluation to yield a numerical estimate of risk. Numerical estimates can be presented in one or more of the following four ways: 1) unit risk, 2) the concentration corresponding to a given level of risk, 3) individual, and 4) population risk. The summary sheets include only unit risk and risk-related air and water concentrations. The numerical risk estimation activity is not dependent on the likelihood of human carcinogenicity, as categorized in the hazard identification process. Instead, it is an independent piece of information which is to be combined with the hazard identification in making regulatory decisions.

As the Guidelines observe, dose-response assessment "usually entails an extrapolation from the generally high doses administered to experimental animals or exposures noted in epidemiologic studies to the exposure levels expected from human contact with the agent in the environment; it also includes considerations of the validity of these extrapolations." Extrapolation is ordinarily carried out first by fitting a mathematical model to the observed data and then by extending either the model or a bound on the risks it predicts in the observed range down toward risks expected at low exposure.

The main elements of a dose-response assessment are: (1) the selection of the appropriate data sets to use; (2) the derivation of estimates at low doses from experimental data at high doses using an extrapolation model; and (3) the choice of an equivalent human dose corresponding to the animal dose used.

---

*IARC (1982) IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 4 Lyon, France.

1. Choice of Data Sets

In choosing the appropriate data sets to use, the main principles are as follows:

(a) Human data are preferable to animal data, provided that quality is adequate.

(b) Data from a species which responds biologically most like humans (with respect to factors such as metabolism, physiology, and pharmacokinetics) are used. When no clear choice is possible on this basis, data corresponding to the most sensitive animal species/strain/sex combination are given the greatest emphasis.

(c) The route of administration which is the most like the route of human exposure is used. When this is not possible, the route differences are noted as a source of uncertainty.

(d) When the incidence of tumors is significantly elevated at more than one site by the agent, risk estimates are made by determining the number of animals with one or more of these tumor sites.

(e) Benign tumors are generally combined with malignant tumors, unless the benign tumors are not considered to have potential to progress to the associated malignancies of the same histogenic origin. See *Guidelines for Combining Neoplasms for Evaluation of Rodent Carcinogenesis Studies* (1986). McConnell, E.E., Solleveld, H.A., Swenberg, J.A., Boorman, G.A. JNCI 86:283-289.

2. Choice of Extrapolation Model

Since risk at low exposure levels cannot be measured directly either by animal experiments or by epidemiologic studies, a number of mathematical models and procedures have been developed to extrapolate from high to low dose. Different extrapolation methods may give reasonable fit to the observed data but may lead to large differences in the projected risk at low doses. In keeping with the Guidelines and the OSTP principles, the choice of low-dose extrapolation method is governed by consistency with current understanding of the mechanism of carcinogenesis and not solely on goodness-of-fit to the observed tumor data. When data are limited, and when uncertainty exists regarding the mechanisms of carcinogenic action, the OSTP principles suggest that models or procedures which incorporate low-dose linearity are preferred when compatible with the limited information available. The Guidelines recommend that the linearized multistage procedure be employed in the absence of adequate information to the contrary.

The first step of the linearized multistage procedure, abbreviated by LM on the summary sheets, calls for the fitting of a multistage model to the data. This is an exponential model approaching 100% risk at high doses with a shape at low doses described by a polynomial function. When the polynomial is of first degree, the model is equivalent to a one-hit or linear model, so called because at low doses it produces an approximately linear relationship between dose and cancer risk.

The second step of the procedure estimates an upper bound for risk by incorporating an appropriate linear term into the statistical bound for the polynomial. At sufficiently small exposures, any higher-order terms in the polynomial will contribute negligibly, and the graph of the upper bound will look like a straight line. The slope of this line is called the slope factor on the summary sheets Since the slope at higher exposures could be different than at low exposures for some chemicals, this slope factor is generally not valid when the exposures are sufficiently high. In the summary sheets the exposure corresponding to a risk of 1/100 is arbitrarily chosen as sufficiently high that the slope factor and the unit risks derived from it should not be used.

Other models that could be used are the Weibull (W), Probit (P), Logit (LO), one-hit (OH), and gamma multihit (GM) models. These models are defined in the IRIS Glossary. . Except for the one-hit model, these models all tend to give the characteristic S-shapes of many biological experiments, with varying curvature and tail length. Their upper bounds tend to parallel the curvature of the models themselves unless a procedure has been devised to provide otherwise, as is the case for the linearized multistage procedure. The slope factor designated on the summary sheets for these models is the slope of the straight line from the upper bound at zero dose to the dose producing an upper bound of 1%.

Two alternative approaches have been used for dealing with the spontaneous background rate of tumor occurrence in risk estimation. Both approaches are summarized by a slope factor.

One approach defines "added risk" as the difference between the total response rate under an exposure condition and the background incidence in the absence of exposure. The corresponding equation is AR = P(d) - P(0). The other approach, called "extra risk", can be described as the "added risk" applied to that portion of the population that did not show background tumors. The corresponding equation is ER = [P(d) - P(0)]/[1-P(0)]. "Extra risk" is the most commonly used approach, but the alternative approach, "added risk", is being explored by the Agency for its utility in certain circumstances and has been used in several cases. When the background response is sizable, "extra risk" is larger than "added risk", and when the background is small, both types of risk are essentially equal.

3. Determination of Human Equivalent Doses

The human dose that is equivalent to the dose in an animal study is calculated using the assumption that different species are equally sensitive to the effects of a toxin if they absorb the same dose per unit body surface area. This assumption is made only in the absence of specific information relevant to equivalent dose for that agent. Since surface area is approximately proportional to the two-thirds power of body weight, the equivalent dose is milligrams per (body weight raised to the two-thirds power) per day. It follows that if the animal dose is expressed in units of mg/kg/day, the equivalent human dose, in the same units, is smaller than the animal dose by a factor equal to the cube root of the ratio of human weight to animal weight. Since the Agency generally assumes a human weight of 70 kilograms, this factor becomes 13 for mice with a weight of 30 grams, and 5.8 for rats with a weight of 350 grams. In the calculation of human equivalent doses, the actual animal weight in the bioassay is used whenever that information is available; otherwise, standard species weights are used.

In using animal inhalation experiments to estimate lifetime human risks for partially-soluble vapors or gases, the air concentration is generally considered to be the equivalent dose between species based on equivalent exposure times; i.e., a lifetime exposure to a 1-ppm concentration in humans is assumed to produce the same effect as a lifetime exposure to a 1-ppm concentration in animals. In the inhalation of particulates or completely-absorbed gases, the amount absorbed per unit of body surface area is considered to be the equivalent dose between species.

In order to evaluate human risks for both air and water contamination when only one route has been tested in animals, additional assumptions with corresponding additional uncertainties must be introduced. For this reason, the summary sheets specify the route of exposure that was used for the calculation of air and drinking water unit risks.

4. Summary of Dose-Response Parameters

Quantitative risk estimates have several uses, and the expression of the results should be tailored to each use. For comparing the carcinogenic characteristics of several agents, the cancer risk per unit absorbed dose is a useful parameter. It could be expressed on a weight basis (e.g., milligrams of the substance absorbed per kilogram body weight per day, mg/kg/day) or on a molar basis (e.g., m moles/kg/day). The low-dose slope factor described on page B-3 is used for this purpose in the IRIS summary.

For determining the concentrations of air or water at certain designated levels of lifetime risk, the ratio of that level of risk/unit risk for water or air is calculated. For example, if the water unit risk is 0.4 E-4 per µg/L, the water concentration corresponding to an upper bound of E-5 risk is E-5/(0.4 E-4) = 0.25 µg/L.

For evaluating risks to environmental agents, the concentrations of the agent in the medium where human contact occurs is the measure of exposure used. Therefore, the appropriate measure of dose-response is risk per concentration unit, with standardized conventions of exposure durations and of intake of each medium being understood. These measures are called the unit risk for air and the unit risk for drinking water. The standardized duration assumption is understood to be continuous lifetime exposure. The concentration units for air and drinking water are usually micrograms per cubic meter (µg/cu m) of air and micrograms per liter (µg/L) of water, respectively. For food, the

agents are usually identified in specific foods (e.g., fish or corn) which constitute characteristic fractions of the daily diet, so the amount of the agents consumed per day in all food known or expected to contain residues of the agent is the most appropriate measure of exposure. For this use, the summary sheets provide the slope factor in units adjusted for body weight (e.g., mg/kg/day). If a different fraction of the agent is absorbed in humans from the human diet than is absorbed from the animal diet, an appropriate correction is needed when applying the animal-derived value to humans.

In summary, the quantities appropriate for calculating upper bound risks for air, drinking water, and food are, respectively, the air unit risk (risk per µg/cu. m of air), the drinking water unit risk (risk per µg/L of drinking water), and slope factor (risk per mg/kg/day of the agent). However, a smaller dose unit (e.g., µg/kg/day for dietary intake risk) is often used if the risk corresponding to the dose unit (e.g., mg/kg/day) exceeds 10^{-2}.

5. Statement of Confidence in Dose-Response Parameters

A judgment about the degree of confidence the Agency has in the accuracy of the risks derived from the data is given in the summary sheets as a high, medium, or low rating. The factors increasing the Agency's confidence in the accuracy of these risk bounds includes the following:

(1) The existence of experimental data to replace default assumptions.

(2) Close agreement in the risk parameters derived from experiments in different animal species.

(3) Similarity in the route of exposure between the tested species and route of interest in humans.

(4) The existence of experimental data on the effective dose for the exposure route of interest.

(5) A large number of animals or people in the studies used.

(6) A large number of dose groups or a large range of doses in the studies being used.

(7) Sufficient purity of the test agent so that contamination is not a factor in interpretation of results.

(8) Similarities between the animal strain and humans as to metabolism and pharmacokinetics of the agent.

(9) For human occupational studies, determination of exposure for different worksites as opposed to an average exposure for the entire workplace.

(10) For epidemiologic studies, exposure measurements concurrent to the period being evaluated (e.g., time period of employment).

(11) Lack of concurrent exposures in epidemiologic studies which would reasonably have been expected to modify the dose-response.

(12) The ranking of epidemiologic study designs according to their usefulness in deriving accurate risk assessments: cohort > case-control > ecologic studies.

(13) The epidemiologic studies provided sufficient information on dose, duration of exposure, and age to permit one to separate the effects of each on the dose-response relationship.

(14) An adequate time period was allowed in epidemiologic studies for a cancer latency period.

(15) Time regimens of animal exposure are similar to those of human exposure.

The factors decreasing the Agency's confidence, in addition to factors contrary to the points above, are as follows:

(1) The use of non-continuous dosing when we have reason to believe that there is an effective continuous dose but pharmacokinetic information is inadequate to estimate it.

(2) The use of vehicles, such as corn oil, which may confound or interact with the agent under study in producing tumors at specific sites.

(3) Situations in which special test systems (such as mouse skin painting, strain A mouse pulmonary adenomas, and *in vitro* tests) are not similar enough to human systems to justify their use as a basis for human quantitative risk estimates.

(4) Lack of concurrent control groups.

(5) Poor animal husbandry.

APPENDIX C
DRINKING WATER HEALTH ADVISORIES

[IN PREPARATION]

APPENDIX D
RISK MANAGEMENT SUMMARIES

NATIONAL AMBIENT AIR QUALITY STANDARDS (NAAQS)

The Clean Air Act requires that NAAQS be set and ultimately met for any air pollutant which, if present in the air, may reasonably be anticipated to endanger public health or welfare and whose presence in the air results from numerous or diverse mobile and/or stationary sources. Two types of NAAQS are provided for: (1) primary standards designed to protect public health, and (2) secondary standards designed to protect public welfare (e.g., vegetation, visibility, materials).

Primary standards must protect the public health with an adequate margin of safety based on a review of air quality criteria which reflects the latest state of scientific knowledge about the pollutant. The requirement for an adequate margin of safety is intended both to address inconclusive scientific and technical information and to provide a reasonable degree of protection against hazards that research has not yet identified. NAAQS are set not only to prevent pollution levels that have been demonstrated to be harmful, but also to prevent lower pollutant levels that the Administrator finds pose an unacceptable risk of harm, even if that risk is not precisely identified as to nature or degree. EPA considers such factors as the nature and severity of the health effects involved, the size of the sensitive population, and the kind and degree of uncertainties in the scientific evidence.

The courts have set limits on the factors EPA may consider in providing an adequate margin of safety. The leading judicial decisions state that the economic and technological feasibility of attaining primary NAAQS are not to be considered in setting them, even in the context of a margin of safety.

REFERENCE

Padgett, J; Richmond, H. (1983) The process of establishing and revising national ambient air quality standards. *JAPCA* 33(1):13-16.

U.S. EPA Contact: Bruce Jordan, Chief
Ambient Standards Branch
Strategies and Air Standards Division
Office of Air and Radiation (MD-12)
Research Triangle Park, NC 27711
(919) 541-5655, FTS 629-5655

EPA AMBIENT WATER QUALITY CRITERIA

Human Health

EPA's ambient water quality criteria for the protection of human health have been developed for 64 out of 65 classes of toxic pollutants (a total of 95 individual chemicals have numerical health criteria). The health criterion is an estimate of the ambient surface water concentration that will not result in adverse health effects in humans. In the case of suspect or proven carcinogens, concentrations associated with a range of incremental cancer risks are provided to supplement a criterion of zero. The EPA criteria are non-enforceable guidelines, which many states have used in the development of enforceable ambient water quality standards.

For most chemicals, EPA water quality criteria to protect human health are available for two different exposure pathways. One criterion is based on lifetime ingestion of both drinking water and aquatic organisms, and the other is based on lifetime ingestion of aquatic organisms alone. The calculations incorporate the assumption that a 70-kilogram adult consumes 2 liters of water and/or 6.5 grams of aquatic organisms daily for a 70-year lifetime.

Derivation of Criteria for Noncarcinogens -- On the basis of a survey of toxicology literature, EPA established a "no observed adverse effect level" (NOAEL) for each chemical. The NOAELs were usually based on animal studies, although human data have been used whenever available. By

applying uncertainty factors to account for the uncertainty in using available data to estimate health effects in humans, a reference dose (RfD) was determined. Criteria (i.e., water concentrations) were then derived from the RfD's and the standard intake assumptions given above.

Derivation of Criteria for Carcinogens--The same exposure and intake assumptions were used for potential carcinogens. A literature search for human and animal carcinogenic effects formed the basis for EPA's estimate of the risk posed by potential human carcinogens. Because methods are not currently available to establish the presence of a threshold for carcinogenic effects, the criteria for all carcinogens state that the recommended concentration for maximum protection of human health is zero. EPA also estimated water concentrations corresponding to incremental risk levels, using a linear, nonthreshold extrapolation model. Extrapolation models provide only an estimate of risk, but represent the best available tool for describing the potential threat of a substance, given certain assumptions. In its published criteria, EPA provides water concentrations corresponding to incremental lifetime cancer risks of 1 in 10,000,000 (E-7), 1 in 1,000,000 (E-6), and 1 in 100,000 (E-5).

Aquatic (Freshwater) and Marine Organisms

Derivation of numerical water quality criteria for the protection of aquatic organisms uses information from many areas of aquatic toxicology. All available information concerning toxicity to, and bioaccumulation by, aquatic organisms is collected, reviewed for acceptability, and sorted. If enough acceptable data on acute toxicity to a sufficiently diverse group of aquatic animals are available, they are used to estimate the highest 1-hour average concentration that should not result in unacceptable effects on aquatic organisms and their uses. This concentration is made a function of water quality characteristics such as pH, salinity, or hardness if a correlation between toxicity and the characteristic can be established. Similarly, data on the chronic toxicity of the material to aquatic animals are used to estimate the highest 4-day average concentration that should not cause unacceptable toxicity during a long-term exposure. This concentration is also related to a water quality characteristic, if appropriate.

Data on toxicity to aquatic plants are examined to determine whether plants are likely to be unacceptably affected by concentrations that should not cause unacceptable effects on animals. Data on bioaccumulation by aquatic organisms are used to determine if residues might subject edible species to restrictions by the U.S. Food and Drug Administration or if such residues might harm some wildlife consumers of aquatic life. All other available data are examined for adverse effects that might be biologically important. The process is discussed in more detail in Stephen et al. (1985).

REFERENCES

Human Health

U.S. EPA. (1980) Water quality criteria documents: availability. Federal Register 45:79318-79379.

U.S. EPA. (1980) Water quality criteria; availability of documents. Federal Register 49:5831.

U.S. EPA. (1985) Draft Superfund public health evaluation manual. Prepared by ICF, Inc., for the Office of Emergency and Remedial Response, Office of Solid Waste and Emergency Response.

U.S. EPA. (1985) Water quality criteria; availability of documents. Federal Register 50:30784-30796.

Aquatic (Freshwater) and Marine Organisms

Stephen, C.E.; Mount, D.I.; Hansen, J.J.; Gentile, J.H., Chapman, G.A.; Brungs, W.A. (1985) Guidelines for deriving numerical national water quality criteria for the protection of aquatic organisms and their uses. U.S. EPA, Office of Research and Development.

U.S. EPA Contact: Dr. Frank Gostomski
Criteria and Standards Division
Office of Water
(WH-584)
Washington, DC 20460
(202) 245-3030

REPORTABLE QUANTITIES

The Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA) establishes broad authority to deal with releases or threats of releases of hazardous substances from vessels or facilities. The Act requires the person in charge of a vessel or facility to notify the National Response Center immediately when there is a release of a designated hazardous substance in an amount equal to or greater than the reportable quantity (RQ) for that substance [sections 103(a) and (b)]. Section 102(b) of CERCLA establishes RQs for releases of designated hazardous substances at 1 pound, unless other reportable quantities were assigned under section 311 of the Federal Water Pollution Control Act. Section 102 authorizes EPA to adjust all of these reportable quantities.

A major purpose of the section 103(a) and (b) notification requirements is to alert the appropriate government officials to releases of hazardous substances that may require rapid response to protect public health and welfare and the environment. Under the Act, the federal government may respond whenever there is a release or a substantial threat of a release into the environment of a hazardous substance or of other pollutants or contaminants which may present an imminent and substantial danger to public health or welfare (section 104). Response activities are to be conducted, to the extent possible, in accordance with the National Contingency Plan (40 CFR Part 300), which was originally developed under the CWA and which has been revised to reflect the responsibilities and authority created by CERCLA. EPA emphasizes that notification based on reportable quantities is merely a trigger for informing the government of a release so that the appropriate federal personnel can evaluate the need for a federal response action and undertake any necessary reponse (removal or remedial action) in a timely fashion. Reportable quantities serve no other purpose; for example, a reportable quantity need not be released before a claim for damages or cleanup costs may be filed against the Hazardous Substance Response Trust Fund. Federal personnel will evaluate all reported releases, but will not necessarily initiate a removal or remedial action in response to all reported releases, because the release of a reportable quantity may not necessarily pose a hazard to public health or welfare or the environment. Government personnel will assess each release on a case-by-case basis.

RQ Adjustment Methodology

EPA has adopted the five RQ levels of 1, 10, 100, 1000, and 5000 lbs originally established pursuant to CWA section 311 (see 40 CRF Part 117). The strategy for adjusting RQs pursuant to CERCLA is described in 50 CFR 13456 (see 40 CFR Part 302) and begins with an evaluation of the intrinsic properties -- called primary criteria -- of aquatic toxicity, mammalian toxicity (oral, dermal, and inhalation), ignitability/reactivity, and chronic toxicity (defined as toxicity resulting from repeated or continuous exposure to either a single release or multiple releases of a hazardous substance). The methodology for adjusting RQs based on potential carcinogenicity will be proposed in the future.

EPA ranks each intrinsic property on a five-tier scale, associating a specified range of values on each scale with a particular RQ value. Thus, each substance receives several tentative RQ values based on its particular properties. The lowest of all of the tentative RQs becomes the "primary criteria RQ" for that substance.

After primary criteria RQs are assigned, substances are further evaluated for their susceptibility to certain extrinsic degradation processes. These extrinsic processes (secondary criteria) are biodegradation, hydrolysis, and photolysis, or "BHP." If the analysis indicates that a substance degrades relatively rapidly to a less harmful compound through one or more these processes when it is released into the environment, the primary criteria RQ is raised one level. The single RQ assigned to each substance on the basis of the primary criteria and BHP becomes the adjusted RQ for that substance.

REFERENCES

U.S. EPA. (1985) Notification requirements; reportable quantity adjustments. Federal Register 50:13456.

U.S. EPA Contact:

K. Jack Kooyoomjian, Ph.D.
Emergency Response Division
Office of Emergency and Remedial Response
Office of Solid Waste and Emergency Response
(202) 382-4130

RCRA/Superfund Hotline
(800) 424-9346
Local/FTS 382-3000

PESTICIDE RISK MANAGEMENT ACTIONS

Three principal "numbers" may be generated by the Office of Pesticide Programs in the course of a registration standard or special review: (1) Toxicity Category; (2) Reference Dose; (3) Tolerance/Action Level. The assignment to a Toxicity Category is based upon an evaluation of acute toxicity. The Reference Dose is derived from a NOAEL or NOEL with the application of appropriate uncertainty factors and assumptions regarding daily intake. A Tolerance is established for every registered pesticide that results in a food residue, while an Action Level is set for pesticides with uses that are canceled or suspended.

Registration Standards

Registration Standards are written for pesticidal active ingredients. They state the conclusions that can be reached concerning human health and/or ecologic effects, based on available data, from pesticide uses, and identify data gaps that must be filled by the registrants. A Registration Standard contains several chapters, including discussions of environmental fate, toxicity, residue chemistry, use patterns of the pesticide products containing the active ingredient, and tolerances.

The principal outcome of a Registration Standard is the identification of data that must be generated by the registrant(s) if they are to retain their registration. However, it can also specify labeling requirements, application procedures, and/or protective clothing requirements.

U.S. EPA Contact:

Registration Division
Office of Pesticide Programs
Office of Pesticides and Toxic Substances
FTS 557-7760

NOTE: Registration Standards can be very complex because of the number of pesticide products that may be involved, and they do not lend themselves to a summary in this format. The database will indicate when a Registration Standard exists, and will provide the appropriate references

Special Review

Special Reviews of registered active ingredients commence when the EPA is concerned that a significant risk may exist to humans or the environment. The initial significant risk determination is based on exposure and specific toxicity criteria only, but economic factors are considered in the final decision. The toxicity criteria are: (1) acute toxicity to humans or domestic animals; (2) oncogenic, teratogenic, fetotoxic, reproductive, and other chronic or delayed toxic effects; (3) heritable genetic effects; (4) hazard to wildlife; (5) hazard to threatened or endangered species; and (6) other adverse effects. The Special Review assessment is specific to the triggering criteria, and will not address other adverse effects or economic benefits unrelated to the triggering criteria.

EPA's initial basis for concern is stated in a Position Document 1 (PD 1) and published in the Federal Register. After public comment, EPA's scientific analysis of adverse effects (PD 2) and regulatory proposal, including an economic benefits analysis (PD 3), are published in the Federal Register. (These two documents are often combined as PD 2/3.) After an additional public comment period, EPA's final regulatory action is issued as a PD 4 in the Federal Register. The final outcome of a Special Review can be a range of use restrictions or cancellation of the pesticide's registration.

U.S. EPA Contact: Special Review Branch
Registration Division
Office of Pesticide Programs
Office of Pesticides and Toxic Substances
FTS 557-7420

NOTE: The outcome of a Special Review can be very complex due to the range of regulatory actions that can be taken. Such complexity does not permit it to be summarized in this format. The database will indicate when a Special Review exists, and will provide the appropriate references.

U.S. EPA Contact: Registration Division
Office of Pesticide Programs
Office of Pesticides and Toxic Substances
FTS 557-7760

Special Review Branch
FTS 557-7420

RCRA APPENDIX VIII LIST

Substances are listed in Appendix VIII of 40 CFR Part 261 (RCRA hazardous waste regulations) only if they have been shown in scientific studies to have toxic, carcinogenic, mutagenic, or teratogenic effects on humans or other life forms. The presence of any of these constituents in the waste is presumed to be sufficient to list the waste unless, after consideration of a number of factors, the EPA Administrator concludes that the waste is not capable of posing a substantial present or potential hazard to human health or the environment when improperly treated, stored, transported or disposed of, or otherwise managed. (Source: 40 CFR Part 261.11.)

NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS (NESHAPs)

Section 112 of the CAA defines a hazardous air pollutant as a pollutant not covered by a NAAQS and exposure to which may reasonably be anticipated to result in an increase in mortality or an increase in serious irreversible, or incapacitating reversible, illness. The Administrator shall list as hazardous those pollutants for which he intends to establish emission standards. No time is specified; listing is at the discretion of the Administrator. The EPA has interpreted section 112 as requiring the listing of pollutants that cause significant risks.

Within 180 days of listing, EPA must propose NESHAPs for new and existing sources. Again, Agency policy is to regulate only those source categories causing significant risks. Section 112(b)(1)(B) requires that NESHAPs be set to provide an ample margin of safety. For nonthreshold pollutants such as carcinogens, EPA has interpreted this provision as requiring protection against unreasonable risks. In making this judgment, EPA considers the feasibility of control, risk reduction, costs, and other impacts as determining which source types to regulate and how much to control. Final regulations must be published within 180 days of proposal. Under EPA policy, this includes decisions on all significant source types the Agency has decided not to regulate.

New sources must comply at start-up. Existing sources covered by the NESHAPs must comply within 2 years of promulgation. NESHAPs may include design, equipment, or work practice standards if an emission standard is not feasible.

CLEAN AIR ACT (CAA) REGULATORY DECISIONS

EPA's Air Toxics Strategy includes an active program to assess the public health risks of potentially toxic air pollutants, develop appropriate regulatory strategies under the CAA (or other federal environmental legislation, if appropriate), and announce the results of the assessment and the Agency's regulatory decision in the Federal Register.

The assessment program involves a tiered approach of increasingly more detailed health and source assessment. The first phase of the program involves a system called the Hazardous Air Pollutant Prioritization System (HAPPS), for screening and ranking large numbers of potential air toxics based on readily available health, production, and volatility information.

For those pollutants selected for further assessment, a short Health Assessment Summary (HAS) is prepared by the Office of Research and Development, and at the same time, the Office of Air and Radiation prepares a preliminary source and exposure assessment. If health information is available from other program offices, it may be used in place of the HAS if air issues are adequately treated. If these documents indicate little or no potential for adverse health effects from routine releases into the ambient air, a decision not to regulate will be published in the Federal Register. If significant health risks appear possible, a more detailed Tier II analysis is conducted. The Tier II Health Assessment Document is generally reviewed by the Science Advisory Board. If, based on the Tier II analysis, nationwide health risks from one or more stationary source categories are significant, EPA will generally publish a Federal Register notice indicating its intent to list the pollutant as a hazardous air pollutant under section 112 of the CAA. These notices indicate that EPA will list under section 112 only after further study of possible control techniques and a determination that federal standards are warranted.

NEW SOURCE PERFORMANCE STANDARDS (NSPS)

Under section 11 of the CAA, EPA sets NSPS for new or modified stationary source categories whose emissions cause or significantly contribute to air pollution which may endanger public health or welfare. NSPS are to be based on the best demonstrated technology, considering costs and other impacts. If an NSPS is set for a pollutant not regulated by an NAAQS, section 111(d) requires that state governments develop regulations to control sources of the same type covered by the NSPS. EPA regulations implementing section 111(d) specify that EPA will issue guidance to the states on best retrofit technology, considering cost and other impacts. If the pollutant is health-related (e.g., sulfuric acid mist from sulfuric acid plants), states must provide strong justification for adopting emission limits less stringent than the guidance specified by EPA. For pollutants subject to section 111(d) that are welfare-related (e.g., fluorides from fertilizer plants), states have more flexibility in adopting regulations for existing sources.

TOXIC SUBSTANCES RISK MANAGEMENT

Under the Toxic Substances Control Act (TSCA), EPA is authorized to take a variety of regulatory actions regarding the manufacture, distribution in commerce, processing, use, or disposal of chemical substances and mixtures. The criterion for action most often addressed by TSCA is termed 'unreasonable risk,' which involves a weighing of both the risks and the benefits associated with a given substance. The Risk Management decisions under TSCA would consider not only the risk factors, such as probability and severity of effects, but also non-risk factors, such as benefits derived from use of the material and availability of alternative substances.

TSCA provides for a wide range of risk management actions to accommodate the variety of risk/benefit situations confronting the Agency. A brief description of these actions follows.

Section 6 - Under §6, EPA may legislate total prohibition or impose limitations on the manufacture, import, processing, distribution in commerce, use, or disposal of a chemical when risk of injury to health or the environment is involved.

Section 7 - In the event that a chemical substance poses an imminent hazard to the general health or environment, EPA is authorized under §7 section to commence civil action or siezure to obtain appropriate relief. This section is used when a §6 rule would be too untimely to be effective.

Section 9 - There are chemical concerns which may be regulated more consistently by federal statutes other than TSCA. When that is the case, the chemical is referred under §9 to the appropriate Agency (e.g. OSHA). If the chemical is referred under §9(a), EPA has concluded that the chemical is likely to present an unreasonable risk; documentation supporting this conclusion is forwarded with the referral and the other Agency must formally respond. In other cases EPA may choose to refer a risk concern informally under §9(d), based on a more limited review.

Section 5(a) - Chemicals may currently be used in ways that do not present an unreasonable risk of injury to health or the environment. However, if certain of those chemicals are used in ways different from their current usage, they may present such a risk. Therefore, EPA has the authority under §5(a) to require manufacturers to submit notification 90 days before manufacturing, importing, or

processing the chemical for such new uses. This is called a significant new use rule. Based on review of new use notifications, the Agency can deny or limit the production of a chemical for such new use.

Chemical Advisory - A less formal method of risk management that the Agency uses is the issuance of a chemical advisory. An advisory is written to give individuals or organizations information on the hazards of specific chemicals, and practical steps that can be used to minimize or eliminate these hazards. The advisory is distributed directly to those who can take action to reduce risk. Advisories are not rules and may be used as interim measures while rules are being developed or in cases where rulemaking is not appropriate to deal with EPA's risk concerns.

APPENDIX E
SUPPLEMENTARY INFORMATION

This section of the IRIS chemical files presents ancillary information which may be of use in risk management decisions. This section is primarily intended for the presentation of nonhealth-risk data, such as chemical and physical properties and acute health hazard data. The information in section V of IRIS is extracted from the EPA Chemical Profile Database. The following paragraphs briefly describe the EPA Chemical Profile Database, as applicable to the information extracted for IRIS. Those who wish to obtain the complete database should contact the appropriate regional EPA office. A complete listing for the references cited in the EPA Chemical Profile Database is provided at the end of the document.

The U.S. Environmental Protection Agency has developed a set of chemical profile reference documents for use in the Chemical Emergency Preparedness Program. These EPA profiles contain a summary of publicly available documented information for chemicals on the EPA list of acutely toxic chemicals. The profiles have been reviewed for accuracy and completeness. However, an exhaustive literature search was not performed for each chemical, and a review of original citations has not been made. The profiles have been marked as INTERIM, and comments and additional data are invited from the users. It is anticipated that the profiles will be reviewed and revised as additional information is made available. Note that none of these data are EPA-generated numbers; they are presented by the EPA for the convenience of the user, not as authoritative scientific information. The user is encouraged to refer to the original literature to totally assess the scientific validity of these data.

A profile is provided for each chemical on EPA's list of acutely toxic chemicals. The CAS number was used to search the automated Toxicology Data Base (TDB) or Hazardous Substance Data Base (HSDB) from the National Library of Medicine (NLM). Available TDB/HSDB files were retrieved. Approximately 65% of the chemicals were listed in the TDB/HSDB files. For these chemicals, the TDB/HSDB files provided the main source of information for the profiles. For those chemicals without a TDB/HSDB file, a limited number of standard reference materials were searched. Such references are cited by author, year, and page number.

Generally, only human data are reported in the Health Hazards section. The information in this section is limited because information on health hazards, and signs and symptoms were often not available or only partially available for specific chemicals. In addition, health hazard and signs and symptoms data sources often did not specify dose or route of entry. In the absence of information on the specific chemical, generic information for the chemical category was provided, wherever possible.

EPA CHEMICAL PROFILES DATABASE REFERENCES (Revised 9/2/86)

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLV threshold limit values for chemical substances and physical agents in the work environment and biological exposure indices with intended changes for 1985-86. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1984. TLV threshold limit values for chemical substances and physical agents in the work environment and biological exposure indices with intended changes for 1984-85. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. TLV threshold limit values for chemical substances and physical agents in the work environment with intended changes for 1983-1984. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1982. TLV threshold limit values for chemical substances and physical agents in the work environment with intended changes for 1982. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1981. TLV threshold limit values for chemical substances in workroom air adopted by ACGIH for 1981. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1980a. Documentation of the threshold limit values, 4th ed., 1980. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1980b. TLV threshold limit values for chemical substances in workroom air adopted by ACGIH for 1980. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1979. TLV threshold limit values for chemical substances in workroom air adopted by ACGIH for 1979. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1971-1979. Documentation of the threshold limit values for substances in workroom air, 3rd ed., 1971. Cincinnati, OH. (Including supplements to 1979.)

Agrochem Dept. Info. Service. 1971. Anthio33 insecticide, Sandoz, Ltd. Basle, AGRO DOK E-4028/DG.

American College of Neuropsychopharmacology. 1968. Psychopharmacology: Review of progress, 1957-1967. Proc. 6th annual meeting, Puerto Rico, December 12-15, 1967. U.S. GPO, Public Health Service Publ. No. 1836, Washington, D.C.

AHFS (American Hospital Formulary Service). 1984. American Hospital Formulary Service, Vols. I and II. American Society of Hospital Pharmacists, to 1984. Washington, DC.

AHFS (American Hospital Formulary Service). 1985. American Hospital Formulary Service-Drug Information 85. American Society of Hospital Pharmacists. Bethesda, MD. (Tentative listing)

American Industrial Hygiene Association Journal. 1964. Vol. 25.

AMA (American Medical Association). 1983. AMA Department of Drugs. AMA Drug Evaluations, 5th ed. Chicago, IL.

AMA (American Medical Association). 1980. AMA Department of Drugs. AMA Drug Evaluations, 4th ed. Chicago, IL.

AMA (American Medical Association). 1977. AMA Department of Drugs. AMA Drug Evaluations, 3rd ed. PSG Publishing Co., Inc., Littleton, MA.

AMA (American Medical Association). 1973. Council on Drugs. AMA Drug Evaluations, 2nd ed. Publishing Sciences Group, Inc., Acton, MA.

AOAC (Association of Official Analytical Chemists). 1965. 1965-1982. Official Methods of Analysis, IOth ed. (including supplements). New editions through 13th edition (including supplements). Washington, DC.

APA (American Pharmaceutical Association). 1976, 1978. Evaluations of Drug Interactions, 2nd ed. (and supplements). Washington, DC.

APA (American Pharmaceutical Association). 1973, 1974. Evaluations of Drug Interactions, Ist ed. (and supplements). Washington, DC.

ASHP (American Society of Hospital Pharmacists). Data supplied on contract from American Hospital Formulary Service and other current ASHP sources.

Arena, J.M. 1974. Poisoning: Toxicology, Symptoms, Treatments, 4th ed. Charles C. Thomas, Springfield, IL.

Arena, J.M. 1979. Poisoning: Toxicology, Symptoms, Treatments, 3rd ed. Charles C. Thomas, Springfield, IL.

Aronson C.E., Ed. 1983. Veterinary Pharmaceuticals and Biologicals, 1982-1983. Veterinary Medical Publishing Co., Edwardsville, KS.

Aronson C.E., Ed. 1980. Veterinary Pharmaceuticals and Biologicals, 1980-1981. Harwal Publishing Co., Media, PA.

Ash, M. and I. Ash. 1984. Encyclopedia of Industrial Chemical Additions, Vol. 1. Chemical Publishing Co , New York, NY.

Beardsley, T. 1984. Ways of death. Nature. 312: 581. Beilstein. 1954. Beilstein's Handbuch der Organischen Chemie, 3rd Supplement Ser. Springer-Verlag, Berlin.

Bergmeyer, H.W., Ed. 1974. Methods of Enzymatic Analysis, 2nd English ed. Academic Press, New York City.

Blacow, N.W., Ed. 1972. Martindale: The Extra Pharmacopoeia, 26th ed. The Pharmaceutical Press, London.

Booth, N.H. and L.E. McDonald, Ed. 1982. Veterinary Pharmacology and Therapeutics, 5th ed. Iowa State University Press, Ames, IA.

Bowman, B.T. and W.W. Saub. 1979. Environmental Science Health. B14: 625-631.

Bretherick, L. 1979. Handbook of Reactive Chemical Hazards, 2nd ed. Butterworth, Woburn, MA.

Brooke, L.T., D.J. Call, D.T. Geiger and C.E. Northcott, Ed. 1984. Acute toxicities of organic chemicals to fathead minnows (*Pimephales promelas*). Center for Lake Superior Environmental Studies, University of Wisconsin, Superior, WI.

Brown, K.W., G.B. Evans, Jr. and B.D. Frentrup, Ed. 1983. Hazardous Waste land Treatment. Butterworth Publishers, Boston, MA.

Browning, E. 1969. Toxicity of Industrial Metals, 2nd ed. Appleton-Century-Crofts, New York.

Browning, E. 1965. Toxicity and Metabolism of Industrial Solvents. American Elsevier, New York.

Brzozowski. 1985. J. Med. Prac. 5: 89.

Buchel, K.H. 1983. Chemistry of Pesticides. John Wiley and Sons, New York.

Carmichael, W.W., Ed. 1981. Environmental Science Research, Vol. 20. The Water Environment-Algal Toxins and Health. Plenum Press, New York/London.

Casarett, L.J. and J. Doull. 1975. Toxicology: The Basic Science of Poisons. MacMillan Publishing Co., New York.

Castegnaro, M., G. Grimmer, G. Hutzinger, et al., Ed. 1983. Laboratory decontamination and destruction of carcinogens in laboratory wastes: Some polycyclic aromatic hydrocarbons. International Agency for Research on Cancer. IARC Publ. No. 49. Lyon, France.

Castegnaro, M., G. Eisenbrand, G. Ellen, et al., Ed. 1982. Laboratory decontamination and destruction of carcinogens in laboratory wastes: Some N-nitrosamines. International Agency for Research on Cancer. IARC Publ. No. 43. Lyon, France.

Castegnaro, M., D.C. Hunt, E.B. Sansone, et al., Ed. 1980. Laboratory decontamination and destruction of aflatoxins B1, B2, G1, G2 in laboratory wastes. International Agency for Research on Cancer. IARC Publication No. 37. Lyon, France:

The Chemical Society. 1981. Foreign compound metabolism in mammals, Vol. 6: A review of the literature published during 1978 and 1979. The Royal Society of Chemistry, London.

The Chemical Society. 1979. Foreign compound metabolism in mammals, Vol. 5: A review of the literature published during 1976 and 1977. The Chemical Society, London.

The Chemical Society. 1977. Foreign compound metabolism in mammals, Vol. 4: A review of the literature published during 1974 and 1975. The Chemical Society, London.

The Chemical Society. 1975. Foreign compound metabolism in mammals, Vol. 3. The Chemical Society, London.

The Chemical Society. 1972. Foreign compound metabolism in mammals, Vol. 2: A review of the literature published between 1970 and 1971. The Chemical Society, London.

The Chemical Society. 1970. Foreign compound metabolism in mammals, Vol. 1: A review of the literature published between 1960 and 1969. The Chemical Society, London.

CHRIS. 1978. U.S. Coast Guard, Department of Transportation. CHRIS -- Hazardous chemical data. Manual 2. U.S. GPO, Washington, DC.

Clarke, E.G. and M.L. Clarke. 1975. Veterinary Toxicology. The Williams and Wilkins Company, Baltimore, MD.

Clarke, E.G. and M.L. Clarke. 1967. Garner's Veterinary Toxicology, 3rd ed. Williams and Wilkins Company, Baltimore, MD.

Clayton, G.D. and F.E. Clayton, Ed. 1981, 1982. Patty's Industrial Hygiene and Toxicology, Vol. 2A, 2B, 2C: Toxicology, 3rd ed. John Wiley and Sons, New York:.

Cole, R.J., and R.H. Cox. 1981. Handbook of Toxic Fungal Metabolites. Academic Press, Inc., New York.

Dagani, R. 1985. Data on MIC's toxicity are scant, leave much to be learned. Chem. Eng. News. 63(6): 37-40.

DASE (Dutch Association of Safety Experts). 1980. Handling Chemicals Safely 1980, 2nd ed. The Dutch Chemical Industry Association and the Dutch Safety Institute, The Netherlands.

Deichman, W.B. and H.W. Gerarde. 1969. Toxicology of Drugs and Chemicals, 4th ed. Academic Press, New York:. DeReuch et al. 1979. Clin. Neurol. Neurosurg. 81(4): 247.

Desktop Analysis Tool for Common Data Base. 1968. Report to the National Science Foundation by Chemical Abstracts Service and American Chemical Society.

Diehl, K.H., et al. 1983. Behavior of tetraalkyleads in the soil and their uptake by plants. Z. Pflanzeneruehr Bodenkd. 146(5): 551-559.

Di Palma, J., Ed. 1971. Drill's Pharmacology in Medicine, 4th ed. McGraw Hill, New York.

Dorland's Illustrated Medical Dictionary 1974, 25th ed. W.B. Saunders, Philadelphia, PA.

DOT (Department of Transportation). 1984. 1984 Emergency response guidebook, guidebook for hazardous materials incidents. DOT Publ. No. P5800.3.

Doull, J. C.D. Klassen and M.D. Amdur, Ed. 1980. Casarett and Doull's Toxicology; The Basic Science of Poisons, 2nd ed. Macmillan Publishing Co., New York:

Dreisbach, R.H. 1977. Handbook of Poisoning, 9th ed. Lange Medical Publications, Los Altos, CA.

Duffy, J.I., Ed. 1983. Treatment, recovery, and disposal processes for radioactive wastes: recent advances. Noyes Data Corporation, Park Ridge, NJ.

Encyclopedia of Occupational Health and Safety. 1983. Encyclopedia of Occupational Health and Safety, Vols. I and II. International Labour Office, Geneva, Switzerland.

Encyclopedia of Occupational Health and Safety. 1971. Encyclopedia of occupational health and safety. Vols. I and II. Geneva, Switzerland: International Labour Office.

Environment Canada. 1982, 1983. Technical information for problem spills.

Farm Chemicals Handbook. 1984. Meister, Willoughby, OH.

Farm Chemicals Handbook. 1983. Meister, Willoughby, OH.

Farm Chemicals Handbook. 1981. Meister, Willoughby, OH.

Farm Chemicals Handbook. 1980. Meister, Willoughby, OH.

Farm Chemicals Handbook. 1979. Meister, Willoughby, OH.

Farm Chemicals Handbook. 1977. Meister, Willoughby, OH.

Farm Chemicals Handbook. 1975. Meister, Willoughby, OH.

Farm Chemicals Handbook. 1974. Meister, Willoughby, OH.

Fazzalari, F.A., Ed. 1978. Compilation of odor and taste threshold values data. ASTM Data Series DS 48A (Committee E-18). American Society for Testing and Materials, Philadelphia, PA.

Friberg, L., G.R. Nordberg and V.B. Vouk. 1979. Handbook on the Toxicology of Metals. Elsevier North Holland, New York.

Friel, J.P., Ed. 1974. Dorland's Illustrated Medical Dictionary, 25th ed. W.B. Saunders, Philadelphia.

Furia, T.E., Ed. 1980. CRC Handbook of Food Additives, 2nd ed., Vol. 2. CRC Press Inc., Boca Raton, FL.

Furia, T.E., ed. 1972. CRC Handbook of Food Additives, 2nd ed. The Chemical Rubber Co., Cleveland, OH.

Furia, T.E. and N. Bellanca, Ed. 1975. Fenaroli's Handbook of Flavor Ingredients, 2nd ed., Vol. I and 2. The Chemical Rubber Co., Cleveland, OH.

Furia, T.E. and N. Bellanca, Ed. 1971. Fenaroli's Handbook of Flavor Ingredients. The Chemical Rubber Co., Cleveland, OH.

Fuscaldo, A., B.J. Erlick and B. Hindman, Ed. 1980. Laboratory Safety- Theory and Practice. Academic Press, New York.

Gardner, W., E.I. Cooke and R.W.I. Cooke, Ed. 1978. Handbook of Chemical Synonyms and Trade Names, 8th ed. CRC Press, Inc., Boca Raton, FL.

General Electric Co. 1978. MSDS (Material Safety Data Sheets). GE Material Information Services, Schenectady, NY.

General Electric Co. 1979. MSDS (Material Safety Data sheets). GE Material Information Services, Schenectady, NY.

GENE-TOX Program: Current Status of Bioassay in Genetic Toxicology. Office of Toxic Substances and Pesticides, U.S. EPA, Washington, DC. Information Center, Oak Ridge National Laboratory, Oak Ridge, TN.

Gilman, A.G., L.S. Goodman, T.W. Rall and F. Murad, Ed. 1985. Goodman and Gilman's the Pharmacological Basis of Therapeutics, 7th ed. Macmillan Publishing Co., New York.

Gilman, A.G., L.S. Goodman and A. Gilman, Ed. 1980. Goodman and Gilman's the Pharmacological Basis of Therapeutics, 6th ed. Macmillan Publishing Co., New York.

Gleason, M.N., R.E. Gosselin, H.C. Hodge and R.P. Smith. 1969. Clinical Toxicology of Commercial Products, 3rd ed. Williams and Wilkins, Baltimore.

Goodman, L.S. and A. Gilman, Eds. 1975. The Pharmacological Basis of Therapeutics, 5th ed. Macmillan Publishing Co., New York.

Goodman, L.S. and A.G. Gilman, Ed. 1970. The Pharmacological Basis of Therapeutics, 4th ed. Macmillan Publishing Co., New York.

Goodwin, B.L. 1976. Handbook of Intermediary Metabolism of Aromatic compounds. Wiley, New York.

Gosselin, R.E., R.P. Smith and M.C. Hodge. 1984. Clinical Toxicology of Commercial Products, 5th ed. Williams and Wilkins, Baltimore.

Gosselin, R.E., R.P. Smith and M.C. Hodge. 1976. Clinical Toxicology of Commercial Products, 4th ed. Williams and Wilkins, Baltimore.

Grant, W.M. 1974. Toxicology of the Eye, 2nd ed. Charles C. Thomas, Springfield, IL.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Acton, MA.

Hansch, C. and A. Leo. 1984. The log p Database. Pomona College Claremont, CA.

Hansten, P.D. 1979. Drug Interactions, 4th ed. Lea and Febiger, Philadelphia.

Hansten, P.D. 1971. Drug Interactions. Lea and Febiger, Philadelphia.

Hartley, D. and H. Kidd, Ed. 1983. The Agrochemicals Handbook. Royal Society of Chemistry/Unwin Brothers Ltd., Old Woking, Surrey, United Kingdom.

Hawley, G.G. 1981. The Condensed Chemical Dictionary, IOth ed. Van Nostrand Reinhold Company, New York:.

Hawley, G.G. 1977. The Condensed Chemical Dictionary, 9th ed. Van Nostrand Reinhold, New York.

Hayes, W.J, Jr. 1982. Pesticides Studied in Man. Williams and Wilkins, Baltimore/London.

Hayes, W.J., Jr. 1975. Toxicology of Pesticides. Williams and Wilkins, Baltimore.

IARC (International Agency for Research on Cancer). 1972-1985. IARC monographs on the evaluation of the carcinogenic risk of chemicals to man. (Multivolume work.) IARC, World Health Organization, Geneva.

Ismagilova, A.K, and V.G. Gilvev. 1971. Evaluation of the toxicity of benzenesulfonyl chloride during chronic inhalation poisoning. Tr Ufim Nauch-Issled Inst. Gig. Prof. Zabol. 6: 151.

ITI and ITII. 1982. The International Technical Information Institute Toxic and Hazardous Industrial Chemicals Safety Manual. The International Technical Information Institute, Tokyo, Japan.

ITI and ITII. 1976. The International Technical Information Institute Toxic and Hazardous Industrial Chemicals Safety Manual. The International Technical Information Institute, Tokyo, Japan.

Izgaronyan, Z.P. and V.A. Amatuni. 1980. Electrical activity of the heart in individuals producing vinyl acetate and its derivatives. Krovoobrashchenie 13, Vol. 4.

Jones, L.M., et al. 1977. Veterinary Pharmacology and Therapeutics, 4 ed. Iowa State University Press, Ames, IA.

Kearney, P.C. and D.D. Kaufman, Ed. 1975. Herbicides: Chemistry, Degradation and Mode of Action, 2nd ed., Vols. I and 2. Marcel Dekke, New York.

Kearney, P.C., and D.D. Kaufman. 1969. Degradation of Herbicides. Marcel Dekker, New York.

Keeler, R.F. and A.T. Tu, Ed. 1983. Handbook of Natural Toxins, Vol. 1. Plant and Fungal Toxins. Marcel Dekker, New York:.

Khan, et al. 1970. Ecological and health effects of the photolysis products of chlorinated hydrocarbon pesticide. In: Dynamics, Exposure and Health Assessment of Toxic Chemicals, R. Haque, ed. Ann Arbor Science Publishers, Ann Arbor, MI.

Kirk-Othmer. 1978. Kirk-Othmer Encyclopedia of Chemical Technology, 1978-1984, 3rd ed., Vols. 1-26. John Wiley and Sons, New York.

LaDu, B.N., H.G. Mandel and E.L. Way. 1971. Fundamentals of Drug Metabolism and Disposition. Williams and Wilkens, Baltimore.

Landrock, A.H. 1983. Handbook of Plastics Flammability and Combustion Toxicology. Noyes Publications, Park Ridge, NJ.

Lefaux, R. 1968. Practical Toxicology of Plastics. CRC Press Inc., Cleveland, OH.

Luckey, T.D. and B. Venugopal. 1977. Metal Toxicity in Mammals, 1. Plenum Press, New York.

Mackay, D. and W.Y. Shiu. 1977. Aqueous solubility of polynuclear aromatic hydrocarbons. Journal of Chemical Engineering Data, Vol. 22.

Marmion, D.M. 1984. Handbook of U.S. Colorants for Foods, Drugs, and Cosmetics, 2nd ed. John Wiley and Sons, New York.

Martin, E.W., Ed. 1978. Hazards of Medication, 2nd ed. J.B. Lippincott Co., Philadelphia.

Martin, E. 1971. Hazards of Medication: A Manual on Drug Interactions, Incompatibilities, Contraindications and Adverse Effects. J.B. Lippincott Co., Philadelphia.

Martin, H, and C.R. Worthing, Ed. 1979. Pesticide Manual, 5th ed. British Crop Protection Council, Worcestershire, England.

Martin, H. and C.R. Worthing, Ed. 1974. Pesticide Manual, 4th ed. British Crop Protection Council, Worcestershire, England.

Martin, H., Ed. 1972 Pesticide Manual: Basic Information on the Chemicals Used as Active Components of Pesticides, 3rd ed. British Crop Protection Council, Worcester, England.

Menzie, C.M. 1978. Metabolism of pesticides, an update 11. U.S. Dept. of the Interior, Fish and Wildlife Service, Special Scientific Report -- Wildlife No. 212. Washington, DC.

Menzie, C.M. 1974. Metabolism of pesticides, an update. U.S. Dept. of the Interior, Fish and Wildlife Service, Special Scientific Report -- Wildlife No. 184. Washington, DC.

Menzie, C.M. 1969. Metabolism of Pesticides. U.S. Dept. of the Interior, Fish and Wildlife Service, Special Scientific Report -- Wildlife No. 127. Washington, DC.

Merck Index. 1983. An Encyclopedia of Chemicals, Drugs, and Biologicals, lOth ed. Merck & Co., Inc., Rahway, NJ.

Merck Index. 1976. An Encyclopedia of Chemicals, Drugs, and Biologicals, 9th ed. Merck & Co., Inc., Rahway, NJ.

Merck Index. 1968. An Encyclopedia of Chemicals and Drugs, 8th ed. Merck & Co., Inc., Rahway, NJ.

Merory, J. 1968. Food Flavorings: Composition, Manufacture, and Use, 2nd ed. Avi Publishing Co., Westport, CT.

Meyers, F.H., E. Jaetz and A. Golfien. 1972. Review of Medical Pharmacology. Lange Medical Publications, Los Altos, CA.

Meyler, L. and A. Herxheimer, Ed. 1955-1971. Side Effects of Drugs, Vol. 1-7. Excerpta Medica, Amsterdam.

Miller, R.R. and D.J. Greenblatt. 1979. Handbook of Drug Therapy. Elsevier North Holland, New York.

Montesano, R., H. Bartsch, E. Boyland, et al., Ed. 1979. Handling chemical carcinogens in the laboratory: Problems of safety. IARC Scientific Publ. No. 33. International Agency for Research on Cancer, Lyon, France.

Morgan, D.P. 1982. Recognition and management of pesticide poisonings. U.S. EPA, Washington, DC. EPA 540/9-80-005.

Morgan, D.P. 1976. Recognition and management of pesticide poisonings. U.S. EPA, Washington, DC. EPA 540/9-76-011.

Mule, S.J. and H. Brill, Ed. 1972. Chemical and Biological Aspects of Drug Dependence. The Chemical Rubber Company, Cleveland.

NFPA (National Fire Protection Association). 1984. Fire Protection Guide on Hazardous Materials, 8th ed. NFPA, Quincy, MA.

NFPA (National Fire Protection Association). 1978. Fire Protection Guide on Hazardous Materials, 7th ed. NFPA, Boston, MA.

NFPA (National Fire Protection Association). 1975. Fire Protection Guide on Hazardous Materials, 6th ed. NFPA, Boston, MA.

NIH EPA, OHM/TADS. 1984. National Institutes of Health, Environmental Protection Agency. Database. Oil and Hazardous Materials Technical Assistance Data Systems.

NIH (National Institute of Health). 1979. Toxicology and carcinogenesis studies of aldicarb. Report #136, NIH Publ. #79.1391. p. 5.

NIOSH (National Institute for Occupational Safety and Health). 1977-Present. NIOSH Manual of Analytical Methods, 2nd ed., Vols. 1-7. U.S. DHEW, PHS, CDC. U.S. GPO, Washington, DC.

NIOSH (National Institute for Occupational Safety and Health). 1980. Registry of toxic effects of chemical substances, 1979 ed., Vols. I and 2. U.S. Dept. Health Human Services, PHS, CDC. U.S. GPO, Washington, DC.

NIOSH (National Institute for Occupational Safety and Health). 1979. Registry of toxic effects of chemical substances, 1978 ed. U.S. DHEW, PHS, CDC. U.S. GPO, Washington, DC.

NIOSH (National Institute for Occupational Safety and Health). 1977. Occupational diseases -- a guide to their recognition. U.S. DHEW. DHEW(NIOSH) Publ. No. 77-181. Washington, DC.

NIOSH (National Institute for Occupational Safety and Health). 1977. Registry of toxic effects of chemical substances, 1977 ed. U.S. DHEW, PHS, CDC. U.S. GPO, Washington, DC.

NIOSH (National Institute for Occupational Safety and Health). 1976. Registry of toxic effects of chemical substances, 1976 ed. U.S. DHEW, PHS, CDC, Washington, DC.

NIOSH (National Institute for Occupational Safety and Health). 1975. Registry of toxic effects of chemical substances, 1975 ed. U.S. DHEW, PHS, CDC. Washington, DC.

NIOSH (National Institute for Occupational Safety and Health). 1974. The toxic substances list. U.S. DHEW, Washington, DC.

NIOSH (National Institute for Occupational Safety and Health). 1973. The toxic substances list. U.S. DHEW, Washington, DC.

NIOSH/OSHA (National Institute for Occupational Safety and Health/Occupational Safety and Health Administration). NIOSH/OSHA -- Occupational health guidelines for chemical hazards, F.W. Mackison, R.S. Stricoff and L.J. Partridge, Jr., Ed. DHHS(NIOSH) Publ. No. 81-123.

NIOSH/OSHA (National Institute for Occupational Safety and Health/Occupational Safety and Health Administration). 1981. Occupational health guide for chemical hazards: Dimethylphthalate. U.S. Dept. Health Human Services, PHS. NIOSH 81.123. p. 1.

NIOSH/OSHA (National Institute for Occupational Safety and Health/Occupational Safety and Health Administration). 1980. NIOSH/OSHA pocket guide to chemical hazards, F.W. Mackison, R.S. Stricoff and L.J. Partridge, Jr., Ed. DHHS(NIOSH) Publ. No. 78-210. Washington, DC.

NIOSH/OSHA (National Institute for Occupational Safety and Health/Occupational Safety and Health Administration). 1978. NIOSH/OSHA pocket guide to chemical hazards. DHEW(NIOSH) Publ. No. 78.210. U.S. DHEW, U.S. Dept. Labor.

NIOSH/RTECS (National Institute for Occupational Safety and Health/Registry of Toxic Effects of Cheical Substances). 1985. Registry of toxic effects of chemical substances (RTECS). National Library of Medicine's current MEDLINE file. U.S. Dept. Health and Human Services, PHS, CDC.

NIOSH/RTECS (National Institute for Occupational Safety and Health/Registry of Toxic Effects of Cheical Substances). 1983. Registry of toxic effects of chemical substances, 1981-1982 ed., Vols. 1-3. DHHS(NIOSH) Publ. No. 83-107.

NRC (National Research Council). 1983. Drinking Water and Health, Vol. 5. National Academy Press, Washington, DC.

NRC (National Research Council). 1982. Drinking Water and Health, Vol. 4. National Academy Press, Washington, DC.

NRC (National Research Council). 1983. Polycyclic aromatic hydrocarbons: Evaluation of sources and effects. National Academy Press, Washington, DC.

NRC (National Research Council). 1981. Prudent Practices for Handling Hazardous Chemicals in Laboratories. National Academy Press, Washington, DC.

NRC (National Research Council). 1980a. Drinking Water and Health, Vol. 3. National Academy Press, Washington, DC.

NRC (National Research Council). 1980b. Drinking Water and Health, Vol. 2. National Academy Press, Washington, DC.

NRC (National Research Council). 1977. Drinking Water and Health, Vol. 1. National Academy Press, Washington, DC.

NRC (National Research Council). 1972. Specifications and Criteria for Biochemical Compounds, 3rd ed. National Academy of Sciences, Washington, DC.

Opavsky, W. and E. MacPherson. 1976. Ger Offen Patent Number 2430193, January I.

Opdyke, D.L.J. and C. Letizia, Ed. 1982. Monographs on fragrance and raw materials. Special Issue VI. Pergamon Press, New York.

Opdyke, D.L.J., Ed. 1979. Monographs on fragrance and raw materials. Pergamon Press, New York.

OSHA (Occupational Safety and Health Administration). 1984. Occupational safety and health standards. Subpart Z. Toxic and hazardous substances. (29 CFR 1910.1000) U.S. Dept. Labor. p. 660-665.

Osol, A., Ed. 1980. Remington's Pharmaceutical Sciences, 16th ed. Mack Publishing Co., Easton, PA.

Osol, A., J.E. Hoover, et al., Ed. 1975. Remington's Pharmaceutical Sciences, 15th ed. Mack Publishing Co., Easton, PA.

Osol, A. and R. Pratt, Eds. 1973. The United States Dispensatory, 27th ed. J.B. Lippincott, Philadelphia.

Parke, D.V. 1968. The Biochemistry of Foreign Compounds. Pergamon Press, Oxford.

Parr, J.F., P.B. Marsh, J.M. Kla, Ed. 1983. Land treatment of hazardous wastes. Noyes Data Corporation, Park Ridge, NJ.

Patty F, Ed. 1963. Industrial Hygiene and Toxicology. Vol. II: Toxicology, 2nd ed. Interscience Publishers, New York.

Peer Review Committee. Updated 1985. Expert opinion on Data Base. National Library of Medicine.

Physicians' Desk Reference. 1980, 1985. 34th ed. and 39th ed. Medical Economics Co. (Litton), Oradell, NJ.

Physicians' Desk Reference. 1974. 28th ed. Medical Economics Co., Oradell, NJ.

Proctor, N.H. and J.P. Hughes. 1978. Chemical Hazards of the Workplace. J.B. Lippincott Co., Philadelphia.

Roberts, N.J. 1983. South Med. J. 76(1): 45.48.

Rodricks, J.V., C.W. Hesseltine and M.A. Mehlman, Ed. 1977. Mycotoxins in human and animal health, proceedings of conference. University of Maryland, October 4-8, 1976. Pathotox Publishers, Inc., Park Forest South, IL.

Rossoff, I.S. 1974. Handbook of Veterinary Drugs. Springer Publishing Company, New York.

Rumack, B.H., Ed. 1975-Present. Poisindex. Microfiche ed. Micromedex, Inc., in association with the National Center for Poison Information, with updates. Denver, CO.

SANSS (Structure and Nomenclature Search System). 1983. Chemical Information Systems, Inc., Baltimore, MD. Last update November 1983.

Sax, N.I. 1984. Dangerous Properties of Industrial Materials, 6th ed. Van Nostrand Reinhold, New York.

Sax, N.I. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold, New York.

Sax, N.I. 1975. Dangerous Properties of Industrial Materials, 4th ed. Van Nostrand Reinhold, New York.

Sax, N.I. 1968. Dangerous Properties of Industrial Materials, 3rd ed. Van Nostrand Reinhold, New York.

Schuckmann, F. 1972. Zentralarbeitsmed Arbeitsschutz. 22(3): 74.

Searle, C.E., Ed. 1976. Chemical carcinogens. ACS Monograph 173. American Chemical Society, Washington, DC.

Shepard, T.H. 1980. Catalog of Teratogenic Agents, 3rd ed. Johns Hopkins University Press, Baltimore, MD.

Soliman, et al. 1979. J. Environ. Sci. Health. Part B B14(1): 27.

Sorahan, T., et al. 1983. Ann. Occup. Hyg. 27(2): 173-182.

Spencer, E.Y. 1973. Guide to the Chemicals Used in Crop Protection, 6th ed. Research Institute, Agriculture Canada. Information Canada, Ottawa, Canada. Publ. No. 1093.

Spencer, E.Y. 1982. Guide to the Chemicals Used in Crop Protection, 7th ed. Research Institute, Agriculture Canada. Information Canada, Ottawa, Canada. Publ. No. 1093.

SRI (Stanford Research Institute International). 1983. 1983 Directory of chemical producers. SRI International, Menlo Park, CA.

Stasik, N.J. 1975. Clinical experience with benzene sulfonyl chloride. Arch. Toxicol. 33(2): 123.

Stockley, I.H. 1981. Drug Interactions. Blackwell Scientific Publications, Boston.

Student, P.J. 1981. Emergency handling of hazardous materials in surface transportation. Bureau of Explosives, Washington, DC.

Sunshine I., Ed. 1969. CRC Handbook of Analytical Toxicology. The Chemical Rubber Company, Cleveland.

Sunshine I., Ed. 1975. Methodology for Analytical Toxicology. CRC Press, Inc., Cleveland.

Talakina, E.T., et al. 1977. Protection of the health of pregnant women working in the production of acetylene-vinyl acetate. Gig. tr Prof. Zabol. Vol. 3.

Testa, B. and P. Jenner. 1976. Drug Metabolism: Chemical and Biochemical Aspects. Marcel Dekker, Inc., New York.

Thienes, C. and T.J. Haley. 1972. Clinical Toxicology, 5th ed. Lea and Febiger, Philadelphia.

Transdermal Indomethacin Pharamaceuticals. 1983 (May 13). Nitto Electric Industrial Co., Ltd. JPN Kokai Tokkyo Koho Patent Number 83 79918.

Tsubura, Y., Kato, Y. (inventors), Kanesho Company, Limited (assignee). 1974 (August 15). Japan Kokai Patent Number 85233.

U.S. Army. 1975. Military chemistry and chemical compounds. Departments of the Army and the Air Force. Headquarters, Department of the Army, Washington, DC. U.S. Army Field Manual No. 3-9/Air Force Regulation No. 355-7.

Usdin, E. and D.H. Efron. 1972. Psychotropic drugs and related compounds, 2nd ed. U.S. DHEW, Washington, DC. Publ. (HSM) 72-9094.

U.S. EPA. 1983. Tolerances for pesticide chemicals in or on raw agricultural commodities; certain pesticide chemicals. (48 FR 44205.6).

U.S. EPA. 1980. Ambient Water Quality Document: Endrin (EPA 440/4-80-047); Chloroform (EPA 44015-80-033).

U.S. EPA. 1983. Drinking Water Criteria Document for Vinyl Chloride. Office of Drinking Water, Washington, DC. p. III-1.

U.S. EPA/Pesticide Index. 1985. EPA Index to Pesticide Chemicals: Use and Limitations. Current file; updated daily. Office of Pesticide Programs, Washington, DC.

U.S. EPA/Active Ingredients. 1985. EPA Chemical Index File: Active Ingredients. Current file; updated as needed. Office of Pesticide Programs, Washington, DC.

U.S. FWS (U.S. Fish and Wildlife Service). 1984. Handbook of toxicity of pesticides to wildlife. Dept. of Interior, Washington, DC. Resource Publ. 153.

U.S. FWS (U.S. Fish and Wildlife Service). 1980. Handbook of acute toxicity of chemicals to fish and aquatic invertebrates. Dept. of the Interior, Washington, DC. Resource Publ. 137.

U.S. FWS (U.S. Fish and Wildlife Service). 1975. Lethal dietary toxicities of environmental pollutants to birds. Dept. of the Interior, Bureau of Sports Fisheries and Wildlife, Washington, DC. Special Scientific Report -- Wildlife No. 191.

U.S. FWS (U.S. Fish and Wildlife Service). 1972. Comparative dietary toxicities of pesticides to birds. Dept. of the Interior, Bureau of Sports Fisheries and Wildlife, Washington, DC. Special Scientific Report -- Wildlife No. 152.

U.S. FWS (U.S. Fish and Wildlife Service). 1970. Handbook of toxicity of pesticides to wildlife. Dept. of the Interior, Washington, DC.

Venugopal, B. and T.D. Luckey. 1978. Metal Toxicity in Mammals, 2. Plenum Press, New York.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Company, New York, NY.

Wagoner, J.K. 1983. Environ. Health Perspect. 52.

Weast, R.C., Ed. 1984. Handbook of Chemistry and Physics, 65th ed. CRC Press, Inc., Boca Raton, FL.

Weast, R.C., Ed. 1983. Handbook of Chemistry and Physics, 64th ed. CRC Press, Inc., Boca Raton, FL.

Weast, R.C., Ed. 1980. Handbook of Chemistry and Physics, 60th ed. CRC Press, Inc., Boca Raton, FL.

Weast, R.C., Ed. 1979. Handbook of Chemistry and Physics, 60th ed. CRC Press, Inc., Boca Raton, FL.

Weast, R.C., Ed. 1976. Handbook of Chemistry and Physics, 57th ed. CRC Press, Inc., Boca Raton, FL.

Weast, R.C., Ed. 1974. Handbook of Chemistry and Physics, 55th ed. CRC Press, Inc., Boca Raton, FL.

Weast, R.C., Ed. 1972. Handbook of Chemistry and Physics, 53th ed. CRC Press, Inc., Boca Raton, FL.

Weed Science Society of America. 1979. Herbicide Handbook, 4th ed. Champaign, IL.

Weed Science Society of America. 1974. Herbicide Handbook, 3rd ed. Champaign, IL.

Weiss, G., Ed. 1980. Hazardous Chemicals Data Book. Noyes Data Corporation, Park Ridge, NJ.

Weiss, R.B. and F.M. Muggia. 1980. Am. J. Med. 68(2): 259.

White-Stevens, R., Ed. 1976a. Pesticides in the Environment: Vol 3. Marcel Dekker, New York.

White-Stevens, R., Ed. 1976b. Pesticides in the Environment: Vol 2. Marcel Dekker, New York.

White-Stevens, R., Ed. 1971. Pesticides in the Environment: Vol 1. Part I, Part 2. Marcel Dekker, New York.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual -- A World Compendium, 7th ed. The Lavenham Press Limited, Lavenham, Suffolk, Great Britain.

Worthing, C.R., Ed. 1979. Pesticide Manual, 6th ed. British Crop Protection Council, Worcestershire, England.

Worthy, W. 1985. Methyl Isocyanate: The Chemistry of a Hazard. Chem. Eng. News. 63(6): 27.33.