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TOXICOLOGICAL PROFILES
GUIDANCE TO CONTRACTORS

This package constitutes the final guidance to the contractors concerning the writing of the Toxicological Profiles required by the Superfund Amendments and Reauthorization Act of 1986. The package consists of five parts:

1. General guidance
2. Outline of the Toxicological Profiles
3. Specific guidance for sections of the Profiles
4. Sample sections written for benzene
5. Attachments

GENERAL GUIDANCE TO CONTRACTORS

General guidance

- Provide more evaluation and interpretation of data, and less description of studies.

- Summarize main points and provide an overview before supporting the claims with details. Follow this principle in organizing all levels of discussion, including individual paragraphs. Do not repeat summaries.

- The length of the document will vary depending on the chemical, but aim at a target of 50 to 60 pages single-spaced rather than hundreds of pages. Notify ATSDR or EPA in advance if you expect the document to be significantly longer than the target. Do not feel obliged to fill up space in order to meet the target; be concise.
(Print out the first and second drafts double-spaced so that there will be space for comments.)

- You must cite original references for key studies, or at least provide the full reference with the notation "as cited in [review]".

- You may cite review articles in place of original references for supplemental studies (i.e., those studies which are not "key studies" but which add significantly to our understanding of a topic).

- When citing both reviews and original literature, distinguish them from each other. For example, "Supplemental studies of neurotoxicity via the oral route include (_____ 1984), (_____ 1980), and (_____ 1923). Much of the data is reviewed in (_____ 1986) and (_____ 1999)."

- If you cite original references for supplemental studies, use them mainly to support general statements rather than specific details of a particular study.

- If there is no information about a topic that is listed in the attached outline, place a statement to that effect under the heading. Do not omit headings that are in the outline from the document.

- The sections on manufacture, use, disposal, and environmental fate shall be present in the toxicological profile only as very short summaries. The purpose for including them is to give the reader an appreciation of how humans might be exposed to the chemical. Note that a new section, called "Potential for human exposure", has been created. See the guidance for this section in the "Specific guidance" part of this package.

- Use the Government Printing Office Style Manual (1984 edition) as the style manual for tables and references. (To the extent that the GPO Style Manual is vague about a specific format for references, use the style to which you are accustomed as long as references are listed with authors' names and year of publication as the first two items.) Use the author-and-date style of referencing in the text. Put all references at the end of the document, not at the end of each chapter.

- ATSDR/EPA has distributed "genetic activity profiles" and summaries of analyses of genotoxicity studies for certain compounds, but not all. These graphs and summaries are for your consideration but are not to be included directly in the documents you are preparing.

- Certain sections (primarily the introductions in several places) will be supplied by ATSDR/EPA at a later date. These sections are identified later in this package. Insert an appropriate statement in parentheses to hold a place for these sections if they have not been distributed by the time a particular document is due.

- Add a header on each page that includes the chemical name (abbreviated if necessary), the title of the chapter, and the page number. Number the pages consecutively from the beginning to the end of the document, rather than within each chapter.

- Begin each chapter on a new page.

- Graphs may be typed or neatly handwritten; the camera-ready copy is not the responsibility of the individual contractors.

- The 3-dimensional graphs in the Specific Guidance section of this document were produced using GEM software for IBM PC-compatible computers. Contractors are not required to provide 3-D graphs for the drafts due on June 8, 1987. They should, however, be provided as soon after that as possible.

- Note on pages 17 and 22 that additional deliverables are requested.

OUTLINE OF THE TOXICOLOGICAL PROFILES

Outline

I. Table of contents

II. Introduction
(To be written by ATSDR/EPA. It will state the purpose of the document, the audience for which it is intended, and limits on its use.)

III. Public health statement
(The non-technical summary for the general public.)
A. What is (CHEMICAL NAME)?
B. How might I be exposed to (CHEMICAL NAME)?
C. How does (CHEMICAL NAME) get into my body?
D. How can (CHEMICAL NAME) affect my health?
E. Is there a medical test to determine whether I have been exposed to (CHEMICAL NAME)?
F. What levels of exposure have resulted in harmful health effects?
G. What recommendations has the federal government made to protect human health?

IV. Health effects summary
(A more technical summary.)
A. Introduction
(To be written by ATSDR/EPA, discussing methodologies for developing the graphs.)
B. Levels of significant exposure
1. Key studies; graphs
2. Biological monitoring as a measure of exposure and effects
a. Exposure
b. Effects
3. Environmental levels as indicators of exposure and effects
a. Levels found in the environment
b. Human exposure potential
C. Adequacy of data base
1. Introduction
(Written by ATSDR/EPA, discussing the purpose of this section and the process for defining research programs to fill critical gaps in information.)
2. Adequacy of the data base for health effect endpoints
a. Introduction and graphic summary
* Introduce 3-D Data Adequacy Charts
* Explain N/A designations
* Define "some" vs. "adequate" data
b. Description of highlights of graphs
* Summarize key features of graphs for the substance
* Explain specific N/A designations
* For systemic toxicity highlight major organ system(s) affected or not adequately studied
c. Summary of relevant on-going research
3. Adequacy of the data base for other information needed

for risk assessment
a. Pharmacokinetics and mechanisms of action
* Mechanisms of action in human and animals
* Pharmacokinetics in humans and animals
* On-going research
b. Monitoring of human biological samples
* Human biomonitoring methods
* On-going research
c. Environmental considerations
* Bioavailability from environmental media
* Environmental transport and fate
* Interactions with other common co-contaminants
* On-going research

V. Chemical and physical information
A. Chemical identity
B. Physical and chemical properties

VI. Toxicological data
A. Toxicokinetics
1. Overview
2. Absorption
a. Inhalation
i. Human
ii. Animal
b. Oral
i. Human
ii. Animal
c. Dermal
i. Human
ii. Animal
3. Distribution
a. Inhalation
i. Human

etc.

4. Metabolism
a. Inhalation
i. Human

etc.

5. Excretion
a. Inhalation
i. Human

etc.

B. Toxicity
1. Lethality and decreased longevity
a. Overview
b. Inhalation
i. Human
ii. Animal

c. Oral
   i. Human
   ii. Animal
d. Dermal
   i. Human
   ii. Animal

2. Systemic/target organ toxicity
   a. Overview
   b. Endpoint 1
      i. Overview
      ii. Inhalation
         1) Human
         2) Animal
      iii. Oral
         1) Human
         2) Animal
      iv. Dermal
         1) Human
         2) Animal
      v. General discussion
   c. Endpoint 2
      i. Overview
      ii. Inhalation
         1) Human

         etc.

3. Developmental toxicity
   a. Overview
   b. Inhalation
      i. Human
      ii. Animal
   c. Oral
      i. Human

      etc.

   d. Dermal
      i. Human

      etc.

   e. General discussion

4. Reproductive toxicity

   etc.

5. Genotoxicity

   etc.

6. Carcinogenicity

   etc.

C. Interactions with other chemicals

VII. Manufacture, import, use, disposal
(A very short summary to lead into the next 2 sections.)
A. Overview
B. Production
C. Import
D. Use
E. Disposal

VIII. Environmental fate
A. Overview
B. Releases to the environment
C. Environmental fate

IX. Potential for human exposure
A. Overview
(This is the place to discuss how the volume of releases is modified by environmental fate processes to result in human exposure.)
B. Levels monitored or estimated in the environment
1. Air
2. Water
3. Soil
4. Other
C. Occupational exposures
D. Populations at high risk

X. Analytical methods
A. Environmental media
1. Air
2. Water
3. Soil
4. Food
B. Biomedical samples
1. Fluids/exudates
2. Tissues

XI. Regulatory and advisory status
A. International (World Health Organization)
B. National
1. Regulations
2. Advisory guidance
3. Data analysis
i. Reference doses (RfDs)
ii. Carcinogenic potency
1) q_1^*
2) Methods used by other agencies
C. State
1. Regulations
2. Advisory guidance

XII. References

SPECIFIC GUIDANCE FOR SECTIONS OF THE PROFILES

Specific guidance for sections of the Profiles

In this section, underlined parts are to be included in the toxicological profile. Parts which are not underlined are comments to the contractors, unless otherwise noted.

I. Table of contents

Use the Style Manual.

II. Introduction

ATSDR/EPA will distribute this section to the contractors.

III. Public Health Statement

This section of the profile, if removed from the rest of the document, should still communicate to the lay public essential information about the chemical. It should be a health effects summary written in layman's terms. The intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. Technical terminology should be avoided. This section should be written for a reading level comparable to a daily newspaper.

The tone of this section should be factual, rather than judgmental. Terms and units should be used consistently throughout this section. Graphics should be used liberally. See "Benzene" example.

Major headings for the lay version will be in a question format. The following questions will be addressed:

A. WHAT IS (CHEMICAL NAME)?
- Provide a physical description of the chemical.
- What are the major natural and man-made sources of the chemical?
- What are general use patterns?

B. HOW MIGHT I BE EXPOSED TO (CHEMICAL NAME)?
- What are environmental sources?
  - Spills, disposal sites.
  - Background levels in soil, air, water, food.
- What are consumer/everyday sources?
- What are consumer/unique sources?
- What are occupational sources?

Manufacturers, processors, users, distributors

C. HOW DOES (CHEMICAL NAME) GET INTO MY BODY?
Discuss ingestion of food and water, inhalation, and dermal exposure.
Describe the most significant pathway first.

D. HOW CAN (CHEMICAL NAME) AFFECT MY HEALTH?
Give a general description of all health effects.
Distinguish
- o health effects associated with brief exposures to high levels
- o health effects associated with long-term exposures at various levels

Answer the following questions, if possible:
Is (CHEMICAL NAME) toxic?
Does (CHEMICAL NAME) cause cancer?
Does (CHEMICAL NAME) cause birth defects?
When can (CHEMICAL NAME) be life-threatening?
What are other major health effects of (CHEMICAL NAME) (e.g., immune system, central nervous system, developmental disability, major organ impairment etc.)?

E. IS THERE A MEDICAL TEST TO DETERMINE IF I HAVE BEEN EXPOSED TO (CHEMICAL NAME)?
This should be a brief paragraph. It should state whether there is a test or not.
What can be measured?
Does the test correlate quantitatively with exposure?
Can the test be used to predict potential health effects or advise changes in exposure?

F. WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?
Provide graphs -- consistent with the LSE chapter -- using the following guidelines and the examples given for benzene:

- o One page for each route of exposure. Titles:
  Health effects from breathing
  Health effects from ingestion
  Health effects from skin absorption
- o Two graphs per page:
  Left side for short-term exposures
  Right side for long-term exposures
  "Short-term" refers to exposures of 14 days or less. "Long-term" refers to exposures greater than 14 days.
- o Exposure plotted on a linear scale, vertically, in the middle of each graph. Units of ppm (spell it out for the lay person) for inhalation, mg substance/kg body weight (ditto) for oral, and mg substance/kg body weight for dermal exposures.

(Use ppb and ug/kg if appropriate.)

- o Brackets to indicate approximately where effects begin. Top of bracket at LOEL for that effect, bottom of bracket at NOEL for that effect. However, do not label these levels explicitly as LOELs and NOELs.
- o Use non-technical terms.
- o Include exposures that are associated with effects other than on health (e.g., odor or taste threshold) for reference.
- o Include a level at which minimal risk is anticipated (for effects other than cancer).

There should be minimal text; use it mainly to refer to the graphs. Include, however, a statement of the exposures associated with 10^{-4} to 10^{-7} risks for cancer (if known). Explain that the reason they are not included on the graph is that these doses are far below the others, and would not fit on the same scale without severe compression of the graph (if that's really true).

Explain that the level marked on the graphs as anticipated to be associated with minimal risk is based on information that is currently available, and that there is some uncertainty associated with it.

G. WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

Provide narrative on guidelines and standards for inhalation, drinking water, food, dermal exposures, etc. For carcinogens, point out that in the absence of information to the contrary, it is assumed that "any exposure involves some risk."

IV. Health Effects Summary

The purpose of this section is to condense information developed in other chapters into an easy-to-access, short and helpful summary using abbreviated text and graphical representations.

A. Introduction

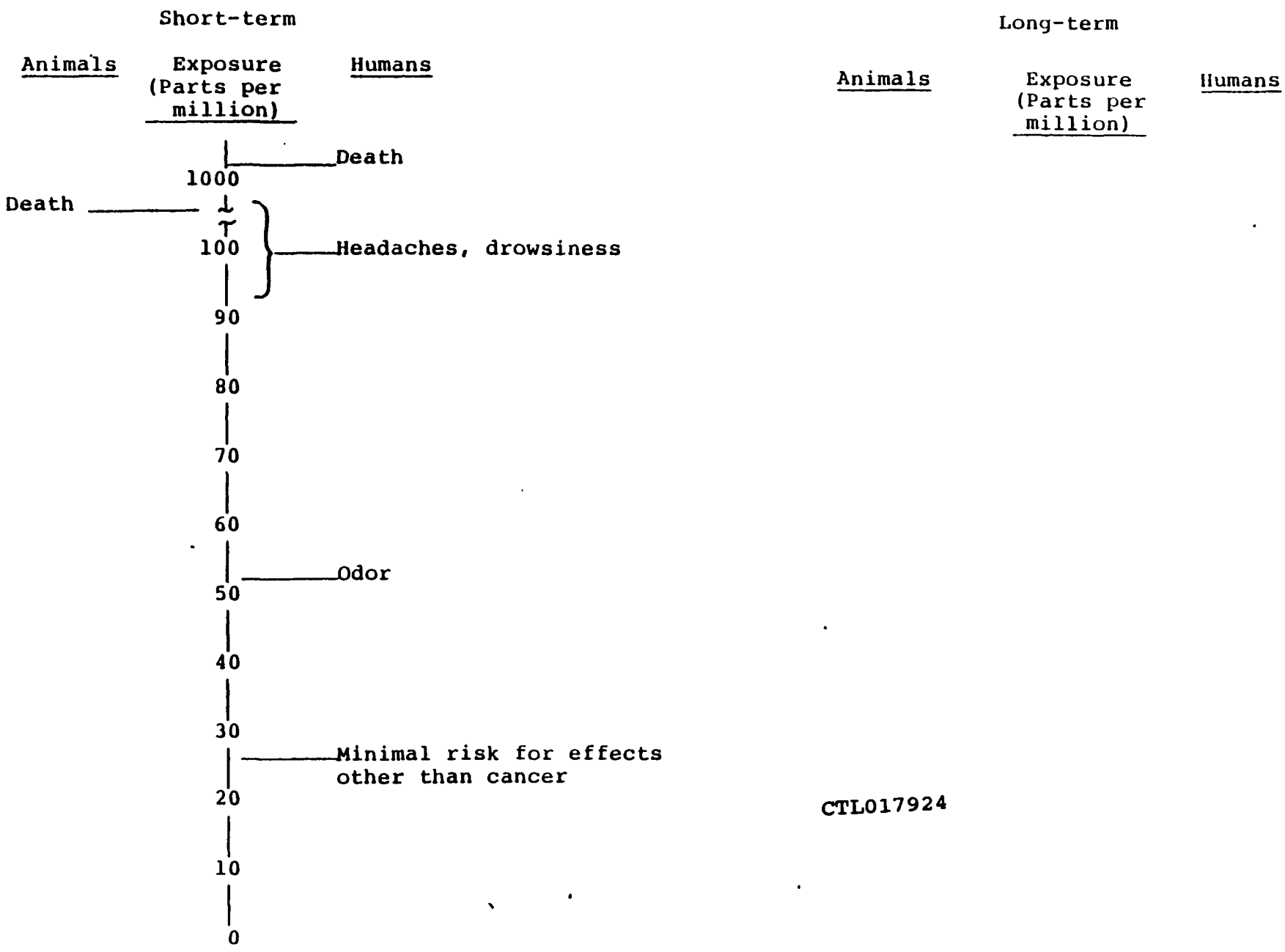
This section will be supplied to the contractors by ATSDR/EPA, and will include a discussion of methodologies used to develop the graphical presentations.

B. Levels of Significant Exposure

1. Key studies; graphs

This section applies the concepts discussed in the Introduction to the chemical in question. Levels of Significant Exposure are to be discussed for specific endpoints, namely lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, genotoxicity and cancer, in that order. All

Health Effects from Breathing



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organ systems must be considered in the evaluation of systemic/target organ toxicity. These include the nervous, dermal, cardiovascular, pulmonary, gastrointestinal, renal, musculoskeletal, immunological, ophthalmic, hematological and hepatic systems. Systemic toxicity should be reported in terms of the most sensitive end organ or system.

Levels of significant exposure will be developed from "key studies". Key studies are those that illustrate best the nature of the adverse effects produced and the doses associated with those effects, both in animals and humans.

Include very brief descriptions of the key studies, with references. State the exposures associated with frank effects, LOAELs and NOAELs.

Organize the discussion first by route of exposure (inhalation, oral, dermal) and within each of those, by duration of exposure (acute, intermediate, and chronic).

In addition to text, use graphs. Two kinds of graphs are expected, as illustrated in the benzene case study:

(1) "Thermometer" graphs for animals and for humans for 3 routes of exposure, which document exposure vs. effect, showing exposure duration. Effects will range from acute lethality at the high exposure end through effects occurring at lower and lower exposures.
There will be a total of six "thermometer" graphs: one page per route, two graphs per page:
one for human data
one for animal data

Exposure on log scale, vertically, in ppm for inhalation, mg/kg for ingestion and dermal exposure (ppb and ug/kg if appropriate).

Plot LOELs and NOELs for each species for each effect, and indicate duration of exposure that caused the effect. Use "i" to denote intermittent exposures, and "c" for continuous exposures.

Generalize effects to the system/target organ level if possible (e.g., renal, hepatic, hematopoietic).

(2) Exposure route graphs (one per page) which separate exposures into three groupings: acute (includes lethality, developmental and organ toxicity), intermediate (organ and reproductive

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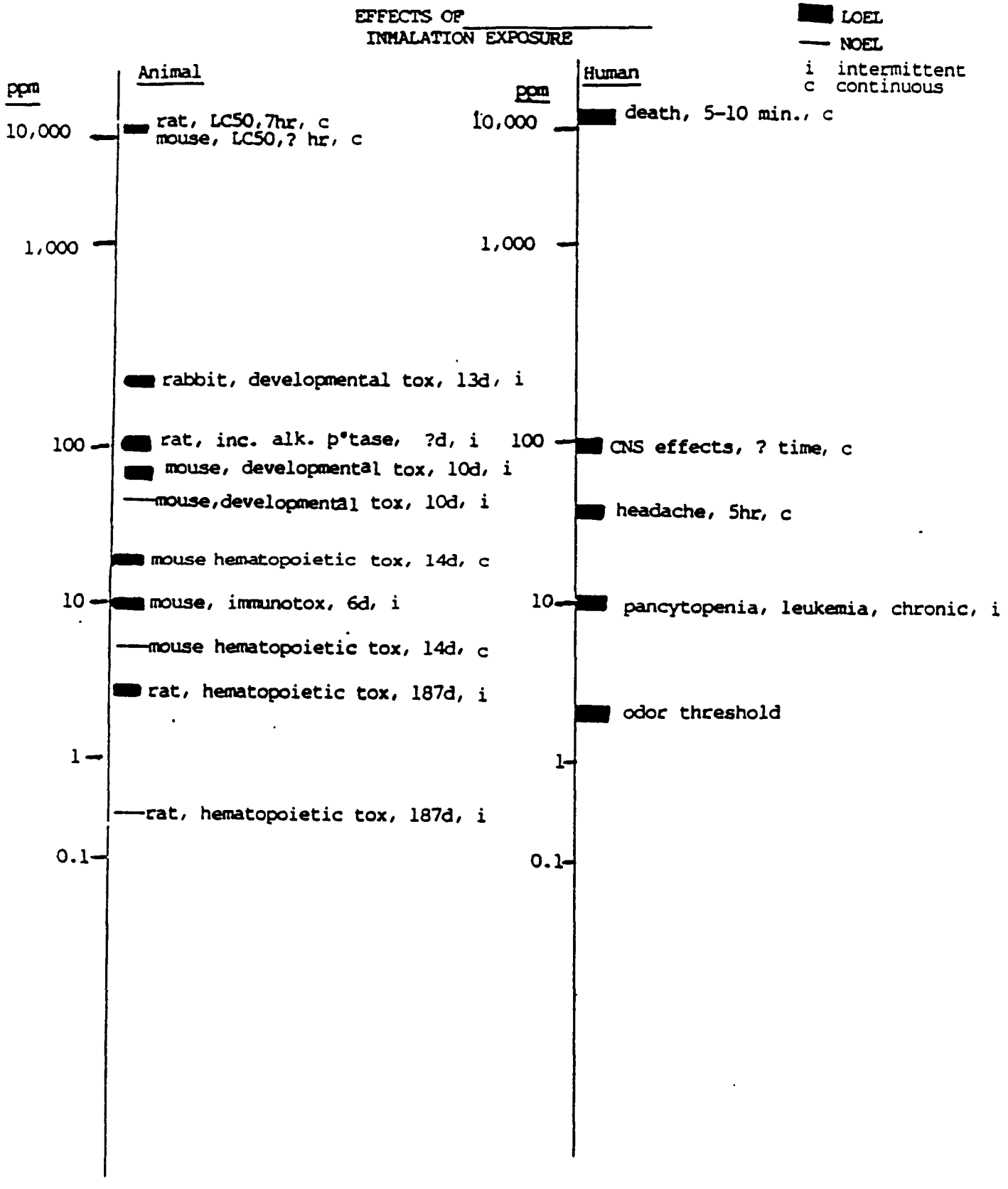

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toxicity) and chronic (organ toxicity and cancer). There will thus be a total of 9 graphs over 3 pages. You may include other effects for an exposure duration if human exposure for that duration would be of concern with respect to that effect.

Use the following definitions of exposure durations: acute = $\leq$ 14 days, intermediate = 15 through 364 days, chronic = $\geq$ 365 days.

Note: genotoxicity will not be included in these graphs.

Exposure on log scale, vertically, at left of page, in units used for the thermometer graph. Plot NOAELs and LOAELs for each species. Join the NOAEL and LOAEL pair for a species with a line. (For humans, exposure is often not known exactly. If only a range is known for the LOAEL or NOAEL, use that range.) Show data from all human studies. Plot the key at the bottom of each graph.

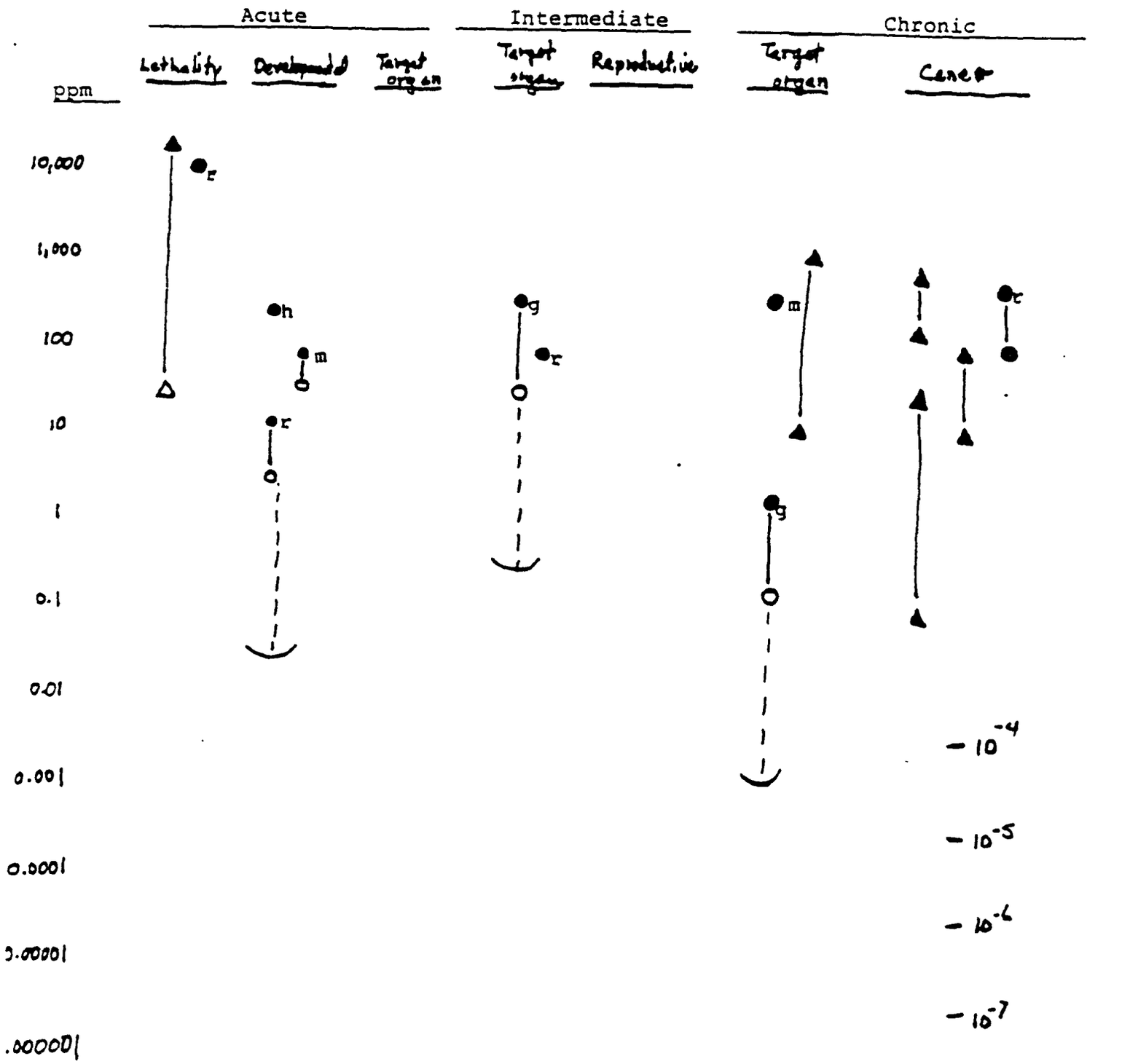
(a) For lethality in humans, graph the LD_{LO} or LC_{LO} values. For animals, graph LD_{50} or LC_{50} values.

(b) For cancer, graph the lowest exposure levels associated with increased tumors in experimental or epidemiological studies. Also graph the exposure levels associated with individual lifetime upper-bound risks of 10^{-4}-10^{-7}, but only if these levels have been derived by the EPA's Carcinogen Assessment Group through the q_1^* methodology. Do not derive q_1^* values for any chemicals which do not have q_1^*s. Plot the 10^{-4} to 10^{-7} ranges for each route of exposure for which a q_1^* is available. (In some cases, q_1^*s will have been extrapolated from one route to another by the EPA. In other cases, such extrapolations will not have been made. Plot the ranges for the second and third routes of exposure if and only if the EPA has done the extrapolation.) Do not plot NOAELs for cancer.

(c) For non-cancer endpoints, show a level below the NOAEL at which there is expected to be minimal risk. The proximity of this level to the NOAEL will vary depending (for example) on the certainty that the animal NOAEL data for that effect are applicable to humans. (See Attachment 1 on RfDs, "reference doses", and the guidance in Section XI.B.3.i.) Connect

LEVELS OF SIGNIFICANT EXPOSURE

INHALATION



Key

Species

r - rat
m - mouse
h - rabbit
g - guinea pig
d - dog
c - cat
s - hamster (Syrian)

r - animal (rat)
▲ - human

- minimal risk for effects other than cancer

Type of observation

▲ - LOEL
Δ - NOEL

- lowest range of exposures associated with effects in humans

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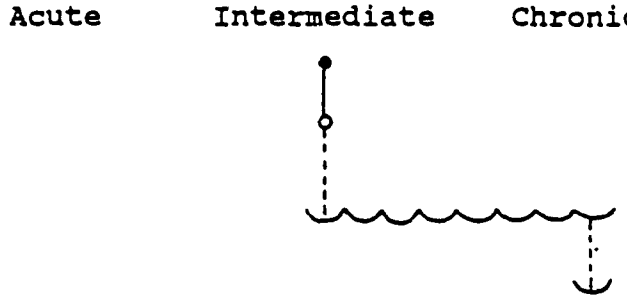
the appropriate NOAEL to this level with a dotted line. Us LOAELs if appropriate NOAELs are not available. Label the level "Minimal risk for effects other than cancer". Use an upward-concave curved line (◡) to denote the level.

If an RfD is available from the EPA, plot it. (It will be the minimal risk level for the chronic exposure duration section of the oral exposure graph.) If an RfD is not available, use the RfD methodology to derive an estimated level of minimal risk. However, do not derive a level if the RfD Work Group considered the chemical and declined to develop an RfD.

Derive a minimal risk level for each exposure duration for which data are available, using the RfD methodology. (The part of the methodology dealing with uncertainty in extrapolating to chronic exposure is not applicable in these cases.) If an RfD has been derived from acute or intermediate exposure data, plot the minimal risk level for the acute or intermediate exposure duration, draw a scalloped line across the graph to th chronic exposure portion, and drop a dotted line from there to the minimal risk level for chronic exposure duration (i.e., the RfD):



Derive minimal risk levels for each exposure route for which data are available, using the RfD methodology. In some cases, an RfD (which is defined only for the oral route) has been derived from inhalation data. In these cases, the minimal risk level for the oral route (i.e., the RfD) will not be anchored to data on the oral-route graph. In the text, explain the connection to the inhalation data. Do not extrapolate from route to route except in those cases where the RfD Work Group has done so.

**** Additional deliverable where applicable ****

Put all derivations of anticipated minimal risk levels, except for the derivation of the EPA's RfD, in a separate document. State the studies used, the effects chosen, and the uncertainty factors used. Show the calculations. In the toxicological profile itself, mention the studies and effects in the LSE section and discuss them more thoroughly in the toxicological data section, but do not include calculations or numerical results in either of these sections.

As noted further on in this Guidance to Contractors package, derivation of RfDs will be shown in detail in the Regulatory section.

2. Biological monitoring as a measure of exposure and effects

Include a short critical evaluation of how accurately and precisely biological monitoring results can be associated with exposure or toxicity. Use graphs, if possible.

Clearly state whether there are tests for exposure. Clearly state whether there are tests for effects.

Attempt to correlate the best available information on biological monitoring with measurable biological alterations. These alterations may have inconsequential and/or unknown effects on health; however, they should be recorded (e.g., ALAD elevations in persons with relatively low serum lead levels). Discuss these ambiguities, and distinguish those alterations which are clearly related to adverse health outcomes.

Briefly review the various biological fluids and/or tissues (blood, urine, fat, etc.) in which the chemical and/or metabolites can be measured. Discuss only the most reliable and predictive biological measurement(s). For example, if measurement of chemical X in the urine is clearly the most sensitive and specific indicator of exposure, only this biological medium should be reviewed in this section. However, if other biological media and measurement techniques are of comparable value, and/or give additional information (e.g., blood lead and blood free erythrocyte protoporphyrin), they should be included.

Graph the relationship between measured levels vs. exposure or effects if the method has sufficient sensitivity, specificity, reliability and

reproducibility, which make it useful to the public health practitioner.

A distinction should be made between measurable biological alterations that represent a clear health effect versus those whose clinical significance is not clear.

3. Environmental levels as indicators of exposure and effects

a. Levels found in the environment

Summarize available data that suggest that levels of the substance found in environmental media (primarily, soil, drinking water, and food) are associated with significant human exposure. It is expected that case studies and epidemiologic investigations will provide the majority of data for this section. For example, the Centers for Disease Control has stated that lead levels in soil greater than 500 ppm may be associated with elevated blood leads in children who have daily contact with that soil. Air levels should be de-emphasized in this section as inhalation data are adequately addressed in graphics presented elsewhere.

[Note to contractors: Two additional databases that should be searched for this section include--(1) CDCBRS and (2) State Health Departments, particularly New Jersey, New York, Wisconsin, Iowa, California, N. Carolina, and Washington].

b. Human exposure potential

Discuss pertinent chemical-specific issues involved in estimating body dose, tissue levels, and health effects from chemical concentrations in soil, water, and food. Emphasize uptake of th substance from commonly-contaminated media at waste sites. For example, studies have shown that the bioavailability of dioxin in Missouri soil may be different from that of soil found in New Jersey-----discuss dioxin-specific properties which may account for this difference.

C. Adequacy of data base

The purpose of this section is to identify gaps in knowledge relevant to developing levels of significant exposure for the substance. Such gaps will be identified for certain of the "endpoints" evaluated in the previous section on Levels of Significant Exposure (lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, and cancer), and also for other areas which are relevant to assessing risk, such as human

biological monitoring, pharmacokinetics, and mechanisms of toxicity. The two groups of information ("endpoint" vs. "other") are treated differently, with the former being graphed and the latter being discussed only in text.

The overall length of the section should not exceed 7 pages single-spaced, including graphs.

1. Introduction

The following standard language shall constitute this subsection:

The Superfund Amendments and Reauthorization Act of 1986 (SARA) states that the toxicological profiles shall include, but not be limited to, each of the following:

> ...(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.
>
> (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This section identifies data gaps in current knowledge relevant to developing levels of significant exposure for [the substance]. Such gaps are identified for certain health effects "endpoints" (lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, and cancer) reviewed in Section IV.B. of this profile in developing levels of significant exposure for [the substance], and for other areas such as human biological monitoring and mechanisms of toxicity. The present section briefly summarizes the adequacy of existing human and animal data, identifies data gaps, and summarizes research in progress that may fill such gaps.

Specific research programs for obtaining data needed to develop levels of significant exposure for [the substance] will be developed by ATSDR, NTP, and EPA subsequent to receipt and review of public comments on this toxicological profile.

2. Adequacy of the data base for health effect endpoints

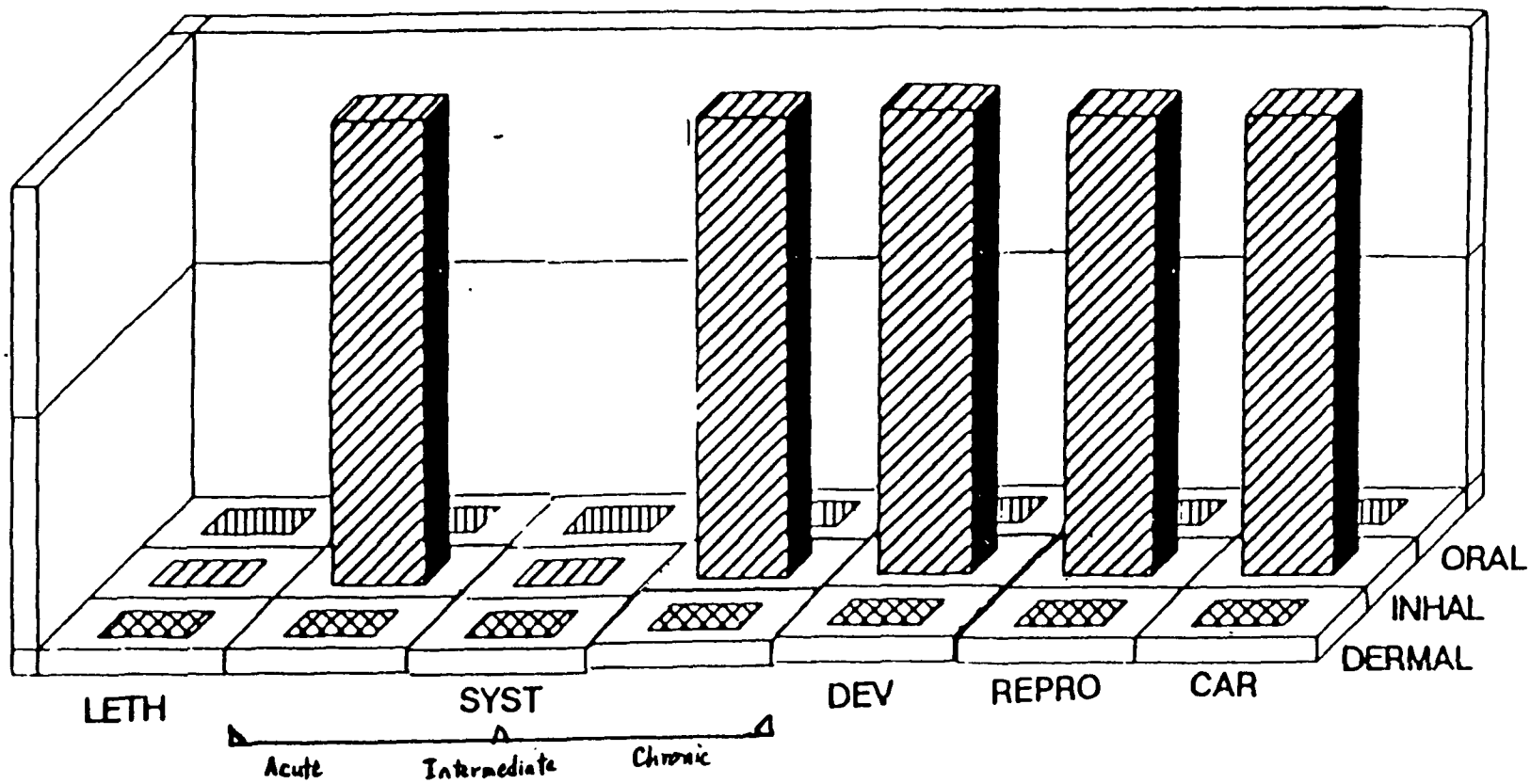
a. Introduction and Graphic Summary

Graph, in the three-dimensional bar graph format illustrated on the next two pages, a summary of the adequacy of the existing data base for the five effect "endpoints" mentioned above. There will be a total of two graphs, as shown (one for animal data and one for human data). The axes of

BASE

ADEQUACY OF DATA ON HEALTH EFFECTS OF

HUMAN DATA



ADEQUATE DATA

SOME DATA

NO DATA OR N/A

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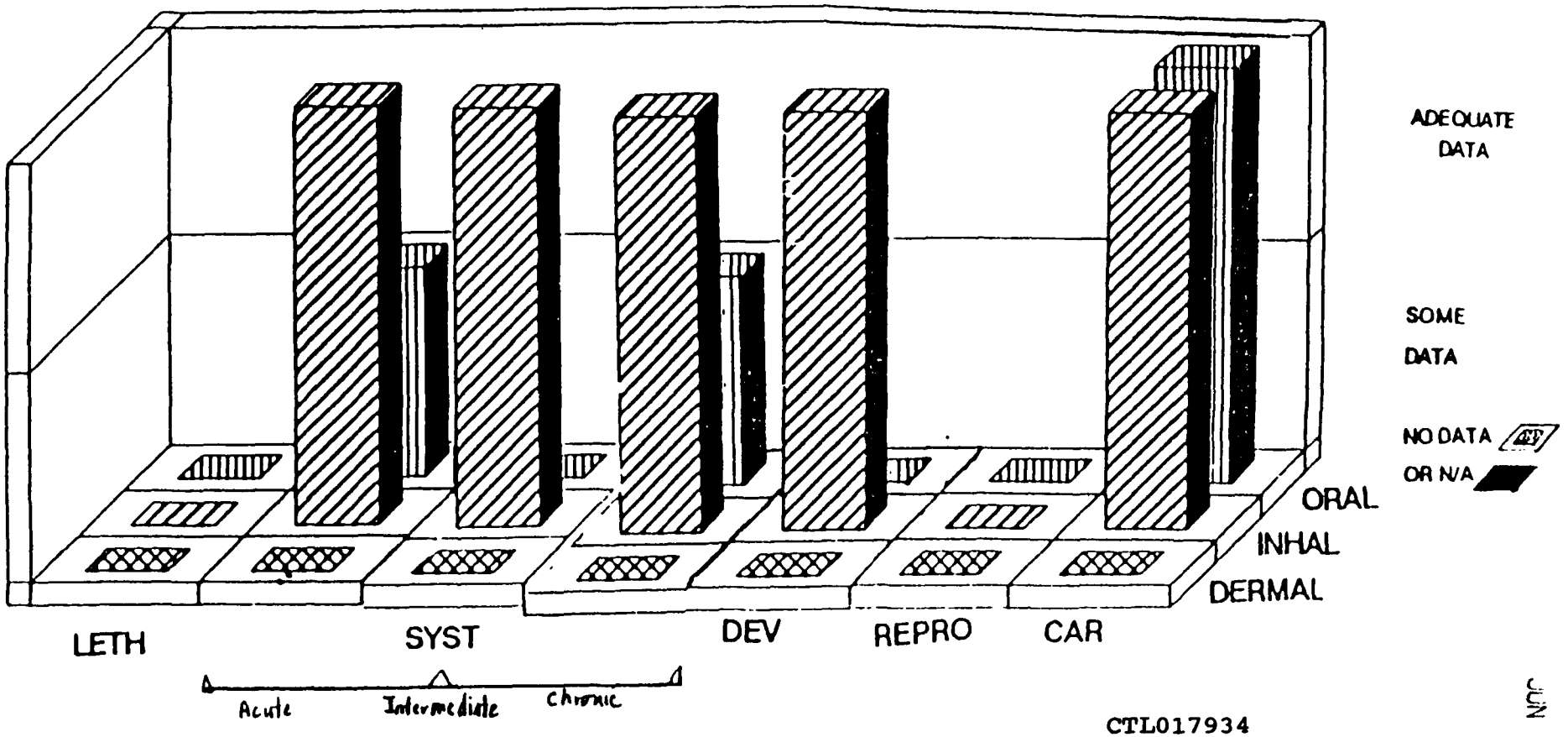
ADEQUACY OF DATA BASE ON HEALTH EFFECTS OF

ANIMAL DATA



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the graphs will be effects vs. exposure route vs. adequacy of data. Divid the information on systemic effects according to exposure duration, as shown. Acute exposure refers to exposures lasting less than or equal to 14 days. Intermediate exposure refers to exposures lasting 15-364 days. Chronic exposure refers to exposures of 1 year or longer.

The data base for an effect/route/duration combination will be considered to be "adequate" if it contains one or more studies that meet current scientific standards and is sufficient to define the range of toxicity encompassing no observed effect, low observed effect, and frank effect levels. When the data base for an effect/route/duration combination is not sufficient to develop LOAELs, NOAELs, and FELs, present it as "some" data. If there are no data, then the corresponding cell of the matrix should not be given any height. If data related to a particular route of exposure would not be applicable in developing levels of significant exposure for a particular substance, even if they were available, blacken that cell on the graph.

For systemic/target organ effects, plot data adequacy for the system/target organ which is most sensitive in that cell.

The graphs shall be accompanied by a paragraph (1/2 page maximum length) that explains the format of the graphs.

b. Descriptions of highlights of graphs
In less than one page, describe the key features of the graphs. An example of the kind of text expected is: "No short-term or long-term data were available regarding the systemic toxicity of acute or chronic exposure to [the substance] by oral or dermal routes." Comment on the human chart first, then the animal chart.

Cover the adequacy of data for systemic effects other than the ones graphed. Give your judgment of whether the data base for systemic effects as a whole is grossly inadequate, remarkably complete, or somewhere in between.

Explain the cells labeled "not applicable" on the graphs; e.g., why the endpoint for that route is deemed not to be relevant to developing levels of significant exposure for the substance.

c. Summary of relevant on-going research

In no more than four sentences per study, describe on-going research related to filling data gaps for the endpoints treated in the graphics in Section 2.a. Include name of principal researcher, institutional affiliation, description of topic, and state which data gap the research is expected to fill or help to fill.

3. Adequacy of the data base for other information needed for risk assessment

Write this section in "bullet" or "narrative" form and address data gap issues that are not considered above. This section should be no longer than 1 1/2 to 2 pages and should address the following issues. No more than 4 sentences per study should be used to describe on-going research.

a. Pharmacokinetics and mechanisms of action
   i. Are the mechanisms of action for human and animal toxicity/carcinogenicity of the substance adequately understood? Gaps in genotoxicity data should be described here.
   ii. Are target organs/pharmacokinetic profiles adequately identified for human and animal exposure to the substance? Is sufficient information available for allowing extrapolation from one route of exposure to another?
   iii. Are there any on-going studies that could fill these data gaps?

b. Monitoring of human biological samples
   i. Does there exist a methodology(ies) of sufficient sensitivity and specificity to test for human exposure to the substance in the body?
   ii. For what conditions of exposure -- route, level, and duration -- are adequate methods not available?
   iii. Are there any on-going studies that could fill these data gaps?

c. Environmental considerations
   i. Does there exist a methodology(ies) of sufficient sensitivity and specificity to measure the level of the chemical in the environment?
   ii. What gaps exist in our understanding of the substance's bioavailability from environmental media (e.g., soil, water, air and food)?
   iii. Is our understanding of environmental fate and transport adequate to predict the movement and degradation of the substance over time in the environment?
   iv. Have studies been conducted on the substance's interaction(s) in vivo or in the environment with other chemicals with which it is commonly

found?

v. Are there any on-going studies that could fill these data gaps?

**** ADDITIONAL DELIVERABLE PRODUCT ****

Section IV.C. of the toxicological profile should be limited to identifying data which are presently unavailable but which would be relevant to developing levels of significant exposure for the substance. The toxicological profile should not contain the contractor's recommendations concerning the specific types of studies that could be conducted to fill the data gaps nor the contractor's recommendations as to the relative priorities for conducting such studies. However, the contractor shall submit such recommendations in a separate report at the same time that the contractor's last version of the toxicological profile is submitted. This separate report will be considered by ATSDR, NTP and EPA in their subsequent development of research programs for the substance.

V. Chemical and physical information

A. Chemical identity
B. Physical and chemical properties

These sections should contain practically no text; all information should be in tables. The formats for the tables are given in attached sheets.

VI. Toxicological Data

The purpose of this section is to provide state and local health officials with evaluations and interpretations of the available toxicological studies on the chemical in question, and to provide some indication of the amount of data and consistency of results where several studies exist. It is neither necessary nor desirable to describe the details of all studies. It is definitely important, however, to provide references that will lead those who are interested to all the detailed information which was evaluated.

Describe in detail only the key study for each effect, route, and species. (There may be more than one key study for each combination.) The purpose of including the detail is to let the reader judge how well the "best" study was performed. Some degree of generalization is acceptable, for the sake of brevity (e.g., "There were approximately 40 animals per sex per dose" rather than "There were 38 female

Chemical Identity of

Chemical Name:	[Value]	[Reference]
Synonyms:		

Trade name:
Chemical Formula:

Wiswesser Line Notation:

Chemical Structure:

22a

Identification Numbers:

CAS Registry Number:

NIOSH RTECS Number:

EPA Hazardous Waste Number:

CHRN-TADS Number

DOT/UN/NA/IMCO Shipping Number:

STCC Number:

CTL017938

Hazardous Substances Data Base Number
National Cancer Institute Number

Physical and Chemical Properties of _____

Property	Value	Reference
Molecular weight		
Color		
Physical state		
Odor		
M lting point		
Boiling point		
Autoignition temperature		
Solubility		
water		
organic solvents		
Density		
Partition coefficients		
Vapor pressure		
Henry's Law constant		
Refractive index		
Flashpoint		
Flammability limits		
Conversion factors (e.g., ppm to mg/m^3 for gases and/or its inverse)		

Notes: 1. More than one value may be cited for any or all of the properties (see benzene example).
2. Other properties may be included in these tables, but the properties above must appear.
3. Use "unknown" and "not applicable" as appropriate.

rats in the 100 ppm group and 40 in the 200 ppm group; the male groups consisted of 39 and 38 animals at the 100 ppm and 300 ppm doses, respectively.") The degree of generalization may ultimately be determined by how much detail can be fit into 3 or 4 graceful sentences.

In some cases, a significant study may have been published (or otherwise made available) after the EPA's RfD Work Group considered a chemical. Discuss the new study in detail, as well as the study which is the basis for RfD. Insert a line of asterisks before and after the discussion of the new study to call the attention of ATSDR/EPA to the study. Remove the asterisks before printing the final copy.

For studies which are not key studies, more generalization is appropriate. The goal is to let the reader know how much support and/or conflicting evidence there is, and whether the support or disconfirming evidence is strong or weak. Condense this description of all other studies and results into a normal-sized paragraph. The generalizations you may be forced to make will probably not be entirely "clean": you may feel that you are combining different units, incomparable results, good and not-so-good studies.

It is assumed that there will be few, if any, studies of effects at the level of the entire organism, with the exception of decrease in body weight gain (DWG). Even this effect is likely to be noted only as part of a study of some other effect. Discuss DWG in the "General discussion" section for the main effect for which the study was conducted (e.g., carcinogenicity). If DWG is seen in studies of several different "main" effects, be sure to note which study provided the LOEL. Determine a NOEL, if possible. In short, treat DWG as an effect. Treat other organism-level effects in the same way as DWG.

For effects other than carcinogenicity, genotoxicity, and lethality, key studies will be used to derive the NOAELs and LOAELs that are graphed on the exposure route graphs in the Health Effects Summary, for each route and each duration of exposure (acute, intermediate, and chronic), for each species of test animal and for humans. Note that for systemic effects, several systems may have been studied in a species but only two systems at most per species will be displayed on the graph (one for the LOAEL and one for the NOAEL. Further guidance on key studies for the carcinogenicity, genotoxicity, and lethality sections are given in those sections below.

Other key studies may be identified which cover important toxicological information such as toxicokinetics or mechanism(s) of action. Describe in detail and discuss these key studies also, but do not graph them in the Health Effects Summary. Discuss the adequacy of such information in the section entitled "Adequacy of data base for other

information needed for risk assessment".

Discuss your choice of "adverse" effect in those cases where you judge the LOEL/NOEL to be different from the LOAEL/NOAEL.

****
* *
* Since the purpose of the document is to evaluate and *
* interpret as well as to describe, it is extremely important *
* that the studies be discussed in terms of what the *
* implications are for human health. It is also important to *
* try to explain apparently inconsistent results (for example, *
* between species) by taking into account other information *
* (e.g., pharmacokinetic data) that may not have been included *
* in the particular study at hand. These discussions should *
* constitute the bulk of the toxicity section. *
* *
****

Existing creditable reviews should be cited if they exist. There should be no hesitation about referencing original literature when a study is so recent that it has not been included in previous reviews, or when there are so few studies in a particular area that no review has been written.

This section is organized using the following scheme:

Effect
Route of exposure
Human vs. animal
Duration of exposure

A. Toxicokinetics

1. Overview

The toxicokinetics section must have an overview which briefly bridges the gap between exposure information and toxicity studies. In addition, this section should focus on similarities and differences in disposition from high vs. low level exposure, on similarities and differences in how humans and animals deal with this substance, and the implications that these similarities and differences have on the interpretation of non-human toxicity studies. Discuss the toxicity of metabolites, if relevant.

2. Absorption

a. Inhalation

i. Human

Order the discussion within this section by exposure duration (acute, intermediate, chronic) if there are enough data to do so. Headings do not need to be provided for exposure durations, however. These comments apply to all subsections in the absorption, distribution, metabolism, and excretion sections.

ii. Animal

b. Oral
   i. Human
   ii. Animal

c. Dermal
   i. Human
   ii. Animal

3. Distribution
...

Include storage sites, rates of deposition, and rates of release from storage.

4. Metabolism
...

The toxicity of metabolic products may be referred to briefly here, and more thoroughly in the appropriate toxicity sections.

5. Excretion
...

Include routes, rates, and products.

B. Toxicity

In the toxicity chapter, "Overview" sections are to contain a summary of results (in keeping with point 2 of the General guidance). "General discussion" sections are to contain evaluations, interpretations, and connections to other sections or chapters.

1. Lethality and decreased longevity
   a. Overview
   b. Inhalation
      i. Human (case reports)
      ii. Animal
   c. Oral
      ...
   d. Dermal
      ...

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The key study for lethality is the study which reports the lowest LD_{50} or LC_{50} for animals, or LD_{Lo} or LC_{Lo} for humans.

2. Systemic/target organ toxicity

Arrange the endpoints from most sensitive/significant to least sensitive/significant.

a. Overview
b. Endpoint 1
   i. Overview
   ii. Inhalation
      1) Human
      2) Animal

      Data in 1) and 2) are to be described in order of increasing duration of exposure (acute, intermediate, chronic) but without headings delineating exposure duration.

   iii. Oral
      ...
   iv. Dermal
      ...

   v. General discussion

      Discussion is strongly encouraged, and is to include considerations about mechanism of action, plausible explanations for differences between human and animal data, possible relationship between this effect and others, etc. Discuss in vitro studies, if any, here. This section should not be a restatement of the evaluations and interpretations found in the previous sections. This is the opportunity to describe the possible interconnections between effects that might otherwise seem discrete (e.g. for benzene, effects on hematopoiesis may be related to induction of chromosomal aberrations, both of which may be related to carcinogenesis). Statements of unproven hypotheses are allowed as long as they are referenced.

c. Endpoint 2
   ...

...

3. Developmental toxicity

a. Overview
b. Inhalation
   i. Human (epidemiological studies, case reports)
   ii. Animal
c. Oral
   ...
d. Dermal
   ...
e. General discussion

4. Reproductive toxicity
   ...

5. Genotoxicity
   ...

Describe the results of non-human genotoxicity studies in a table in the format described in the attached page. In vitro genotoxicity studies using human cell lines should also be described in this table. Generalize the results; do not list the results of each individual study. List results as +, -, or mixed, with the understanding that the + and - mean "predominantly" positive or negative, rather than "completely" positive or negative. Interpret the results in the text.

It is possible that there will be no key study for genotoxicity. However, if there is an epidemiology study which investigated genotoxicity, it should be described in detail. Any other genotoxicity study which is particularly important may also be discussed in detail.

ATSDR/EPA has distributed "genetic activity profiles" for certain chemicals for your consideration. They are not to be included directly in the toxicological profiles at this time.

6. Carcinogenicity
   ...

As stated previously in the guidance for the Health Effects Summary, "key studies" are those studies that illustrate best the nature of the adverse effects produced and the dose associated with those effects, both in animals and humans. There may be several key studies for cancer. Summarize the weight of the evidence for carcinogenicity here, in half a page or less, and describe the studies which contributed to the weight of the evidence.

Describe in detail at least the study on which the q_1^* is based (if it exists). If a significant new study

Genotoxicity of [Chemical Name]

In vitro
In vivo

Endpoint	Species (Test system)	Result with activation/ without activation	Reference
Gene mutation	[lower] ↓ phylogenetically [higher]		
Chromosomal aberration	[lower] ↓ phylogenetically [higher]		
Other effects			

Notes: 1. Make one table for in vitro results and a separate table for in vivo results.
2. Results for in vivo studies will not have the distinction "with activation/without activation".

is now available which was not available at the time the q_1^* was developed, discuss that study in detail also. Insert a line of asterisks before and after the discussion of the new study to call the attention of ATSDR/EPA to the study. Remove the asterisks in the final copy.

C. Interactions with other chemicals

Discuss studies that have investigated the effect that this chemical has when administered with other chemicals. Highlight effects that are not simply additive.

VII. Manufacture, Import, Use, Disposal

Keep the level of detail appropriate to an overview. The text should be brief (2-3 pages), and should summarize the most pertinent information. Restrict discussion to major use categories, import quantities, and domestic production processes and quantities unless other topics substantially affect human exposure and health. Present information in narrative form; extensive listing of tabular information is to be avoided. There should rarely be a need to cite specific information; a string of references that support general statements will usually be more appropriate.

A. Overview
Normally this will not exceed 1 paragraph.

B. Production

C. Import

D. Use

E. Disposal

VIII. Environmental Fate

The purpose of this section is to help the reader understand what happens to the chemical after release. The text should be succinct summaries of the data, focussing on media most important for exposure to humans. Less important media should be noted only. Transformation products should be identified for the important media. There should rarely be a need to cite specific information; a string of references that support general statements will usually be more appropriate. The section will normally be no more than 2-3 pages. Direct the reader to texts, reports, and other sources where a fuller discussion of the subject may be found.

A. Overview
This will normally be no more than 1 paragraph.

B. Releases to the environment

C. Environmental fate

IX. Potential for human exposure

In this section, use the information on environmental fate to give perspective on production volumes and release volumes. Note, however, that the toxicological profiles are not intended to be complete risk assessment documents.

A. Overview

This is the place to discuss how the volume of releases is modified by environmental fate processes to result in human exposure.

B. Levels monitored or estimated in the environment

Provide ranges of concentrations; indicate "usual" values (also as a range, rather than as a specific mean or median). Identify categories with unusually high levels.

1. Air
2. Water
3. Soil
4. Other (food, cigarettes, etc.)

C. Occupational exposures

D. Populations at high risk

Discuss populations that have unusually high exposure, and populations that are unusually susceptible.

X. Analytical methods

The purpose of this section is to show the reader, very briefly, the methods that are available for detecting and/or measuring the chemical in environmental media and in biological samples. It is intended to serve as a quick reference for state and local health officials who need to know which samples are the best to take in order to measure exposure or monitor effects. It is not intended to be a full description of the methods, or a recommendation for using specific methodologies.

Identify the most commonly used methods. Show which methods are the most sensitive. Indicate which methods have been standardized by ASTM or promulgated by federal agencies. Discuss important idiosyncracies of the method, particularly

as they apply to this chemical. (For example, discuss specificity, reproducibility, accuracy, the reliability of the method for showing past exposure, peculiarities of sample stability, etc.) Note where methods are lacking for important environmental media. Include methods for measuring key metabolites, if that is an acceptable way of measuring exposure. Direct the reader to references where a fuller description of the methods can be found.

Refer the reader to descriptions of sample preparation techniques for biological samples, but do not describe the techniques in detail.

Use tables (format attached).

A. Environmental media
   1. Air
   2. Water
   3. Soil
   4. Food

B. Biomedical samples
   1. Fluids/exudates
   2. Tissues

XI. Regulatory and advisory status

All applicable national and state regulations and guidelines should be included, whether a number or not. (E.g., include the listing of a chemical as a Hazardous Air Pollutant under Section 112 of the Clean Air Act.)

Do not include international regulations, either from individual countries or international organizations. However, do include guidance from the World Health Organization.

A. International (World Health Organization)
B. National
   1. Regulations
   2. Advisory guidance

Check to see if any of the following regulations or guidelines apply to the chemical in question. This list may not be exhaustive; you may add to it.

NATIONAL
MEDIA SPECIFIC
a. AIR

AGENCY	STD/ADV
OSHA	TLV-TWA (PEL)
"	TLV-Ceiling (PEL)
"	IDLH
NIOSH	TLV-TWA

Analytical Methods
Biological Samples

Sample matrix	Sample prep.	Analytical method	Detection limit	Accuracy	References
Blood/plasma	[?]	GC/MS	<0.5 ppb	5% CO at 2 ppb	Antoine et al. 1986

Include methods for measuring key metabolites if that is an acceptable way of measuring exposure.

Use asterisks to the left of sample prep/detection method pairs to denote common methods of measuring exposure.

"	TLV-Ceiling	
"	IDLH	
ACGIH	TLV	
"	STEL	
EPA	q_1^* (inhalation)	
"	NAAQS	

b. WATER

AGENCY	STD/ADV
EPA	1-day Health Advisory
EPA	10-day Health Advisory
EPA	Longer-term Health Advisory
EPA	Lifetime Health Advisory
EPA	MCL --- (CHECK WHICH OF THESE
EPA	SMCL --- ARE STILL APPLICABLE)
EPA	MCLG
EPA	AWQC
NAS	SNARL

c. FOOD

AGENCY	STD/ADV	
FDA	Action levels.	(Note: List only range of various action levels for food. Refer reader to FDA documents for specifics for each food type.)
EPA	Tolerances	(Note: List only the range of the tolerances for agricultural products.)

NON MEDIA-SPECIFIC

AGENCY	STD/ADV
EPA	q_1^* (oral)
EPA	RfD (oral)

CATEGORIES

AGENCY	STD/ADV
IARC	GROUP (Cancer ranking)
EPA	GROUP (Cancer ranking)
ACGIH	GROUP (Cancer ranking)
EPA	Hazard ranking

OTHERS

AGENCY	STD/ADV
EPA	Reportable Quantity
CPSC	Consumer product limits
ACGIH	Biological Exposure Index

3. Data analysis
   i. Reference dose

If a "reference dose" (RfD) has been derived by the EPA, discuss its derivation here. State which study and which effect was used to derive the RfD. Note which uncertainty factors were used. Show the calculation. Refer the reader to [U.S. EPA 1987. Reference Dose (RfD): Description and use in health risk assessments. Appendix A of the Integrated Risk Information System (IRIS)] for more information about what RfDs mean and how they are derived. A copy of the Appendix is attached to this Guidance to Contractors. Refer also to the EPA document which describes the derivation of the RfD for this particular chemical. The current list of chemicals for which reference doses have been derived can be obtained from the Office of Health and Environmental Assessment, Office of Research and Development, EPA.

Use the level whose derivation is shown here in the Health Effects Summary graphs described in Section IV.B.1.(2)(c).

ii. Carcinogenic potency

1) q_1^*

State details of the specific data used: which study, which tumor site in which sex, etc. Describe the method of combining results from several studies, if applicable. Refer the reader to a reference (which ATSDR/EPA will provide) for a fuller discussion of how q_1^*s are derived. Include the reference for the EPA document in which the q_1^* is derived. Include a qualitative statement of the IARC classification if it exists, and a qualitative statement of the EPA carcinogenicity classification if it exists. Include one sentence explaining what that classification means.

2) Other

If other federal agencies have derived estimates of carcinogenic potency, describe them here, to the same degree of detail that was used for q_1^*s.

C. State
1. Regulations
2. Advisory guidance

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XII. References

In the reference list, use asterisks in the left margin to denote key studies. Use daggers in the left margin to denote Confidential Business Information. Footnote the meaning of these symbols on the bottom of the first page of the reference list.

SAMPLE SECTIONS WRITTEN FOR BENZENE

CONTRACTORS:

THE MODEL DOCUMENT ON BENZENE WHICH FOLLOWS IS NOT A COMPLETE DOCUMENT. IT IS BEING PROVIDED ONLY TO GIVE YOU AN IDEA OF THE AMOUNT OF DESCRIPTION WHICH IS APPROPRIATE FOR THE TOXICOLOGICAL PROFILES. YOU ARE EXPECTED TO PROVIDE A GREATER DEGREE OF ANALYSIS AND INTEGRATION OF INFORMATION THAN IS DISPLAYED HERE.

Examples are not given for every section.

Not all of the examples show the proper degree of referencing.

Chapter II, the Public Health Statement, can be regarded as nearly complete. It lacks only the final graphs. The format of the graphs has already been given in the Specific Guidance section of this package.

Chapter V, Toxicological Data, is the most incomplete, both in terms of the numbers of sections missing, and in terms of the level of analysis shown.

PUBLIC HEALTH STATEMENT FOR BENZENE

WHAT IS BENZENE?

Benzene is a naturally occurring substance. It can be produced by volcanoes and forest fires, and is present in many plants and some animals. Most of the benzene we use comes from coal and oil. As a pure chemical, benzene is a clear, colorless liquid. In industry, the main use of benzene is to make other chemicals, but it is also used to make some types of plastics, detergents, pesticides, and as an additive in gasoline.

HOW MIGHT I BE EXPOSED TO BENZENE?

The two main sources of exposure to benzene are environmental and occupational.

Environmental

- Gasoline filling stations and vehicle exhaust fumes are the greatest single environmental source of benzene exposure. Other sources include:
- Underground storage tanks that leak,
- Wastewater from industries that use benzene,
- Poorly maintained toxic waste sites, and
- Chemical spills.
- Also, benzene has been found in the ground water adjacent to landfills containing benzene, and
- In food grown on benzene-contaminated soil.

Some consumer products such as:

- Glues,
- Adhesives,
- Household cleaning products,
- Paint strippers, and
- Some art supplies contain benzene.
- Cigarette smoke also contains benzene.

Occupational

By far the greatest exposures to benzene occur in the workplace. Benzene is used in the:

- Rubber industry,
- Oil refineries,
- Chemical plants,
- Shoe manufacturing, and
- Gasoline storage, shipment, and retail gas stations.

Most of what is known about how benzene affects health is based on studies of workers.

HOW DOES BENZENE GET INTO MY BODY?

- Because benzene evaporates very quickly, the most common exposures to benzene come from breathing air containing benzene.
- It is less common to eat or drink benzene, but is possible because very small amounts of benzene are found in some food products such as boiled eggs and canned beef, and in drinking water contaminated by hazardous wastes.
- Although benzene penetrates the skin easily, it is rare to come into contact with liquid benzene, and exposures through the skin are not likely in day-to-day life.

HOW CAN BENZENE AFFECT MY HEALTH?

Benzene is clearly toxic. How benzene affects your health would depend on how much you are exposed to and for how long.

Brief Exposures at High Levels

The main effects of short-term exposure to high levels of benzene are drowsiness, dizziness, and headaches. These symptoms disappear after exposure stops.

Long-Term Exposures at Varying Levels

Long-term exposures to benzene may affect normal blood production. Some workers exposed to high levels of benzene over a long period of time have developed leukemia (cancer in the white blood cells). Other effects include anemia and internal bleeding. There is even evidence that suggests benzene is toxic to the body's natural defense system (immune system), increasing the chance for infections.

There is also some evidence that benzene may be associated with spontaneous abortions and miscarriages in pregnant women. Animal studies indicate effects on unborn test animals such as low birth weight and delayed bone production. The evidence for human reproductive effects, however, is too limited to establish a clear association.

IS THERE A MEDICAL TEST TO TELL WHETHER I HAVE BEEN EXPOSED TO BENZENE?

Benzene can be measured in the blood and breath. The body changes benzene to a chemical called phenol, which can be measured in urine.

HOW MUCH BENZENE IS HARMFUL?

The graphs below show the relationship between exposure to

benzene and known health effects. In the first graph labeled "Health Effects from Breathing Benzene," the scale on the 1 ft represents exposure. Exposure here is measured in parts of benzene per million parts of air (ppm). The three bars or columns represent the known health effects of benzene exposure. Those health effects followed by an asterisk or star are based on animal studies, all others are known health effects to humans.

The first column, called "Short-Term," means the known health effects from exposure to benzene for less than two weeks. Th second column, "Long-Term," means known health effects for exposures lasting over two weeks.

In the second graph, the same relationship is represented for the known health effects from eating or drinking foods containing benzene. The last graph shows the same for absorbing benzene through the skin.

WHAT RECOMMENDATION HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

Because most benzene exposures occur in the workplace, the government's emphasis thus far has been to protect workers. And because benzene has been shown to cause leukemia, and any exposure involves some risk, the occupational exposure standards for benzene are very strict.

The National Institute for Occupational Safety and Health (NIOSH) has recommended an occupational exposure limit for benzene in air of 1 part of benzene per 1 million parts of air (ppm) for an 8-hour workday, 40-hour workweek. The Occupational Safety and Health Administration's (OSHA's) legally enforcible limit is 10 ppm for the same time period.

The environmental criteria for benzene exposure are more difficult to set. This is because exposures are not likely to be from benzene in the air, but from benzene in the drinking water or in the foods we eat. The Environmental Protection Agency (EPA) has developed guidelines for what they consider permissible levels of benzene in drinking water. The EPA guidelines are:

- 0 parts of benzene per billion parts of air (ppb) as a goal, based on benzene's ability to cause leukemia.
- 5 ppb as a practical limit in municipal drinking water supplies.
- 233 ppb as a level above which benzene in water may cause health effects if drunk for 1 day.

HEALTH EFFECTS SUMMARY

A. Introduction

[Standard language will be provided by ATSDR/EPA.]

B. Levels of significant exposure

[Standard language will be provided by ATSDR/EPA to be included here.]

1. Key studies and graphical presentations

a. Inhalation exposure
Hematopoietic suppression and the induction of cancer seem to be the key endpoints for inhalation exposure to benzene for long-term exposure, while effects on the central nervous system are the main concern for short-term exposures to high levels.

1) Lethality - Death in humans is anticipated in humans after exposure to about 20,000 ppm for 5-10 minutes, while LC50 values about 10,000 ppm have been demonstrated for rats and mice.

No acute exposure-induced symptoms occur in humans following exposure to 25 ppm.

2) Developmental toxicity

3) Heritable mutations

4) Reproductive toxicity

5) Systemic toxicity
There are few target organ effects following acute exposures. There is ample evidence in humans and animals, however, of adverse effects on the hematopoietic system following intermediate and chronic exposures. Decreases in all the formed elements -- red and white cells and thrombocytes -- may occur alone or in combination (pancytopenia). In rats exposed for 126 days, significant leukopenia occurred at exposures greater than 61 ppm; lowest effect levels were 44 ppm; and 31 ppm constituted no-observed-adverse-effect level. In humans, pancytopenia has been observed following long-term exposures to benzene at levels in excess of 10 ppm, ranging up to about 1000 ppm. Effects on the immune system may also be sensitive endpoints of benzene toxicity; further study might contribute to an

understanding of this potential.

6) Carcinogenicity
Studies in humans and animals demonstrate the ability of benzene to produce cancer via inhalation. In humans exposed to levels of benzene in excess of about 10 ppm for long periods of time, a series of steps seem to characterize the carcinogenic process: first there is depression of formed elements in the blood, followed by pancytopenia and bone marrow shut down, and finally the development of acute myelogenous leukemia (and possibly other tumors). Using the human data and a linear extrapolation of risks, the combined risk estimate of benzene is estimated to be 2.6×10^{-2} for exposure to benzene at 1 ppm.

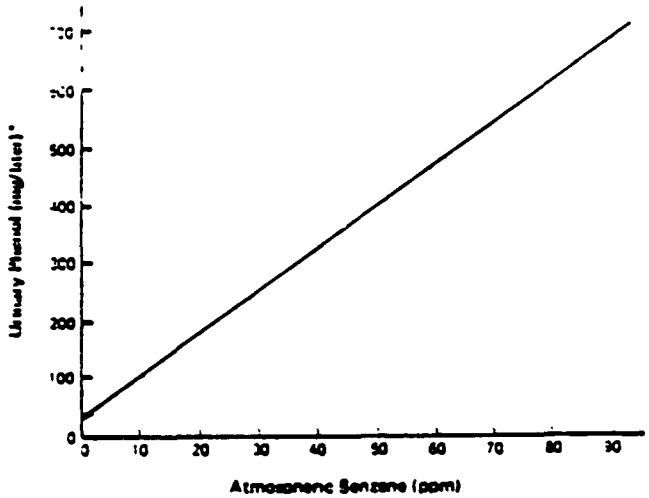
Animal inhalation studies also illustrate the carcinogenic potential of benzene....

b. Oral exposure

etc.

2. Biological Monitoring

Currently available biological monitoring techniques are summarized in Chapter X. Urinary phenol measurement (others if appropriate) is commonly used. The sensitivity, specificity, and method reliability and reproducibility are reviewed in Chapter X. The following graph plots exposure levels (inhalation-ppm benzene) by mg phenol/liter measured in urine (NIOSH 1974).



Urinary phenol may originate from non-benzene sources such as diet or pharmaceuticals as discussed in Chapter VI; therefore this graphic relationship may

not be valid at levels below ____. At levels abov 5 ppm, daily benzene exposure and urinary phenol may be approximately related, based on the NIOSH 1974 data, as follows:

mg phenol/liter urine = 26.6 + [(7.2) (ppm benzene in air)]

No similar relationships have been developed for oral or dermal exposure to benzene, and no correlation between urinary phenol and any endpoints of toxicity have been made.

3. Environmental levels

[This section is not being supplied for the benzene model.]

IV. Chemical and Physical Information

A. Chemical Identity

The chemical formula, structure, synonyms, and identification numbers for benzene are listed in Table 1.

B. Physical and chemical properties

Important physical and chemical properties of benzene are given in Table 2.

V. Toxicological Data

[The following guidance suggests th kind of analysis that would be expected in the benzene document.]

A. Toxicokinetics

2. Absorption

a. Inhalation

i. Human: Expand definition and/or discussion regarding meaning of respiratory absorption (uptake); e.g., uptake equals inhaled concentration minus exhaled concentration divided by exhaled concentration. Similarly expand discussion regarding respiratory retention.

ii. Animal: Direct discussion to emphasize those animal data which support or add clarification to the human data.

b. Oral

General: Although definitive scientific data and epidemiological studies are not available on oral absorption of benzene, case studies of accidental or intentional poisoning indicate that benzene is readily and rapidly absorbed by the oral route. This should be detailed and discussed.

c. Dermal

General: In reference to dermal absorption in humans, discuss absorption of both benzene vapor and liquid. Assess the importance (quantitative relationship) of these exposures compared to inhalation. Since cutaneous physiology is so much different in animal species compared to humans, animal data should be discussed only in regards to its support of human data.

3. Distribution

General; both human and animal: Discuss and emphasize data which keys on distribution to sites of action; e.g., the CNS, bone marrow. This may also require a tie-in with the following Section on Metabolism.

4. Metabolism

General: Briefly detail metabolic pathways, intermediates and products. Discuss briefly sites of metabolism, both primary and secondary (Liver, bone marrow) and discuss their importance. Emphasize importance of toxic intermediates. Also describe and discuss alterations in metabolism, particularly those which may

substantially impact or affect the ultimate toxicity of benzene. More specifically, indicate that benzene induces or increases its own metabolism, thereby increasing the rate of toxic metabolite formation, and thus its own toxicity. Other compounds such as ethanol do the same. Conversely, compounds such as aniline and toluene inhibit benzene metabolism, thus reducing benzene toxicity. Such information will be important for the following Toxicity Section, particularly in regards to chronic benzene exposure and/or benzene exposure in combination with other substances commonly found at Superfund Sites.

5. Excretion

General: List all routes (exhaled air, urine, bile, feces), excretion products, relative amounts and relative importance of each route. Discuss those excretory products which may be useful for assessing exposure.

B. Toxicity

General Comments

1. Overview

- emphasize that benzene per se is not the primary toxicant (except at extremely high, narcotic doses), but that several metabolic intermediates and end products have been identified as the primary toxicants
- indicate that since benzene must be absorbed, distributed and metabolized in order to exert toxicity (other than acute CNS depression at extremely high doses), route of exposure is important only in regards to the ultimate magnitude of effect, not the type of effect.
- discuss importance of repeated benzene exposure (e.g., the potential for benzene inducing/increasing its own toxicity) relative to the potential for toxicity from chronic benzene exposure.

2. Specific Exposure Route/Endpoint Toxicity

- discuss mechanisms of toxicity studies relevant to each route/endpoint, particularly those which provide information that expands or clarifies the understanding of that particular toxic endpoint.
- in vitro data, if it substantially adds

to or clarifies specific endpoint toxicity, should also be discussed.
- other toxicity endpoints not specified, e.g., immunotoxicity, should also be discussed if relevant and meaningful information is available.

3. Interactions with Other Chemicals
   - detail and discuss interactions with other chemicals which either increase or decrease the toxicity of benzene, with particular emphasis on those chemicals which may be commonly found in association with benzene at Superfund Sites.

     Such information may also be relevant to discussions in Section IX. D., "Potential for Human Exposure, Populations at High Risk." More specifically, chemicals which induce benzene metabolism (e.g., ethanol, phenobarbital) may reduce susceptibility to acute CNS toxicity/lethality, whereas these same chemicals may increase susceptibility to the toxic manifestations of chronic benzene exposure.

[The following sections should be used mainly as a guide to the amount of description, not analysis, that should be present in the benzene example.]

A. Toxicokinetics

1. Overview

Benzene is volatile and lipid-soluble, and can be absorbed by all exposure routes: oral, inhalation and dermal. Once benzene is absorbed and in the blood, it is widely distributed to tissues, the relative uptake dependent on the perfusion rate of the tissue by blood. For example, accumulation in fat is slow because of low perfusion, but the total potential uptake is high in these tissues because of the lipid solubility of benzene.

Available data in both animals and humans indicate that benzene must undergo metabolic transformation via a variety of routes to exert its toxicity. Metabolism of benzene occurs primarily in the liver where it is converted to benzene oxide, a highly reactive and unstable intermediate which forms phenol. Other metabolites include catechol, hydroquinone, and conjugated phenolic compounds.

Benzene is excreted both unchanged via the lungs and as metabolites in the urine. Phenol and its conjugated sulfates, esters, and glucuronides are excreted in the urine, with unconjugated phenol comprising the major urinary metabolite. The rate and percent of excretion via the lungs is dependent on exposure dose and route.

2. Absorption

a. Inhalation

i. Human

Data regarding the inhalation absorption of benzene by humans consistently suggest an absorption factor of 40 to 50% of a continuous dose of 50 to 100 ppm for several hours (IARC 1982, Nomiyama and Nomiyama 1974, Sato and Nakajima 1979, Snyder et al. 1981, Teisinger et al. 1985, Hunter 1968, Hunter and Blair 1972, Srbova et al. 1950). Absorption is greatest in the first 5 minutes, and reaches a constant level somewhere between 15 minutes (Srbova et al 1950) and 3 hours (Nomiyama and Nomiyama 1974a and b) of continuous exposure.

ii. Animal

Inhalation studies in dogs, rabbits, mice, and rats confirm that benzene is rapidly absorbed through the lungs, although retention is not complete (EPA 1985a, IARC 1982b). The percentage retained after inhalation appears to be similar to that of man -- approximately 10% to 50% in rats and mice (Sabourin et al. 1987).

B. Toxicity

2. Systemic/organ toxicity

a. Overview

Evaluation of the existing toxicological data base for benzene suggests that hematopoietic effects may be the most sensitive non-cancer endpoint of toxicity for this substance. However, very recent studies in animals suggest that the immune system may also be quite susceptible to perturbation following benzene exposure, and is, thus, deserving of continued evaluation.

Central nervous system depression and narcosis have been demonstrated to be the critical effects observed during acute, high level exposure to benzene in humans and animals. Additional effects observed include cardiovascular, ocular, dermal, hepatic and renal.

b. Hematopoietic effects

i. Overview

...

ii. Inhalation

1) Human

As described below, exposure to benzene, principally in the occupational setting, has been associated with the production of acute myelogenous leukemia. There also is a strong link between benzene exposure and other tumors of the hematopoietic system.

Benzene also induces a broad spectrum of other, non-cancer hematological effects, generally described as pancytopenia (reviewed in Goldstein and Laskin, 1977; U.S. EPA, 1978; U.S. EPA, 1980). While none of the published studies report actual measurements of benzene in the air, estimated exposures at which effects were noted range from 10 (a nominal LOAEL) to >1000 ppm.

For example, in 332 rotogravure workers exposed to benzene for 3-5 years at levels ranging from 11 to 1060 ppm (median = 132 ppm), anemia, macrocytosis and thrombocytopenia were observed in 65 individuals (Greenburg et al., 1939; Goldwater 1941; Goldwater and Tewksbury, 1941). Also,in a Korean study reported by Chang (1972) and summarized in U.S. EPA (1978), of 119 workers exposed to benzene, 21 developed anemia, 2 developed leukopenia and 5 developed both. While the authors proposed a "threshold" of 10 ppm benzene, insufficient data were presented to ascertain adequately actual exposure levels in the workplace.

Doskin (1971), as cited in U.S. EPA (1978), evaluated 365 workers in a chemical factory with estimated benzene exposure levels ranging from 10-40 ppm for hematological disorders. The number of hematological abnormalities decreased over a three year study period concomitant with a decrease in estimated benzene exposure levels. In the first year, 40% of the workers developed hematological disorders, principally thrombocytopenia, but also anemia.

2) Animal

No data describing adverse hematological effects following acute exposure was found in the literature.

Wolf, et al. (1956) exposed groups of 10-25 male and female Wistar rats and 5-15 male guinea pigs to 88 ppm benzene and 1-2 male rabbits to 80 ppm benzene 7 hr/day, 5 days/week for 204-269 days. Leukopenia and other evidence of adverse hematopoietic effects were seen in all species. The 88 ppm level is considered to be a LOAEL.

Deichmann (1963) exposed groups of 40 Sprague-Dawley rats/sex to 0, 15, 31, 44, 47, 61 or 831 ppm benzene 5 or 7 hours/day, 5 days/week for 88-126 days. Significant leukopenia, but no bone marrow alterations, was observed > 61 ppm for 126 days (FEL). Slight to moderate leukopenia was observed at the 44 ppm dose

(LOAEL). No adverse effects were observed at 31 ppm (NOAEL).

The hematotoxic effects of benzene were studied in C57Bl/BN6 mice exposed to concentrations of 10, 25, 100, 300 or 400 ppm, 6 hours/day, 5 days/week for up to 16 weeks, then observed over their lifetime (Cronkite, et al. 1985). [Must read original article to identify potential NOAELs, LOAELs and FELs].

iii. Oral

1) Human

No data describing adverse hematopoietic effects in humans following oral exposure of any duration were found in the literature.

2) Animals

No data describing adverse hematological effects following acute exposure were found in the literature.

Wolf, et al. (1956) dosed groups of 10 female Wistar rats with 0 (20 animals), 1, 10, 50 or 100 mg/kg benzene in olive oil by gavage 5 days/week for 187 days. No effects were observed at the 1 mg/kg/day level; however, very slight leukopenia was observed at the 10 mg/kg/day level, and leukopenia and erythrocytopenia were reported at both the 50 and 100 mg/kg/day doses. A NOAEL of 1 mg/kg/day, a LOAEL of 10 mg/kg/day and a FEL of 50 mg/kg/day can be identified for this study.

Two-year carcinogenicity bioassays were conducted by NTP (1986) in which F344N rats and B6C3F1 mice of both sexes received benzene in corn oil, 5 days/week for 103 weeks. In rats, lymphoid depletion of the splenic follicles (both sexes) and thymus (males only) was observed at all doses (50, 100 or 200 mg/kg for males and 25, 50 or 100 mg/kg for females). In both sexes of mice, bone marrow hematopoietic hyperplasia was observed at all doses (25, 50 or 100 mg/kg). All doses can be considered FELs.

iv. Dermal

No adequate data describing adverse hematopoietic effects in humans or animals following dermal exposure of any duration were found in the literature.

c. Nervous system effects

i. Overview

...

ii. Inhalation

etc.

d. Cardiovascular effects

i. Overview

ii. Inhalation

etc.

etc.

6. Carcinogenicity

a. Overview

Benzene is carcinogenic in humans via inhalation, and in animals by inhalation and gavage. Data are insufficient to make direct conclusions about carcinogenicity via ingestion in humans, or by the dermal route in humans or animals. However, it is reasonable to assume that benzene can cause cancer in humans if ingested. The risk of cancer after dermal exposure is probably less than from other routes since absorption through the skin is low. Summaries and reviews of the animal studies can be found in IARC 1982, Van Raalte and Grasso 1982, NTP 1986, and NRC 1986. Studies reviewed include both positive and negative findings.

b. Inhalation

i. Human

...

ii. Animal

Animal studies of the carcinogenicity of benzene via inhalation have generally been positive. Table __ presents the details of the key inhalation study for benzene. This study is the most appropriate inhalation study because _____. Other inhalation studies are described in Table __.

The finding of cancer in animals after inhalation of benzene supports the conclusion that benzene is carcinogenic in humans via inhalation. Inhalation studies are particularly important because this is the most common exposure route for humans.

c. Oral

i. Human

No studies are available.

ii. Animal

Benzene has been shown to cause cancer in animals after oral administration (see the reviews cited above). Doses tested range from 25 to 500 mg/kg given 5 days/week to rats and mice by

gavage. Tumors at various sites have been observed, in addition to hematopoietic neoplasms. Oral studies have not consistently shown leukemias, but the reason and significance of this is unknown.

Although benzene may be ingested by humans in food or water, caution should be used in extrapolating from the oral studies in animals to the human situation. It is conceivable, for example, that the large, relatively infrequent doses given to experimental animals causes effects through metabolic routes that are not operative when multiple low doses (such as occur when humans eat or drink) are used.

d. Dermal

i. Human

No studies are available.

ii. Animal

IARC (1982) cited 6 investigations in which there was no indication that topical application of benzene induces tumors. These studies were actually studies of other chemicals in which benzene was used as the vehicle control. Several of these studies were limited by the fact that not all possible tumor sites were examined histologically. Also, the negative results may reflect the poor absorption of benzene across the skin (see absorption section) rather than a lack of carcinogenic potential. These studies are not considered to be adequate studies of the carcinogenicity of benzene and are not described in Table __.

XI. Regulatory and advisory guidance
B. National
3. Data analysis
i. Reference dose

EPA has proposed an oral RfD of 0.0007 mg/kg/day using the Wolf et al. (1956) study, using leukopenia as the adverse effect of concern. The RfD_o is calculated as follows:

$$RfD_o = \frac{(1 \text{ mg/kg/day})\ (5/7)}{(100)\ (10)} = 0.0007 \text{ mg/kg/day}$$

Where: 1 mg/kg/day = NOAEL

5/7 = Conversion for 5 day/week dosing regimen to continuous 7 day/week exposure

100 = uncertainty factor appropriate for use with NOAEL from animal data (inter- and intra-species extrapolation)

10 = uncertainty factor for use of data from less-than-lifetime study

ii. Carcinogenic potency

The U.S. EPA (198_) has developed a quantitative unit cancer risk estimate based upon three sets of data described in epidemiologic studies of workers exposed to benzene vapors (Aksoy, et al. 1974, 1977, 1978; Infante, et al., 1977; Ott, et al., 1978). Using an average derived from the application of several mathematical models, a combined risk estimate of 2.6 x 10^{-2} was determined for exposure to benzene at 1 ppm.

[This last paragraph must be confirmed by re-reading the document received from CAG recently].

Benzene has been classified by IARC (1982) in Group 1: Human carcinogen.

Benzene has been classified by EPA in Group A: Human Carcinogen (U.S. EPA, 1986 (FR notice)). This category is for agents for which there is sufficient evidence to support the causal association between exposure to the agents and cancer.

ATTACHMENTS

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

DISCLAIMER

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, (in this document the term "systemic" refers to an effect other than carcinogenicity or mutagenicity induced by a toxic chemical) 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.)

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. (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 ration of the toxic dose to the theraputic dose, and to avoid the use of the value-laden term "safety").

Section IV examines how these new concepts can be applied in reaching risk management decisions, whil 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.

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 appropriat "no-observed-adverse-effect-level (NOAEL)" by a "safety factor (SF)" as follows:

ADI (human dose) = NOAEL (experimental dose) / SF (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.

(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.)

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 a 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.

While the original selection of SFs appears to have been rather arbitrary (Lehman, A.J. and Fitzhugh, O.G.(1954). Association of Food Drug Officials. USQ Bulletin 18:33-35.), subsequent analysis of data as reviewed by Dourson and Stara (1983) lends theoretically (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" lev l 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 which is 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 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.

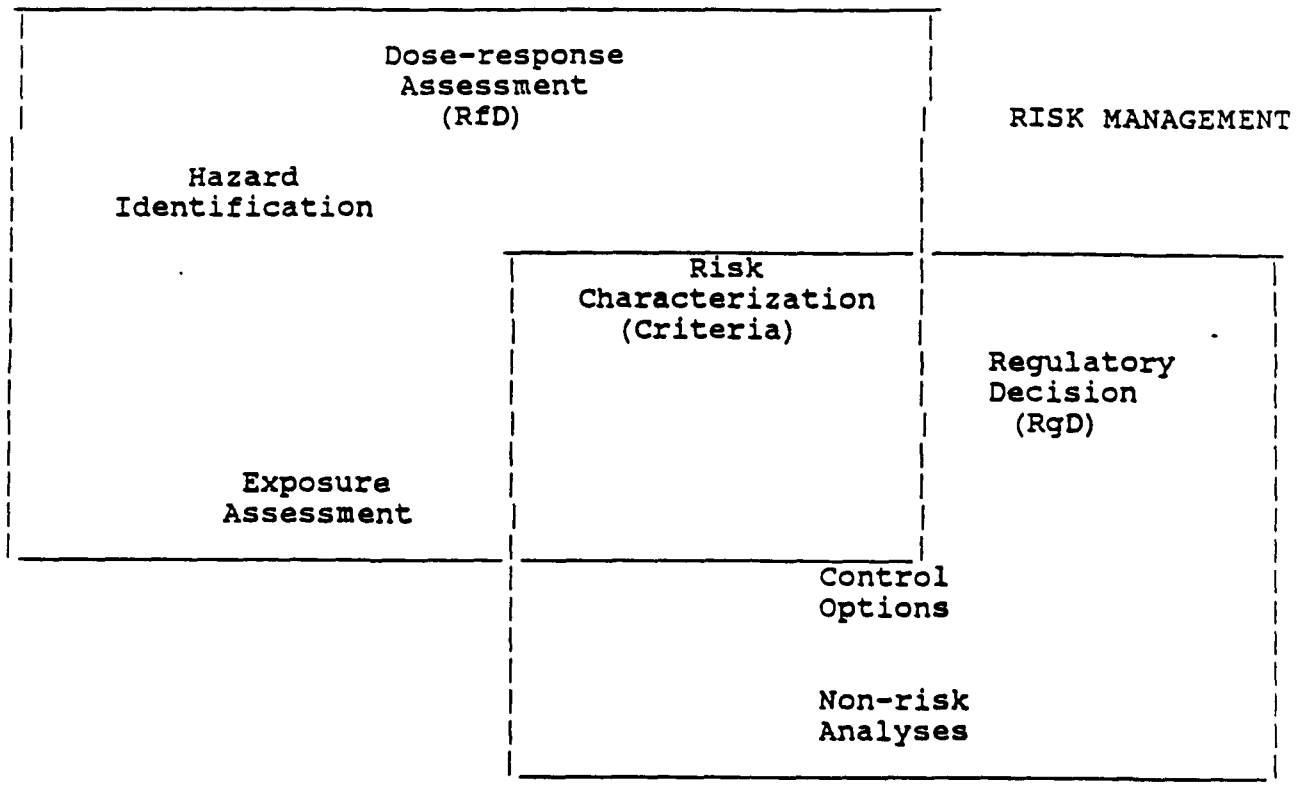
Such practices, as employed by a number of scientists in different programs, exercising their best scientific judgment, have in many cases resulted in different ADIs for the same chemical. The fact that different ADIs were generated (e.g., by adopting different SFs) can be a source of considerable confusion 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 U.S. 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?"

RISK ASSESSMENT



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.

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. 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. Supportive studies

Supportive 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 non-humans. 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 supportive 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 which 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. 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" 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-fold) 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.

TABLE A-1. GUIDELINES FOR THE USE OF UNCERTAINTY FACTORS

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 (MFO 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 not explicity treated above; e.g., the completeness of the overall data base and th number of species tested. The default value for the MF is 1.

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

("Uncertainty factor" is the new description applied to the term "safety factor". 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 judgments regarding scientific uncertainties n t covered under the standard UF, such as the completeness of the overall data base and the number of animals in the study.)

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 or greater) 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." (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 th 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 r ader 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 the 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)", 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:

MOE = NOAEL (experimental dose) / EED (human dose) (3)

In parallel to the statements above on EED and RfD, the risk assessment should contain a discussion of the assumption underlying the estimates of the RfD and the degree of possible conservatism of the UF and MF factors. 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, non-risk 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 non-technical 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 which protect the public "to the xtent 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:

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

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:

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

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. above. 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 Planing 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 1 ss-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 statistically or biologically significantly differences between treated and control animals:	NOEL
5	2% decrease* in body weight gain (not considered to be of biological significance). Increased ratio of liver weight to body weight. Histopathology indistinguishable from controls Elevated liver enzyme levels	NOAEL
25	20% decrease* in body weight gain Increased* liver weight to body weight Enlarged, fatty liver with vacuole formation Increased* liver enzyme levels	LOAEL

* = 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 non-risk factors, in reaching a decision on the regulatory dose (RgD).