ENDANGERMENT ASSESSMENT HANDBOOK

Errata

Certain changes have been made to the draft Endangerment Assessment Guidance since this Handbook was written. These changes should be kept in mind while reading the Handbook, especially Sections 2.0 and 4.0:

- The endangerment assessment is not necessary to support cost recovery for CERCLA Section 104 remedial actions.
- The endangerment assessment is normally developed as part of an enforcement lead RI/FS.
- In evaluation of public health impacts, human health standards and criteria should be included.
- At remedial sites subsequently targeted for CERCLA Section 106 or RCRA Section 7003 enforcement action, all of the elements of an endangerment assessment will be provided by completing the contamination assessment, public health assessment and environmental assessment during the RI/FS process.

Specific changes to this Handbook include the following:

1. Page 4-11, Section 4.3.2, Paragraph 2

   Delete the third sentence which reads: "Intermedia transport processes . . . characterized in the Level 1 endangerment assessment."

   Delete the last sentence which reads: "An overview . . . Figure 4-2."

2. Page 4-13, Figure 4-13

   Change the title of the figure to read: "Figure 4-2 Overview of Environmental Fate and Transport Analysis for Level 2 Endangerment Assessments."

3. Page 4-14, First Line

   Add this sentence following the first line: "An overview of the environmental fate and transport analysis for Level 2 endangerment assessments is shown in Figure 4-2."

4. Page 4-14, First Full Paragraph, First Sentence

   Add this sentence after the first full sentence: "Intermedia transport processes (e.g., adsorption, volatilization, infiltration, bioaccumulation) and intramedia transformation processes (e.g.,

photolysis, hydrolysis, oxidation and biodegration) which potentially affect migration of the contaminants of concern are identified and characterized in the Level 2 and 3 endangerment assessments."

5. Page 4-22, Section 4.4.1, Paragraph 2

Add these sentences at the end of the second paragraph: "How extensive the toxicity profiles are will depend on the amount of time available to prepare the profile and the level of detail of the endangerment assessment. Thus, the toxicity profiles prepared for Level 1 endangerment assessments may not be as extensive as the profiles prepared for Level 2 or 3 endangerment assessments. A Level 1 toxicity profile would include, at a minimum, identification of applicable standards and guidelines for the contaminants of concern. Table 4-8 provides guidance for the preparation of toxicity profiles for endangerment assessments of varying levels of detail."

6. Page 4-28, Table 4-8

Change Step 2.1 to read: "Estimate 'Acceptable Levels'"

7. Page 4-39, Section 4.5.2, Paragraph 1

Change the first sentence to read: "One method that toxicologists use to characterize noncarcinogenic risks involves comparing the expected exposure level (E) to the "acceptable level" (AL) (USEPA 1985a). This proposed method has not been adopted as official EPA policy."

8. Page 4-39, Section 4.5.3, Paragraph 2

Replace the final sentence ("As within . . . risks increases.") with the following: "This is an oversimplification of the procedures used to estimate noncarcinogenic risks associated with exposure to multiple chemicals. There are many assumptions made in developing these calculation procedures which the user should be aware of. These assumptions are detailed in the mixture guidelines in Appendix 3 of this Handbook (USEPA 1985a)."

9. Page 4-40, Paragraph 2

Add this sentence at the end of the second paragraph: "Qualitative risk characterization methods include a comparison of actual or potential exposure levels to background levels, analytical detection limits, technically based criteria and standards and health based criteria and standards. Quantitative risk characterization methods include all of the above in addition to a quantitative estimation of the actual or potential risks at the site."

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THE ENDANGERMENT ASSESSMENT HANDBOOK

Prepared For

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office Of Waste Programs Enforcement
Washington, D.C. 20460

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ENDANGERMENT ASSESSMENT HANDBOOK

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August, 1985

DISCLAIMER

This document has not undergone final review within EPA and is for internal Agency use/distribution only.

There has been an EPA Workgroup review of the development of this document prior to this draft. This final draft is being distributed to EPA personnel for a six-month review period after which changes will be made based on the comments received.

FOREWORD

This Endangerment Assessment Handbook was prepared by ICAIR, Life Systems, Inc., under U.S. Environmental Protection Agency (EPA) Contract 68-01-7037 during the period February 1, 1985 to August 16, 1985. The program was directed by Mr. Timothy E. Tyburski. The handbook was compiled by Ms. Lee Ann Smith with technical support from Mr. Kevin Gleason, Ms. Yvonne Hales and Mr. Jon Hellerstein.

Mr. R. Charles Morgan and Ms. Kathleen Plourd, Health Sciences Section, Technical Support Branch, Office of Waste Programs Enforcement (OWPE) were the lead EPA Technical Contacts. ICAIR would also like to acknowledge the contributions of the EPA Workgroup members to this program: Cheryl Peterson, Compliance Branch, OWPE; Linda Southerland, Guidance and Oversight Branch, OWPE; Libby Clemens, Resource Conservation and Recovery Act (RCRA) Enforcement Division, OWPE; Kurt Lamber, Physical Sciences Section, Technical Support Branch, OWPE; Craig Zamuda, Office of Emergency and Remedial Response (OERR); John Schaum, Exposure Assessment Group, Office of Health and Environmental Assessment (OHEA); Jim Kohanek, Office of Enforcement and Compliance Monitoring (OECM); Ralph Jennings, EPA Region 4; and Sally Edwards, EPA Region 1.

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LIST OF ACRONYMS

ADI	Acceptable Daily Intake
AO	Administrative Order
ATSDR	Agency for Toxic Substances and Disease Registry
CASR	Chemical Activities Status Report
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act
ECAO	Environmental Criteria and Assessment Office
EPA	Environmental Protection Agency
FS	Feasibility Study
GEMS	Graphical Exposure Modeling System
HI	Hazard Index
LOAEL	Lowest-Observed-Adverse-Effect Level
NCP	National Contingency Plan
NEIC	National Enforcement Investigations Center
NOAEL	No-Observed-Adverse-Effect Level
NOEL	No-Observed-Effect Level
OAQPS	Office of Air Quality Planning and Standards
ODW	Office of Drinking Water
OECM	Office of Enforcement and Compliance Monitoring
OERR	Office of Emergency and Remedial Response
OHEA	Office of Health and Environmental Assessment
ORD	Office of Research and Development
OSW	Office of Solid Waste
OTS	Office of Toxic Substances
OWPE	Office of Waste Programs Enforcement
OWRS	Office of Water Regulations and Standards
QA/QC	Quality Assurance/Quality Control
RCRA	Resource Conservation and Recovery Act
REM/FIT	Remedial Planning/Field Investigation Team
RI	Remedial Investigation
SPHAM	Superfund Public Health Assessment Manual
TAT	Technical Assistance Team
TES	Technical Enforcement Support

GLOSSARY

Acceptable Daily Intake - The amount of toxicant, in mg/kg body weight/day, that will not cause adverse effects after chronic exposure to the general human population.

Administrative Action - Any action that a statute or regulation authorizes EPA to take, but does not involve filing papers with a court and is not part of prosecuting a case already filed. Examples of administrative actions are issuance of orders under Section 106 of CERCLA and Section 7003 of RCRA.

Dose-Response Assessment - The second step in the toxicity assessment process which involves defining the relationship between the exposure level (dose) of a chemical and the incidence of the adverse effect (response) in the exposed populations.

Endangerment Assessment - A site-specific assessment of the actual or potential danger to public health or welfare or the environment from the threatened or actual release of a hazardous substance or waste from a site. The endangerment assessment document is prepared in support of an enforcement action under CERCLA or RCRA.

Enforcement Action - Any action taken pursuant to Section 106 of CERCLA or Section 7003 of RCRA to compel responsible parties to respond to hazardous conditions. An enforcement action may include administrative actions and/or judicial actions.

Exposure Assessment - One of the components of the endangerment assessment process, the exposure assessment is a four-step process to identify actual or potential routes of exposure, characterize populations exposed and determine the extent of the exposure.

Exposure Evaluation - The section of the endangerment assessment document which reports the results of the exposure assessment process.

Judicial Action - Any action that involves filing papers with a court or is part of prosecuting a case already filed. Examples of judicial actions are actions taken to seek injunctive relief or actions taken when a party fails to comply with an administrative order.

LC_{50} - Lethal concentration at which 50% of the test organisms die.

LD_{50} - Lethal dose at which 50% of the test organisms die.

Lowest-Observed-Adverse-Effect Level (LOAEL) - The lowest dose of a chemical in a study that produces statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and an appropriate control.

No-Observed-Adverse-Effect Level (NOAEL) - That dose of a chemical at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and an appropriate control.

No-Observed-Effect Level (NOEL) - That dose of a chemical at which there are no statistically or biologically significant increases in the frequency or severity of effects between the exposed population and an appropriate control.

Risk Characterization - The final component of the endangerment assessment process which integrates all of the information developed during the exposure and toxicity assessments to yield a complete characterization of the actual or potential risk at a site.

Risk and Impact Evaluation - The section of the endangerment assessment document which reports the results of the risk characterization process.

Toxicity Assessment - One of the components of the endangerment assessment process, the toxicity assessment is a two-step process to determine the nature and extent of health and environmental hazards associated with exposure to contaminants of concern present at the site. It consists of toxicological evaluations and dose-response assessments for contaminants of concern.

Toxicity Evaluation - The section of the endangerment assessment document which reports the results of the toxicity assessment process.

Toxicity Profile - A summary of the available human health or environmental toxicity data on a contaminant. This document considers doses used, routes of exposure, types of adverse effects manifested and definitive statements of quantitative indices of toxicity.

Toxicological Evaluation - The first step in the toxicity assessment process which is a qualitative evaluation of the scientific data to determine the nature and severity of actual or potential health and environmental hazards associated with exposure to a chemical substance. The end product of the toxicological evaluation is a toxicity profile for each of the contaminants of concern.

Unit Cancer Risk - Excess lifetime risk of cancer due to a continuous lifetime exposure of one unit of carcinogen concentration.

1.0 INTRODUCTION

Current U.S Environmental Protection Agency (EPA) policy states that an endangerment assessment is required to support all administrative and judicial enforcement actions under Section 106(a) of the Comprehensive Environmental Response, Compensation and Liability Act of 1980 (CERCLA) and Section 7003 of the Resource Conservation and Recovery Act of 1976 (RCRA).

This Handbook makes a distinction between:

- The endangerment assessment process which evaluates the collective demographic, geographic, physical, chemical and biological factors at a site to determine whether there is a significant risk to public health or welfare or the environment as a result of a threatened or actual release of a hazardous substance or waste; and

- The endangerment assessment document which summarizes the findings of the assessment process in a concise format and documents EPA's assertion that an imminent and substantial endangerment to public health or welfare or the environment may exist at a site targeted for enforcement actions.

1.1 Purpose and Scope of the Endangerment Assessment Handbook

This Handbook provides guidance to EPA regional, state and contractor personnel on conducting endangerment assessments and preparing the necessary documentation. Its primary purpose is to assist individuals in the preparation of endangerment assessment documents which will satisfy the enforcement needs of each case. This Handbook is intended only as a supplement to the "Draft Endangerment Assessment Guidance" prepared and distributed by EPA's Office of Waste Programs Enforcement (OWPE) (USEPA 1985d) and should be used in conjunction with that document, which is included in its entirety in Appendix 1 to this Handbook.

The Handbook explains the use of the endangerment assessment as an enforcement tool and its relationship to the remedial investigation (RI) and feasibility study (FS) processes at a site. It provides guidance on how to develop an endangerment assessment and discusses the timing, scope and level of detail that are required and how these factors may be affected by site-specific enforcement concerns.

The Handbook also describes the relationship of the endangerment assessment document to other documents generated for a site and provides instructions for preparing the document. Finally, it identifies key references and other sources of information and assistance.

A distinction between the endangerment assessment process and endangerment assessment document is made throughout this Handbook to clarify the difference between the complex, multi-disciplinary assessment process and the fairly straightforward task of preparing a document which reports the conclusions of the assessment process.

EPA has recently completed guidance documents for planning and performing RI and FS studies at Superfund sites:

- Guidance on Remedial Investigations Under CERCLA (USEPA 1985c)
- Guidance on Feasibility Studies Under CERCLA (USEPA 1985b)

A detailed instruction manual is being developed, designed to accompany the RI and FS guidance documents, for conducting public health assessments at Superfund sites:

- Superfund Public Health Assessment Manual (ICF 1985)

Since the endangerment assessment process is similar to the public health and environmental assessments which are conducted as part of the RI and FS, this manual should be used as a technical reference when performing endangerment assessments. To avoid unnecessary duplication of technical detail provided in the Superfund manual, this Handbook directs the reader to this manual for additional information where appropriate.

1.2 Handbook Organization

This Handbook is divided into six sections and five appendices in addition to this Introduction:

2.0 Legislative and Programmatic Framework
3.0 Overview of the Endangerment Assessment Process
4.0 Guidelines for Conducting Endangerment Assessments
5.0 Preparation of the Endangerment Assessment Document
6.0 Sources of Information and Assistance
7.0 References

Appendix 1 Draft Endangerment Assessment Guidance
Appendix 2 Examples of Endangerment Assessments
Appendix 3 EPA's Proposed Assessment Guidelines
Appendix 4 Test Protocol Criteria for Animal Assays
Appendix 5 Definition of Toxicological Endpoints

Section 2.0 provides an overview of the legislative and programmatic framework in which the endangerment assessment fits. It summarizes the legislative background of the endangerment assessment process and discusses when an endangerment assessment should be prepared and who should prepare it. The relationship of the endangerment assessment process to the RI and FS processes and the role of the endangerment assessment document in enforcement cases is also discussed in this section.

Section 3.0 provides an overview of the endangerment assessment process and its components: contaminant identification, exposure assessment, toxicity assessment and risk characterization. This section briefly describes the objectives of each component and the information needed to complete each of the assessments.

Section 4.0 provides guidelines for conducting endangerment assessments. It contains a discussion of the levels of detail required in an endangerment assessment and discusses the steps required to complete the contaminant identification, exposure assessment, toxicity assessment and risk characterization components introduced in Section 3.0.

Section 5.0 describes the format, scope and content of the endangerment assessment document. It provides specific instructions for completing each required section of the document, sources of information and factors to be addressed.

Section 6.0 provides information on the points of contact at EPA Headquarters for additional information on the endangerment assessment process and the requirements of an endangerment assessment document.

Section 7.0 is a list of references cited in this Handbook.

2.0 LEGISLATIVE AND PROGRAMMATIC FRAMEWORK

2.1 Applicable Legislation

Section 106(a) of CERCLA states that ". . . when the President determines that there may be an imminent and substantial endangerment to public health or welfare or the environment because of an actual or threatened release of a hazardous substance from a facility, he may . . . secure such relief as may be necessary to abate such danger and threat . . . ."

Section 7003 of RCRA states that ". . . upon receipt of evidence that the handling, storage, treatment, transportation or disposal of any solid waste or hazardous waste may present an imminent and substantial endangerment to health or the environment, the Administrator may bring suit . . . to immediately restrain any person contributing to such handling, storage, treatment, transportation, or disposal or to take such other action as may be necessary."

Thus, Section 106(a) of CERCLA authorizes EPA to take judicial or administrative action to compel responsible parties to respond to hazardous conditions resulting from an actual or threatened release of a hazardous substance. Likewise, Section 7003 of RCRA may be used as the authority under which EPA may issue orders or file civil actions to compel responsible parties to respond to hazardous conditions resulting from the handling, storage, treatment, transportation or disposal of solid wastes or hazardous wastes.

2.2 Role of the Endangerment Assessment in Enforcement Cases

Before taking enforcement actions (i.e., judicial actions, administrative actions) under Section 106(a) of CERCLA or Section 7003 of RCRA, EPA must be able to properly document and justify its assertion that an imminent and substantial endangerment to public health or welfare or the environment may exist. The endangerment assessment provides this justification and documentation.

It is important to note at this juncture that "imminent" does not mean immediate harm, rather, it means an impending risk of harm. Sufficient justification for a determination of an imminent endangerment may exist if harm is threatened; no actual injury need have occurred or be occurring. Similarly, "endangerment" means something less than actual harm (USEPA 1985d).

The data collected at a site (i.e., contaminants present, quantities present, environmental media affected, etc.) does not stand on its own; it must be interpreted. The endangerment assessment document provides an interpretation of the data which supports the "Findings of Fact" sections in the administrative or judicial enforcement documents that may be prepared for a site.

2.2.1 When to Perform an Endangerment Assessment

The endangerment assessment document must be prepared before a CERCLA Section 106(a) or RCRA Section 7003 action is filed or issued. Therefore, the endangerment assessment process should be initiated as soon as a site is

identified as an enforcement site and administrative or judicial actions are considered. The requirement for an endangerment assessment document should not slow down the enforcement process at a site.

Only one endangerment assessment document should be prepared for a site. The original document may then be revised, updated or amended throughout the site development process as additional data become available.

Figure 2-1 illustrates the points in time when an enforcement action under CERCLA, and the required endangerment assessment, may be initiated at a site. The endangerment assessment may be performed:

1. Before issuance of an administrative order (AO) for removal actions;

2. As part of the RI/FS;

3. Before issuance of an AO or consent decree for responsible party RI/FS or cleanup (i.e., remedial actions);

4. Before issuance of an AO to a Federal facility for cleanup; or

5. Before any judicial action is taken (i.e., case is filed).

Figure 2-1 also illustrates what site documentation may be available to provide input to the endangerment assessment. Finally, since the endangerment assessment may be performed at varying points in time to support different enforcement actions, the level of detail in the document will vary on a case-by-case basis. Figure 2-1 indicates what level of detail may be appropriate for endangerment assessments supporting CERCLA enforcement actions performed at different points of time. The concept of varying levels of detail in endangerment assessments is discussed more fully in Section 4.0.

While an endangerment assessment document must be prepared to support both RCRA Section 7003 actions and CERCLA Section 106 actions, the circumstances when Section 7003 orders are used and endangerment assessments must be prepared differ under RCRA and CERCLA. Whereas the CERCLA Section 106 authority initially relies on the discovery or notification of a release of hazardous substances, the RCRA Section 7003 authority can be activated when the Administrator possesses evidence "that the past or present handling, storage, treatment, transportation or disposal of any solid waste or hazardous waste <u>may present</u> (emphasis added) an imminent and substantial endangerment to health or the environment" (42 USC Section 6973). Additionally, the Section 7003 authority extends to imminent hazards presented by a wider range of hazardous constituents than CERCLA Section 106 authority. Section 7003 orders cover constituents that fall under the definition of "solid wastes" (RCRA Section 1004(27)) and "hazardous wastes" (RCRA Section 1004(5)) while CERCLA Section 106 orders cover "hazardous substances" (CERCLA Section 104(14)).

Endangerment assessments must be prepared to support the issuance of an administrative order or before judicial action is taken under RCRA Section 7003. But, unlike the CERCLA program, the RCRA program does not have a

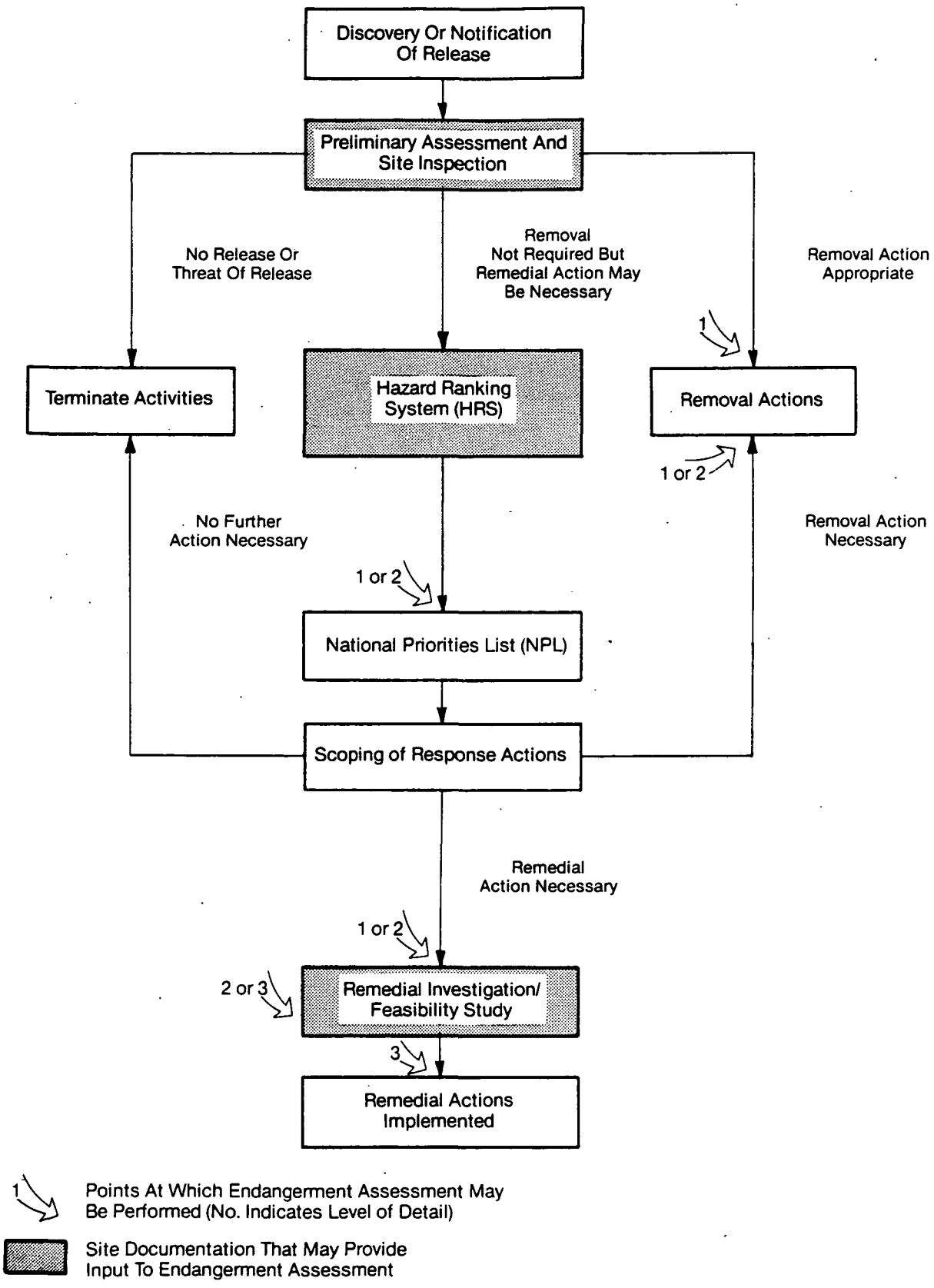


FIGURE 2-1 ROLE OF THE ENDANGERMENT ASSESSMENT IN CERCLA ENFORCEMENT CASES

formalized RI/FS study process. Hence, the detailed information contained in an RI/FS study that is available for use in the CERCLA endangerment assessment may not be readily available to include in an endangerment assessment for supporting Section 7003 orders.

For more information on Section 7003 orders, please see the "Final Revised Guidance Memorandum on the Use and Issuance of Administrative Orders under Section 7003 of the Resource Conservation and Recovery Act (RCRA)," dated September 26, 1984.

2.2.2 Who Performs an Endangerment Assessment

Agency policy states that the Regions have the responsibility to assure that endangerment assessments are performed. For assistance in performing endangerment assessments, the Regions can draw on technical expertise available in their Regional offices, OWPE's Technical Support Branch, the Office of Research and Development (ORD), the Agency for Toxic Substances and Disease Registry (ATSDR) and/or contractor personnel available through the Technical Enforcement Support (TES), Remedial Planning/Field Investigation Team (REM/FIT) or Technical Assistance Team (TAT) contracts.

The only exception to EPA (Regions) performing the endangerment assessment is if the responsible parties elect to perform the RI/FS pursuant to an AO. In these cases, they will also, in effect, perform an endangerment assessment because they will develop many or all of the elements of an endangerment assessment as part of the RI/FS. Since subsequent enforcement actions (i.e., AOs requiring responsible parties to perform cleanup) rely on this endangerment assessment for justification, close Regional oversight should be given to this responsible party work.

2.2.3 Confidentiality of an Endangerment Assessment

The endangerment assessment document, and all supporting documentation, must be considered enforcement confidential as long as an enforcement action is pending. Document control procedures which should be implemented may include:

- Marking the cover page of all documents as "Privileged Work Product Prepared in Anticipation of Litigation"
- Marking each page of all documents as "Enforcement Confidential"
- Limiting the distribution of all documentation
- Limiting the number of copies distributed
- Utilizing standard chain-of-custody procedures for the documents per the National Enforcement Investigations Center (NEIC) manual

The endangerment assessment is no longer considered confidential when the finalized document is distributed to the public.

2.3 Relationship of Enforcement Actions to Superfund Actions

The Hazardous Substance Response Trust Fund, commonly known as Superfund, was established by CERCLA to finance the discovery of actual or threatened

releases of hazardous substances into the environment and the development and implementation of response actions at these uncontrolled hazardous waste sites. To ensure that Superfund is used as effectively as possible, procedures for use of the fund were incorporated into the revised National Contingency Plan (NCP) (USEPA 1985c).

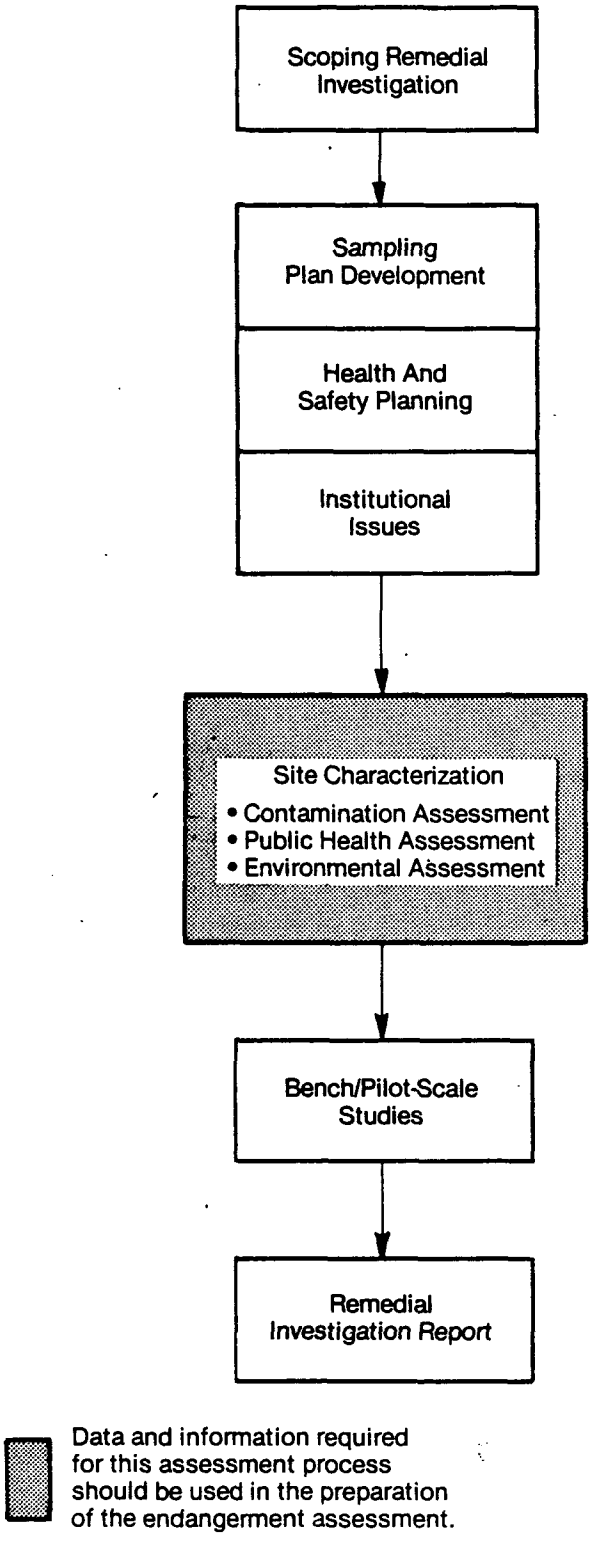
Section 104 of CERCLA authorizes EPA to initiate Superfund-financed response actions as soon as an actual or threatened release of a hazardous substance is discovered. All Superfund-financed response actions must be in accord with the NCP.

As discussed previously, Section 106(a) of CERCLA authorizes EPA to take any necessary enforcement actions to compel responsible parties to respond to hazardous conditions resulting from an actual or threatened release of a hazardous substance. Thus, if a potentially responsible party is identified at any time during the development and implementation of Superfund-financed response actions at a site, enforcement actions may be taken to compel the potentially responsible party to conduct the cleanup itself or provide funds for the government-conducted cleanup (i.e., reimburse Superfund costs). Any response actions or remedies resulting from enforcement actions at Superfund sites must be in accord with the procedures outlined in the NCP.

2.3.1 The RI and FS Processes

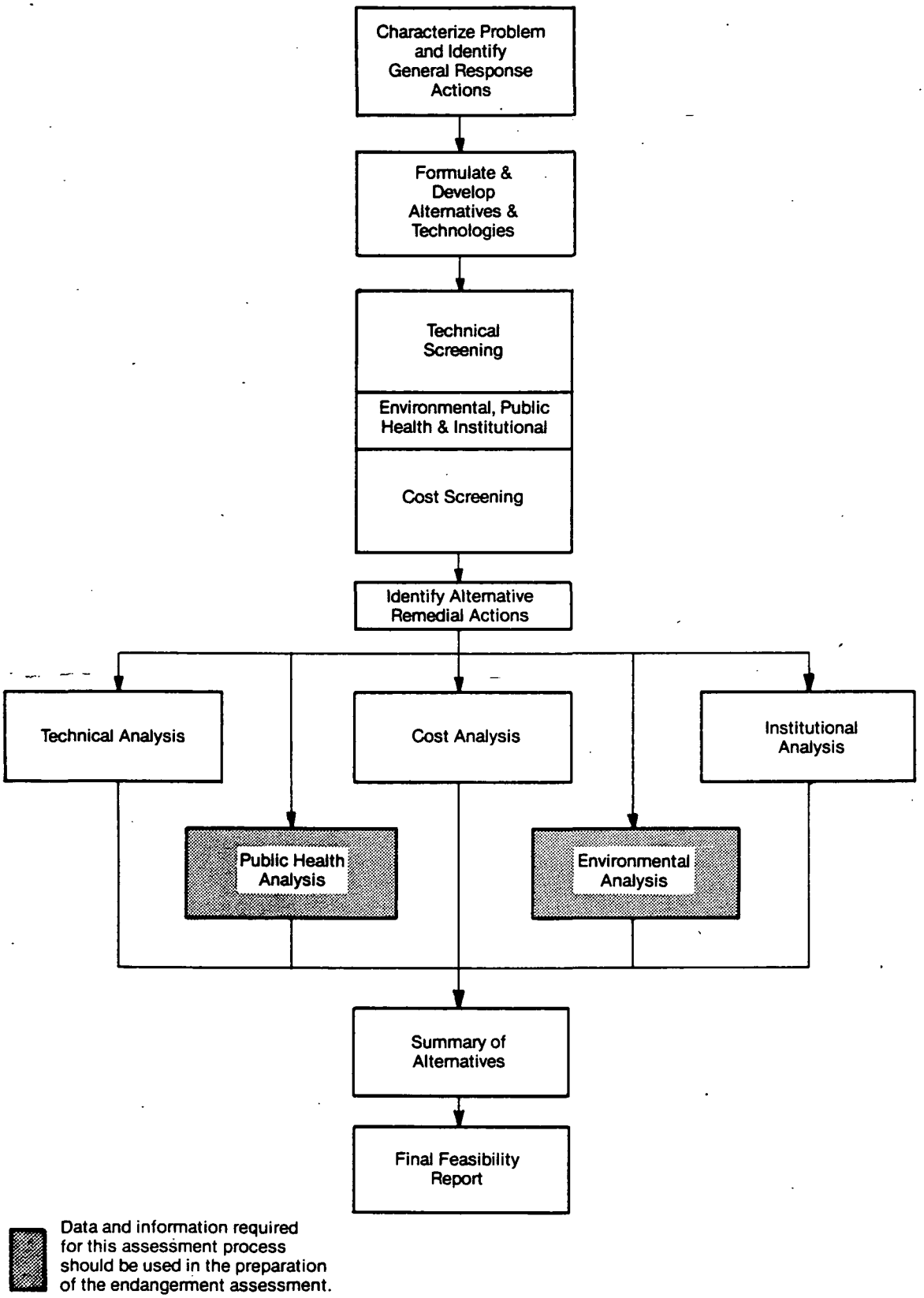
The NCP requires that a detailed RI and FS be conducted at each site targeted for remedial response action under Sections 104 and 106 of CERCLA. The goal of the RI is to obtain the necessary site data so the potential impacts on public health or welfare or the environment can be evaluated and remedial alternatives can be developed and selected. The goal of the FS is to develop and evaluate alternative remedial actions (including the no-action alternative) in terms of cost, effectiveness and their engineering feasibility. Thus, the RI emphasizes data collection and site characterization while the FS emphasizes data analysis and an evaluation of alternative remedial actions.

For Superfund-financed sites, the NCP requires an analysis of impacts on public health, welfare and the environment. Therefore, the RI and FS processes require an assessment of the contamination at the site and the potential impacts on public health or the environment from that contamination. The RI assessments focus on the existing conditions at the site in performing a baseline assessment or complete site characterization. Figure 2-2 illustrates when the site characterization assessments are performed in the RI process. The FS assessments evaluate the potential impacts at the site associated with each remedial alternative, including the no-action alternative. The no-action alternative analysis is, essentially, a baseline assessment at the site against which all remedial alternatives are compared. Figure 2-3 illustrates when this analysis of alternatives is performed in the FS process.



Adapted from EPA 1985c

FIGURE 2-2 THE REMEDIAL INVESTIGATION PROCESS



Adapted from EPA 1985b

FIGURE 2-3 THE FEASIBILITY STUDY PROCESS

2.3.2 Relationship of the Endangerment Assessment Process to the RI and FS Assessment Processes

The assessments performed during the RI and FS processes are very similar to the endangerment assessment. Although the assessments are performed for different reasons, the information requirements are similar and the assessment methods used should be consistent. Therefore, in addition to this Handbook, the guidance documents and instruction manuals prepared in support of the RI and FS processes should be utilized when performing endangerment assessments.

Since a Superfund-financed site may become an enforcement site at any time during the development and implementation of remedial response actions (see Figure 2-1), documentation prepared for each program (e.g., Superfund and Enforcement) should be complementary. Thus, if the RI and FS are essentially complete when an enforcement action is initiated, the requirement for an endangerment assessment may be fulfilled by the "Site Characterization" and "Analysis of No-Action Alternative" sections of the RI and FS reports, respectively. In this situation no separate endangerment assessment document is required. Conversely, if an endangerment assessment is prepared prior to completion of the RI and FS reports, it should address all the issues that are required in the assessment sections of the RI and FS reports. The objective should always be to reduce duplication of assessment efforts and documentation at any given site. Figure 2-4 illustrates the interrelationship of the endangerment assessment document required at enforcement sites and the RI and FS reports required at Superfund sites.

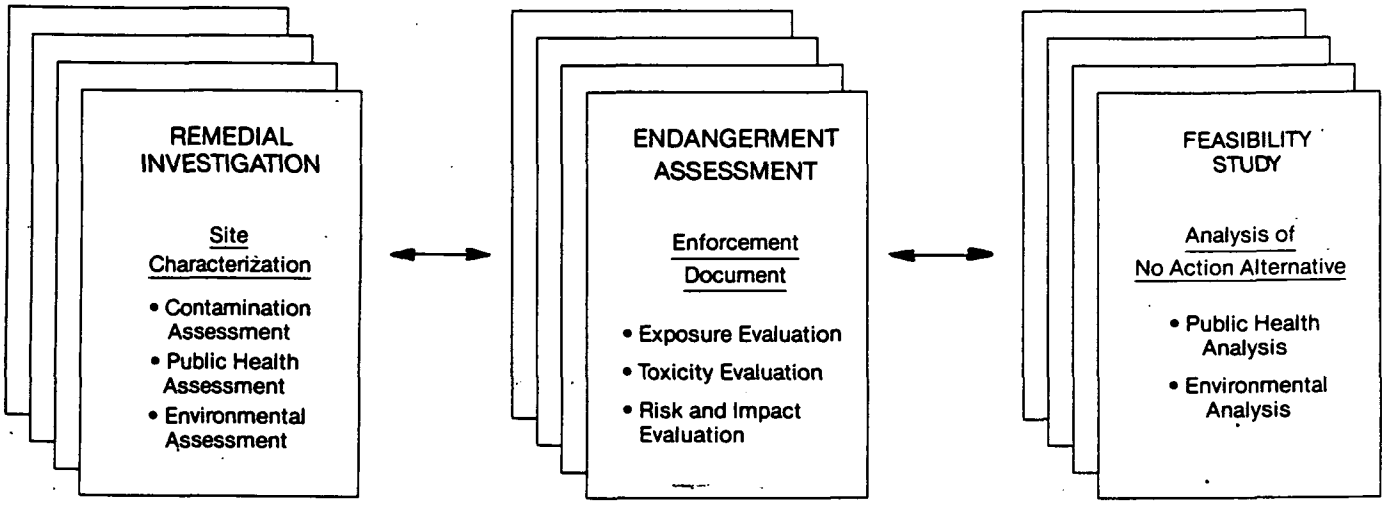


FIGURE 2-4 THE INTERRELATIONSHIP OF THE ENDANGERMENT ASSESSMENT DOCUMENT, REMEDIAL INVESTIGATION REPORT AND FEASIBILITY STUDY REPORT

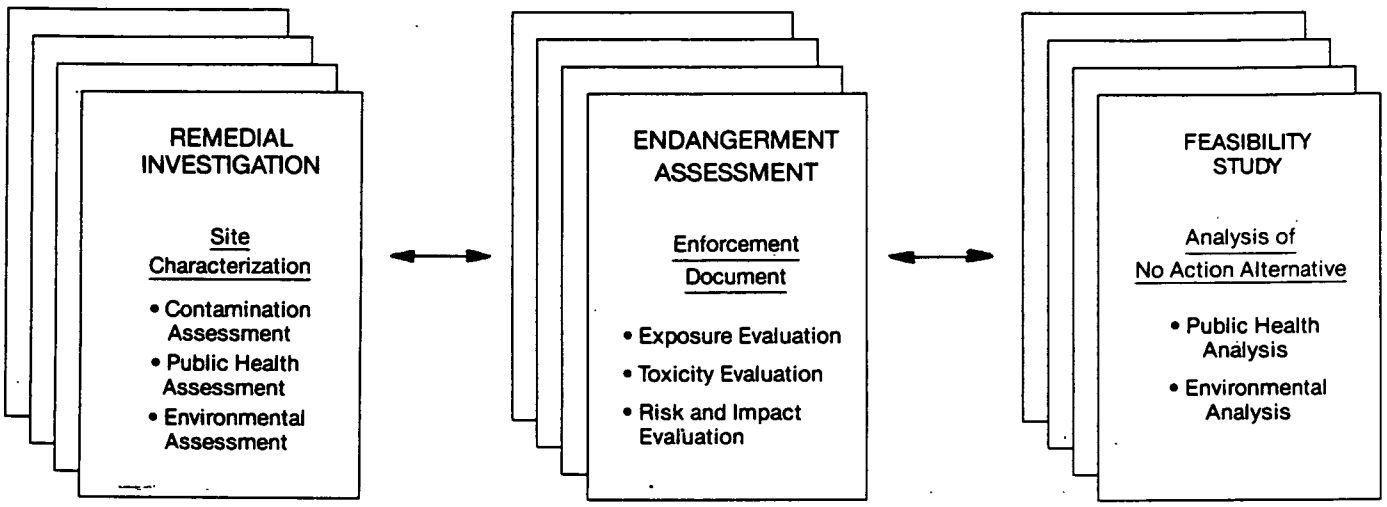


FIGURE 2-4 THE INTERRELATIONSHIP OF THE ENDANGERMENT ASSESSMENT DOCUMENT, REMEDIAL INVESTIGATION REPORT AND FEASIBILITY STUDY REPORT

3.0 OVERVIEW OF THE ENDANGERMENT ASSESSMENT PROCESS

The overall objective of an endangerment assessment is to provide a determination of the magnitude and probability of actual or potential harm to public health or welfare or the environment by the threatened or actual release of a hazardous substance (for a CERCLA action) or a hazardous waste (for a RCRA action). In general, this objective may be attained by identifying and characterizing the following:

1. Hazardous substances and/or hazardous wastes present in all relevant media (e.g., air, water, soil, sediment, biota);

2. Environmental fate and transport mechanisms within specified environmental media, such as physical, chemical and biological degradation processes and hydrogeological evaluations and assessments;

3. Exposure pathways and extent of expected exposure;

4. Populations at risk;

5. Intrinsic toxicological properties of specified hazardous substances or hazardous wastes; and

6. Extent of expected harm and the likelihood of such harm occurring (i.e., risk characterization).

An endangerment assessment is an evaluation and interpretation of the collective demographic, geographic, physical, chemical and biological factors at a site which describe the extent of the potential or actual harm. Thus, the process of evaluating endangerment is multi-disciplinary, requiring the expertise of scientists in several technical areas.

The endangerment assessment process is comprised of four separate components which, collectively, address each of the six key areas identified above. The endangerment assessment process is divided into these four components based on the areas of technical expertise required to perform each. The four components of the endangerment assessment process are:

1. Contaminant Identification
2. Exposure Assessment
3. Toxicity Assessment
4. Risk Characterization

Figure 3-1 illustrates the endangerment assessment process and its four components. The following sections provide a brief overview of each component. Section 5 of this handbook describes how the information developed during each component of the endangerment assessment process is presented in a concise endangerment assessment document.

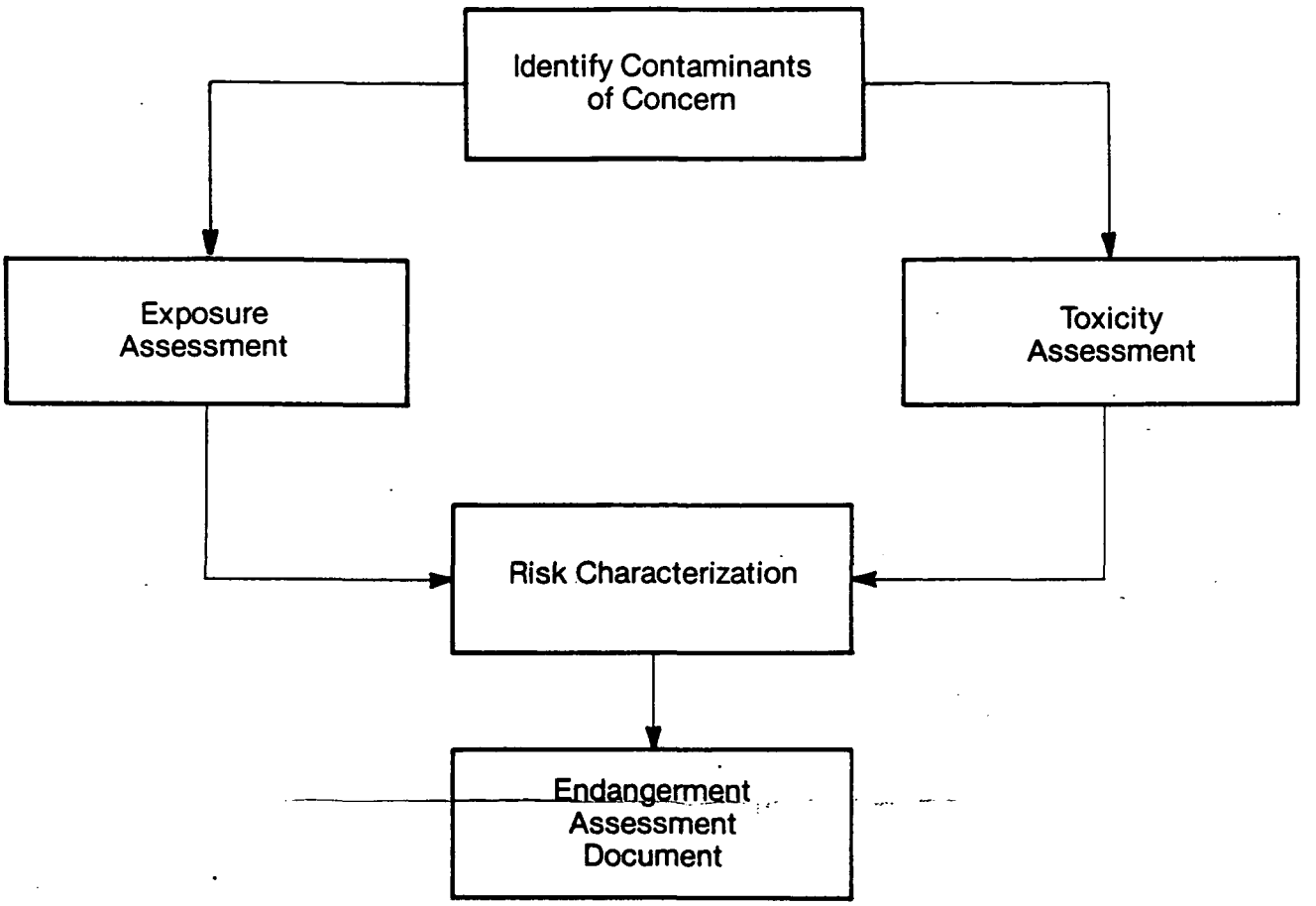


FIGURE 3-1 THE ENDANGERMENT ASSESSMENT PROCESS

3.1 Contaminant Identification

The objective of this component is to screen the information available on hazardous substances or wastes present at the site and identify contaminants of concern. This screening process is necessary in order to focus subsequent efforts in the endangerment assessment process on a few, selected contaminants.

Contaminants of concern may be selected based on their intrinsic toxicological properties or because they are present in large quantities or because of potentially critical exposure routes (i.e., being released into a drinking water supply).

"Indicator chemicals" may have been selected as part of the RI/FS. In this case, the endangerment assessment should focus on those chemicals. If "indicator chemicals" have not yet been selected, the enforcement team must select the contaminants of concern. The enforcement team may choose to select the contaminants based on the methodology for selecting "indicator chemicals" discussed in Chapter 4 of the SPHAM (2 CF 1985). The goal of the selection process is to select the contaminants which encompass all of the relevant physiochemical and toxicological properties of the contaminants present at the site.

3.2 Exposure Assessment

The objectives of an exposure assessment are to identify actual or potential routes of exposure, characterize the exposed populations and determine the extent of the exposure. These objectives may be attained by performing the following four steps:

1. Analyze contaminant release
2. Analyze environmental fate and transport
3. Analyze exposed populations
4. Estimate or calculate expected exposure levels (or doses incurred)

The first step, an analysis of contaminant releases from the hazardous waste site, involves characterizing the contaminants of concern at the site and determining the amount of each contaminant released to each environmental medium.

In the second step the environmental fate and transport of the contaminants are analyzed. The results of these analyses provide information on the magnitude and extent of environmental contamination. The exposure routes identified during this step will have varying levels of proof supporting their evaluation, depending on the amount of field data available at the time the exposure assessment is being performed.

The third step of an exposure assessment involves an analysis of exposed populations. Exposed populations may include human populations, sensitive subsets of the human population and/or fish and wildlife populations which may be at risk. This analysis yields data on the magnitude of exposure and identifies potential high-risk populations (i.e., children, women of child-

bearing age, endangered or threatened wildlife populations, etc.). This step may also involve the application of exposure coefficients. An exposure coefficient combines information on the frequency, mode and magnitude of exposure to yield a value representative of the amount of contaminated medium contacted per day.

The final step in an exposure assessment integrates the results of the preceding three steps to yield a qualitative or quantitative estimate of the expected exposure levels resulting from actual or potential releases of contaminants from the site. Figure 3-2 illustrates the exposure assessment process.

3.3 Toxicity Assessment

The objectives of the toxicity assessment are to determine the nature and extent of health and environmental hazards associated with exposure to contaminants present at the site. It is a two-step process consisting of:

1. Toxicological Evaluation
2. Dose-Response Assessment

The first step in the toxicity assessment, the toxicological evaluation, is a qualitative evaluation of the scientific data to determine the nature and severity of actual or potential health and environmental hazards associated with exposure to a chemical substance. The toxicological evaluation involves a critical evaluation and interpretation of toxicity data from epidemiological, clinical, animal and *in vitro* studies and results in a toxicity profile for each contaminant of concern. Toxicity profiles present a review of the primary literature on the types of adverse effects manifested (e.g., chronic, acute, carcinogenic, etc.), doses employed, routes of administration (e.g., oral, dermal, inhalation, etc.), the quality and extent of test data, the reliability of the test data and other factors. Toxicity profiles provide the weight-of-evidence that the contaminants of concern pose potential hazards to human health or the environment.

Once the toxicological evaluation determines that a chemical is likely to cause a particular adverse effect, the next step is to determine the potency of the chemical. The second step in the toxicity assessment, the dose-response assessment, is a quantitative estimation of risk from exposure to a toxic chemical. It defines the relationship between the dose of a chemical and the incidence of the adverse effect.

The dose-response assessment for noncarcinogenic chemicals utilizes the quantitative indices of toxicity (e.g., NOEL, NOAEL, LOAEL, LC_{50}, etc.), which were identified during the toxicological evaluation, and their respective margins of safety to determine "acceptable levels" for the contaminants of concern. "Acceptable levels" are defined as exposure levels which are not anticipated to cause adverse effects. These "acceptable levels" may be expressed in a variety of ways such as Acceptable Daily Intakes (ADIs), Ambient Air Standards, Water Quality Criteria, etc.

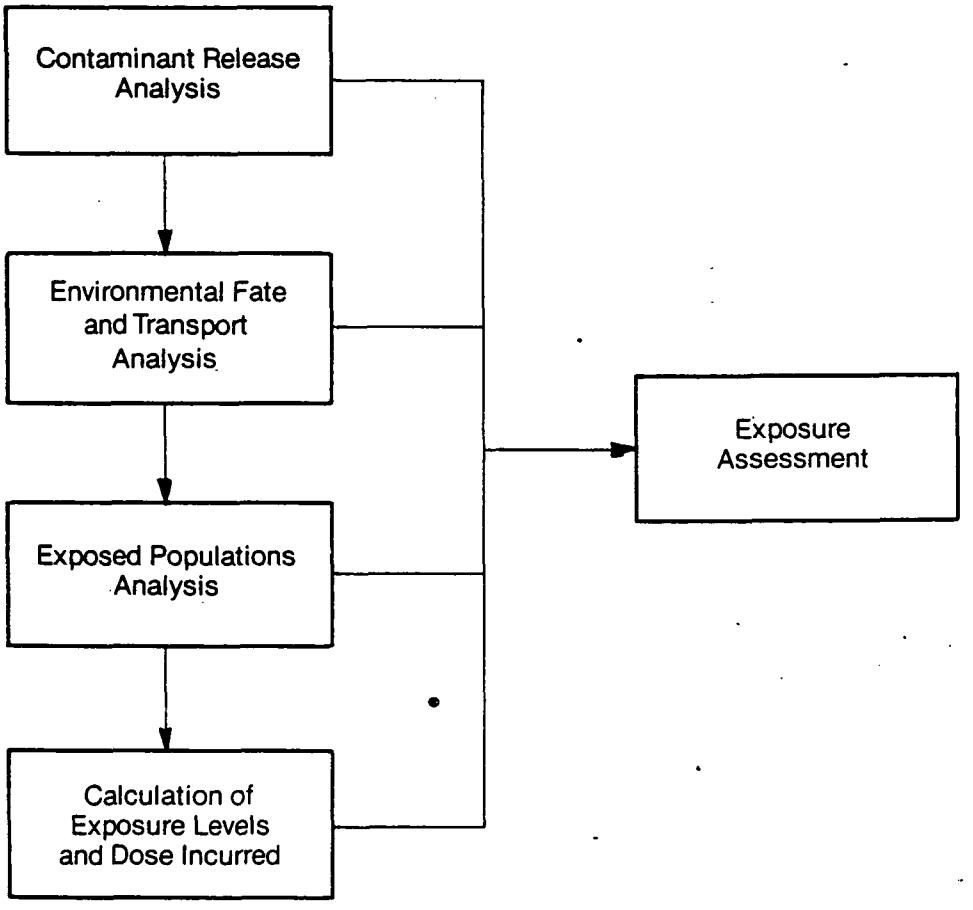


FIGURE 3-2 THE EXPOSURE ASSESSMENT PROCESS

The dose-response assessment for carcinogenic chemicals provides estimates of the probability that a specific adverse effect will occur (e.g., unit cancer risk or carcinogenic potency values). These estimates of probability are derived using mathematical models of the dose-response relationship.

The end-product of a toxicity assessment is a qualitative description of the toxic properties of the contaminants of concern at the site and a quantitative index of the toxicity for each contaminant at the site, if the data are sufficient for such an assessment.

EPA has developed toxicity profiles on a large number of the contaminants that are found at hazardous waste sites (see Section 4.4 of this Handbook for a discussion of the available toxicity profiles). These toxicity profiles characterize the adverse health and environmental effects that are anticipated to result from exposure to these contaminants. Additionally, these profiles define the "acceptable levels" for noncarcinogenic chemicals and the estimates of unit cancer risk for carcinogenic chemicals. Endangerment assessments should always utilize existing EPA toxicity profiles when they are available. If there are no appropriate toxicity profiles available for the contaminants and exposure routes of concern, then the members of the endangerment assessment team with the appropriate expertise will have to develop toxicity profiles based on the current scientific literature.

Figure 3-3 illustrates the toxicity assessment process.

3.4 Risk Characterization

The final component of the endangerment assessment process, risk characterization, is the process of estimating the incidence of an adverse health or environmental effect under the various conditions of exposure defined in the exposure assessment. This objective is attained by integrating all of the information developed during the exposure and toxicity assessments to yield a complete characterization of potential or actual risk. The risk characterization should address all types of potential or actual risks at the site including:

1. Carcinogenic risks
2. Noncarcinogenic risks
3. Environmental risks
4. Risks to public welfare

The final assessment should include a summary of the risks associated with a site and such factors as the weight-of-evidence associated with each step of the process, the estimated uncertainty of the component parts, the distribution of risk across various sectors of the population, the assumptions contained within the estimates, etc.

For carcinogens where risk estimation data are available (e.g., carcinogenic potency values), crude estimates of the excess cancer risk at a site can be obtained by multiplying the carcinogenic potency value by the current and projected chronic exposure levels. The estimated excess cancer risks are then

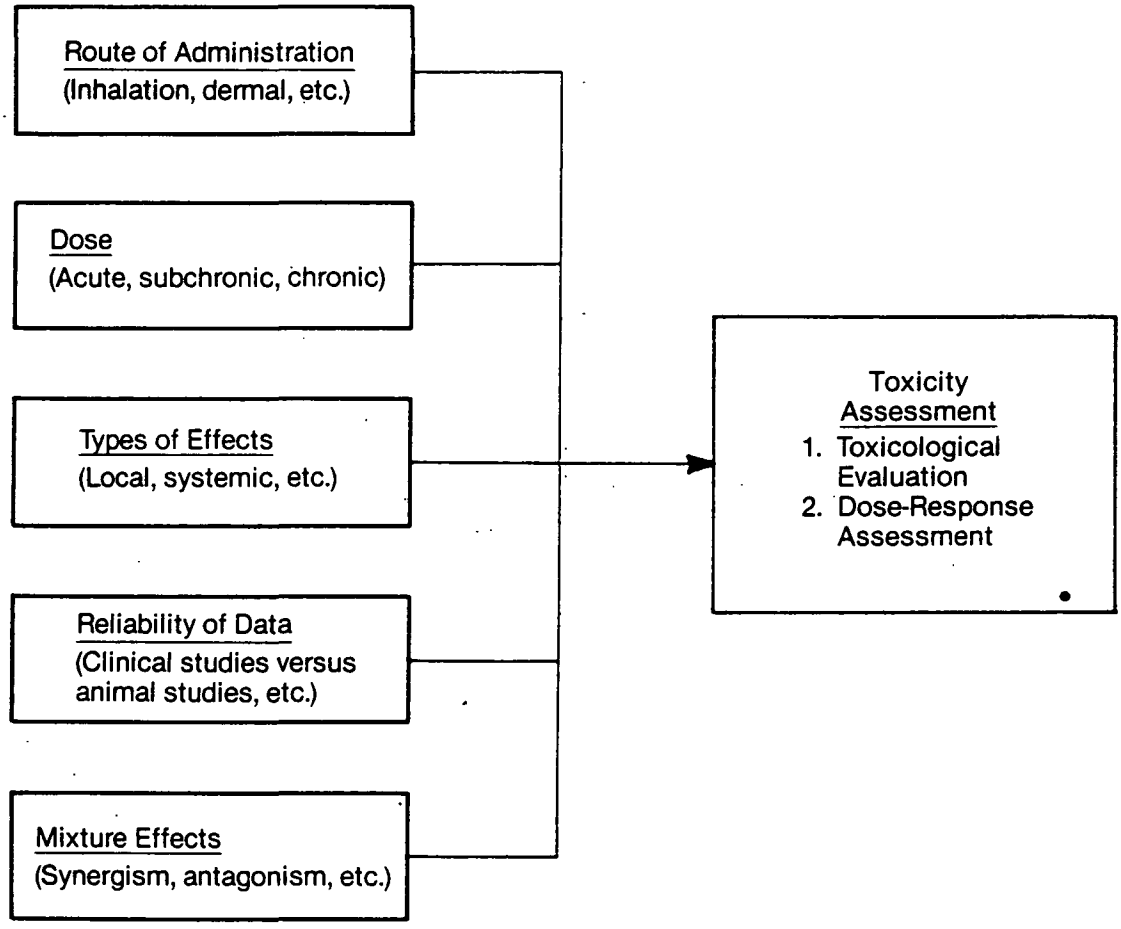


FIGURE 3-3 THE TOXICITY ASSESSMENT PROCESS

compared to acceptable risk levels defined in regulatory legislation and guidelines.

For noncarcinogenic effects, projected exposure levels are compared to "acceptable levels" (e.g., ADI values or established criteria and standards) identified during the toxicity assessment. Any time there is an actual or projected exposure level which exceeds an "acceptable level" for that contaminant and exposure route, the risk at the site is considered unacceptable. The risk characterization should evaluate the risks associated with each projected exposure route for each contaminant of concern at a site.

Characterization of the environmental risks involves identifying the toxic effects of exposures to the chemicals of concern to fish or wildlife populations. The environmental risk evaluation should also discuss what the effects of exposure will be on indigenous species, on the food chain and on the habitat, since all of these factors affect the environmental quality at a site.

The risk characterization should also include an evaluation of the potential or actual risks to public welfare. Welfare risks may include adverse effects on property values, future land uses, recreational and commercial activities, public perception and opinion, quality of life, etc.

Figure 3-4 illustrates the risk characterization process.

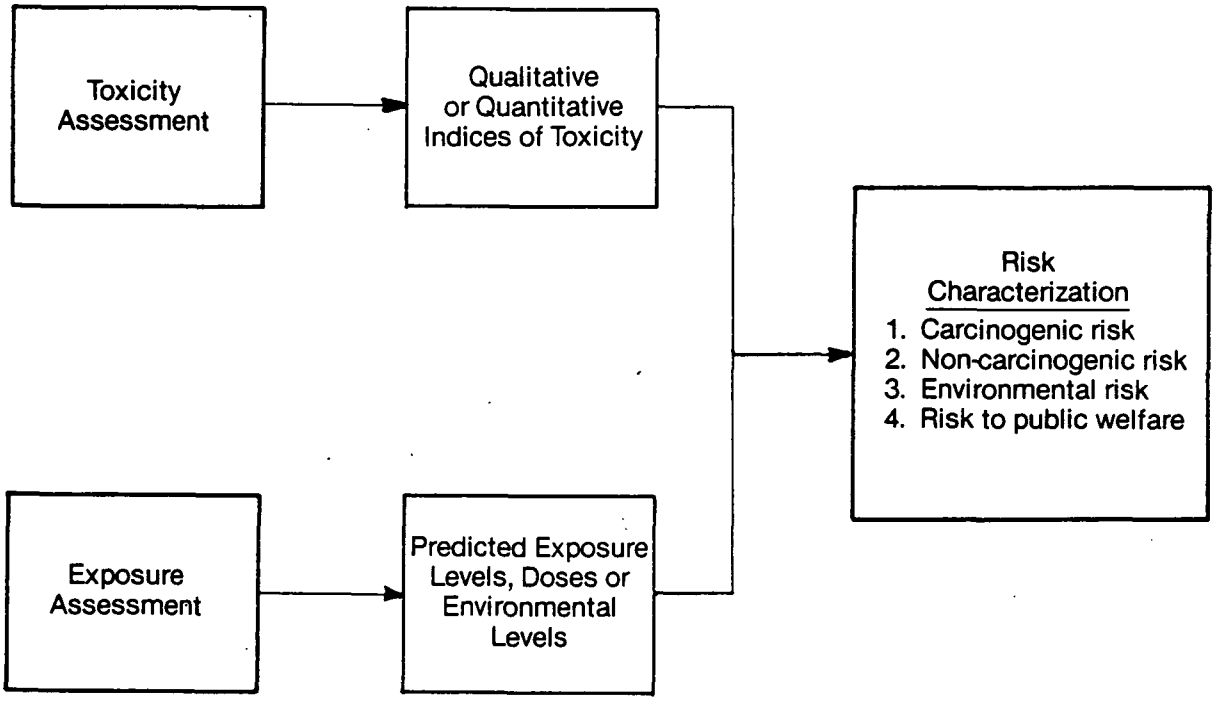


FIGURE 3-4 THE RISK CHARACTERIZATION PROCESS

4.0 GUIDELINES FOR CONDUCTING ENDANGERMENT ASSESSMENTS

This section provides guidelines for conducting the few components of an endangerment assessment, beginning with a discussion of the level of detail required for each type of enforcement action. Although the steps required for conducting the exposure and toxicity assessments and risk characterization are identified, the details of how they are to be performed are not included in this Handbook. The "Superfund Public Health Assessment Manual" (ICF 1985), currently under development as an instruction manual to accompany the RI and FS guidance documents, will provide details for performing the components of the endangerment assessment process.

The endangerment assessment process is very similar to the baseline assessments performed during the RI and FS process. Although the assessments at Superfund and enforcement sites are performed for different reasons, the information requirements for each type of assessment are similar and the assessment methods used should be consistent. Therefore, the assessment methodologies detailed in the RI and FS instruction manuals cited above should be utilized, in conjunction with this Handbook, when performing endangerment assessments. Table 4-1 outlines the relationship between the endangerment assessment steps identified in this Handbook and the appropriate chapters in the RI and FS instruction manuals.

4.1 Level of Detail

It is EPA policy that endangerment assessments should be undertaken only to the extent "necessary and sufficient" to fulfill the requirements of legal enforcement proceedings. The endangerment assessment level of detail should be limited to the amount of information needed to sufficiently demonstrate an actual or potential imminent and substantial endangerment.

The level of detail required to sufficiently demonstrate endangerment will vary depending on:

1. Type of enforcement action (e.g., AO for removal versus litigation)
2. Type of response action (e.g., removal versus remedial action)
3. Stage of response action (e.g., RI/FS workplan versus RI/FS completed)

The level of detail required to support a particular enforcement action will ultimately be determined on a case-by-case basis by the litigation team.

The levels of detail required actually represent a continuum from the qualitative to the quantitative. For simplicity's sake, however, three succinct levels of detail have been defined: Level 1 (qualitative), Level 2 (semi-quantitative) and Level 3 (quantitative).

4.1.1 Level 1 ("Qualitative")

Level 1 endangerment assessments are generally prepared to support AOs for removal actions, a responsible party RI/FS or preliminary scoping activities.

TABLE 4-1 RELATIONSHIP BETWEEN THE ENDANGERMENT ASSESSMENT HANDBOOK AND THE SUPERFUND PUBLIC HEALTH ASSESSMENT MANUAL (SPHAM)

Steps Identified in the Endangerment Assessment Handbook	Chapters in the SPHAM[a] in which the Steps are Discussed
1.0 CONTAMINANT IDENTIFICATION	4
2.0 EXPOSURE ASSESSMENT	5
2.1 Contaminant Release Analysis	5
2.2 Environmental Fate Analysis	5
2.3 Exposed Population Analysis	5
2.4 Calculation of Dose Incurred	6
3.0 TOXICITY ASSESSMENT	7
3.1 Toxicological Evaluation	7
3.2 Dose-Response Assessment	7
4.0 RISK CHARACTERIZATION	8
4.1 Noncarcinogenic Risks	8
4.2 Carcinogenic Risks	8
4.3 Environmental Risks	--
4.4 Public Welfare Risks	--

(a) SPHAM = Superfund Public Health Assessment Manual (ICF 1985).

Level 1 endangerment assessments are also applicable for those cases when time becomes a factor in the enforcement action. An example of a situation in which a "quick and dirty" assessment may be necessary is a case where the responsible party is going to declare bankruptcy and EPA must file an enforcement action very quickly in order to assure the financial liability of the responsible party.

Basically, the information to satisfy the requirements for a Level 1 endangerment assessment can be covered by the Action Memorandum developed by the regions to support emergency removal actions. It is based entirely on existing data which may include the Hazard Ranking System evaluation, preliminary site assessment and site inspection report (if available). The "Findings of Fact" in an AO for remedial actions may serve as a Level 1 endangerment assessment and vice versa.

A Level 1 endangerment assessment must characterize the physical description of the site and identify contaminants detected or suspected to be at the site. A brief discussion of the toxic properties of the contaminants present should be sufficient to justify EPA's contention that imminent and significant risk of harm to human life or health or the environment may exist or exists.

4.1.2 Level 2 ("Semi-Quantitative")

A Level 2 endangerment assessment may be developed to support an AO or consent decree for responsible party cleanup. It will be based on existing information on the site, including the Hazard Ranking System evaluation, preliminary site assessment and site inspection reports. Additional information that may be available include the RI/FS workplan and preliminary health effects and exposure studies.

A Level 2 endangerment assessment must completely characterize the site contamination and provide preliminary exposure and toxicity assessments. The toxicity assessment will generally rely on existing standards and guidelines for the contaminants of concern at the site. The risk characterization will be "semi-quantitative" in nature and should identify any data gaps and recommend additional studies, if necessary.

4.1.3 Level 3 ("Quantitative")

A Level 3 endangerment assessment is required for sites targeted for litigation after completion of the RI/FS and will be used to support any subsequent AOs or judicial actions seeking design and construction remedies.

It will be based on all existing data gathered during the RI/FS. For sites with enforcement potential, EPA regions should review the RI/FS workplan to ensure that information developed as part of the RI/FS will be sufficient to perform a quantitative endangerment assessment.

A Level 3 endangerment assessment must provide a detailed characterization of the site and, when possible, quantitative exposure and toxicity assessments for the contaminants present. The Level 3 endangerment assessment differs

from the Level 2 in that actual exposure levels should be developed, using state-of-the-art modeling techniques. Likewise, in the absence of existing standards and guidelines for the contaminants of concern, the Level 3 endangerment assessment should generate quantitative indices of toxicity (e.g., "acceptable levels," unit cancer risk estimates, etc.) for use in the characterization of risks at the site. The risk characterization will be a quantitative evaluation of the risk assessment values for each probable exposure scenario.

A Level 3 endangerment assessment may be performed concurrently with the FS evaluation of the no-action alternative. The FS may provide input to the endangerment assessment although the purposes and objectives of the two documents are different. In some cases, a quantitative assessment will still not be possible at the RI/FS stage due to data limitations.

Table 4-2 presents a summary of guidelines for determination of the levels of detail required for each type of enforcement action. The guidelines are flexible and may shift on a case-by-case basis as required to support a particular enforcement action. The matrix should help determine what constitutes an adequate endangerment assessment for a particular enforcement action. Table 4-3 summarizes the site-specific documentation that may be available to prepare the endangerment assessment document for each level of detail.

4.2 Contaminant Identification Guidelines

The first component of the endangerment assessment process is the identification of contaminants of concern. The objective of this component is to narrow the field of contaminants at the site to those that either pose the greatest potential of release or the greatest toxic threats.

Identification of contaminants of concern is an informal screening process performed with the input of all members of the endangerment assessment team. The best professional judgment of the endangerment assessment team results in selection of contaminants of concern which represent a range of the physiochemical and toxicological properties of the contaminants at the site.

This screening process corresponds to the "Selection of Indicator Chemicals" process described in the Superfund Public Health Assessment Manual (SPHAM) (ICF 1985). The Superfund process for selecting indicator chemicals is a four-step process which evaluates the environmental concentrations and toxicological properties of the contaminants. The steps of this process are:

1. Identify contaminants present at the site.
2. Record environmental concentrations from site sampling data.
3. Calculate indicator scores for all chemicals (based on concentration and toxicity).
4. Select indicator chemicals (based on indicator scores).

If indicator chemicals have been selected at a site (i.e., site was a Superfund site prior to the initiation of enforcement actions), they should be used as the contaminants of concern for the endangerment assessment. If indicator

TABLE 4-2 GUIDELINES FOR LEVEL OF DETAIL IN ENDANGERMENT ASSESSMENTS[a]

Level of Detail	Enforcement Action	Data Base	Type of Assessment	Remarks
Level 1	AO for removal action, AO for PRP RI/FS, preliminary scoping.	May be limited, probably consisting of information from the Preliminary Site Assessment, Site Inspection Report, and Hazard Ranking System evaluation, if completed. No health studies available; no demographic studies available. Preliminary sampling data will probably be available on pollutants present. Data on extent of release or concentrations of materials at the point of exposure may be available.	Qualitative assessment of exposure routes, population at risk and probability of harm. Critical pollutants and their toxicological properties can be readily identified and quantity of pollutants estimated. Reasonable and prudent to conclude that an exposure may exist because of the release.	For removal actions where the normal site ranking process has not been completed or undertaken, information for the assessment may be available from record searches, State-sponsored investigations, written reports from inspections by Government authorities and notification in accordance with CERCLA Section 103.
Level 2	Issuance of AO or consent decree for responsible party cleanup.	Remedial Investigation complete or other quantitative data available on nature/extent of release. Data available on magnitude and demographics of population at risk. Possibly some preliminary health effects studies. Sources and specific materials associated with release are identified.	Semi-quantitative appraisal considering specific exposure routes and critical pollutants. The assessment should identify any data gaps and recommend additional studies, if necessary.	This assessment must be able to support legal action in the event it is challenged by a recalcitrant responsible party. Should be conclusive enough that responsible parties will be encouraged to make a firm commitment to complete remedial action.

continued-

(a) The guidelines are flexible and may shift on a case-by-case basis as required to support a particular enforcement action.

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Table 4-2 - continued

Level of Detail	Enforcement Action	Data Base	Type of Assessment	Remarks
Level 3	Litigation (site-by-site basis).	RI and FS complete. All required geological and hydrogeological studies complete. Health studies may be available.	Detailed, quantitative review to identify potential health effects, critical exposure levels and necessary follow-up health studies. Critical pollutants and exposure routes identified and existing exposure levels defined or estimated. Constitutes an appraisal based on the best expertise and knowledge and an estimate of the uncertainty.	This assessment must be able to support legal action in the event it is challenged by a recalcitrant responsible party. Should be conclusive enough that responsible parties will be encouraged to make a firm commitment to complete remedial action.

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TABLE 4-3 SITE-SPECIFIC DOCUMENTATION AVAILABLE FOR THE PREPARATION OF ENDANGERMENT ASSESSMENTS

Site-Specific Documentation	Availability for Levels of Detail		
	Qualitative (Level 1)	Semi-Quantitative (Level 2)	Quantitative (Level 3)
Preliminary Site Assessment	Probable	Yes	Yes
Site Inspection Report	Probable	Yes	Yes
Hazard Ranking System Evaluation	Probable	Yes	Yes
Remedial Investigation/ Feasibility Study	No	Possible	Yes
Epidemiological Studies	No	Possible	Possible
Demographic Studies	No	Possible	Yes
Sampling Studies	Possible	Probable	Yes
Exposure Studies	Possible	Probable	Yes
Health Effects Studies	No	Possible	Possible
Geological Studies	Possible	Probable	Yes
Hydrogeological Studies	Possible	Probable	Yes

chemicals have not been selected, the endangerment assessment team will select the contaminants of concern, possibly based on the methodology discussed in Chapter 4 of the SPHAM (ICP 1985).

4.3 Exposure Assessment Guidelines

This section of the Handbook is intended to serve as a guide for individuals responsible for conducting exposure assessments. It identifies and describes the necessary steps in an exposure assessment and provides general information for performing each of the required steps. This section is not intended to serve as a definitive guide on how to perform specific exposure assessment procedures. For this type of information, the reader is referred to the SPHAM (ICF 1985). Additional guidance documents for performing exposure assessments include Callahan et al. (1983), McNells et al. (1984), Schultz et al. (1984) and USEPA (1984).

The exposure assessment should evaluate all existing exposure routes and those which may reasonably be anticipated to exist in the future. For example, if land use development documents indicate that a site located in a currently rural or industrial area is scheduled for residential development, then the exposure assessment should develop exposure scenarios evaluating the current risk, as well as the risks associated with predicted residential use patterns.

The exposure scenarios developed will depend on site-specific technical and legal considerations. Generally, an exposure assessment for an endangerment assessment should present the "worst probable case" exposure scenarios. The exposure assessment at a site prior to any removal or remedial actions may be significantly different from an exposure assessment at the same site following completion of the RI/FS (i.e., a removal action at the site may have altered the exposure routes). Thus, the exposure assessment should always consider the type of enforcement action the endangerment assessment is intended to support. The best professional judgment of the experts on the endangerment assessment team will be the basis for establishing which exposure scenarios should be developed for each site.

The objectives of an exposure assessment are to identify actual or potential routes of exposure, characterize the populations exposed and determine the extent of the exposure. These objectives may be attained by performing the following four steps:

1. Analyze contaminant release
2. Analyze environmental fate and transport
3. Analyze exposed populations
4. Estimate or calculate expected exposure levels (or doses incurred)

This section presents information on conducting each of these analyses. Table 4-4 identifies the individual steps required to complete an exposure assessment, the endangerment assessment level of detail to which they apply and the locations in this Handbook where they are discussed.

TABLE 4-4 EXPOSURE ASSESSMENT STEPS

Exposure Assessment Step	Level of Detail[a] 1	2	3	Applicable Handbook Sections 4.0	5.0
1.0 Contaminant Release Analysis	X	X	X	4.3.1	5.1
1.1 Identify Information Required	X	X	X		
1.2 Evaluate Contaminant Release to Environmental Media		X	X		
1.3 Quantify Contaminant Release to Environmental Media			X		
2.0 Environmental Fate and Transport Analysis	X	X	X	4.3.2	5.2
2.1 Identify Potential Points of Environmental Contamination	X	X	X		
2.2 Evaluate Environmental Fate and Transport Processes		X	X		
2.3 Quantify Environmental Fate and Transport Processes			X		
3.0 Exposed Population Analysis	X	X	X	4.3.3	5.3
3.1 Identify Exposed Populations	X	X	X		
3.2 Characterize Populations	X	X	X		
3.3 Analyze Population Activity		X	X		
3.4 Identify/Develop Exposure Coefficients			X		
4.0 Calculation of Dose Incurred		X	X	4.3.4	5.3
4.1 Determine Population Exposure Level		X	X		
4.2 Estimate Dose Incurred		X	X		

(a) X indicates the level of endangerment assessment (e.g., Level 1, 2 or 3) for which this step must be performed.

4.3.1 Contaminant Release Analysis

The contaminant release analysis involves the identification of each on-site source of release for the contaminants of concern. The results of this analysis provide the basis for the next step in the exposure assessment process, environmental fate analysis.

In order to evaluate the probability and extent of contaminant releases from a hazardous waste site, the following information is required:

1. Identity of contaminants at the site
2. Physical/chemical properties of the contaminants
3. Climatological site parameters
4. Hydrogeological site parameters
5. Location and manner of waste placement

Each potential source of contaminants must be identified and evaluated to determine its likely contribution to overall contaminant release. The nature of the contaminants involved and the probable magnitude of release are also evaluated.

Contaminant release analysis for Level 1 endangerment assessments consists of identifying and characterizing the information identified above. A qualitative description of the sources of contaminants and the relative importance of each source is sufficient for a Level 1 endangerment assessment.

Quantitative analyses of contaminant releases from hazardous waste sites (for Level 2 and 3 endangerment assessments) are initiated by an evaluation of the available data to determine their accuracy and completeness. Following this initial evaluation, each source of contaminant release is analyzed and total releases (i.e., mass loadings) to each environmental medium (e.g., atmosphere, surface water, soil, ground water) are evaluated and quantified. Potential sources of contaminant release to each medium are outlined below:

1. Atmospheric Contamination - Emissions of contaminated fugitive dusts (airborne wastes and contaminated soil particles) and volatilization of contaminants are the most likely sources of atmospheric contamination

2. Surface-Water Contamination - Contaminated runoff and overland flow of contaminants (from leaks, spills, etc.) are the most likely sources of surface water contamination.

3. Ground-Water Contamination - The leaching of toxic contaminants from contaminated soils or vertical migration of toxics from lagoons and ponds are the most likely sources of ground-water contamination.

4. Soil Contamination - Sources of surface soil contamination include intentional placement of waste on or in the ground, or as a result of spills, lagoon failure or contaminated runoff. Toxic contaminants can also be leached from surface soils to subsurface layers.

Schultz et al. (1984) discusses the methods available to evaluate and quantify each of these factors (e.g., atmospheric, surface-water, ground-water and soil contamination).

Level 2 endangerment assessments should report the results of any monitoring studies available for each of these factors. If there are insufficient monitoring data available to quantify contaminant releases to these media, the Level 2 endangerment assessment should present a discussion of the site characteristics which affect the probability or likelihood of contamination of each media occurring at the site.

Level 3 endangerment assessments may utilize computer modeling techniques to arrive at estimates of the average and maximum contaminant release to each media. These quantitative estimates are required for the subsequent calculations of actual and projected exposure levels at the site.

An overview of the contaminant release analysis process is shown in Figure 4-1.

4.3.2 Environmental Fate and Transport Analysis

The purpose of the environmental fate and transport analysis is to determine the potential for off-site migration of contaminants from on-site sources identified during the qualitative release analysis. The analysis of environmental fate and transport results in identification of probable points of contamination associated with a hazardous waste site. The results of this analysis provide the basis for the next step in the exposure assessment process, the exposed population analysis.

A qualitative environmental fate and transport analysis (i.e., Level 1 endangerment assessment) is based on information on the physical/chemical properties of the contaminants, the manner of their placement at the site and relevant climatological and hydrogeological site parameters. This information was identified during the contaminant release analysis. Intermedia transport processes (e.g., adsorption, volatilization, infiltration, bioaccumulation) and intramedia transformation processes (e.g., photolysis, hydrolysis, oxidation and biodegradation) which potentially affect migration of the contaminants of concern are identified and characterized in the Level 1 endangerment assessment. This information is used to identify potential points of environmental contamination. An overview of the environmental fate and transport analysis for Level 1 endangerment assessments is shown in Figure 4-2.

Level 2 and 3 endangerment assessments require a more quantitative environmental fate and transport analysis to generate estimates of the direction of movement of contaminants and the ambient concentrations of contaminants in various environmental media. The average release rate estimates derived during the contaminant release analyses are used as input.

In general, the environmental fate and transport analysis for Level 2 endangerment assessments evaluates the transport pathways within each medium but does not take into consideration transfer and transformation processes. The Level 2 endangerment assessment should report any ambient monitoring data and

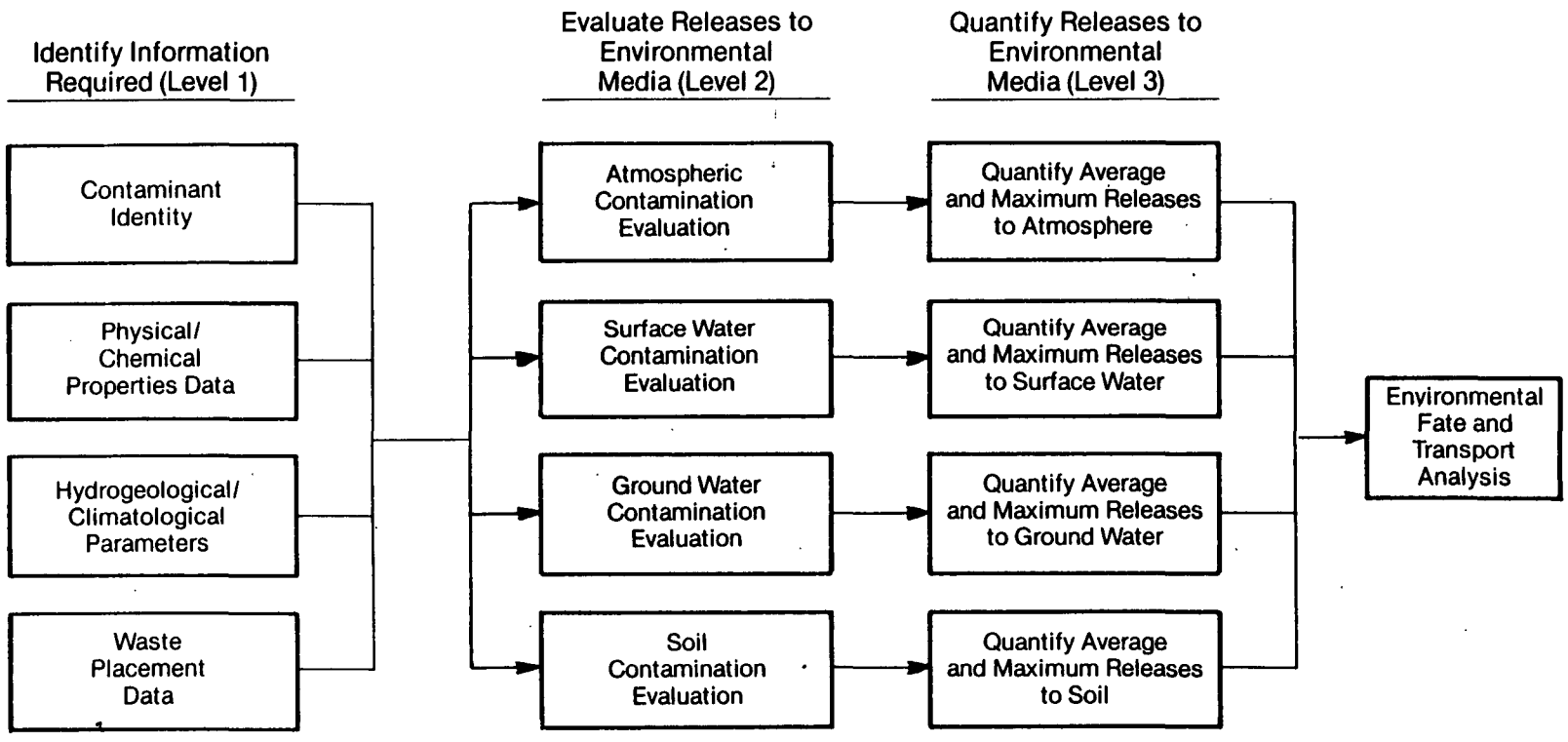

FIGURE 4-1 OVERVIEW OF CONTAMINANT RELEASE ANALYSIS

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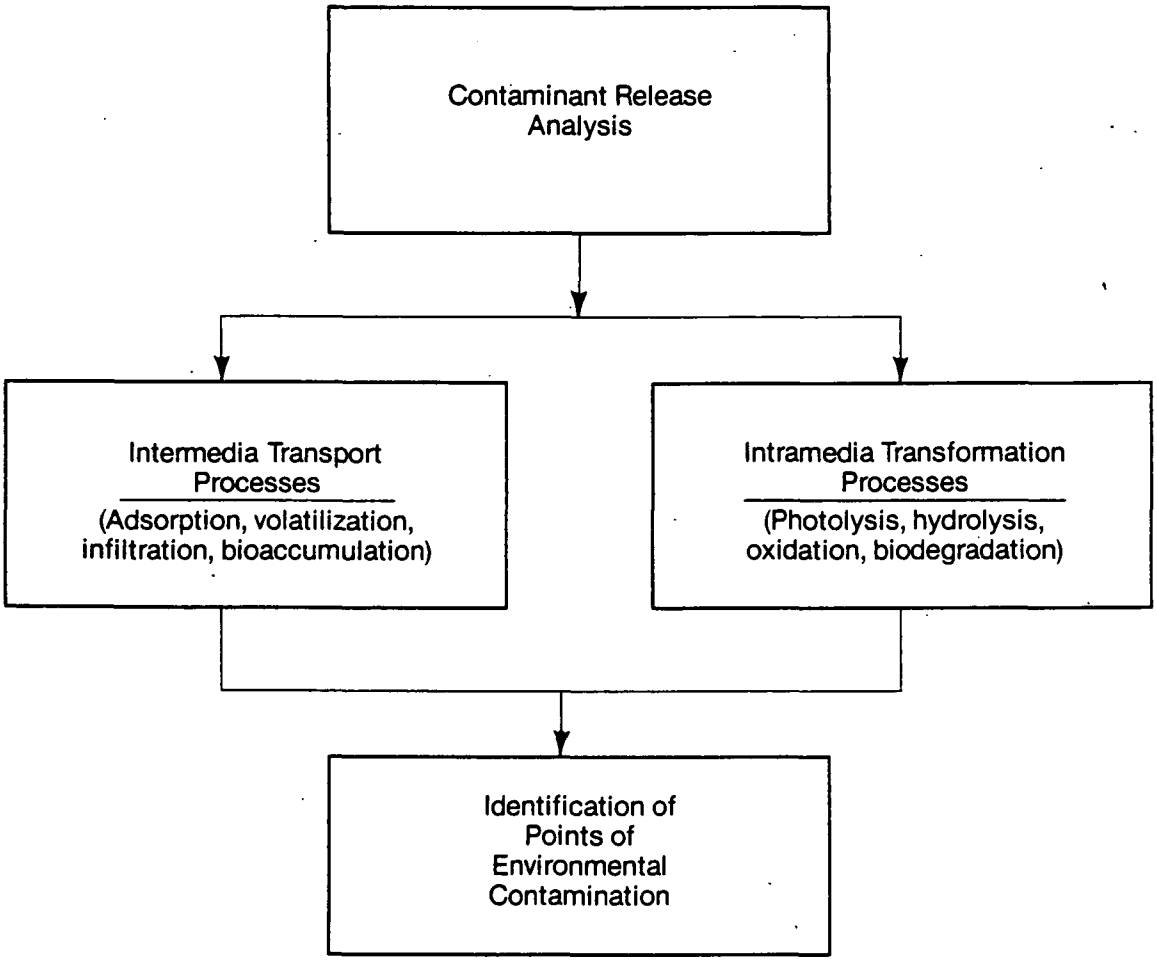

FIGURE 4-2 OVERVIEW OF ENVIRONMENTAL FATE AND TRANSPORT ANALYSIS FOR LEVEL 1 ENDANGERMENT ASSESSMENTS

provide conservative estimates of final ambient concentrations and the extent of hazardous substance migration.

Level 3 endangerment assessments require more in-depth assessments of environmental fate and transport. Modeling procedures usually must be applied to quantify atmospheric fate, surface-water fate, ground-water fate and biotic pathways. One relevant set of models for this purpose is the Graphic Exposure Modeling System (GEMS) (USEPA 1982). GEMS provides access to models capable of assessing the fate of contaminants in air, surface water, ground water and soil. Table 4-5 identifies the current components of GEMS. Schultz et al. (1984) discuss further the available methods for quantitative environmental fate and transport analyses.

An overview of the environmental fate and transport analysis process for Level 2 and 3 endangerment assessments is shown in Figure 4-3.

4.3.3 Exposed Population Analysis

The exposed population analysis provides an evaluation of the expected degree of human population contact with contaminants emanating from the site. The results of this analysis are used in estimating or calculating exposure levels and doses incurred by the exposed populations.

The exposed population analysis involves the following four steps:

1. Identification of exposed populations
2. Characterization of population
3. Analyses of population activities
4. Development of exposure coefficients

The first step requires comparing data on environmental contamination with population data in order to identify and enumerate those populations (human and environmental) that will potentially or actually be exposed to the contaminant(s) of concern. The second step, population characterization, involves identifying those groups (e.g., infants, elderly, women of child-bearing age, endangered or sensitive wildlife species) within the exposed populations which may experience a greater risk than the average population as a result of a given exposure level. The third step, activity analysis, involves an examination of the activities (e.g., employment, recreation) of potentially or actually exposed populations in order to define the extent or level of exposure of the previously identified and characterized populations.

The final step of the exposed population analysis is the identification of exposure coefficients. The exposure coefficient combines information on the frequency and magnitude of contact with contaminants to yield a quantitative value of the amount of contaminated medium contacted per day. Exposure coefficients are developed for each exposure route and are used as input in calculating the dose incurred. An example of an exposure coefficient would be the average daily intake of drinking water or pounds of fish consumed in a week, etc. Schultz et al. (1984) provide lists of exposure coefficients that may be required for exposure assessments at hazardous waste sites.

TABLE 4-5 COMPONENTS OF EPA's GRAPHICAL EXPOSURE MODELING SYSTEM (GEMS)

Models	
ATM/SECPOP:	Atmospheric transport model (ATM) and a population distribution retrieval program (SECPOP).
PTMAX:	Produces analysis of maximum atmospheric concentration as a function of wind speed and atmospheric stability.
PTDIS:	Calculates downwind atmospheric concentration at ground level at various downwind distances.
BOXMOD:	Interactive simple atmospheric box model for screening chemicals.
EXAMS:	Evaluates behavior of synthetic organic chemicals in aquatic ecosystems.
SESOIL:	Long-term environmental fate simulation model for water, sediment and pollutant transport/transformation.
ENPART:	Environmental partitioning model.
Physiochemical Property Estimation Programs	
SFILES:	Molecular structure diagrams.
CLOGP:	Estimates octanol-water partition coefficient (log P).
CHEMEST:	Estimates physiochemical properties of organics.
Data Files	
GEOECOLOGY DATA BASE:	County-level data on a variety of environmental parameters.
IFD/GAGE:	Point source discharges and stream gaging stations.
MASTER AREA REFERENCE FILE 1980 CENSUS:	U.S. Census data for small geographic areas.
METEOROLOGICAL DATA:	Stability Tubular Array (STAR) data for >300 first-order weather stations.
ZIP CODE FILE:	Associates zip codes with Federal Information Processing System (FIPS) codes.
CANONICAL ENVIRONMENTS DATA:	Model input parameters for major U.S. river systems, lakes and reservoirs.

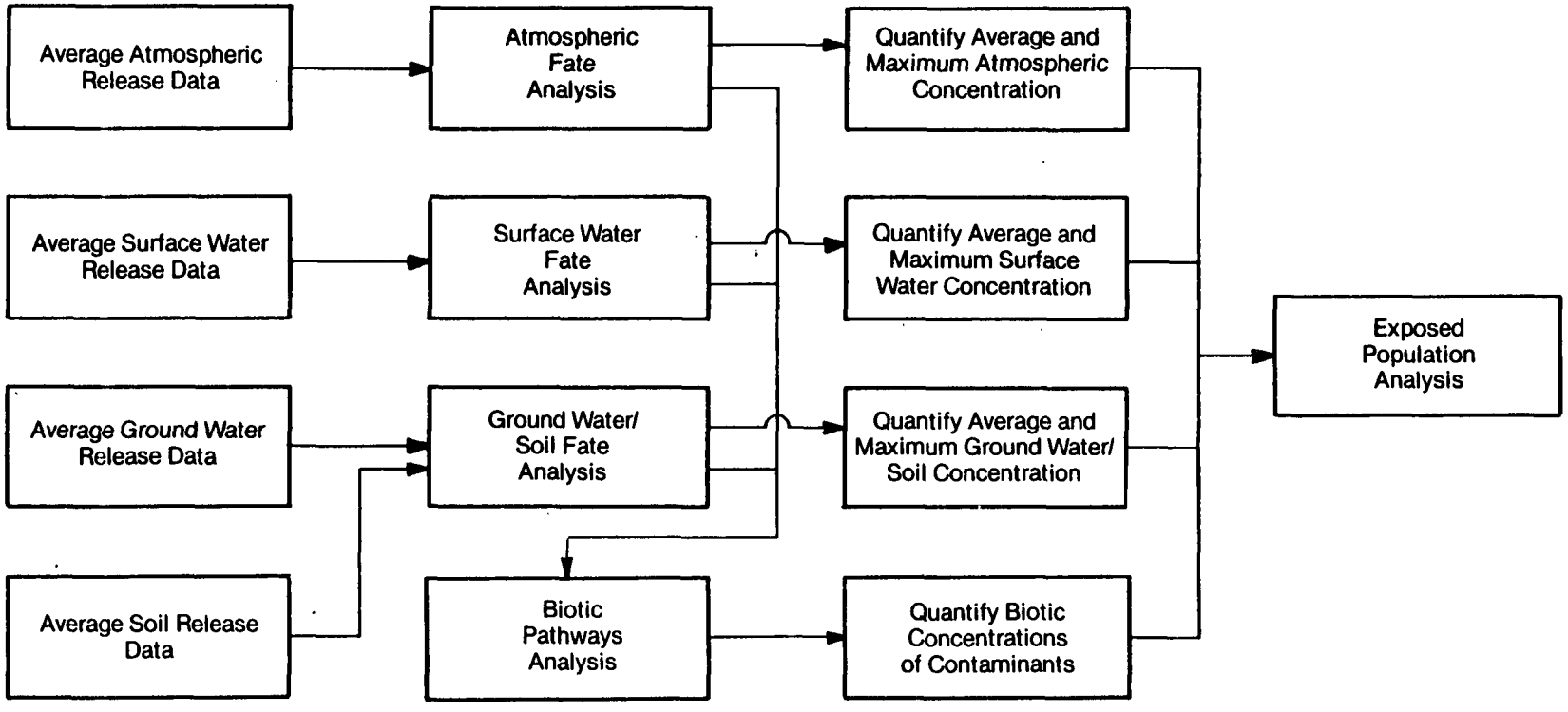

FIGURE 4-3 OVERVIEW OF ENVIRONMENTAL FATE AND TRANSPORT ANALYSIS FOR LEVEL 2 AND 3 ENDANGERMENT ASSESSMENTS

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Level 1 endangerment assessments should identify the exposed populations and provide a brief characterization of the population. This is a descriptive analysis which should not require quantitative census or survey data. Level 2 and 3 endangerment assessments will utilize available census and survey data to provide quantitative assessments of the exposed populations.

An overview of the exposed population analysis process is shown in Figure 4-4.

4.3.4 Calculation of Exposure Level and Dose Incurred

Schaum (1984) presents a discussion of the specific exposure assessment methods that should be used in estimating the dose incurred. The following discussion outlines the general steps that are required in performing this ultimate step in an exposure assessment.

The term "exposure" may be defined as the amount of a contaminant that contacts the boundaries of an organism (e.g., skin, lungs, or gastrointestinal tract), while "dose" may be defined as the amount of that contaminant absorbed by the organism. The fourth and final step in conducting an exposure assessment requires a quantitative determination of the dose of contaminants incurred by receptor populations. Accomplishing this task involves integrating the results obtained during the first three steps of the exposure assessment (Contaminant Release Analysis, Environmental Fate Analysis and Exposed Population Analysis) to determine the cumulative dose of each contaminant incurred by each population segment.

In calculating the dose incurred, an exposure coefficient is multiplied by the chemical-specific environmental concentration values derived during the Contaminant Release Analysis. This calculation provides a route-specific estimate of the total amount of each contaminant to which the population is exposed on a daily basis. Summing the exposures for each exposure route yields a total daily exposure level for each contaminant.

This exposure value must be adjusted to account for the extent to which each chemical is transferred across the membranes of the exposed organism (i.e., the extent of absorption). This adjustment is accomplished by multiplying total daily exposure values by an absorption factor. Absorption factors are generally available in the toxicity profiles discussed in Section 4.4 of this Handbook. When empirically derived absorption factors are not available, an absorption factor of unity is applied, thereby generating a conservative, worst-case estimate of the dose incurred. Finally, this whole-body dose estimate (mg/day) is converted to terms of mg of contaminant/kg of body mass/day by dividing it by the body mass representative of the receptor population. EPA's Exposure Assessment Group has prepared a report which contains ranges of standard factors (i.e., body mass, surface area, etc.) for use in performing exposure assessments. Use of these standard factors promotes consistency among all exposure assessment activities (Anderson et al. 1984).

Since the risk characterization portion of a quantitative (Level 3) endangerment assessment requires the development of average daily dose and maximum daily dose estimates, two calculations of dose incurred must be performed. Estimates

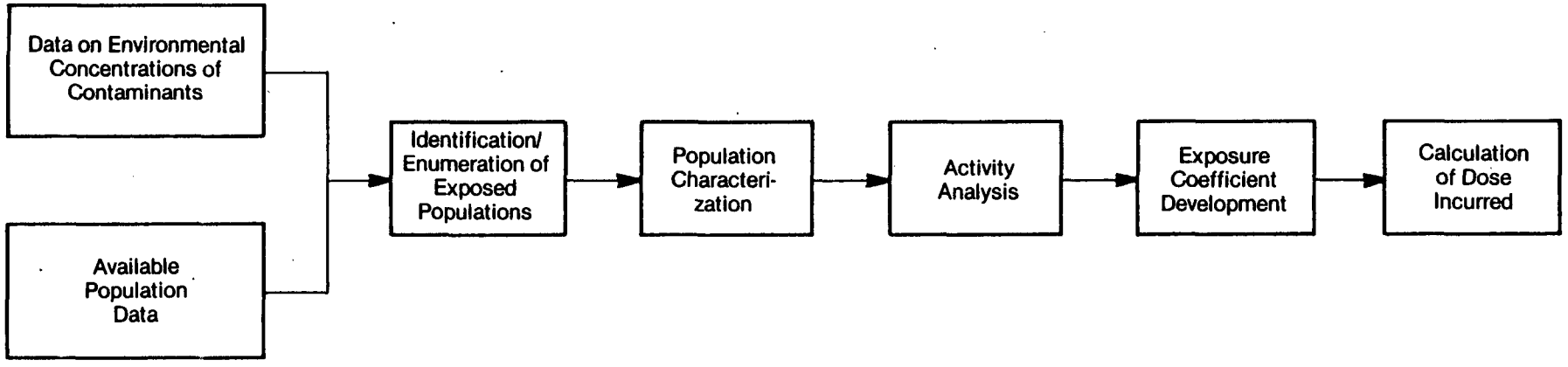

FIGURE 4-4 OVERVIEW OF EXPOSED POPULATION ANALYSIS

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of average daily dose are calculated by multiplying the exposure coefficients derived during the exposed populations analysis by the average environmental concentration values. Estimates of maximum daily dose are calculated by multiplying the exposure coefficients by the maximum environmental concentration values.

Level 1 endangerment assessments are qualitative assessments which do not require a calculation of estimated exposure levels or doses incurred. Level 2 and 3 endangerment assessments require an integrated exposure assessment which quantifies exposure via all routes of exposure (inhalation, ingestion and dermal) and all exposure pathways (e.g., surface water, atmosphere, ground water, etc.). The uncertainty associated with the exposure values is a function of the input parameters throughout the exposure assessment process. Level 2 and 3 exposure assessments must characterize the uncertainty associated with the final exposure and dose calculations. Whitmore (1984) provides a methodology for characterizing the uncertainty in exposure assessments. All exposure calculations for the endangerment assessment must be adequately documented. Assumptions made in support of these calculations require justification in writing as part of the endangerment assessment.

An overview of the process for calculating the dose incurred is shown in Figure 4-5.

4.3.5 Exposure Assessment References

Anderson E, Browne N, Duletsky S et al. GCA Corporation. 1984. Development of statistical distributions or ranges of standard factors used in exposure assessment. Revised Draft Final Report. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Exposure Assessment Group. Contract No. 68-02-3510.

Callahan MA, Johnson RH, McGinnity JL et al. 1983. Handbook for performing exposure assessments. Draft. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment.

ICF Incorporated. 1985. Superfund public health assessment manual. Draft. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. Contract No. 68-01-6872.

McNells DN, Barth DC, Khare M et al. Environmental Research Center, University of Nevada at Las Vegas. 1984. Exposure assessment methodologies for hazardous waste sites. Las Vegas, NV: Office of Research and Development. Environmental Monitoring Systems Laboratory. CR810550-01.

Schaum J. 1984. Short course on integration of exposure and risk assessment. Part 3. Exposure assessment methods. Paper presented at the Annual Meeting of the Society for Environmental Toxicology and Chemistry, Arlington, VA.

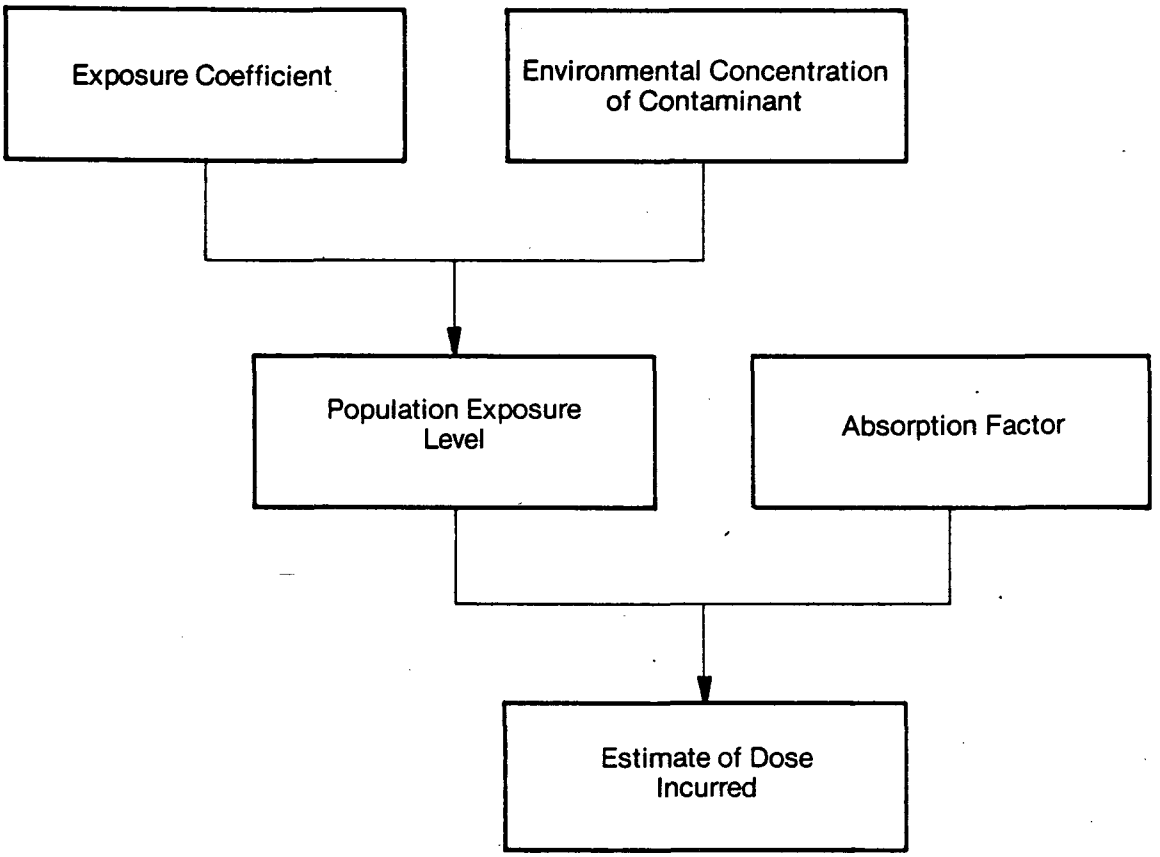

FIGURE 4-5 OVERVIEW OF PROCESS FOR CALCULATING POPULATION EXPOSURE LEVELS AND DOSE INCURRED

Schultz HL, Palmer WA, Dixon GH et al. Versar Inc. 1984. Superfund exposure assessment manual. Final Draft. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances, Office of Solid Waste and Emergency Response. Contract Nos. 68-01-6271 and 68-03-3149.

USEPA. 1984. U.S. Environmental Protection Agency. Office of Health and Environmental Assessment. Proposed guidelines for exposure assessment. Fed. Regist., Nov. 23, 1984, 49 46314.

USEPA. 1982. U.S. Environmental Protection Agency. Office of Pesticides and Toxic Substances. Graphical exposure modeling system (GEMS) user's guide. Draft. Washington, DC: U.S. Environmental Protection Agency.

Whitmore RW. Research Triangle Institute. 1984. Methodology for characterization of uncertainty in exposure assessments. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Exposure Assessment Group. Contract No. 68-01-6826.

4.4 Toxicity Assessment Guidelines

This section of the Handbook is intended to serve as a guide for individuals responsible for conducting toxicity assessments. It identifies and describes the necessary steps required in a toxicity assessment and provides general information on performing each of the required steps. The toxicity assessment process is discussed briefly in the SPHAM (ICF 1985). A more detailed discussion of the components of the toxicity assessment process is provided in "Toxicology Handbook: Principles Related to Hazardous Waste Site Investigations" (ICAIR 1985) which is currently being prepared under the direction of the Health Sciences Section, OWPE.

The objectives of the toxicity assessment are to determine the nature and extent of health and environmental hazards associated with exposure to contaminants present at the site. The end-product is a toxicity profile for each contaminant of concern. The toxicity profile is derived from current toxicological literature on a contaminant. The profile includes considerations of doses used, routes of exposure, types of adverse effects manifested and definitive statements on quantitative indices of toxicity for the contaminant.

The Office of Emergency and Remedial Response (OERR) and OWPE have prepared toxicity profiles specifically for use in assessing toxicological risk at hazardous waste sites. The Chemical Profiles prepared by OWPE briefly summarize the chemical and physical properties, fate and transport, health effects and environmental toxicity levels for chemicals found most often at hazardous waste sites. There are currently 183 Chemical Profiles available in draft form from OWPE. OERR is preparing Health Effects Assessments on the most commonly occurring chemicals at hazardous waste sites. The Health Effects Assessments, being prepared for OERR by EPA's Environmental Criteria and Assessment Office (ECAO), contain information on acceptable intake levels for sub-chronic and chronic exposure from both ingestion and inhalation pathways of exposure. There are currently 58 Health Effects Assessments

available in draft form from OERR. Table 4-6 lists the chemicals for which Chemical Profiles and Health Effects Assessments are currently available.

Other EPA offices have also prepared toxicity profiles on numerous chemicals. The EPA Chemical Activities Status Report (CASR), a guide to EPA activities on specific chemical substances, provides information on the status of the activities and a point-of-contact in the appropriate EPA program office responsible for the preparation of the toxicity profile (USEPA 1984f). The types of toxicity profiles included in CASR are listed in Table 4-7. For information on the availability of specific toxicity profiles, contact the program office identified in Table 4-7.

If an acceptable EPA toxicity profile exists for a contaminant at the site in question, it is unnecessary to re-create one for the Toxicity Assessment. The existing profile should be briefly summarized and referenced in the endangerment assessment document. However, if the existing profile focuses on a different exposure route, or is more than three years old, it should be supplemented with a search of the current literature.

When no toxicity profile is available, or the existing toxicity profile is inadequate, the toxicologist on the endangerment assessment team must review the current toxicological literature on the contaminant of concern and prepare a suitable toxicity profile. This toxicological review and evaluation process is known as the toxicity assessment. It is a two-step process consisting of a toxicological evaluation and a dose-response assessment. Table 4-8 summarizes the steps in the toxicity assessment process and identifies the endangerment assessment level of detail to which they apply and the locations in this Handbook where they are discussed.

4.4.1 Toxicological Evaluation

The toxicological evaluation is the first step in the toxicity assessment process. It is a qualitative evaluation of the scientific data to determine the nature and severity of potential health and environmental hazards associated with exposure to a chemical substance.

The toxicological evaluation involves a critical evaluation and interpretation of toxicity data from epidemiological, clinical, animal and *in vitro* studies when human health effects are of concern and of ecotoxicity studies when environmental effects are of concern. The toxicological evaluation results in either a health or environmental toxicity profile (or both) for each contaminant of concern. The toxicity profile presents a review of the primary literature on the types of adverse effects manifested (e.g., chronic, acute, carcinogenic, etc.), routes of administration (e.g., dermal, oral, inhalation, etc.), dose employed, the quality and extent of test data, the reliability of the test data and other factors.

The toxicity profile also identifies any quantitative indices of toxicity reported in the literature, such as NOEL (no-observed-effect level), NOAEL (no-observed-adverse-effect level), LOAEL (lowest-observed-adverse-effect level), LC_{50} (concentration at which 50 percent of the test organisms die),

TABLE 4-6 TOXICITY PROFILES PREPARED SPECIFICALLY FOR USE AT HAZARDOUSE WASTE SITES

Chemical	OWPE Chemical Profile	OERR Health Effects Assessment
Acenaphthene	X	
Acenaphthylene	X	
Acetic acid	X	
Acetone	X	X
Acrolein	X	
Acrylonitrile	X	
Aldrin	X	
Anthracene	X	
Antimony	X	
Arsenic	X	X
Asbestos	X	X
Barium	X	X
Benzene	X	X
Benzidine	X	
Benzo(a)anthracene	X	
Benzo(a)pyrene		X
Benzothiazole	X	
Beryllium	X	
alpha-BHC	X	
beta-BHC	X	
gamma-BHC (lindane)	X	X
delta-BHC	X	
Butanol	X	
Butyl acetate	X	
Cadmium	X	X
Carbon tetrachloride	X	X
cis-Chlordane	X	X
trans-Chlordane	X	X
Chlorine	X	
Chlorobenzene	X	X
Chlorobenzilate	X	
Chloroethane	X	
Chloroform	X	X
p-Chloro-m-cresol	X	
1-Chloro-3-nitrobenzene	X	
bis(2-Chloroethoxy)ethane	X	
Chromium (total)	X	
Chromium (hexavalent)		X
Chromium (trivalent)		X
Chrysene	X	
Coal tars		X
Cobalt	X	
Copper	X	X
Cresol	X	X
Cyanides	X	X
Cyanuric acid	X	
p,p'-DDD	X	
o,p'-DDD	X	
p,p'-DDE	X	
p,p'-DDT	X	X
o,p'-DDT	X	X
Dibromochloropropane	X	
1,2-Dichlorobenzene	X	
1,3-Dichlorobenzene	X	
1,4-Dichlorobenzene	X	
1,1-Dichloroethane	X	X
1,2-Dichloroethane	X	X
1,1-Dichloroethylene	X	X
1,2-cis-Dichloroethylene		X
1,2-trans-Dichloroethylene	X	X
2,4-Dichlorophenol	X	
2,4-Dichlorophenoxyacetic acid	X	
1,2-Dichloropropane	X	

continued-

Table 4-6 - continued

Chemical	OWPE Chemical Profile	OERR Health Effects Assessment
1,3-Dichloropropane	X	
1,3-Dichloropropene	X	
Dicofol	X	
Dieldrin	X	
Diethyl benzene	X	
Diethylene glycol	X	
Diethyl phthalate	X	
Diisobutyl ketone	X	
Dimethylaminoethyl methacrylate	X	
Dimethyl aniline	X	
Dimethylnitrosamine	X	
2,4-Dimethyl pentane	X	
2,4-Dimethylphenol	X	
n-Dioctyl phthalate	X	
1,4-Dioxane	X	
Diphenyl ethane	X	
Endrin	X	
Ethanol	X	
bis(2-Chloroethyl) ether	X	
Ether	X	
Ethyl acetate	X	
Ethylbenzene	X	X
Ethylene glycol	X	
Ethyl hexanediol	X	
bis-2-Ethylhexyl phthalate	X	
Ethyl toluene	X	
Fluoranthene	X	
Formaldehyde	X	
Glycol ethers		X
Heptachlor	X	
Heptane	X	
Hexachlorobenzene	X	X
Hexachlorobutadiene	X	X
Hexachlorocyclohexane	X	
Hexachlorocyclopentadiene		X
Hexachloroethane	X	
Hexachlorophene	X	
Hexane	X	
Iron	X	X
Isobutyl alcohol	X	
Isopropyl benzene	X	
Isopropyl ether	X	
Lead	X	X
Lithium	X	
Magnesium	X	
Manganese	X	X
Mercury	X	X
Methacrylic acid	X	
Methanol	X	
Methyl chloride	X	
2-Methyl dodecane	X	
Methylene chloride	X	X
Methyl ethyl benzene	X	
Methyl ethyl ketone	X	X
3-Methyl hexane	X	
Methyl isobutyl ketone	X	
Methyl methacrylate	X	
Methyl parathion	X	
2-Methyl pentane	X	
3-Methyl pentane	X	
2-Methyl-1-pentene	X	
2-Methyl tetradecane	X	
2-Methyl tridecane	X	

continued-

Table 4-6 - continued

Chemical	OWPE Chemical Profile	OERR Health Effects Assessment
Monethanolamine	X	
Naphthalene	X	X
Nickel	X	X
Nitrocellulose	X	
2-Nitrophenol	X	
Pentachlorophenol	X	X
Pentadecane	X	
Phenanthrene	X	X
Phenol	X	X
Phenyl ether	X	
Phosphoric acid	X	
Phosphorus	X	
Picric acid	X	
Polychlorinated biphenyls (PCBs)	X	X
Polychlorinated dibenzo-p-dioxin	X	
Polycyclic aromatic hydrocarbons (PAHs)		X
Pyrene		X
Selenium	X	X
Silver	X	
Sodium chlorate	X	
Sodium cyanide		X
Sodium	X	
Stoddard solvent	X	
Sulfuric acid		X
1,2,4,5-Tetrachlorobenzene	X	
2,3,7,8-Tetrachloro-dibenzo-p-dioxin (TCDD)	X	X
1,1,2,2-Tetrachloroethane	X	X
Tetrachloroethylene	X	X
Tetraethyl lead	X	
Tetrahydrofuran	X	
Tetramethyl benzene	X	
Thallium	X	
Titanium	X	
Toluene	X	X
Toxaphene	X	
1,2,3-Trichlorobenzene	X	
1,2,4-Trichlorobenzene	X	
1,3,5-Trichlorobenzene	X	
2,3,6-Trichlorobenzoic acid	X	
1,1,1-Trichloroethane	X	X
1,1,2-Trichloroethane	X	X
Trichloroethylene	X	X
Trichlorofluoromethane	X	
2,4,5-Trichlorophenol	X	X
2,4,6-Trichlorophenol		X
2,4,5-Trichlorophenoxyacetic acid	X	
2,4,5-Trichlorophenoxy propionic acid	X	
Trimethylbenzene	X	
1,3,5-Trimethylbenzene	X	
1,2,4-Trimethylbenzene	X	
tris(2,3-Dibromopropyl)phosphate	X	
Undecane	X	
Vanadium	X	
Vinyl chloride	X	X
Xylene	X	X
m-Xylene	X	
o-Xylene	X	
p-Xylene	X	
Zinc	X	X

TABLE 4-7 EPA SOURCES OF TOXICITY PROFILES

Document	Availability	Description
Criteria Document - Air	Office of Air Quality Planning and Standards (OAQPS)	Summary of the latest scientific knowledge on the effects of varying quantities of a substance in the air. Usually prepared for OAQPS by the Office of Health and Environmental Assessment (OHEA).
Criteria Document - Drinking Water	Office of Drinking Water (ODW)	Summary of important experimental results from the literature relevant to the chemistry and health effects of a specific drinking water contaminant. Serves as a foundation to support regulatory standards or guidelines for the acceptable concentration of the contaminant in the drinking water.
Criteria Document - Ambient Water Quality	Office of Water Regulations and Standards (OWRS)	Information on the type and extent of identifiable toxic effects on health and welfare expected from the presence of pollutants in any body of water. Objective of document is to protect most species in a balanced and healthy aquatic community. To date, 65 have been completed, covering all priority pollutants.
Chemical Hazard Information Profile (CHIP)	Office of Toxic Substances (OTS)	Summary of readily available information concerning the health and environmental effects and potential exposure to a chemical.
Chemical Profile	Office of Waste Programs Enforcement (OWPE)	Brief summary of the chemical/physical properties, fate and transport, health effects and environmental toxicity levels for 202 chemicals identified at hazardous waste sites. Currently 183 of the planned Chemical Profiles are available in draft form.

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Table 4-7 - continued

Document	Availability	Description
Health Advisory	ODW	Develops toxicological analyses to establish an acceptable level in drinking water for unregulated contaminants for various exposure durations. Used in transient situations (spills, accidents) therefore, does not consider chronic exposure data (e.g., carcinogenicity).
Health Assessment Document	Office of Health and Environmental Assessment (OHEA)	Inventories the scientific literature and evaluates key studies. Discusses dose-response relationships so that the nature of the adverse health response is evaluated in perspective with observed environmental levels. Usually prepared by OHEA for another office.
Health and Environmental Effects Profile	Office of Solid Waste (OSW)	Profiles are "mini-" criteria documents prepared usually as summaries of existing water quality criteria documents. They serve as a support for the listing of hazardous wastes in the RCRA program.
Health Effects Assessments	Office of Emergency and Remedial Response (OERR)	Summary of the pertinent health effects information on 58 chemicals found most often at hazardous waste sites. Developed by the Environmental Criteria and Assessment Office (ECAO) for OERR.

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TABLE 4-8 TOXICITY ASSESSMENT STEPS

Toxicity Assessment Step	Level of Detail[a] 1	2	3	Applicable Handbook Sections 4.0	5.0
1.0 Toxicological Evaluation	X	X	X	4.4.1	5.4
1.1 Prepare Health Toxicity Profile	X	X	X	4.4.1.1	
a. Conduct literature search b. Evaluate adequacy of each study c. Review studies to obtain information on dose, biological end points and exposure d. Summarize information on each contaminant					
1.2 Prepare Environmental Toxicity Profile	X	X	X	4.4.1.2	5.4
a. Conduct literature search b. Evaluate adequacy of each study c. Review studies to obtain information on dose, toxic effects and thoroughness of study d. Summarize information on each contaminant					
2.0 Dose-Response Assessment		X[b]	X	4.4.2	5.4
2.1 Estimate ADI levels			X	4.4.2.1	5.4
a. Select appropriate quantitative index of toxicity (e.g., NOEL, NOAEL, LOAEL, etc.) b. Determine uncertainty factor c. Calculate ADI					
2.2 Estimate unit cancer risks			X	4.4.2.2	5.4
a. High-to-low dose extrapolation b. Interspecies extrapolation					

(a) X indicates the level of endangerment assessment (e.g., Level 1, 2 or 3) for which this step must be performed.
(b) Generally, a Level 2 endangerment assessment will utilize ADI and unit cancer risk values calculated in existing toxicity profiles. Only a Level 3 endangerment assessment will require calculation of new values.

etc. It also reports data on mixture effects and discusses the limitations, if any, of each study that could potentially impact its selection as the basis for deriving an ADI and unit cancer risk (for humans) or determination of levels of environmental concern (for aquatic and terrestrial organisms). In the development of an endangerment assessment, it may be necessary to use an interim ADI value (or other index of toxicity) with caveats indicating it may require updating in the future if the Agency revises the value.

4.4.1.1 Health Toxicity Profile

The first step in preparing a health toxicity profile is to conduct a thorough search of the current health effects literature on the contaminants of concern and to identify and acquire candidate studies for the profile. The next step is an evaluation of the adequacy of each study for the toxicity assessment. It is imperative that studies contain sufficient quantitative data to provide the basis for risk characterization. Accordingly, the studies should follow established test protocol criteria for determining biological or toxicological endpoints. Parameters to be considered include: (1) dose levels, (2) duration and frequency of compound administration, (3) route of compound exposure, (4) species selection, (5) the number of test animals, etc. Guidelines for evaluating test protocol criteria for specific endpoints have been established by EPA. These guidelines are summarized in Appendix 4.

The next step in preparing a toxicity profile is to review the studies which have been determined to be adequate to obtain the following data: (1) specific dose levels used, (2) all biological endpoints manifested, (3) route of exposure or (4) any limitations of the study which may compromise positive or negative outcomes. Important data to be considered when reviewing the studies include the following:

1. Dose: Studies of noncarcinogenic effects should report (a) the dose of the test substance at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed animals and an appropriate control (NOAEL) or (b) the lowest dose of the test substance that produces a statistically or biologically significant increase in the frequency or severity of adverse effects between the exposed animals and an appropriate control (LOAEL). These values provide the basis for deriving the ADI for noncarcinogenic effects.

   Studies of carcinogenic effects should report the frequency of tumor formation as a function of exposure level (dose). From this dose-response data, mathematical models are employed to predict cancer frequency rates at very low exposure levels.

2. Biological Endpoints: Results of a variety of studies report a wide range of adverse effects manifested. These include hepatotoxicity, renal toxicity, blood toxicity, neurotoxicity, behavioral toxicity, reproductive toxicity, teratogenicity, mutagenicity and carcinogenicity. Appendix 5 defines these biological endpoints.

3. Route of Exposure: The most relevant routes of exposure are oral, dermal and inhalation. Those studies which include the route of major concern for human exposure are the most useful.

The final step in the preparation of a toxicity profile is to briefly summarize the toxicological information on each contaminant of concern at a site. This summary should focus on those studies examining the exposure routes of concern at the site (i.e., oral dose if contaminants are expected to be found in the drinking water).

4.4.1.2 Environmental Toxicity Profile

The first step in preparing an environmental toxicity profile is to conduct a search of the environmental literature on the contaminants of concern and to identify and acquire candidate toxicity studies on fish and wildlife for the profile. The next step is an evaluation of the adequacy of each study for an environmental toxicity evaluation. An adequate study includes considerations of dose levels tested and toxic effects manifested, as well as thoroughness of reporting environmental parameters (e.g., temperature, photoperiod, dissolved oxygen concentration and pH).

The next step is to review the studies which have been determined to be adequate to obtain the data that should be summarized in the profile. Important data to be considered when reviewing the studies include the following:

1. Dose: The studies should report quantitative indices of environmental toxicity such as the NOAEL, LOAEL, LC_{50}, etc. These toxicity values may be used in deriving various levels of environmental concern.

2. Types of Effects: Environmental effects include effects of contaminants on growth, reproduction or survival which would either temporarily or permanently alter population levels of wild plants and animals. Accordingly, hazardous waste discharges may result in fish kills or other deleterious effects such as decreased reproductive potential, abnormal larval growth, systemic pathological effects or tumorigenesis. Environmental effects on birds can be manifested in three major forms: direct mortality/morbidity (via bioconcentration in the food chain or volatilization), indirect mortality/morbidity (via elimination of food sources such as phytoplankton) and reproductive effects (such as eggshell thinning). Behavioral changes can occur as well (e.g., migratory patterns, feeding habits and social population size). Other effects include bioconcentration in aquatic species all along the food chain (e.g., fat soluble compounds) and aesthetic considerations such as impartation of unpleasant taste to water and edible fish/shellfish.

The final step in the preparation of an environmental toxicity profile is to briefly summarize the toxicological information on each contaminant of concern at a site. This summary should focus on those studies examining ecosystems and/or species which are present at the site.

4.4.2 Dose-Response Assessment

Once the toxicological evaluation determines that a chemical is likely to cause a particular adverse effect, the next step is to determine the potency of the chemical. The second step, then, in the toxicity assessment, the dose-response assessment, is a quantitative estimation of risk from exposure to a chemical. It defines the relationship between the dose of a chemical and the incidence of the adverse effect.

The objective of the dose-response assessment is to use the quantitative indices of toxicity (e.g., NOEL, NOAEL, LOAEL, LC_{50}, etc.) presented in the toxicity profiles to determine ADI levels (for noncarcinogens) and unit cancer risk (for carcinogens) or levels of environmental concern (for aquatic and terrestrial organisms).

4.4.2.1 Estimation of Acceptable Daily Intake Levels

The dose-response assessment for noncarcinogenic chemicals produces an estimation of the NOEL, NOAEL or LOAEL and the margin of safety associated under the prescribed conditions of exposure. These quantitative indices of toxicity may be used to derive an exposure level which is considered "acceptable" or which is not expected to cause adverse effects. This exposure level may be expressed in a variety of ways such as the ADI, Ambient Air Standard, Water Quality Criteria, etc. The term "acceptable level" will be used in this Handbook to indicate any such derived criteria, standard or advisory level.

The toxicity profile should identify any quantitative indices of toxicity as well as any derived "acceptable levels" for noncarcinogens. A Level 2 endangerment assessment should utilize only available values in characterizing the risks at a site. A Level 3 endangerment assessment may require the estimation of an "acceptable level" for contaminants present at the site. Following is a brief discussion of the methodology for deriving an ADI.

A widely accepted procedure for evaluating noncarcinogenic toxic endpoints is to estimate the ADI. An ADI is defined as the amount of toxicant, in mg/kg body weight/day (or in mg/day for a 70-kg person) that is not expected to result in any adverse effects following chronic exposure to the general human population. Adverse effects are considered to be functional impairment or pathological lesions that may affect the biological integrity of the whole organism or that reduce an organism's ability to respond to an additional toxic insult. It is assumed in an ADI estimation that there are threshold doses below which no adverse effects will occur. The ADI is calculated by dividing the quantitative index of toxicity (e.g., NOEL, NOAEL, LOAEL, etc.) derived from human or animal toxicity studies, by one or more uncertainty factors. The parameters for calculation of the ADI are defined as follows:

1. The NOEL (No-Observed-Effect Level) is defined as that dose of a chemical at which there are no statistically or biologically significant increases in the frequency or severity of effects between the exposed population and an appropriate control.

2. The NOAEL (No-Observed-Adverse-Effect Level) is defined as that dose of a chemical at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and an appropriate control. Effects are produced at this dose, but they are not considered to be adverse.

3. The LOAEL (Lowest-Observed-Adverse-Effect Level) is defined as the lowest dose of a chemical in a study or group of studies that produces statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and an appropriate control.

Either the NOEL, NOAEL or the LOAEL may be used in estimating the ADI. The formula for calculating the ADI is shown below:

$$ADI = \frac{\text{NOEL x Body Weight}}{\text{Uncertainty Factor}}$$

If the NOEL is taken to be a safe dose for the species tested, an uncertainty factor must then be applied to allow for the potentially higher sensitivity of exposed humans and differences in sensitivity among exposed individuals. Uncertainty factors are adjustments of the NOEL, NOAEL, or LOAEL reported for small populations of humans or experimental animals in order to estimate the comparable NOEL from chronic exposure to a chemical by a large human population that includes sensitive subgroups. The size of the uncertainty factor used depends on the severity of the biological effects observed in toxicological studies. For example, an uncertainty factor of 100 might be used for a reversible effect, while an uncertainty factor of 1,000 might be employed if a chemical causes an irreversible effect such as teratogenicity.

Several considerations that influence the selection of an uncertainty factor are the species and strain of the test animals, the quality and sensitivity of the experimental data, the availability of comparative pharmacokinetic data and information on the absorption, distribution, biotransformation, binding and excretion of the test chemical in the animal species and in man.

Table 4-9 summarizes several uncertainty factors currently in use by the EPA to estimate ADI's for toxicants.

4.4.2.2 Estimation of Unit Cancer Risk

The dose-response assessment for carcinogenic chemicals should provide an estimation of the probability or range of probabilities that a specific adverse effect (i.e., tumor growth) will occur under the prescribed conditions of exposure. These estimates of probability are derived using mathematical models of the dose-response relationship. One way of expressing this numerical estimate of risk is as a "unit cancer risk" which is defined as the excess risk due to a continuous lifetime exposure to one unit of carcinogen concentration.

The toxicity profile should identify any numerical estimates of risk which have been derived. Level 2 endangerment assessments should utilize only

TABLE 4-9 GUIDELINES FOR SELECTION OF UNCERTAINTY FACTORS

Uncertainty Factor [a,b]
1. Use a 10-fold factor when extrapolating from valid experimental results from studies on prolonged ingestion by man. This 10-fold factor protects the sensitive members of the human population estimated from data garnered on average healthy individuals.
2. Use a 100-fold factor when extrapolating from valid results of long-term feeding studies on experimental animals with results of studies of human ingestion not available or scanty (e.g., acute exposure only). This represents an additional 10-fold uncertainty factor in extrapolating data from the average animal to the average man.
3. Use a 1,000-fold factor when extrapolating from less than chronic results on experimental animals with no useful long-term or acute human data. This represents an additional 10-fold uncertainty factor in extrapolating from less-than-chronic to chronic exposures.
4. Use an additional uncertainty factor of between 1 and 10 depending on the sensitivity of the adverse effect when deriving an ADI from LOAEL. This uncertainty factor drops the LOAEL into the range of a NOAEL.

(a) In calculating an ADI when no indication of carcinogenicity of a chemical exists, these factors are to be applied to the highest valid NOAEL or NOEL that does not have a valid LOAEL equal to or below it. In some cases, an additional variable uncertainty factor should be applied. The EPA has recommended that this variable uncertainty factor reflect a scientific judgment of the difference between the observed LOAEL and the hypothesized NOAEL. This difference will not necessarily be the same from experiment to experiment. In lieu of specific data, the value of this additional uncertainty factor utilized by the EPA ranges from one through ten, based on the severity of the adverse effect at the LOAEL.

(b) Uncertainty factors one and two are supported by the FDA and the WHO/FAO; uncertainty factors one through three have been established by the NAS and are used in a similar form by the FDA; uncertainty factors one through four are recommended by the EPA.

established risk estimates. Level 3 endangerment assessments may require the derivation of a quantitative risk estimate for carcinogenic contaminants of concern at a site. The following is a brief discussion of the estimation of unit cancer risk. For further details on quantitative carcinogenic risk assessment, the reader is referred to EPA's Proposed Guideline for Carcinogen Risk Assessment (USEPA 1984). These Guidelines are attached in their entirety as Appendix 3, Part 1.

There are three main types of evidence which may be used to determine whether a substance poses a carcinogenic hazard: (1) epidemiologic data from exposed human populations, (2) experimental evidence derived from long-term bioassays of animals and (3) supportive or suggestive evidence derived from studies of chemical structure or from other short-term tests. Ideally, this assessment would be based on epidemiological studies of human populations. However, epidemiological studies are often unsatisfactory because it is difficult to measure individual exposure patterns, it may be impossible to eliminate the confounding effects of other factors and the time between exposure and occurrence of an observable effect may be very long (up to several decades). Consequently, it is often necessary to rely on tests carried out on laboratory animals exposed to much higher levels of the toxic agent than humans are expected to experience. The results of such tests have to be subjected to two types of extrapolation:

1. The results obtained for laboratory animals at relatively high exposure levels have to be extrapolated down to predict the effects of relatively low exposure on those animals (high-to-low dose extrapolation).

2. The resulting predicted effects of low-level exposure on laboratory animals are then used to predict the effects on human health (interspecies extrapolation).

The experimental results are extrapolated from the high, observed doses to low, expected doses by fitting a mathematical model to the data and using the model to predict the low-dose response. The Proposed Guidelines for Carcinogen Risk Assessment (USEPA 1984b) recommends the use of the linearized multistage model for high-to-low dose extrapolation unless there is mechanistic, statistical or other biological evidence that indicates the greater suitability of an alternative extrapolation model or statistical or biological evidence that excludes the use of the multistage model. The point estimate and the 95% upper confidence limit of excess risk are calculated by using the computer program GLOBAL 79, developed by Crump and Watson (1979). This model approximates the dose-response curve by a straight line with slope determined by the linear term of the model. The linearized multistage model estimates a plausible upper limit to risk and is consistent with some mechanisms of carcinogenesis. However, it should be emphasized that such an estimate does not necessarily represent the actual risk. USEPA (1984b) provides a discussion of the application of this model as well as a list of additional references on quantitative risk assessment.

The results of animal studies, having been extrapolated from high to low dose, then have to be extrapolated to humans. Differences in the metabolism of chemicals between species often creates the greatest problem in obtaining meaningful extrapolations. Methods of scaling animal doses to equivalent human doses have been based on body weight, concentration in the diet and body surface area. Additional uncertainty is introduced when the route of exposures differs from one species to another.

High-to-low dose and interspecies extrapolation involves a series of assumptions, some of which are impossible to verify, and necessarily involves a high degree of uncertainty. Nevertheless, it is important to obtain as realistic an estimate as possible so that appropriate decisions can be made regarding the risk of exposure to toxic substances.

4.4.2.3 Interpretation of Unit Cancer Risk

For several reasons, the unit cancer risk estimate based on animal bioassays is only an approximate indication of the absolute risk in populations exposed to known carcinogen concentrations. First, there are important species differences in uptake, metabolism and organ distribution of carcinogens, as well as species differences in target site susceptibility, immunological responses, hormone function, dietary factors and disease. Second, the concept of equivalent doses for humans compared to animals on a mg/surface area basis is virtually without experimental verification regarding carcinogenic response. Finally, human populations are variable with respect to genetic constitution and diet, living environment, activity patterns and other cultural factors.

The unit cancer risk estimate can give a rough indication of the relative potency of a given agent compared with other carcinogens. The comparative potency of different agents is more reliable when the comparison is based on studies in the same test species, strain and sex and by the same route of exposure, preferably by inhalation. However, it should be recognized that the estimation of cancer risks to humans at low levels of exposure is uncertain. At best, the linear extrapolation model recommended by EPA provides a rough, but plausible, estimate of the upper-limit of risk (i.e., it is not likely that the true risk would be much higher than the estimated risk, but it could very well be considerably lower).

4.4.3 Toxicity Assessment References

ICAIR, Life Systems, Incorporated. 1985. The hazardous waste site toxicology handbook. Draft. Washington, DC: U.S. Environmental Protection Agency, Office of Waste Programs Enforcement. Contract No. 68-01-7037.

ICF Incorporated. 1985. Superfund public health assessment manual. Draft. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. Contract No. 68-01-6872.

ICF Incorporated. 1983a. Scientific support document: the scientific basis for the risk evaluation process. Draft. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response.

ICF Incorporated. 1983b. Superfund feasibility study guidance, chapter 4, risk evaluation. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response.

USEPA. 1985a. U.S. Environmental Protection Agency. Environmental Criteria and Assessment Office. Proposed guidelines for the health risk assessment of chemical mixtures. Fed. Regist., Jan. 9, 1985, 50 1170.

USEPA. 1984b. U.S. Environmental Protection Agency. Office of Health and Environmental Assessment. Proposed guidelines for carcinogen risk assessment. Fed. Regist., Nov. 23, 1984, 49 46294.

USEPA. 1984d. U.S. Environmental Protection Agency. Office of Health and Environmental Assessment. Proposed guidelines for mutagenicity risk assessment. Fed. Regist., Nov. 23, 1984, 49 46314.

USEPA. 1984e. U.S. Environmental Protection Agency. Office of Health and Environmental Assessment. Proposed guidelines for the health assessment of suspect developmental toxicants. Fed. Regist., Nov. 23, 1984, 49 46324.

4.5 Risk Characterization Guidelines

The final component of the endangerment assessment process is risk characterization. The objective of risk characterization is to estimate the incidence of an adverse health or environmental effect under the various conditions of exposure defined in the exposure assessment. It is performed by integrating information developed during the exposure and toxicity assessments to yield a complete characterization of risk at the site. Four discrete steps are required to develop this information:

1. Characterize carcinogenic risks at the site
2. Characterize noncarcinogenic risks at the site
3. Characterize environmental risks at the site
4. Characterize public welfare risks at the site

The final assessment should include a summary of the risks associated with a site and such factors as the weight-of-evidence associated with each step of the process, the estimated uncertainty of the component parts, the distribution of risk across various sectors of the population, the assumptions contained within the estimate, etc.

Typically, releases from a hazardous waste site result in exposure to a mixture of chemicals rather than a single compound. This phenomenon occurs when a series of unrelated compounds, placed in the same area for disposal or storage, eventually come in contact with each other and are released to the environment as a mixture. The EPA has published "Proposed Guidelines for Health Risk Assessment of Chemical Mixtures" (USEPA 1985a) which provide guidelines for assessing the effects of multiple toxicant or multiple carcinogen exposure.

The preferred approach for predicting the effects of exposure to mixtures is to use health effects data on the mixture of concern or on a similar mixture

(i.e., same components but in slightly different proportions) and adapt the same assessment procedures as used for single compounds. Most frequently, the toxicological properties of the mixtures are poorly characterized. When health effects data are not available on an identical or similar mixture, the risk assessment may be based on the toxic or carcinogenic properties of the individual components of the mixture. The use of dose additive models is recommended by EPA for combining the risk estimates for individual chemicals in the mixture to estimate the risk for the mixture.

The methodology for risk characterization is based on existing and proposed guidelines for performing carcinogenic, mutagenic, teratogenic and mixture risk assessments (USEPA 1984b,d,e; 1985a). These guidelines are included in their entirety as Appendix 3 of this Handbook. Additional guidance on risk characterization at hazardous waste sites is contained in the SPHAM (ICF 1985). Further information on risk assessment in general is available in the following publications: ICF 1983a,b, NAS 1982, Schaum 1984 and USEPA 1984a.

Table 4-10 lists the steps required to complete the risk characterization and identifies the endangerment assessment level of detail to which they apply and the locations in this Handbook where they are discussed.

4.5.1 Characterize Carcinogenic Risks

In order to obtain a quantitative estimate of carcinogenic risk, the results of the dose-response assessment must be combined with an estimate of the exposures to which the population is subject. Depending on the needs of the endangerment assessment, quantitative estimates of risk can be presented in one or more of the following ways:

1. Unit Cancer Risk - Under an assumption of low-dose linearity the unit cancer risk is the excess lifetime risk due to a continuous lifetime exposure of one unit of carcinogen concentration.

2. Dose Corresponding to a Given Level of Risk - This approach is useful when using nonlinear extrapolation models where the unit risk differs at various dose levels.

3. Individual Risks - Risk is characterized in terms of excess individual lifetime risks.

4. Population Risks - Risk is characterized in terms of the excess number of cancers produced per year in the exposed population.

In characterizing the risk due to concurrent exposure to several carcinogens, the risks are combined on the basis of additivity unless there is specific information to the contrary (USEPA 1985a). Interactions with enzyme inducers or inhibitors, cocarcinogens, promoters and initiators should be considered on a case-by-case basis.

TABLE 4-10 RISK CHARACTERIZATION STEPS

Risk Characterization Step	Level of Detail[a] 1	2	3	Applicable Handbook Sections 4.0	5.0
1.0 Characterize carcinogenic risk	X	X	X	4.5.1	5.5
1.1 Compare site-specific exposure levels to estimates		X	X	4.5.1	5.5
1.2 Compare site-specific exposure levels to existing regulatory guidelines and standards for carcinogens		X	X	4.5.1	5.5
1.3 Characterize uncertainties associated with risk estimates		X	X	4.5.1	5.5
2.0 Characterize noncarcinogenic risk	X	X	X	4.5.2	5.5
2.1 Compare site-specific exposure levels to "Acceptable Levels"		X	X	4.5.2	5.5
2.2 Compare site-specific exposure levels to existing regulatory guidelines and standards for noncarcinogens		X	X	4.5.2	5.5
2.3 Characterize uncertainties					
3.0 Characterize environmental risk	X	X	X	4.5.3	5.5
3.1 Compare site-specific exposure levels to ecotoxicity data		X	X	4.5.3	5.5
3.2 Compare estimated environmental concentrations to existing environmental concern levels and regulatory guidelines and standards		X	X	4.5.3	5.5
3.3 Characterize uncertainties		X	X	4.5.3	
4.0 Characterize public welfare risk	X	X	X	4.5.4	5.5

(a) X indicates the level of endangerment assessment (e.g., Level 1, 2 or 3) for which this step must be performed.

The results of every risk estimation are subject to uncertainties. These uncertainties may be due to limitations in the human and animal studies, lack of adequate exposure data, and the assumptions of the high-to-low dose and interspecies extrapolation procedures used. Risk estimates should be presented together with a summary of the toxicity and exposure assessments to ensure that the weight-of-evidence that provides a basis for site-specific risks is adequately described. All of the key findings of the qualitative assessment and the interpretative rationale that forms the basis for conclusions should be summarized. In addition, uncertainties in the evidence as well as factors that affect the relevance of animal studies to humans should be discussed.

To characterize carcinogenic risks at the site, compare site-specific exposure levels for each contaminant at the site to quantitative estimates of risk identified or developed during the dose-response assessment. Exposure levels should also be compared to existing regulatory guidelines and standards for carcinogens. The risk characterization should be accompanied by a discussion of the uncertainties associated with the risk estimate used.

A method for determining incremental risk at a site resulting from exposure to carcinogens is proposed by ICF (1985). Site-specific exposure levels (chronic daily intake) are multiplied by the quantitative risk estimates (carcinogenic potency factors) to obtain an estimate of incremental risk for each chemical. Total incremental risk at the site is obtained by summing this incremental risk estimate for each chemical.

4.5.2 Characterize Noncarcinogenic Risks

Characterizing risks from noncarcinogenic compounds involves comparing the expected exposure level (E) to the "acceptable level" (AL) (USEPA 1985a). The resultant ratio (referred to as the Hazard Index (HI) provides a numerical indicator of the transition between acceptable and unacceptable exposure levels. (Note: When making this comparison (E/AL), it is important to ensure that the units for the exposure level and the "acceptable level" are the same. It may be necessary to apply a scaling factor or exposure coefficient to the estimated exposure level, as appropriate, to standardize the units in the ratio.) Thus, when HI >1 (where HI = E/AL), there is a potential health risk to the exposed populations.

EPA guidelines assume dose additivity for exposure to multiple noncarcinogens. Therefore, the HI of a mixture may be defined as:

$$HI = E_1/AL_1 + E_2/AL_2 + \ldots E_i/AL_i$$

As with single chemicals, any time the HI approaches unity, concern for potential risks increases.

This assumption of additivity is most properly applied to compounds that induce the same effect by the same mechanism. Thus, it may be desirable to group the compounds by type of critical effect and derive a separate HI for each group to avoid overestimating risk at a site.

For the purposes of the endangerment assessment, an HI should be estimated for each contaminant of concern and each exposure scenario using all "acceptable levels" identified in the toxicity profile. The resulting HI scores (or sum of HI scores) characterizes the risk to human populations from the noncarcinogenic chemicals at the site. ICF (1985) proposes a similar methodology for characterizing noncarcinogenic risk.

The noncarcinogenic risk characterization should include an explanation of the "acceptable levels" which were used, a determination of the "acceptability" of the risks and a discussion of the uncertainties associated with the assessment.

4.5.3 Characterize Environmental Risks

For ecological risks, the ecotoxicity assessment and the environmental exposure assessment are integrated to quantify the probability that adverse effects may occur, will occur or are occurring as a result of exposure. The methods used to integrate such information can vary from a simple comparison of exposure and toxicity data (quotient or ratio approach) to more complex methods, which utilize comparative toxicology/exposure and effects models. Estimated environmental concentrations of contaminants at the site should be compared to existing environmental concern levels and existing regulatory guidelines and standards.

The ecological risk characterization should include an explanation of the extrapolations that have been made, a determination or estimation of the ecological significance of any adverse effects and a discussion of the uncertainties associated with the assessment.

4.5.4 Characterize Public Welfare Risks

Risks to public welfare are not easily quantifiable. Obvious impacts would include a decrease in property values, adverse impacts on recreational facilities (i.e., lakes, streams, wildlife areas, etc.), decreases in commercial fisheries, etc. Health and environmental risks could, directly or indirectly, have adverse effects on the public welfare. Risks to public welfare should be a considered throughout the endangerment assessment process and characterized in the endangerment assessment document.

4.5.5 Risk Characterization References

ICF Incorporated. 1985. Superfund public health assessment manual. Draft. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. Contract No. 68-01-6872.

ICF Incorporated. 1983a. Scientific support document: the scientific basis for the risk evaluation process. Draft. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response.

ICF Incorporated. 1983b. Superfund feasibility study guidance, Chapter 4, risk evaluation. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response.

NAS. 1982. National Academy of Sciences, National Research Council. Risk and decision making: perspectives and research. Washington, DC: National Academy Press.

Schaum J. 1984. Short course on integration of exposure and risk assessment. Part 3. Exposure assessment methods. Paper presented at the Annual Meeting of Society for Environmental Toxicology and Chemistry, Arlington, VA.

USEPA. 1985a. U.S. Environmental Protection Agency. Environmental Criteria and Assessment Office. Proposed guidelines for the health risk assessment of chemical mixtures. Fed. Regist., Jan. 9, 1985, 50 1170.

USEPA. 1984a. U.S. Environmental Protection Agency. Risk assessment and management: framework for decision making. Washington, DC: U.S. Environmental Protection Agency.

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USEPA. 1984d. U.S. Environmental Protection Agency. Office of Health and Environmental Assessment. Proposed guidelines for mutagenicity risk assessment. Fed. Regist., Nov. 23, 1984, 49 46314.

USEPA. 1984e. U.S. Environmental Protection Agency. Office of Health and Environmental Assessment. Proposed guidelines for the health assessment of suspect developmental toxicants. Fed. Regist., Nov. 23, 1984, 49 46324.

5.0 PREPARATION OF THE ENDANGERMENT ASSESSMENT DOCUMENT

This section presents and discusses the content and recommended format for the endangerment assessment document. This format has been designed to:

1. Ensure that all major issues are adequately addressed.
2. Ensure adequate documentation and support for EPA's enforcement actions.
3. Produce comparable documents from different sites.
4. Promote high-quality documents.

The recommended format consolidates information from the individual assessments into a single, concise document. Thus, the endangerment assessment document is an "executive summary" of the endangerment assessment process which fully characterizes the site and supports the EPA's contention that an endangerment may exist at the site.

The endangerment assessment document should not repeat site information reported elsewhere. The author should reference existing documents, such as the RI and FS reports, which contain detailed site or assessment information, and maintain complete records and notes during the assessment process. These can be used, if necessary, to substantiate the conclusions reported in the endangerment assessment document. Referencing existing documents should aid in keeping the endangerment assessment document brief. The length of the document will vary depending on the site characteristics and the point in time the assessment is being made (i.e., the amount of data available). As a rule, the average endangerment assessment document should not exceed 20 typewritten pages excluding Appendices. Appendix 2 provides examples of Level 1, 2 and 3 endangerment assessment documents.

Table 5-1 presents the recommended endangerment assessment document outline. This outline should be followed when preparing all endangerment assessments, no matter what level of detail. Obviously, a Level 1 document will not be as lengthy as a Level 2 or 3; however, all data requirements must be addressed. The endangerment assessment document should contain seven major sections:

Section 1.0 is an introduction briefly describing the site, site history and contaminants found at the site.

Section 2.0 identifies the environmental fate and transport of contaminants at the site.

Section 3.0 evaluates the results of the exposure assessment.

Section 4.0 evaluates the results of the toxicity assessment.

Section 5.0 evaluates the results of the risk characterization of the site.

Section 6.0 draws conclusions based on expected exposures and toxic properties of contaminants of concern at the site.

TABLE 5-1 ENDANGERMENT ASSESSMENT DOCUMENT OUTLINE

Disclaimer

1.0 Introduction

- 1.1 Site description and history
- 1.2 Contaminants found at site

2.0 Environmental Fate and Transport

- 2.1 Factors affecting migration
- 2.2 Movement and environment fate

3.0 Exposure Evaluation

- 3.1 Routes of exposure
- 3.2 Populations exposed
- 3.3 Extent of exposure

4.0 Toxicity Evaluation

5.0 Risk and Impact Evaluation

- 5.1 Human Health
- 5.2 Environmental
- 5.3 Public Welfare

6.0 Conclusions

7.0 References

Appendices (documentation)

Section 7.0 is a list of references used in preparing the endangerment assessment document. Appendices should consist of any support documentation.

Table 5-2 presents a summary of the key factors that should be addressed in each section of the document at each level of detail.

All draft endangerment assessment documents should include a Disclaimer indicating that the document has not yet been approved by EPA and is not available for public distribution. The disclaimer may read:

"This document has not been peer and administratively reviewed within EPA and is for internal Agency use/distribution only"

Draft endangerment assessments should also be clearly marked as being "Enforcement Confidential." When the endangerment assessment is final (i.e., EPA and responsible parties have agreed to release it to the public or the litigation is settled) the Disclaimer and "Enforcement Confidential" should be removed from the document.

The following are instructions for preparing each of the major sections of the endangerment assessment document.

5.1 Section 1.0 Introduction

The purpose of this section of the endangerment assessment document is to acquaint the reader with the site characteristics and contaminants present at the site.

Sections 1.0 and 2.0 are important in establishing the "point in time" at which the endangerment assessment was performed. Since an endangerment assessment may be performed at varying points in time, the degree of endangerment may vary. It is helpful to illustrate, to the best extent possible (based on the information available at the time the endangerment assessment is being performed) what types of chemicals and what quantities were disposed of at the site, the manner of disposal, and any prior actions taken at the site, to help provide a setting for the "point in time" concept. This setting should also be carefully segregated from other parts of the endangerment assessment in a separate introductory section. Care should also be taken not to mix the manner of disposal information with exposure scenarios. Environmental fate information and any removal actions must be taken into account in order to clearly set forth exposure to chemicals being evaluated.

Preparation of the Introduction and subsequent sections of the endangerment assessment document begins with a thorough review of the available documentation on the site. Notes should be taken as the documents are reviewed, focusing on the pertinent factors identified on Table 5-2. This section contains two subsections: Site Description and Site History and Contaminants Found at the Site.

TABLE 5-2 FACTORS TO BE CONSIDERED IN ENDANGERMENT ASSESSMENTS

Level of Detail

Level 1

1.0 Introduction

1.1 Site Description and Site History
- a. geographic location
- b. management practices/site use/site modifications
- c. chronological survey
- d. facility description/containment systems
- e. substances brought on site (identity, quantity, form manner of disposal

1.2 Contaminants found at site
- a. identity of substances detected

2.0 Environmental Fate and Transport
- a. identity of possible transport pathways

3.0 Exposure Evaluation
- a. identity of potential exposure routes
- b. identity of populations at risk

4.0 Toxicity Evaluation
- a. characterize key toxicological properties

5.0 Risk and Impact Evaluation
- a. risk may exist because of potential exposure to toxic chemicals

6.0 Conclusions

7.0 References

Level 2

1.0 Introduction

1.1 Site Description and Site History
- a. geographic location
- b. management practices/site use/site modifications
- c. chronological survey
- d. facility description/containment systems
- e. substances brought on site (identity, quantity, form and manner of disposal)

1.2 Contaminants found at site
- a. identity of substances detected
- b. concentration of substances detected
- c. analytical methodology and QA/QC

2.0 Environmental Fate and Transport
- a. physical-chemical properties of specified chemicals/substances (e.g., soil/sediment adsorption coefficients, vapor pressures, solubility, etc.) [preliminary]
- b. photodegradation rates, decomposition rates, hydrolysis rates, chemical transformations, etc. [preliminary]
- c. local topography [preliminary]
- d. description of the hydrological setting and flow system [preliminary]
- e. soil analyses [preliminary]
- f. climatic factors, other factors affecting fate and transport [preliminary]

3.0 Exposure Evaluation
- a. demographic profile of populations at risk including subpopulation at special risk [preliminary]
- b. background chemical exposures [preliminary]
- c. life style and occupation histories [preliminary]
- d. population macro- and micro-environments [preliminary]
- e. exposure routes [preliminary]
- f. magnitude, source, and probability of exposure to specified substances [preliminary]

4.0 Toxicity Evaluation
- a. metabolism [preliminary]
- b. acute toxicity [preliminary]
- c. subchronic toxicity [preliminary]
- d. chronic toxicity [preliminary]
- e. carcinogenicity [preliminary]
- f. mutagenicity [preliminary]
- g. teratogenicity/reproductive effects [preliminary]
- h. other health effects as relevant including neurotoxicity, immuno-depressant activity, allergic reactions, etc. [preliminary]
- i. epidemiological evidence (chemical specific or site specific) [preliminary]
- j. aquatic/non-human terrestrial species toxicity/environmental quality impairment [preliminary]

5.0 Risk and Impact Evaluation
- a. qualitative description of risk to public health, welfare and the environment

6.0 Conclusions

7.0 References

Level 3

1.0 Introduction

1.1 Site Description and Site History
- a. geographic location
- b. management practices/site use/site modifications
- c. chronological survey
- d. facility description/containment systems
- e. substances brought on site (identity, quantity, form and manner of disposal

1.2 Contaminants found at site
- a. identity of substances detected
- b. concentration of substances detected
- c. analytical methodology and QA/QC
- d. survey of environmental monitoring studies (detailed discussion of environmental media and contamination levels)

2.0 Environmental Fate and Transport
- a. physical-chemical properties of specified chemicals/substances (e.g., soil/sediment adsorption coefficients, vapor pressures, solubility, etc.) [final]
- b. photodegradation rates, decomposition rates, hydrolysis rates, chemical transformations, etc. [final]
- c. local topography [final]
- d. description of the hydrological setting and flow system [final]
- e. soil analyses [final]
- f. climatic factors, other factors affecting fate and transport [final]
- g. prediction of fate and transport (where necessary using modeling methods)

3.0 Exposure Evaluations
- a. demographic profile of populations at risk including subpopulation at special risk [final]
- b. background chemical exposures [final]
- c. life style and occupation histories [final]
- d. population macro- and micro-environments [final]
- e. exposure routes [final]
- f. magnitude, source, and probability of exposure to specified substances [final]

4.0 Toxicity Evaluation
- a. metabolism [final]
- b. acute toxicity [final]
- c. subchronic toxicity [final]
- d. chronic toxicity [final]
- e. carcinogenicity [final]
- f. mutagenicity [final]
- g. teratogenicity/reproductive effects [final]
- h. other health effects as relevant including neurotoxicity, immuno-depressant activity, allergic reactions, etc. [final]
- i. epidemiological evidence (chemical specific or site specific) [final]
- j. aquatic/non-human terrestrial species toxicity/environmental quality impairment [final]

5.0 Risk and Impact Evaluation
- a. carcinogenic risk assessment
- b. probability of non-carcinogenic human health effects
- c. non-human species risk assessment
- d. environmental impacts/ecosystem alterations

6.0 Conclusions

7.0 References

5.1.1 Section 1.1 Site Description and Site History

This subsection should summarize background site description and history information. The purpose of this section is to provide a framework in time and place for the endangerment assessment. A map of the site should also be included in this introductory section.

Review the background material on the site, being alert for chronological events, such as removal actions, which may have significantly altered the site characteristics or probable exposure routes. Refer to the available documents (i.e., RI and FS reports) for detailed information and maps of the site.

The site history information presented in this subsection must be clearly referenced. Identify and cite any affidavits, inspection reports, surveys, etc. that have been previously prepared on this site. This documentation of previous events is critical in an enforcement document, especially if it is to support a judicial action.

5.1.2 Section 1.2 Contaminants Found at the Site

This subsection should identify and, to the extent possible, quantify the contaminants present at the site. A primary objective of this section is to focus the remaining sections of the endangerment assessment document on the contaminants of concern which are present in significant quantities.

To complete this section, review all available monitoring reports. Level 1 assessments will probably not have monitoring data available so contaminant identification information must be developed from the disposal logs at the site. Level 2 assessments will have preliminary monitoring data available from the RI, and Level 3 assessments should have the complete RI to work from. A critical evaluation of the analytical methodology and QA/QC (quality assurance/quality control) procedures for the sampling effort should be included in all Level 3 assessments.

The QA/QC procedures that were used during the data collection and analysis phases must be discussed in Level 3 endangerment assessments because the existence of, or lack of, QA/QC data is very important in determining how valid the conclusions based on the sampling data are. If the QA/QC procedures are known, they should be documented; if the QA/QC procedures are not known or the data are unavailable, this should be stated. This discussion and evaluation of the QA/QC procedures is in keeping with the concept that the endangerment assessment is an interpretive document. It provides a critical evaluation of the available site information in order to reach a justifiable conclusion regarding the potential for endangerment at a site.

This section should contain information on the identity, quantity and form of contaminants present at the site and the concentrations of contaminants in the environmental media. Level 1 assessments will typically identify contaminants present and, possibly, quantities disposed of. Level 2 and 3 assessments will provide more quantitative information on the concentrations of contaminants at the site.

5.2 Section 2.0 Environmental Fate and Transport

The purpose of this section is to describe the potential for off-site migration of contaminants and provide estimates of the direction of movement of contaminants and ambient concentrations of contaminants in various environmental media. This section of the endangerment assessment should summarize the results of the environmental fate analysis portion of the exposure assessment.

The discussion should include information on any factors which may significantly affect the environmental fate and transport of contaminants released from the site. The assumptions upon which the environmental fate analysis was based should be stated, as well as any limitations of the environmental fate analysis. Again, bear in mind that if the environmental fate and transport characteristics at the site have been fully characterized in existing documentation, it is not necessary to repeat that information in this document. Cross-referencing existing documents will satisfy the requirements of this section.

A Level 1 environmental fate and transport analysis may only go as far as identifying possible transport pathways. A Level 2 analysis should characterize the physical and chemical and properties of the contaminants, transformation processes (e.g., photodegradation, decomposition and hydrolysis) and site factors which affect transport such as local topography, the hydrological setting, climatological setting and geological setting of the site. A Level 3 analysis will continue this characterization through a prediction of fate and transport pathways, using modeling methods when necessary. This level of detail is necessary to provide input to the quantitative Exposure Evaluation characteristic of a Level 3 endangerment assessment.

5.3 Section 3.0 Exposure Evaluation

The purpose of this section is to identify actual or potential routes of exposure, characterize the populations exposed and determine the extent of the exposure. Section 3.0 should evaluate the results of the exposure assessment and may contain up to three separate subsections: Populations Exposed, Routes of Exposure and Extent of Exposure. The information presented should basically be a summary of the results of the Exposed Population Analysis and Estimation/Calculation of Dose Incurred steps of the exposure assessment. Information on expected doses incurred should include a summation of the total dose of each contaminant received as a result of exposures by multiple routes.

This section should also identify anticipated or potential pathways of exposure. The exposure routes should be presented in the order of those routes with the highest amount of proof first (i.e., most field data supporting the exposure route, highest level of confidence, etc.). This assures that EPA presents its strongest, most defensible case first in the endangerment assessment document.

The Exposure Evaluation for a Level 1 endangerment assessment will identify potential exposure routes and populations at risk. It is not necessary to

quantify the exposure or populations in a Level 1 endangerment assessment. A Level 2 Exposure Evaluation will compile all the demographic data available on the site; this information will have been collected during the RI and FS studies. Based on this data, a series of exposure estimates may be presented. The Level 3 Exposure Evaluation may use available modeling methods to predict the extent of future exposure at the site. It is important that this section include a discussion of all the assumptions upon which the calculations of exposure were based. Data limitations should also be discussed.

A summary table identifying exposed populations, exposure routes and extent of exposure is an ideal way to summarize the exposure assessment information. Keep in mind that the Exposure Evaluation should define as many of the factors listed in Table 5-2 as possible. If a factor cannot be defined, identify the data gap but do not attempt to collect additional data for the sole purpose of completing the endangerment assessment. Such original data collection is beyond the scope of the endangerment assessment effort.

5.4 Section 4.0 Toxicity Evaluation

The purpose of Section 4.0 is to provide the toxicological weight-of-evidence that the contaminants at the site pose actual or potential risks to public health or the environment. This section, which evaluates the results of the toxicity assessment, will comprise the bulk of the endangerment assessment document, since the toxic properties of contaminants are usually not completely characterized in any other documents prepared for the site.

Toxicological factors identified in Table 5-2 should be defined for each of the contaminants of concern. If there are a large number of contaminants being evaluated, then a tabular summary of the toxic properties of each contaminant, is appropriate. As discussed previously, this information should be derived from existing toxicity profiles or the primary literature.

The Toxicity Evaluation for a Level 1 assessment should be a brief characterization of the key toxicological properties for the contaminants at the site with the greatest risk of potential exposure. The Level 2 and 3 assessments should identify any quantitative indices of toxicity (e.g., NOEL, NOAEL, LC_{50}, etc.), derived "acceptable levels" (e.g., ADIs, recommended standards, criteria, etc.) or unit cancer risk estimates available from the literature. A Level 3 assessment may go on to calculate ADIs and unit cancer risk estimates for contaminants at the site when these values are not available in the current literature. The studies that provide the basis for the quantitative indices of toxicity and risk estimations should be identified and discussed in this section as well as any assumptions or data gaps.

5.5 Section 5.0 Risk and Impact Evaluation

The purpose of this section is to integrate the findings of the exposure and toxicity assessments to estimate site-specific risks. Section 5.0 evaluates and summarizes the information developed during the risk characterization process.

The results of the exposure assessment should be summarized in a tabular form for each medium, population group and route of exposure for which dose estimates have been calculated. The risk estimates are then tabulated in duplicate tables that report the probability of harm or margins of safety. These data should be accompanied by a statement of the nature and severity of the risks, the major assumptions used, the uncertainties that result and the guidelines and standards that may be exceeded by potential exposure values and the associated risks.

It may be sufficient for a Level 1 Risk and Impact Evaluation to simply state that risk may exist because of potential exposure to toxic chemicals. A Level 2 Risk and Impact Evaluation should contain a qualitative description of potential adverse effects and a quantitative estimate of risk based on existing guidelines and standards (e.g., Ambient Water Quality Criteria, Drinking Water Standards, etc.). A Level 3 Risk and Impact Evaluation should provide a quantitative risk assessment for all carcinogenic and noncarcinogenic chemicals and an evaluation and summary of the adverse effects on public health or welfare or the environment.

5.6 Section 6.0 Conclusions

The purpose of Section 6.0 is to present the results of the entire endangerment assessment process in a very brief statement of the problems that could occur at a site if no action is taken. This section should also contain a clear explanation as to whether the site may present an endangerment based on the risk assessment that was performed.

Data gaps, assumptions and uncertainties that affect the risk assessment should be fully qualified in the conclusion section. The endangerment assessment document should not address risk management options at the site. Rather, this document should clearly and objectively state the existing and potential risks to public health or welfare or the environment that may exist at the site.

6.0 SOURCES OF INFORMATION AND ASSISTANCE

The bibliographies provided at the end of Sections 4.3, 4.4 and 4.5 of this Handbook are a primary source of information on the endangerment assessment process and its component parts. Additional guidance and assistance may be obtained from the points of contact identified in this section.

6.1 Endangerment Assessment Process

The primary points of contact for specific questions on the endangerment assessment process and the enforcement requirements at a site are:

R. Charles Morgan, Chief
Health Sciences Section
Office of Waste Programs Enforcement
USEPA
401 M Street, SW
Washington, DC 20460
Telephone: (202) 382-5611

Kathleen Plourd
Health Sciences Section
Office of Waste Program Enforcement
401 M Street, SW
USEPA
Washington, DC 20460
Telephone: (202) 382-5646

Additional questions or comments on the endangerment assessment process or this Handbook may be directed to:

Lee Ann Smith or
Timothy E. Tyburski
ICAIR Life Systems, Inc.
24755 Highpoint Road
Cleveland, OH 44122
Telephone: (216) 464-3291

6.2 RI and FS Processes

The primary point of contact for specific questions on Superfund requirements at a site and the RI and FS guidance documents and instruction manuals is:

Craig Zamuda
Office of Emergency and Remedial Response
USEPA
401 M Street, SW
Washington, DC 20460
Telephone: (202) 382-2470

6.3 Toxicity Profiles

Questions on the availability of toxicity profiles prepared specifically for use at hazardous waste sites should be addressed to the OWPE and OERR contacts identified above. Mr. R. Charles Morgan or Ms. Kathleen Plourd should be contacted for information on the OWPE Chemical Profiles; Craig Zamuda is the point of contact for the OERR Health Effects Assessments.

6.4 EPA Risk and Exposure Assessment Guidelines

The EPA has recently published a series of draft guidelines for risk and exposure assessment. These draft guidelines are reproduced in their entirety as Appendix 3 of this Handbook. Each of the draft guidelines contain a complete reference list as well as a point of contact at EPA for questions on the individual assessment processes. The point of contact at EPA for each set of assessment guidelines is identified below:

Carcinogen Risk Assessment

Dr. Robert McGaughy
Carcinogen Assessment Group (RD-689)
Office of Health and Environmental Assessment
USEPA
401 M Street, SW
Washington, DC 20460
(202) 382-5952

Exposure Assessment

Dr. James W. Falco
Exposure Assessment Group (RD-689)
Office of Health and Environmental Assessment
USEPA
401 M Street, SW
Washington, DC 20460
(202) 475-8909

Mutagenicity Risk Assessment

Dr. David Jacobson-Kram
Reproductive Effects Assessment Group (RD-689)
Office of Health and Environmental Assessment
USEPA
401 M Street, SW
Washington, DC 20460
(202) 382-7336

Health Assessment of Suspect Developmental Toxicants

Dr. Carole A. Kimmel
Reproductive Effects Assessment Group (RD-689)
Office of Health and Environmental Assessment
USEPA
401 M Street, SW
Washington, DC 20460
(202) 382-7331

Health Risk Assessment of Chemical Mixtures

Dr. Richard Hertzberg
Environmental Criteria and Assessment Office
USEPA
26 West St. Clair
Cincinnati, OH 45268
(513) 684-7531

7.0 REFERENCES

Anderson E, Browne N, Duletsky S et al. GCA Corporation. 1984. Development of statistical distribution or ranges of standard factors used in exposure assessment. Revised Draft Final Report. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Exposure Assessment Group. Contract No. 68-02-3510.

Callahan MA, Johnson RH, McGinnity JL et al. 1983. Handbook for performing exposure assessments. Draft. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment.

ICAIR, Life Systems, Inc. 1985. Toxicology handbook: Principles related to hazardous waste site investigations. Draft. Washington, DC: U.S. Environmental Protection Agency, Office of Waste Programs Enforcement. Contract No. 68-01-7037.

ICF Incorporated. 1985. Superfund public health assessment manual. Draft. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. Contract No. 68-01-6872.

ICF Incorporated. 1983a. Scientific support document: the scientific basis for the risk evaluation process. Draft. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response.

ICF Incorporated. 1983b. Superfund feasibility study guidance, chapter 4, risk evaluation. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response.

McNells DN, Barth DC, Khare M et al. Environmental Research Center, University of Nevada at Las Vegas. 1984. Exposure assessment methodologies for hazardous waste sites. Las Vegas, NV: Office of Research and Development. Environmental Monitoring Systems Laboratory. CR810550-01.

Morgan RC, Clemens R, Davis BD et al. 1984. Endangerment assessments for superfund enforcement actions. Washington, DC: U.S. Environmental Protection Agency, Office of Waste Programs Enforcement.

NAS. 1982. National Academy of Sciences, National Research Council. Risk and decision making: perspectives and research. Washington, DC: National Academy Press.

Nisbet ICT. Clement Associates, Inc. 1984. Seminar presentation on endangerment assessment. Final Report. Washington, DC: U.S. Environmental Protection Agency, Office of Waste Programs Enforcement. Contract No. 68-01-6769.

Schaum J. 1984. Short course on integration of exposure and risk assessment. Part 3. Exposure assessment methods. Paper presented at the Annual Meeting of Society for Environmental Toxicology and Chemistry, Arlington, VA.

Schultz HL, Palmer WA, Dixon GH et al. Versar Inc. 1984. Superfund exposure assessment manual. Final Draft. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances, Office of Solid Waste and Emergency Response. Contract Nos. 68-01-6271 and 68-03-3149.

USEPA. 1985a. U.S. Environmental Protection Agency. Environmental Criteria and Assessment Office. Proposed guidelines for the health risk assessment of chemical mixtures. Fed. Regist., Jan. 9, 1985, 50 1170.

USEPA. 1985b. U.S. Environmental Protection Agency. Office of Emergency and Remedial Response. Guidance on feasibility studies under CERCLA. Draft. Washington, DC: U.S. Environmental Protection Agency.

USEPA. 1985c. U.S. Environmental Protection Agency. Office of Emergency and Remedial Response. Guidance on remedial investigations under CERCLA. Final Draft. Washington, DC: U.S. Environmental Protection Agency.

USEPA. 1985d. U.S. Environmental Protection Agency. Office of Waste Programs Enforcement. Draft endangerment assessment guidance. Memorandum from Jack W. McGraw. Washington, DC: U.S. Environmental Protection Agency. May 28, 1985.

USEPA. 1984a. U.S. Environmental Protection Agency. Risk assessment and management: framework for decision making. Washington, DC: U.S. Environmental Protection Agency.

USEPA. 1984b. U.S. Environmental Protection Agency. Office of Health and Environmental Assessment. Proposed guidelines for carcinogen risk assessment. Fed. Regist., Nov. 23, 1984, 49 46294.

USEPA. 1984c. U.S. Environmental Protection Agency. Office of Health and Environmental Assessment. Proposed guidelines for exposure assessment. Fed. Regist., Nov. 23, 1984, 49 46304.

USEPA. 1984d. U.S. Environmental Protection Agency. Office of Health and Environmental Assessment. Proposed guidelines for mutagenicity risk assessment. Fed. Regist., Nov. 23, 1984, 49 46314.

USEPA. 1984e. U.S. Environmental Protection Agency. Office of Health and Environmental Assessment. Proposed guidelines for the health assessment of suspect developmental toxicants. Fed. Regist., Nov. 23, 1984, 49 46324.

USEPA. 1984f. U.S. Environmental Protection Agency. Office of Pesticides and Toxic Substances. Chemical activities status report, fourth edition, volume 2. Washington, DC: U.S. Environmental Protection Agency. EPA 560/TIIS-84-0016.

USEPA. 1982. U.S. Environmental Protection Agency. Office of Pesticides and Toxic Substances. Graphical exposure modeling system (GEMS) user's guide. Draft. Washington, DC: U.S. Environmental Protection Agency.

Whitmore RW. 1984. Research Triangle Institute. Methodology for characterization of uncertainty in exposure assessments. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Exposure Assessment Group. Contract No. 68-01-6826.

APPENDIX 1

DRAFT ENDANGERMENT ASSESSMENT GUIDANCE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DRAFT

SEP 20 1985

OFFICE OF
SOLID WASTE AND EMERGENCY RESPONSE

MEMORANDUM

SUBJECT: Endangerment Assessment Guidance

FROM: J. Winston Porter
Assistant Administrator

TO: Addressees

PURPOSE

This memorandum clarifies the requirement that an endangerment assessment be developed to support all administrative and judicial enforcement actions under Section 106 of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and Section 7003 of the Resource Conservation and Recovery Act (RCRA). Before taking enforcement action under these provisions to abate the hazards or potential hazards at a site, the Environmental Protection Agency (EPA) must be able to properly document and justify its assertion that an imminent and substantial endangerment to public health or welfare or the environment may exist. The endangerment assessment provides this documentation and justification. The endangerment assessment is not necessary to support cost recovery for Section 104 remedial actions.

This memorandum also provides guidance on the content, timing, level of detail, format, and resources required for the preparation of endangerment assessments.

WHAT IS AN ENDANGERMENT ASSESSMENT

An endangerment assessment is a determination of the magnitude and probability of actual or potential harm to public health or welfare or the environment by the threatened or actual release of a hazardous substance (for a CERCLA action) or a hazardous waste (for a RCRA action).

An endangerment assessment evaluates the collective demographic, geographic, physical, chemical, and biological factors which describe the extent of the impacts of a potential or actual release of a hazardous substance and/or hazardous waste.

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In general, the endangerment assessment should identify and characterize:

(a) Hazardous substances and/or hazardous wastes present in all relevant environmental media (e.g., air, water, soil, sediment, biota);

(b) Environmental fate and transport mechanisms within specified environmental media, such as physical, chemical and biological degradation processes and hydrogeological evaluations and assessments;

(c) Intrinsic toxicological properties or human health standards and criteria of specified hazardous substances or hazardous wastes;

(d) Exposure pathways and extent of expected or potential exposure;

(e) Populations at risk; and,

(f) Extent of expected harm and the likelihood of such harm occurring (i.e., risk characterization).

WHY PERFORM AN ENDANGERMENT ASSESSMENT

Under Section 106(a) of CERCLA, if the President determines that there may be an imminent and substantial endangerment to public health or welfare or the environment from an actual or threatened release of a hazardous substance, the President may secure such relief as may be necessary to abate such danger or threat. Such relief may be in the form of a judicial action or an administrative order to compel responsible parties to respond to hazardous conditions.

Before an order can be issued under §106 of CERCLA, EPA must be able to document and justify its assertion that an imminent and substantial endangerment to public health or welfare or the environment may exist. The endangerment assessment provides this documentation and justification. It is the basis for the findings of fact in administrative orders, consent decrees, and complaints.

In situations dealing with hazardous wastes or solid wastes under RCRA, rather than hazardous substances under CERCLA, Section 7003 of RCRA may be used as the authority under which EPA may issue orders or file civil actions 1/. Section 7003 of RCRA requires a similar finding of imminent and substantial endangerment and, therefore, EPA must also document and justify such an assertion with an endangerment assessment before taking enforcement action.

1/ "Final Revised Guidance Memorandum on the Use and Issuance of Administrative Orders Under Section 7003 of the Resource Conservation and Recovery Act", September 26, 1984 signed by Courtney Price and Lee Thomas.

It is important to note that "imminent" does not mean immediate harm. Rather, it means an impending risk of harm. Sufficient justification for a determination of an imminent endangerment may exist if harm is threatened; no actual injury need have occurred or be occurring. Similarly, "endangerment" means something less than actual harm.

WHEN TO PERFORM AN ENDANGERMENT ASSESSMENT

At remedial sites subsequently targeted for CERCLA §106 or RCRA §7003 enforcement action, all of the elements of an endangerment assessment will be provided by completing the contamination assessment, public health evaluation, and environmental assessment during the RI/FS process. As such, these assessments are equivalent to the endangerment assessment for enforcement sites. The information from the contamination assessment, public health evaluation, and environmental assessment will be considered sufficient to issue an order although additional work may be needed prior to litigation (See Attachment 1 and the RI/FS guidance documents referenced on Page 6 of this guidance).

Where an RI/FS has not been initiated or completed, an endangerment assessment must be prepared to justify an administrative order or judicial action under CERCLA §106 or RCRA §7003. For example, orders issued to govern responsible party conduct of an RI/FS or to compel responsible party performance of immediate response actions will require an endangerment assessment prior to issuance. In both cases, the endangerment assessments will demonstrate that there may be an imminent and substantial endangerment which justifies either further investigative action to determine the appropriate remedy for a site or an immediate response action.

In isolated cases, EPA has negotiated with potentially responsible parties for the site remedy before it has developed the RI/FS. In these few cases, an endangerment assessment must be developed independently of the RI/FS and completed prior to issuance of the order or decree for remedial action.

An endangerment assessment is required for all future RCRA §7003 actions, as well as older RCRA §7003 cases to which CERCLA §106 authority has been or will be added. An endangerment assessment is not required for older RCRA §7003 cases already filed by the Department of Justice without an endangerment assessment. The litigation team, however, may determine on a case-by-case basis that the preparation of an endangerment assessment or its equivalent would substantially strengthen the government's case.

Endangerment assessments must be prepared for all RCRA §7003 or CERCLA §106 orders issued to another Federal agency for cleanup of a Federally-owned facility. Normally, EPA will seek response action at a Federal facility through a site-specific compliance agreement with the appropriate Federal agency or other responsible parties. If, however, a compliance agreement is not complied with by Federal owners or responsible parties, EPA may issue an order.

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WHAT LEVEL OF DETAIL

The determination that an imminent and substantial endangerment to public health or welfare or the environment may exist is a legal prerequisite that must be met before an order can be issued. It is EPA policy that endangerment assessments should be undertaken only to the extent "necessary and sufficient" to fulfill the requirements of legal enforcement proceedings. At any site, there is the potential for conducting studies beyond the level of detail needed for enforcement actions. The level of detail of the endangerment assessment should be limited to the amount of information needed to sufficiently demonstrate an actual or potential imminent and substantial endangerment. The level of detail to sufficiently demonstrate endangerment will vary from case to case based on the following factors:

- the type of enforcement action (e.g., AO for removal vs litigation);
- the type of response action (e.g., removal vs remedial); and
- the stage of response action (e.g., RI/FS workplan vs RI/FS completed).

The level of detail required to support a particular enforcement action will ultimately be determined on a case-by-case basis by Regional program personnel in consultation with Regional Counsel. As a general guide, the matrix on page 5 defines these levels of detail based on the factors listed above. The matrix should help the Regions to both (1) determine what constitutes an adequate endangerment assessment for a particular enforcement action, and (2) plan their intramural and extramural resources accordingly.

When endangerment assessments are developed to support administrative orders for private party RI/FS or immediate removal actions, information already available about the site will generally be sufficient. Where sites are targeted for enforcement action after completion of an RI/FS, the endangerment assessments developed as part of the RI/FS will be more detailed and generally more quantitative as they will be based on information obtained from the remedial investigation. Such endangerment assessments will be used to support any subsequent CERCLA §106 orders or judicial actions seeking design and construction of site remedies.

The information gathered in an RI/FS is generally similar to the type of information needed for an endangerment assessment. However, RI/FS and endangerment assessments are developed for different purposes. RI/FS are used to determine appropriate response actions under CERCLA §104, while endangerment assessments are used for enforcement actions under CERCLA §106 or RCRA §7003. For sites with CERCLA §106 or RCRA §7003 enforcement potential, Regions should review the RI/FS workplan to determine whether information developed as part of the RI/FS will be sufficient for an endangerment assessment. In certain complex cases, additional information may be needed and a separate endangerment assessment workplan may be required.

GUIDELINES FOR LEVELS OF ENDANGERMENT ASSESSMENT

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Complexity	Type of Action	Data Base	Type of Assessment	Remarks
Level I	AO for removal action, AO for private party RI/FS, preliminary scoping	May be limited, probably consisting of information from the Preliminary Site Assessment, Site Inspection Report, and Hazard Ranking System evaluation, if completed. No health studies available; no demographic studies available. Preliminary sampling data will probably be available on pollutants present. Data on extent of release or concentrations of materials at the point of exposure may be available.	Qualitative assessment of exposure routes, population at risk, and probability of harm occurring. Critical pollutants and their toxicological properties can be readily identified and quantity of pollutants estimated. Reasonable and prudent to conclude that an exposure may exist because of the release.	For removal actions where the normal site ranking process has not been completed or undertaken, information for the assessment may be available from record searches, State sponsored investigations, written reports from inspections by government authorities, and notification in accordance with CERCLA §103.
Level II	Issuance of AO or consent decree for private party cleanup	Remedial Investigation complete or other quantitative data available on nature/extent of release. Data may be available on magnitude and demographics of population at risk. Possibly some preliminary health effects studies. Sources and specific materials associated with release are identified.	Semi-quantitative appraisal considering specific exposure routes and critical pollutants. The assessment should be able to identify any data gaps and recommend additional studies, if necessary.	This assessment must be able to support legal action in the event that it is challenged by a recalcitrant PRP. Should be conclusive enough that PRPs will be encouraged to make a firm commitment to complete remedial action, but not necessarily detailed and complete if based on RI/FS.
Level III	Litigation (site-by-site basis)	RI and FS complete. All required geological, hydrogeological, and health studies complete.	Detailed, quantitative review to identify potential health effects, critical exposure levels, and necessary follow-up health studies. Critical pollutants and routes identified, and existing exposures defined or estimated. This will constitute an appraisal to the best of expertise and knowledge and an estimate of the uncertainty.	May require endangerment assessment work in addition to information generated during RI/FS.

Note:
The matrix is flexible and may shift on a case-by-case basis as required to support a particular enforcement action.

DRAFT

The endangerment assessment should evaluate the adequacy, accuracy, precision, comprehensiveness, reliability, and overall quality of identified information and data.

Emergency actions do not require the same depth of assessment as planned or remedial activities. By definition, an immediate and significant risk of harm to human life or health or the environment will be present in an emergency, making the assessment of endangerment easier to prepare. Further, EPA is justifying only the need for immediate action, not the long-term remedial solution. Thus, the endangerment assessment may be much briefer, although the Regions should attempt to use as much available information as feasible. The Action Memorandum supporting the emergency action will normally be considered adequate to serve as an endangerment assessment in support of an enforcement action under §106 of CERCLA for an immediate response.

Attachment 2 is an abstract of a detailed paper on "Endangerment Assessments for Superfund Enforcement Actions", prepared by Technical Support Branch, CERCLA Enforcement Division, the Office of Waste Programs Enforcement (OWPE). This paper, previously distributed to the Regions, will provide technical assistance in preparing qualitative and quantitative assessments. OWPE is also preparing a handbook on preparation of endangerment assessments.

Methodologies used for performance of such aspects of the endangerment assessment as exposure and risk assessment should be consistent with the concepts and methods currently in use by the EPA Office of Research and Development (ORD).

Attachment 3 shows how the various toxicity, exposure, and risk evaluations are used to define the overall problems and hazards (endangerment) at a site. Although the use of these evaluations is possible at every site, the need for a detailed analysis, as outlined, is likely to be appropriate at only a limited number of sites to sufficiently demonstrate an actual or potential imminent and substantial endangerment.

The Office of Emergency and Remedial Response (OERR) has developed guidance manuals covering the performance of remedial investigations and feasibility studies. The chapters listed below from these documents and the OWPE handbook will provide guidance in preparing endangerment assessments:

<u>Guidance on Remedial Investigations Under CERCLA</u> (OERR, May 1985)

Chapter 7 - Site Characterization
Chapter 9 - Remedial Investigation Report Format

<u>Guidance on Feasibility Studies Under CERCLA</u> (OERR, April 1985)

Chapter 5 - Evaluate Protection of Public Health Requirements

<u>Handbook on Preparation of Endangerment Assessments</u> (OWPE - Technical Support Branch, Summer 1985)

Attachment 4 is a list of references that can be used in preparation of the endangerment assessment.

FORMAT

The endangerment assessment generally should follow a standard framework as provided in Attachment 5 and use qualitative and/or quantitative terms as appropriate.

The Action Memorandum will normally be considered adequate to serve as the endangerment assessment document in support of an order under §106 for an emergency action.

The endangerment assessment document may be the order itself (where the order contains all of the elements of an endangerment assessment) or a separate document. In deciding whether to develop a separate document or to include the elements of the endangerment assessment in the order, Regions should consider the following factors:

1. Are the responsible parties more likely to consent to an order if the endangerment assessment is part of the body of the order, or a separate document?

2. Is the order likely to be issued unilaterally or on consent? A separate document will, of course, be more important in adversarial settings.

We strongly urge that the endangerment assessment in support of an administrative order for private party cleanup be a separate document. Where all of the elements of an endangerment assessment are in the RI/FS documents, a separate document may consist simply of a brief statement cross-referencing the appropriate elements of the RI/FS.

WHO SHOULD PERFORM AN ENDANGERMENT ASSESSMENT

The Regions have the responsibility to assure that endangerment assessments are performed. The Regions can draw on technical expertise available in their Regional offices, OWPE - Technical Support Branch, ORD, the Agency for Toxic Substances and Disease Registry (see MOU between ATSDR and EPA), and/or contractor personnel available through the Technical Enforcement Support (TES) or REM/FIT and TAT contracts.

Endangerment assessments used to justify administrative orders or judicial actions issued or filed before development of the RI/FS should normally be drafted by Regional personnel with the assistance of the TES contractor. The Regions and TES contractor also have the lead in preparation of endangerment assessments for older cases where an RI/FS has not been completed.

DRAFT

If responsible parties elect to perform the RI/FS, they will, in effect, perform an endangerment assessment because they will develop many or all of the elements of an endangerment assessment as part of the RI/FS. Regions should review the RI/FS workplan to determine whether information developed as part of the RI/FS will be sufficient to show that an imminent and substantial endangerment may exist. Because subsequent enforcement actions will rely on the endangerment assessment developed as part of the RI/FS, close Regional oversight should be given to this responsible party work.

The authority for determinations of imminent and substantial endangerment relating to emergency response actions costing up to one million dollars has been delegated to the Regions, subject to the directives issued by the Office of Solid Waste and Emergency Response. (See Delegation 14-1-A, Selection and Performance of Removal Actions Costing Up to $1,000,000 and the Memorandum "Waiver of Advance Concurrence Requirements for Certain Consent Administrative Orders, Gene A. Lucero, January 3, 1985).

When exercising the authority to determine that an imminent and substantial endangerment exists for the purposes of taking enforcement action, the Region must consult with OWPE as outlined in the November 30, 1984 Regional Assignment Memo (also see the Memorandum "Superfund Delegations of Authority - ACTION MEMORANDUM", Howard Messner, April 4, 1984). In contacting OWPE, Regional staff should be prepared to discuss the details of the endangerment assessment for each determination. In certain cases involving complex health and environmental endangerment issues, OWPE may request a copy of the draft endangerment assessment for review. OWPE will complete a review of this document within 14 days of receipt, to ensure consistent, timely response.

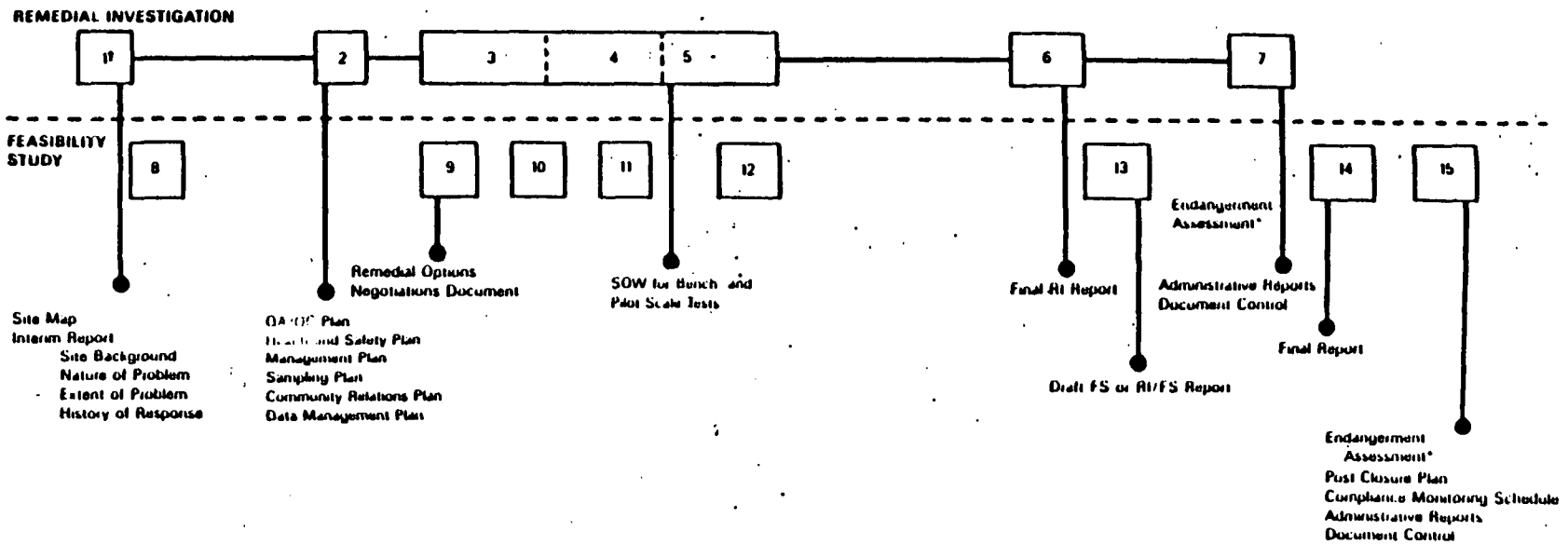
USE OF THIS GUIDANCE

The policy and procedures set forth here, and internal office procedures adopted in conjunction with this document, are intended for the guidance of staff personnel, attorneys, and other employees of the U.S. Environmental Protection Agency. They do not constitute rulemaking by the Agency, and may not be relied upon to create a right or benefit, substantive or procedural, enforceable at law or in equity, by any person. The Agency may take any action at variance with the policies or procedures contained in this memorandum or which are not in compliance with internal office procedures that may be adopted pursuant to those materials.

If you have any questions or concerns regarding this guidance, please have your staff contact Chuck Morgan (FTS-475-6690), Chief of the Environmental Health Sciences Section of OWPE or Linda Southerland (FTS-382-2035) of the Guidance and Oversight Branch.

Attachment 1

RI/FS Process



Remedial Investigation

Model Statement of Work for Remedial Investigations	Guidance Document for Remedial Investigations Under CERCLA
	CH 1 Introduction
Task #1 Description of Current Situation	CH 2 Scoping
Task #2 Plans & Management	CH 3 Sampling Plan Development
	CH 4 Data Management Procedures
	CH 5 Health and Safety Planning for Remedial Investigations
Task #3 Site Investigation	CH 6 Institutional Issues
Task #4 Site Investigation Analysis	CH 7 Site Characterization
Task #5 Laboratory & Bench Scale Studies	CH 8 Pilot and Bench Studies
Task #6 Reports	CH 9 Remedial Investigation Report Format
Task #7 Community Relations Support	

Feasibility Study

Model Statement of Work for Feasibility Studies	Guidance Document for Feasibility Studies Under CERCLA
	CH 1 Executive Summary
Task #8 Description of Proposed Response	CH 2 Develop a Range of Remedial Alternatives
Task #9 Preliminary Remedial Technologies	
Task #10 Development of Alternatives	CH 3 Conduct a Detailed Technical Evaluation
Task #11 Initial Screening of Alternatives	
	CH 4 Evaluate Institutional Requirements
	CH 5 Evaluate Protection of Public Health Requirements
Task #12 Evaluation of Alternatives	CH 6 Evaluate Environmental Impacts
	CH 7 Cost Analysis
Task #13 Preliminary Report	CH 8 Summarize Alternatives
Task #14 Final Report	
Task #15 Additional Requirements	CH 9 Feasibility Study Report Format

† Numbers in the boxes refer to tasks described in the Model Statement of Work for RI/FS under CERCLA Guidance issued February 1985. See Appendix A

* Endangerment assessments may be prepared at any point in the RI/FS process in support of enforcement actions

Attachment 2

ENDANGERMENT ASSESSMENTS FOR SUPERFUND ENFORCEMENT ACTIONS[1]

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Robert Clemens
Thomas T. Evans
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ABSTRACT

The Comprehensive Environmental Response, Compensation and Liablity Act of 1980 (CERCLA) gave the Environmental Protection Agency (EPA) new responsibilities and powers to take actions in response to releases of hazardous substances into the environment which may present an imminent and substantial endangerment to the environment, or the public health or welfare.

In an action to abate an endangerment, an assessment is made of the hazards or potential hazards at a site according to methods outlined in the National Contingency Plan. Information needed to perform an endangerment assessment includes the site history and management practices, identification and quantification of hazardous substances at a site, and their likely transport and fate. Estimates of actual or potential human and environmental exposures are compared to toxicological data to describe the kind and degree of endangerment.

This paper discusses the many factors that should be considered in an endangerment assessment and streses the need for strict quality assurance and sound scientific judgment.

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[1] The information presented in the paper is based on the technical enforcement case development experiences of the authors.

[2] Contact to whom comments should be addressed:
(WH-527), 401 M. Street, S.W. Washington, D.C. 20460

Attachment 3

Data Collection/Problem Characterization

Data Collection/Problem Characterization

I. Site Characterization

A. physical description of the site
B. geographical location
C. demographic surroundings
D. type of facility (landfill, incinerator, impoundment)
E. management practices

II. Contaminants Found at the Site

A. identity/type
B. quantity
C. form
D. manner of disposal
E. ambient levels

III. Factors Affecting Migration

A. topography
B. soil parameters
C. geological parameters
D. hydrological characteristics
E. climate

IV. Environmental Fate of Contaminants

A. physical and chemical degradation characteristics
B. movement between environmental media
C. hydrogeological/geochemical characteristics
D. evidence migration

V. Hazard Identification (site/population specific)

A. Toxicological evaluation, e.g.

- organ toxicity, carcinogenic
- mutagenic, teratogenic
- neurotoxic, etc.

B. Impact Evaluation (actual)

1. Environmental impacts

a. determination of need
b. literature searches
c. lab tests
d. food chain studies
e) environmental effect observation
- stressed vegetation
- wildlife or aquatic life morbidity/mortality
- domestic animal morbidity/mortalilty
f) natural resource damages

2. Public Health Impacts (actual)

a) health assessment/advisory (short-term)

1. determination of need?
2. literature searches
3. lab tests, pilot biological testing
4. testing of food chain contamination
5. health assessment document
6. health advisories

b) human health studies (long-term)

- epidemiological studies
- clinical studies
- registries

c) human health standards and criteria

Data Interpretation

I. Dose-Response Assessment (predictive)

A. quantitative component of cancer mathematical modeling- probability

B. ADI calculations for non-carcinogens

II. Exposure Assessment

A. locate potential populations at risk of exposure
B. determine routes and pathways of exposure for each in various environmental media, and environmental transport and fate data

C. calculate maximum short-term dose and average dose expected over a lifetime

III. Risk Characterization (predictive)

A. combining exposure, hazard and dose-response assessments for a specific site

B. estimation of the magnitude of the public health problem at a particular site including Medical Panel concerns.

Risk Management
process of evaluating and selecting options; environmental, economic, social and political consequences may be considered

Attachment 4

BIBLIOGRAPHY

Proposed Guidelines for Carcinogen Risk Assessment, EPA, 49 FR 84-30724 November 23, 1984.

Proposed Guidelines for Exposure Assessment, EPA, 49 FR 84-30723 November 23, 1984.

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Proposed Guidelines for the Health Assessment of Suspect Developmental Toxicants, EPA, 49 FR 84-30721 November 23, 1984.

Proposed Guidelines for the Health Risk Assessment of Chemical Mixtures, EPA, 50 FR 85-589 January 9, 1985.

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Interim Procedures and Guidelines for Health Risk and Economic Impact Assessments for Suspected Carcinogens, EPA, 41 FR 24102 May 25, 1976.

Scientific Bases for Identification of Potential Carcinogens and Estimation of Risks, Report by the Work Group on Risk Assessment of the Interagency Regulatory Liaison Group, 44 FR 39858 July 6, 1979.

Guidelines and Methodology Used in the Preparation of Health Assessment Chapters of the Consent Decree Water Criteria Documents, Appendix C of Water Quality Criteria Documents: EPA, 45 FR 79347 November 28, 1980.

Appendix E: Response to Comments on the Human Health Effects Methodology for Deriving Ambient Water Quality Criteria, 45 FR 79368.

Endangerment Assessments for Superfund Enforcement Actions, HMCRI Compendium of Papers, November, 1984.

Risk Assessment and Management: Framework for Decision Making U.S. EPA, December 1984.

* Further references are forthcoming in the Feasibility Study Guidance Document, the Superfund Exposure Assessment Manual, the Superfund Public Health Evaluation Process: Procedures Manual, the Superfund Risk Evaluation Manual, and the Office of Research and Development Handbook for Performing Exposure Assessments.

APPENDIX 2

EXAMPLES OF ENDANGERMENT ASSESSMENT

Part 1 - Level 1 Endangerment Assessment

Part 2 - Level 2 Endangerment Assessment

Part 3 - Level 3 Endangerment Assessment

PREFACE

The following examples of Level 1, 2 and 3 endangerment assessments are based on data from a real enforcement case. They were prepared exclusively for illustrative purposes and are not intended to definitively reflect current endangerment posed by the site. It was necessary to selectively include information from a substantial number of documents in the EPA's case files to reflect the scope and type of information that typically would be available at the times Level 1, 2 or 3 assessment documents are prepared. As a result, some data were considered not to exist during preparation of the Level 1 or 2 examples which were subsequently used to prepare the Level 3 example. Some descriptions and information in these example documents may not fully reflect actual site conditions at the present time but are intended to represent conditions that may have existed at the time each assessment would have been prepared.

Although a substantial information base was available, some key information was still not available. The example endangerment assessment documents illustrate several approaches to deal with an incomplete or a less than ideal data base. The scope, quality and type of information available and site specific features influenced the level of detail, content, length and focus of the example endangerment assessment documents. The example endangerment assessments focused on a single chemical (dioxin) due to its extreme toxicity. The type of monitoring data available and existing exposure assessment and risk assessment documents precluded addressing multiple chemicals in the example endangerment assessments. More information on other contaminants may become available to enable expansion of the scope of these assessments. Future revisions of these examples endangerment assessments or preparation of real endangerment documents on other sites may require addressing several chemicals of concern. These documents should contain correspondingly less detailed toxicity information for individual chemicals (relative to the amount of information provided on dioxin in the example documents) to keep the entire document's length of a manageable size.

The Vertac site is probably more complex than the typical site since it contains several landfill areas, drum storage areas, discharges to surface waters, spill areas, drainage ditches and adjacent residences. Several removal and remedial actions implemented at the site further complicate the example.

Existing exposure evaluation documents for the Vertac site have focused on dioxin exposures via consumption of contaminated fish or inhalation of airborne dioxin contaminated dust. Assessments of direct dermal exposures, direct ingestion (i.e. pica in children) and ingestion of contaminated drinking water were limited by the available information and the resources available and the schedule for completion of the examples. Future revisions of the example endangerment assessments may address these routes in more detail (i.e., in the Levels 2 and 3 example) and possibly consider exposures to other contaminants as appropriate. This may include rough exposure calculations in the Level 2 example and some original exposure modeling for the Level 3 example as appropriate data become available.

The risk and impact evaluation may require expansion in future revisions pending results of the exposure evaluations. This is especially relevant for the Level 3 example which should ideally provide quantitative assessments for direct dermal and ingestion exposures, and ingestion of contaminated drinking water. The risk and impact evaluation may also need to address adverse effects posed by other contaminants from the site.

PART 1 - LEVEL 1 ENDANGERMENT ASSESSMENT

Submitted to:

Office of Waste Programs Enforcement
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Attention: Chief, Health Sciences Section, R. Charles Morgan (2 copies)

VERTAC SITE ENDANGERMENT ASSESSMENT

(Level 1 Example)

Prepared Under

Program No. 1393

for

Contract No. 68-01-7037

Work Assignment No. 12

PRC Work Assignment No. 136

Contact: Timothy E. Tyburski

Telephone: (216) 464-3291

July 25, 1985

DISCLAIMER

This document has not been peer and administratively reviewed within EPA and is for internal Agency use/distribution only.

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1.0 INTRODUCTION

The disposal of chemical waste and discharges of process wastewater at the Vertac hazardous waste site over a 30-year period has resulted in contamination of soils, groundwater and surface waters. This contamination may endanger human health, welfare and the environment.

1.1 Site Description and History

The Vertac site (about 93 acres), located in Jacksonville, AR, is currently used to manufacture the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D). Munitions and numerous pesticides including DDT, aldrin, dieldrin, toxaphene, 2,4-D, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4,5-trichlorophenoxypropionic acid (Silvex or 2,4,5-TP) and Agent Orange have been previously manufactured on site. The site is bounded by the Rocky Branch Creek and the East Branch of the Rocky Branch Creek, an old artillery booster line and an adjacent housing subdivision (see Figure 1). The creek flows to Bayou Meto, a tributary of the Arkansas River.

1.2 Contaminants Found On-Site

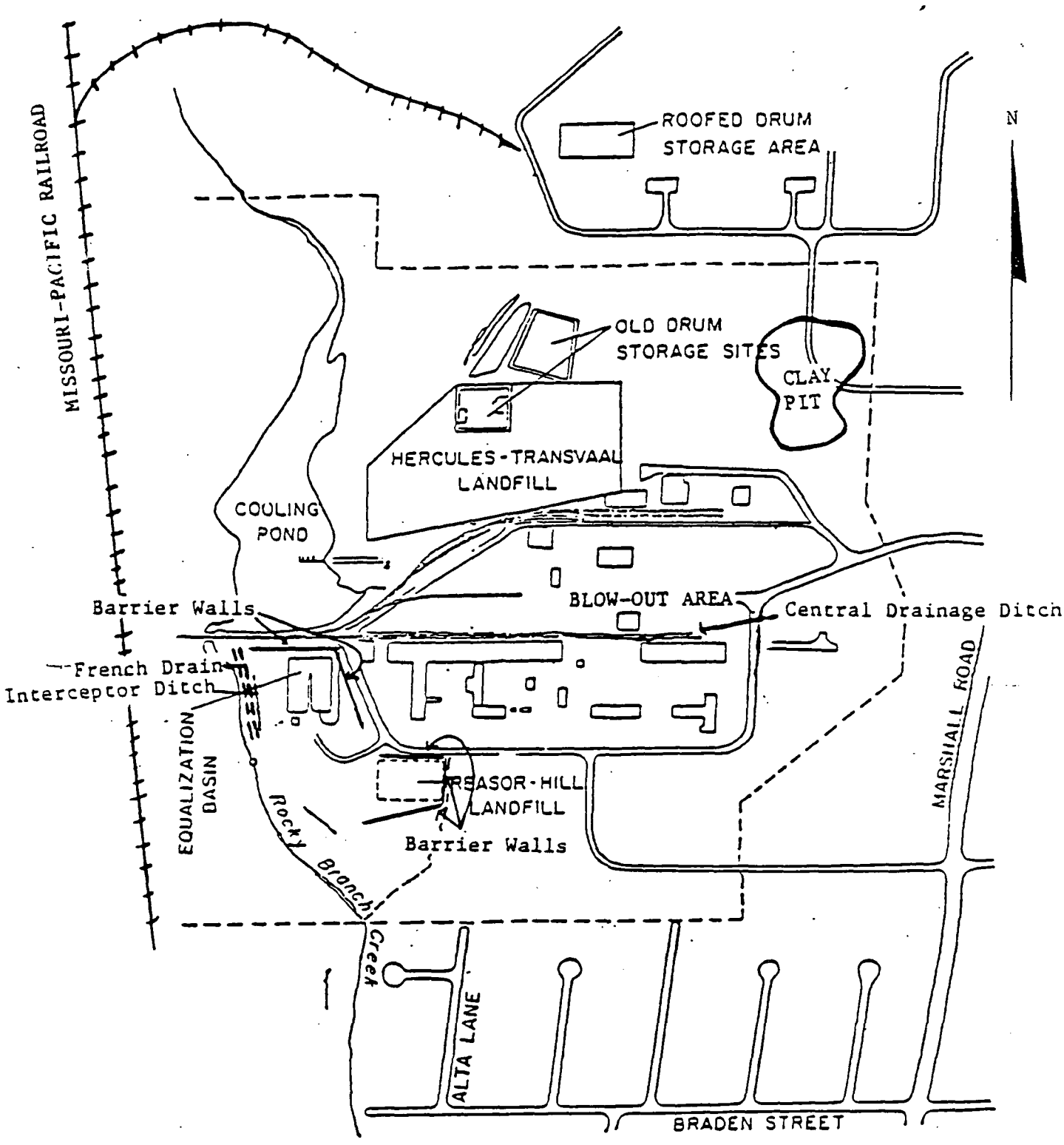
The site contains about 30,000 yd^3 of chlorinated phenols, benzene and toluene wastes in the Reasor-Hill Landfill, 20,000 yd^3 of materials (containing dioxin) in the equalization basin, 100,000 yd^3 of toluene still bottoms in the Hercules-Transvaal Landfill and 3,000 drums of 2,4,5-T still bottoms and contaminated soils in a roofed and diked warehouse. Discharges of process wastewaters, disposal of pesticide manufacturing wastes, reactor spills and other plant operations have caused the actual or potential release of the following contaminants:

- 2,3,7,8-TCDD
- 2,4,5-T
- 2,4-D
- 2,4,5-TP
- Chlorophenols
- Chlorobenzenes
- Toluene
- Methanol

This endangerment assessment focuses on dioxin because it is the most highly toxic substance at this facility and is very persistent in soils and aquatic systems. Dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin or 2,3,7,8-TCDD) has been detected as an impurity in waste products from the manufacture of 2,4,5-T and Agent Orange, in soils on-site and in sediments and fish tissues from adjacent surface waters.

2.0 ENVIRONMENTAL FATE AND TRANSPORT

Dioxin is very persistent (estimated half-life of 10 years) in the environment and resists biodegradation, photodegradation, oxidation and hydrolysis (USEPA 1984). Dioxin is adsorbed on particles (suspended or sediments) and soils and is only slightly soluble (0.2 μg/L) in water (USEPA 1984). Since dioxin tends to remain bound to soils, the vertical migration of dioxin in soil is usually minimal. The primary route of transport is via horizontal transfer of dioxin adsorbed to soils and dust particles. Wind erosion and surface runoff erosion



Adapted from Walton 1982 as cited in JRB (1983)

FIGURE 1 VERTAC SITE MAP

processes are anticipated to be the primary mechanisms of natural horizontal transport. Vertical migration of dioxin through the soil is unlikely to occur unless the capacity of the soils are saturated or dioxin is solvated by organic solvents (NRCC 1981). Dioxin solvated by organic solvents may be more readily transported through soil to the groundwater.

Dioxin released to aquatic systems bioaccumulates in a number of species and may accumulate up to four orders of magnitude above environmental concentrations (Isensee and Jones 1975). Bioaccumulation and bioconcentration factors for dioxin are being reassessed by the U.S. Environmental Protection Agency. Anthropogenic activities involving disturbance of soils and frequent vehicular movement (associated with routine on-site land fill operations) are expected to cause emission of dust potentially bearing dioxin. Wet and dry deposition of this dust may contaminate surface soils and surface water bodies (Rocky Branch Creek, Bayou Meto and Lake Dupree) adjacent to the site.

The direct discharge of process wastewaters to the cooling pond and transport of dioxin on suspended particles has caused substantial contamination of the Rocky Branch Creek and Bayou Meto. Flooding of the Rocky Branch Creek south of the Vertac site has potentially transported dioxin-particulate to Lake Dupree, a man-made recreational lake about 1.3 miles south of Vertac.

3.0 EXPOSURE EVALUATION

3.1 Routes of Exposure

The potential routes of exposure are:

1. Consumption of contaminated fish from the Bayou Meto and Rocky Branch Creek.

2. Consumption of groundwater or surface water downgradient of the Vertac site.

3. Inhalation of dust-contaminated with dioxin that becomes airborne due to wind erosion or anthropogenic activities.

4. Direct contact with waters, sediments or soils adjacent to the site that have been contaminated by surface runoff, erosion processes and direct releases. Direct contact includes direct dermal exposures as well as direct ingestion exposures (i.e. pica in children).

The route of primary concern is anticipated to be consumption of contaminated fish from the Bayou Meto because of the probability for dioxin to bioaccumulate in fish (as indicated by the high bioconcentration factors). Preliminary environmental monitoring data has detected high concentrations of dioxin in fish from Lake Dupree (810 ppt) and Bayou Meto (300 ppt) (Schaum and Falco 1982). Bayou Meto was classified as a warm water fishery according to the 1975 Arkansas Water Quality Standards and was considered suitable for desirable species of fish, wildlife and other aquatic and semi-aquatic life and

potentially as raw water source for public water supplies. However, pollution problems in Bayou Meto and its tributaries (including the Rocky Branch Creek) date back to 1955 when massive fish kills were first reported to be associated with releases of contaminants from the Vertac site.

3.2 Populations Exposed

The population that consumes fish caught from the Bayou Meto is potentially exposed to high concentrations (about 300 ppt) of dioxin (Schaum and Falco 1982). Individuals who may consume large (5 to 16 lb/year) amounts of fish from the Bayou have the highest exposure potential. Complaints of "medicinal" taste and odor problems in fish caught from the Bayou registered with the Arkansas Game and Fish Commission indicate that there have been chronic pollutional problems and provide evidence of real exposure potential via this route. Further complaints about taste and odor of fish from the Bayou registered in 1963 and in 1965 were also traced to contaminants released from the Vertac site.

Insufficient data on the prevailing wind direction, wind speed and geographical features affecting wind patterns are available to determine which populations are at an increased exposure potential for airborne dust. The population living in the subdivision to the south of the Vertac site is potentially at risk for exposure to dioxin-dust emissions. The size of the population living near the site has not been determined. It is assumed that the proximity of the population to the site subjects the nearest residents to an increased risk of exposure to dioxin since airborne dust concentrations are expected to be greatest close to the site and to diminish with increasing distance from the site. People that are homebound during the daytime, and especially those that are outside during site activities that create dust emissions are expected to be at highest risk; however, the concentration indoors and outdoors may equalize over time.

Preliminary contacts with state and local permitting agencies have not identified a substantial number of domestic or industrial wells within the vicinity of the site. Populations that consume groundwater may be at increased risk of exposure to dioxin or other contaminants that may percolate into the water table and migrate off-site.

Off-site migration via wind and water erosion processes or direct releases creates the potential for direct contact exposures. Populations that are in close proximity to the site (i.e., in the housing subdivision) and/or people that may use the area for recreation are expected to be at higher risk for direct contact exposures.

Aquatic organisms, avian species and terrestrial organisms may be exposed to dioxin and other contaminants released from the site. Preliminary monitoring data on fish indicate substantial dioxin exposures have occurred and resulted in bioaccumulation of high dioxin levels in tissues. Aquatic species that are benthic feeders are expected to be at higher risk due to high concentrations of dioxin detected in sediments of the Rocky Branch Creek, Bayou Meto and Lake Dupree.

4.0 TOXICITY EVALUATION

Dioxin is a highly toxic compound which causes liver damage, skin lesions (chloracne), renal function impairment, hematologic effects, adrenal atrophy, reproductive system damage, immunosuppression, fetotoxicity, teratogenicity and cancer in laboratory animals. The effects of greatest concern associated with exposure to dioxin are liver damage, thymic atrophy, fetotoxicity, teratogenicity and carcinogenicity. McConnell et al. (1978a,b) observed that orally administered dioxin induced mortality in various laboratory animals at doses (LD_{50}) ranging from 0.6 µg/kg to about 280 µg/kg.

Chronic toxicity studies identify the liver as the primary organ affected by dioxin (Kociba et al. 1978, 1979, NTP 1980). Oral administration of dioxin doses in less than 0.1 µg/kg/day produced hepatitis in rodents.

Dioxin has been experimentally shown to produce fetal abnormalities and teratologic effects in mice, rats and rabbits. Cleft palet and kidney abnormalities were observed in offspring from dams (mice) receiving very low doses of dioxin (0.1 µg/kg/day) for nine to ten days during gestation (Smith et al. 1976). Hemorrhages edema and kidney abnormalities have also been reported in fetal rats (Courtney and Moore 1971) and bone and soft tissue malformations in fetal rabbits (Giavini et al. 1982) following maternal exposure to dioxin. A study in rhesus monkeys observed a statistically significant increase in early abortions in animals exposed to dioxin (McNulty 1978).

Conflicting evidence is available concerning the potential teratogenicity of dioxin in humans. Some epidemiological studies show a positive association between exposures to the herbicide 2,4,5-T (which contains dioxin as an impurity) and the occurrence of birth defects or abortions while other studies have found no association.

Numerous studies in laboratory animals indicate that dioxin is a potent carcinogen when administered via ingestion or dermal exposure (Van Miller 1977, Toth et al. 1978, Kociba et al. 1978 and NTP 1980a,b). The U.S. EPA Carcinogen Assessment Group has identified dioxin as the most potent chemical carcinogen evaluated to date using animal tumorigenesis models.

A substantial number of studies indicate an association between exposure to dioxin and development of cancer in humans, however, human data are not available to definitively demonstrate that dioxin causes cancer. Most of the studies examined people who were occupationally exposed to dioxin along with phenoxyherbicides (2,4-D, 2,4,5-T and chlorophenols). Soft-tissue carcinomas were observed in workers exposed to phenoxy acids (Hardell 1977) and malignant lymphomas in workers exposed to phenoxy acids and chlorophenols (Hardell et al. 1981). Other epidemiological studies (Zack and Suskind 1980, Cook et al. 1980, Smith 1982, 1983) also found increased tumor frequencies in dioxin exposed populations. However, since dioxin was usually a contaminant of pheynoxy acids and/or chlorophenols, human exposures were always to multiple chemicals. Therefore, the evidence for human carcinogenicity is only suggestive due to problems associated with the evaluation of risks from chemical mixtures.

The toxic properties of the other site contaminants, 2,4,5-T, 2,4-D, Silvex, chlorophenols, chlorobenzenes, toluene and methanol, are summarized in NAS (1977, 1980, 1983).

5.0 RISK AND IMPACT EVALUATION

Contamination from the Vertac site presents endangerment to human health and the environment due to exposure potential and toxicity. Consumption of contaminated fish from the Bayou Meto may substantially increase the cancer risks in humans due to dioxin exposures. Preliminary data indicate an apparent lack of exposure potential via groundwater; however, groundwater contamination with dioxin or more environmentally mobile chemicals is probable and may preclude future use of groundwater as a drinking water resource. Residents adjacent to the Vertac site in the housing subdivision are potentially subjected to dioxin exposure via inhalation of contaminated dust and are therefore subjected to an increased risk of cancer. Potential exposures via direct contact with contaminated soils and sediments caused by offsite erosion and/or release of dioxin presents increased risks of cancer and various acute and chronic effects, such as chloracne, to populations that may garden, play or be in contact with soils or sediments.

Release of dioxin from the Vertac site also poses potential risks to aquatic and terrestrial species because of its tendency to bioaccumulate in aquatic organisms. Contaminant releases from the Vertac facility have caused massive fish kills (acute toxicity) and may potentially cause chronic toxicity.

Contamination from the Vertac site also has a major impact on the public welfare since it is probable that surface waters may not be useable for fishing and/or recreation. Additionally, properties adjacent to the site which are contaminated or may be contaminated will potentially have decreased values.

6.0 CONCLUSIONS

On-site disposal of large quantities of pesticide manufacturing waste, discharges of process wastewaters, spills and other plant operations at the Vertac site have caused substantial chemical contamination both on-site and off-site. The actual or potential release of dioxin and other toxicants to the environment may present a substantial endangerment to humans, aquatic organisms, terrestrial organisms and avian species. The most significant threat to human health may be due to the potential consumption of dioxin that accumulates in fish caught from the Bayou Meto, although other routes may be important for other individuals. Potential dioxin exposures via direct contact (direct dermal exposure on direct ingestion) with contaminated soils and sediments may potentially endanger human health. The contamination of groundwater may preclude its use as a drinking water resource. Residents adjacent to the site may be exposed to dioxin via inhalation of dust-emissions from anthropogenic activities at the site or from wind erosion. Adverse health effects including cancer have or potentially may occur in populations exposed to dioxin from the Vertac site. The release of dioxin to aquatic systems and soils may lead to bioaccumulation in organisms throughout the food

chain and present risk to the environment. The potential loss of fishing in the Bayou Meto, decrease in value of property adjacent to the site and the loss of groundwater as a potential drinking water resource impact the public welfare.

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PART 2 - LEVEL 2 ENDANGERMENT ASSESSMENT

Submitted to:

Office of Waste Programs Enforcement
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Attention: Chief, Health Sciences Section, R. Charles Morgan (2 copies)

VERTAC SITE ENDANGERMENT ASSESSMENT

(Level 2 Example)

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July 25, 1985

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1.0 INTRODUCTION

Disposal of chemical wastes and discharges of process wastewater over a 30-yr period has resulted in contamination of soils, groundwater and surface waters at the Vertac Chemical Corporation herbicide manufacturing facility in Jacksonville, AR. The release or potential release of contaminants from this site may endanger human health, welfare and the environment. Human health is at risk due to the potential for consumption of contaminated fish, inhalation of airborne contaminants, direct contact with contaminanted soils/sediments and ingestion of contaminated groundwater. Contaminants released to surface waters have been bioaccumulated to substantial levels in fish and other aquatic species.

1.1 Site Description and History

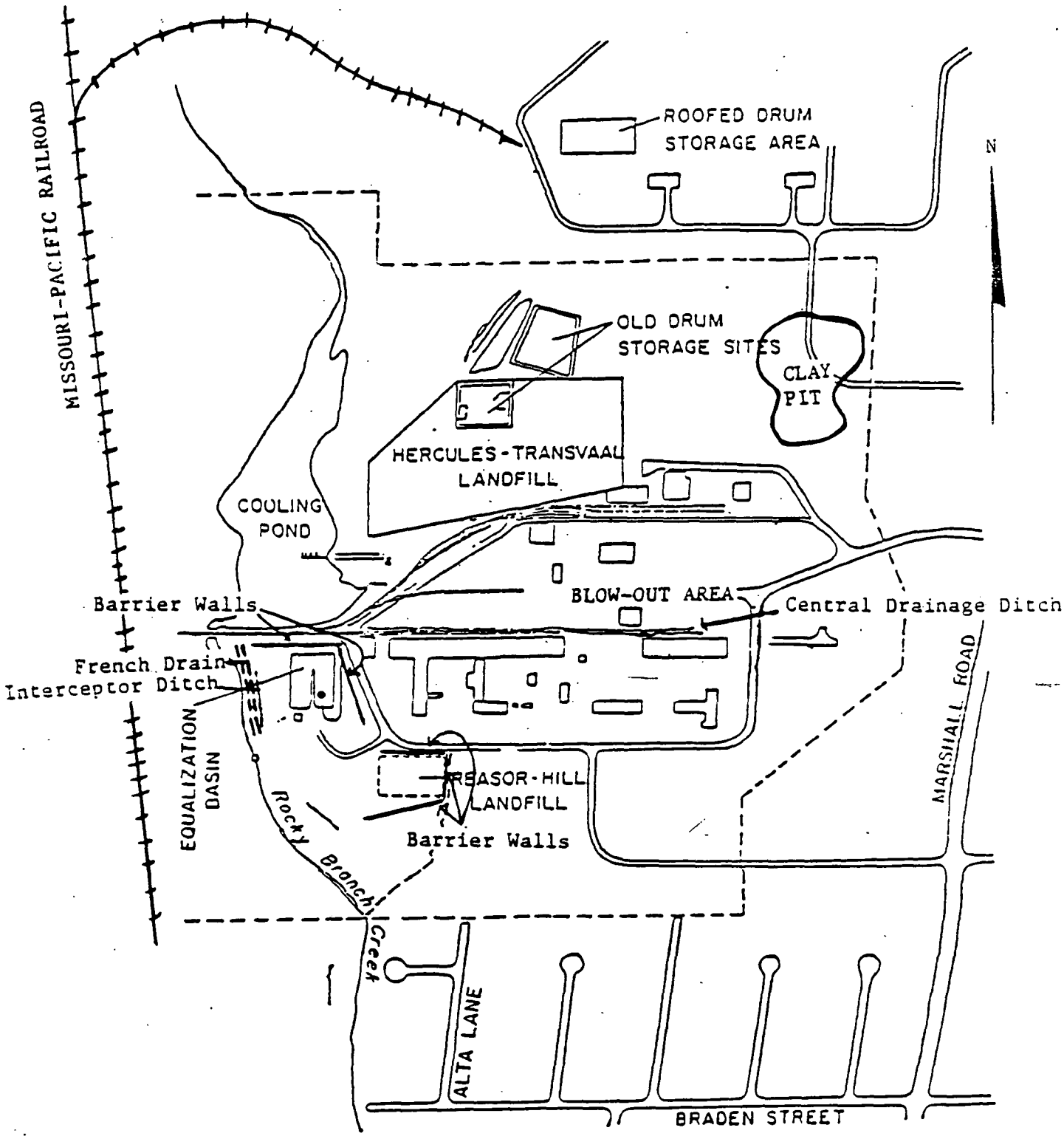
The Vertac hazardous waste site is located in northwest Jacksonville, AR (Pulaski County), approximately 20 mi northeast of Little Rock. The site (about 93 acres in size) is bounded by Marshall Road to the east and the Missouri-Pacific Railroad to the west. The old artillery booster line is on the northern boundary and an adjacent housing development is to the south. The Rocky Branch Creek flows along the western edge of the site and the East Branch of the Rocky Branch Creek flows to the east of the site. The cooling pond located along the western edge of the site was formed by construction of an earthen dam across the Rocky Branch Creek. The Rocky Branch Creek flows into Bayou Meto (a tributary of the Arkansas River) about two miles south of the Vertac site. There is a fence around the entire site with a main gate facing Marshall Road. Figure 1-1 demonstrates the site features and boundaries.

The site is a herbicide manufacturing plant owned by the Vertac Chemical Corporation which currently produces 2,4-dichlorophenoxyacetic acid (2,4-D). The site has been used since the 1930s by a variety of companies for the manufacture of munitions and pesticides including DDT, aldrin, dieldrin, toxaphene, 2,4-D, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 2,4,5-trichlorophenoxypropionic acid (Silvex or 2,4,5-TP) and Agent Orange (a mixture of 2,4-D and 2,4,5-T). The herbicides 2,4,5-T and Agent Orange are known to contain 2,3,7,8-tetrachlorodibenzo-p-dioxin (hereafter referred to as dioxin, 2,3,7,8-TCDD or TCDD) as an impurity. Waste disposal, cooling water discharges and other plant operations apparently resulted in on-site and off-site releases of pesticides and herbicides manufactured on site, chemicals used in manufacturing processes and manufacturing impurities/by-products, including TCDD.

Estimates of the quantity and types of contaminated materials at the Vertac site were reported (JRB 1983) as follows:

1. Thirty thousand (30,000) yd^3 (22,800 m^3) of chlorinated phenols, benzene and toluene wastes within the Reasor-Hill landfill.

2. Twenty thousand (20,000) yd^3 (15,200 m^3) of still bottoms, contaminated with 2,3,7,8-TCDD, presently contained in the equalization



Adapted from Walton 1982 as cited in JRB (1983)

FIGURE 1-1 VERTAC SITE MAP

basin wastewater treatment system. This amount includes the clay cap placed on the basin at closure.

3. One hundred thousand (100,000) yd^3 (76,000 m^3) of material, including toluene still bottoms, in the Hercules-Transvaal landfill area.

4. Three thousand (3,000) drums (55 gallons each) of 2,4,5-T still bottoms (repacked in 85 gallon overpack drums) and contaminated soils from the former above-ground storage area, stored in the concrete diked warehouse.

The U.S. Environmental Protection Agency (USEPA) has initiated enforcement actions against the site owners and required a number of remedial actions to be implemented. The major remedial actions completed as of 1984 are summarized below:

1. The Reasor-Hill landfill was capped with clay, covered with soil and seeded with grass. Clay barrier walls were installed on three sides and the downgradient side was left open.

2. The Hercules-Transvaal landfill was capped with clay, covered with soil and seeded with grass. No barrier walls were installed.

3. The former above-ground drum storage area was capped with clay, covered with soil and seeded. The old drums were repacked and placed in the roofed storage warehouse.

4. Two-thirds of the blow-out area (where spills from reactors had occurred) was paved with asphalt and the remainder was capped with clay, covered with soil and seeded.

5. The equalization basin has been subjected to extensive remedial actions including dewatering and lime solidification of sludges, installation of clay barrier walls, installation of a "French drain" on the downgradient side, capping with clay, covering with soil and seeding.

Under the proposed remedial action (Alternative IV), the Reasor-Hill Landfill and North Burial Area (includes old drum storage sites and Hercules-Transvaal Landfill) will be excavated and contaminated materials/soils will be redisposed of in a new on-site secure landfill in an area to the north of and overlapping with the North Burial Area. This proposed remedial action will involve excavation of 50,000 yd^3 of soil from the Reasor-Hill Landfill and 100,000 yd^3 from North Burial Areas.

1.2 Contaminants Found at the Site

Contaminants found at the site include pesticides and herbicides manufactured on site, chemicals used in the manufacture of DDT, aldrin, dieldrin, toxaphene, 2,4-D, 2,4,5-T, 2,4,5-TP (Silvex) and Agent Orange (2,4-D and 2,4,5-T mixture). Dioxin, an impurity resulting from synthesis of 2,4,5-T, is also present at

the Vertac facility. Environmental monitoring surveys from the period of 1978 to 1983 have detected chemical contaminants in groundwater, surface water, soils and sediments. The USEPA Office of Waste Programs Enforcement has identified the following "indicator" chemicals for the Vertac site on the basis of their toxic properties, presence in large quantities or potential and actual releases to the environment:

- 2,3,7,8-TCDD
- 2,4,5-T
- 2,4-D
- 2,4,5-TP
- Chlorophenols
- Chlorobenzenes
- Toluene
- Methanol

This endangerment assessment will focus on dioxin because it is the most highly toxic substance at the facility and is very persistent in soils and aquatic systems. Dioxin has been detected in waste products, groundwater and soils on site and in sediments and fish tissue in adjacent surface waters (see Table 1-1). Refer to CH2M Hill (1984a), JRB (1983) and Walton et al. (1982) for data on individual sampling sites, dates and maps indicating sampling locations and groundwater monitoring wells. A site map showing these locations (which is normally provided in an endangerment assessment) is not included because of the complexity of the several monitoring studies performed at this site. The values presented in Table 1-1 are a composite of the available monitoring data from the period 1979 to 1983.

These data have not been subjected to a comprehensive quality assurance and quality control review but a preliminary review of available data reports indicates that quality control and quality assurance procedures were implemented. These procedures included the chain of custody, split samples, replicate analyses, sample spiking with an internal radiolabelled dioxin standard, routine instrument calibration, methodological (extraction) blanks, adherence to recommended sample holding times and storage temperature, etc.

TABLE 1-1 RANGES OF DIOXIN CONTAMINATION DETECTED ON-SITE AT THE VERTAC FACILITY AND IN ADJACENT WATER BODIES

Sample Type	Location/Description	Dioxin Concentration, ppb	Total Number of Samples Analyzed	Number with Dioxin Not Detected	Detected Dioxin Concentrations, ppb Mean ± SD(n)[a]	Reference
Sediments	Equalization basin	0.063 to 1,200	5	0	460.2 ± 459.1 (5)	CH2M Hill (1984a)
	Cooling pond	0.236 to 102.0	18	0	18.2 ± 24.2 (18)	CH2M Hill (1984a)
	Drainage ditches, on-site	0.600 to 34.1	6	0	16.1 ± 12.9 (6)	CH2M Hill (1984a)
	On-site groundwater monitoring well	ND[b] to 12.1	4	2	10.0 ± 3.0 (2)	CH2M Hill (1984a)
	Rocky Branch Creek	0.500	NA[c]	NA[c]	NA[c]	Falco (1982)
	Rocky Branch Creek, on-site	0.236 to 17.4	5	0	4.1 ± 7.5 (5)	CH2M Hill (1984a)
	Sewer and interceptors off-site	18.4 to 33.4	3	0	28.3 ± 8.6 (3)	CH2M Hill (1984a)
	Creek bed adjacent to private residences	1	NA	NA	NA	JRB (1983)
	Lake Dupree	0.150	1	0	NA	Schaum and Falco (1982)
Soils	Surface soils on-site	ND[d]	NA	NA	NA	JRB (1983)
	Surface soils on-site	100 to 14,000	NA	NA	NA	Falco and Schaum (1984)
	Hercules-Transvaal area/surface dirt	559	1	0	NA	CH2M Hill (1984a)
	Reasor Hill landfill/dirt	3.42	1	0	NA	CH2M Hill (1984a)
	Reasor Hill landfill/mud	0.505	1	0	NA	CH2M Hill (1984a)
	Reasor Hill landfill area	NR[e]	NA	NA	NA	JRB (1983)
	Blow-out area	0.99 to 45	2	0	22.5 ± 31.7 (2)	CH2M Hill (1984a)
Surface Waters	Rocky Branch Creek, on-site	ND	1	1	NA	CH2M Hill (1984a)
	Discharge in combined sewer at Braden and Alta Lane	0.017	1	0	NA	CH2M Hill (1984a)
Ground Water	Monitoring wells down gradient of Hercules-Transvaal Landfill	"High"	NA	NA	NA	JRB (1983)
	Monitoring wells, on-site	ND to <0.03	35	21	0.005 ± 0.010 (13)	CH2M Hill (1984a)
Wastes	Toluene still bottoms disposed on-site	37,000	NA	NA	NA	JRB (1983)
	Seeps from Reasor Hill	0.045 to 5.5	3	0	2.4 ± 2.7 (3)	CH2M Hill (1984a)
	Equalization basin liquid	445	1	0	NA	CH2M Hill (1984a)
	Equalization basin discharge	<10	1	0	NA	CH2M Hill (1984a)
Fish	Caught in Bayou Meto	<0.025 to 0.300	6	0	0.087 ± 0.110 (6)	Schaum and Falco (1982)
	Caught in Lake Dupree	0.810	1	0	NA	Schaum and Falco (1982)

(a) The mean and standard deviation of samples with detected levels of dioxin were calculated. Samples with "not detected" (ND) levels of dioxin were not used in the calculations. The value in parentheses is the number of samples with detected dioxin levels used in the calculations.
(b) ND = Not detected. Detection limit was not reported.
(c) NA = Not applicable due to insufficient information.
(d) Not detected in measurable quantity. Detection limits 50 to 100 ppt.
(e) NR = detected but concentration not reported.

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2.0 ENVIRONMENTAL FATE AND TRANSPORT

2.1 Factors Affecting Migration

2.1.1 Geology

The Vertac site is situated very near or possibly on the fall line of the Interior Highlands and Coastal Plain physiographic regions. The geologic maps show that the Vertac site is slightly to the west of the fall line suggesting that it is in the Interior Highlands but evidence (the northern part of the site contains clays of the Midway Group which are present in the Coastal Plain) suggests it is also in the Coastal Plain or in the transition zone. The surface soils near the eastern portion of the site are sedimentary. The subsoils are part of the Atoka Formation characteristics of the Interior Highlands.

The site is underlain by the consolidated rock of the Atoka Formation which surfaces in the Interior Highlands and underlies the sediments of the Coastal Plain. The Vertac site is located on the south flank of a westward plunging syncline. The bedrock is alternating gray to black shales and sandstones of the Atoka Formation which dips to the northeast at a rate of about 30 degrees. There are many discrepancies regarding the strike and dip of the rock strata on-site since the site is so close to the fall line. The overlying unweathered bedrock in ascending order is weathered bedrock approximately five feet thick, clays and alluvium.

The soil is classified as a Leadvale-Urban land complex with a 1 to 3% slope. The Leadvale Urban land complex are areas of Leadvale soils that have been modified by urban development. The Leadvale soils are moderately well-drained, nearly level and gentle-sloping soils in valleys. They are formed mainly of loamy sediment washed from uplands composed of sandstone, shale and in some areas from weathered siltstone. The Leadvale soils have moderately low permeability and maintain a medium level of available water capacity. The level of runoff from the Leadvale Urban land complex is medium and the erosion hazard is moderate if the soils are not protected by vegetation. Soil borings indicate the presence of yellowish brown silty sands in the northeast corner of the site and yellowish brown or tan silty clays in the southeast portion of the site (CH2M Hill 1984a).

2.1.2 Hydrology

Surface drainage patterns at the Vertac site are predominantly westerly and easterly. The western 55 acres drain directly to the Rocky Branch Creek. The Rocky Branch Creek enters the Vertac site at the northwest boundary and flows into a man-made cooling pond. About 700,000 gallons/day of process waste-waters enter the cooling pond. Waters from the cooling pond flow out a concrete outlet structure at the southwest extremity of the pond. A central ditch (no longer present) acted as a surface drainage channel from the plant production area and flowed into the cooling pond. The combined flow of surface runoff and process waters enters Rocky Branch Creek and flows south about two miles to Bayou Meto.

The eastern 38 acres of the site drain east to numerous small ditches caused by natural erosion. Along adjacent driveways and roads are a few man-made ditches. The catch basins located on the eastern portion of the site drain to a storm sewer which empties into an open ditch near the main plant entrance. All surface runoff east of the drainage divide eventually flows into the East Branch of the Rocky Branch Creek. Most of this runoff is carried by the "East Ditch" to the East Branch. The East Branch flows into Rocky Branch Creek south of the Vertac Site.

During heavy spring rains it is not uncommon for the Rocky Branch Creek to flood the area south of the Vertac Site. This is important because there is a manmade recreational lake (Lake Dupree) 1.3 mi south of the Vertac site. Lake Dupree and the Rocky Branch Creek are not normally connected but, the low terrain and tendency for flooding in the area potentially enables contaminants discharged into Rocky Branch Creek to be deposited in Lake Dupree (JRB 1983).

2.1.3 Hydrogeology

The Interior Highlands are hilly and underlain by consolidated sediments which dip slightly in a southeasterly direction. The consolidated rock of the Interior Highlands underlies unconsolidated sediments of the Coastal Plain. Above the lowest level of the water table, the consolidated rock of the Highlands has been weathered. Soil and "rotten rock" (i.e., weathered rock) in this region are present to a total depth of about 20 ft (maximum). This weathered rock area is more permeable and porous than unweathered rock. Water is present in intergranular voids of "rotten rocks" and soil while water is only present in joints, fractures and other secondary openings in unweathered rock.

The sediments of the Coastal Plain vary from high plasticity clays to sands and gravels with varying permeabilities. There are three units within the sediments which are major water sources in some areas of Pulaski County. Beds of claystone, calcareous sandstone, sandy limestone, marl and conglomerate (about 7 to 60 ft) comprise one aquifer unit. Fine to medium sand with some interbedded clay lenses (about 320 ft thick) comprise another aquifer unit. Terrace deposits and alluvium (deposited by the Arkansas and Mississippi rivers) composed of fine-grain top stratum and deeper coarser stratum (about 120 ft) is the third aquifer unit. Refer to Walton et al. (1982), CH2M Hill (1984a) and JRB (1983) for further hydrogeologic information and a diagram of the locations of aquifers in the Coastal Plain and Interior Highland regions.

The general horizontal groundwater flow is from north to south (CH2M Hill 1984a). Two groundwater divides are evident on site with one running from the northeast boundary of the site along the east side, across the plant and then due south. The second divide runs from the northwest along the western edge of the cooling pond and south along Rocky Branch. The contaminated water table flows toward the cooling pond and the Rocky Branch Creek at a rate of <1 to 10 in/yr (CH2M Hill 1984a). The vertical groundwater flow rates in bedrock were calculated to range from 2×10^{-2} in/yr to 6.0 in/yr (CH2M Hill 1984a) which indicates potential downward migration of contaminants.

Little is known about the hydrogeology of bedrock deposits at the Vertac site and the structure of bedrock has not been evaluated.

The Rocky Branch Creek receives groundwater inflows from the water table from both the east and west. These flows have passed under or through the Reasor-Hill area. Contaminants entering the groundwater east of the divide may eventually enter the Coastal Plain aquifers (off-site) (CH2M Hill 1984a). The recharge and inflow upgradient of contaminant sources flows toward western surface water bodies and are conveyed off-site above ground or in the water table.

2.1.4 Climatology

Precipitation is fairly well distributed throughout the year; however, May is normally the wettest month. The annual precipitation averages about 48 in and about 31% of total precipitation occurs from March through May. August through October are the driest months with a total of 3 in of rain.

Winters are mild with average winter temperatures of 41 F and an average annual snowfall of 5.7 in. The greatest monthly snowfall reported was 12 in in January 1966. The summers are hot with an average daily temperature of 82 F and maximum temperatures of over 100 F occurring frequently in July and August.

2.2 Environmental Fate and Transport of Dioxin

2.2.1 Environmental Fate

Dioxin is not readily biodegraded. Dioxin is persistent in freshwater aquatic environments with a half-life of 550 to 590 days in sediment containing lake waters (Ward and Matsumura 1977). The biodegradation half-life of dioxin was estimated to be greater than one year based on theoretical biotransformation rate values and assumed concentrations of microorganisms (USEPA 1984). The biodegradation half-life of 0.5 yr for dioxin in soils was based on data from a rural Missouri incident involving accidental spraying of dioxin contaminated oils (IARC 1977). Recent data suggest that the half-life may be closer to 10 yr (USEPA 1984).

Dioxin in the presence of organic solvents (Crosby et al. 1971) or other hydrogen donators is photodegraded (Crosby and Wong 1977). Insufficient information is available on reactions of dioxin in aquatic media under environmental conditions to predict the photodegradation half-life in natural waters. Assessment of photodegradation in natural waters is complicated by the tendency for dioxin to be strongly adsorbed on particles in sediments that are not exposed to ultraviolet (UV) light.

Information on photodegradation of airborne dioxin adsorbed on particulates is conflicting. The importance of photodegradation relative to deposition (dry or wet) in the fate of airborne dioxin is uncertain but may be important. Dioxin sorbed to solid surfaces and exposed to the atmosphere yielded negligible

photodegradation (Crosby et al. 1971), while photolysis was evident for dioxin in a condensed phase on glass or silica.

The photodecomposition of dioxin on wet or dry soils under artificial and natural sunlight (UV radiation) was observed to be negligible in soils (Crosby et al. 1971). However, photodecomposition may occur when dioxin and other pesticides (hydrogen donators) are present as a mixture in soils (Crosby and Wong 1977).

No information on the oxidation of dioxin in aquatic systems was available but its strong electropositive nature suggests it may be more resistant than nonchlorinated or less chlorinated aromatics. The potential for oxidation of dioxin (sorbed on airborne particulates) by atmospheric compounds (NO_x, O_3, etc.) is unknown. Hydrolysis is unlikely to occur under environmental conditions in aquatic systems (USEPA 1984).

Quantitative information on volatilization of dioxin from aquatic systems is not available although several references have mentioned volatilization as a possible loss process (Callahan et al. 1979). The validity of these estimates has not been assessed with experimental data. Volatilization of dioxin adsorbed on soils is expected to be at a very slow rate due to the extremely low vapor pressure of dioxin (Falco and Schaum 1984).

Sorption on particles (suspended or sediments) and in microorganisms appears to be an important fate for dioxin in aqueous environments. Isenee and Jones (1975) observed that ~~85% to 99% of dioxin remained~~ adsorbed on sediments in an aquatic system and the majority of dioxin not on sediments was in aquatic organisms. Ward and Matsumura (1978) observed that more than 90% of dioxin in aquatic medium remained bound to sediments. The low water solubility and high octanol/water partition coefficient of dioxin support these observations.

Many aquatic species bioaccumulate dioxin. In a static experimental test chamber, the accumulation appeared to be dependent upon initial dioxin concentrations. The bioconcentration factors (determined experimentally in a static system) vary with species and may range from about 2,000 (algae or snail) to 9,000 (catfish) to 26,000 (mosquitofish) (Isenee and Jones 1975, Isenee 1978).

2.2.2 Environmental Transport

Kearney et al. (1973) examined the mobility of dioxin in five soil types and observed that decreased mobility was associated with increased organic content of soils. Dioxin was relatively immobile in all test soils and Kearney et al. (1973) concluded that leaching to underground water supplies would be unlikely. Matsumura and Benezet (1973) postulated that dioxin transport would be via horizontal transfer of contaminated soils and dust particles.

Dioxin does not readily migrate vertically in soils (USEPA 1984). Nash and Beall (1980) observed that 80% of dioxin applied to soils in a microagroecosystem remained in the upper 2 cm of soils and that only trace amounts were detected at 8 to 15 cm. The NRCC (1981) suggested that vertical migration of

dioxin may result when the sorption capacity of soils are saturated or as a result of biotic mixing (i.e., action of earthworms or other soil invertebrates). Dioxin solvated by organic solvents may be more readily transported through soils to the groundwater.

Wet and dry deposition of particulate-bound dioxins appear to be an important fate-determining process in the transport of airborne dioxins.

2.3 Contaminant Movement On Site and Off Site

The summary of the Vertac site history indicates that contaminants (dioxin and others) were discharged in untreated wastewaters and process wastes, transported and released to the Rocky Branch Creek possibly as early as 1955 (JRB 1983). Dioxin and other contaminants were also released by seepage from underground burial areas and by erosion of contaminated surface soils.

Contaminants from the Hercules-Transvaal Landfill have migrated to the process cooling pond. The central drainage ditch and surface runoff also transported dioxin to the cooling pond. Contaminants that leaked into the cooling pond and/or settled there probably flowed into the Rocky Branch Creek since the pond is in its steam course. Spills and/or valve ruptures of the trichlorophenol reactor in the "blow-out" area or other areas released dioxin which may have percolated underground or have been transported via surface runoff to the East Branch. Leachates from the equalization basin along the western edge of the site also contributed to contamination of the Rocky Branch Creek. Transport of dioxin to Dupree Lake probably occurred as a result of flooding of the Rocky Branch Creek during periods of heavy spring rains.

Implementation of remedial actions involving disturbance of soils and vehicular movement may have promoted contaminant transport particularly during remediation of the equalization basin. The remedial actions implemented (clay caps, barrier walls, French drain, etc.) may reduce the potential for further contamination by preventing infiltration of surface precipitation, runoff and wind erosion.

There is some uncertainty about the vertical migration of contaminants to groundwaters. Unexpectedly, "high" concentrations of dioxin were detected in groundwater monitoring wells downgradient from the Hercules-Transvaal Landfill area (JRB 1983). There is potential for lateral subsurface movement in this landfill since no barrier walls have been installed. The closure of the equalization basin appears to contain lateral leachate seeps but the effectiveness over time is uncertain since the French drain and barrier walls were constructed over weathered rock (with fissures). Installation of the above-grade neutralization wastewater treatment system and discharge to the local wastewater treatment plant has reduced or eliminated the potential for further release of process waste to the Rocky Branch Creek.

The proposed remedial action (Alternative IV) which involves excavation of contaminated soils/materials and redisposal in a secure landfill on-site) will disturb soils and create the potential release of contaminants as dust

emissions. Primary sources of dust emissions are expected to be from vehicle travel over contaminated soils, loading/unloading operations and spreading excavated soil in the new landfill. The release and movement of contaminated dust may be reduced by implementation of dust control measures. It is assumed that "clean-dirt" will be applied to roadways between the excavation sites and the secure landfill and covered trucks will be used to reduce contaminant releases. The wind-only generated dust emissions are expected to be negligible compared to mechanically generated dusts occurring during truck travel, loading/unloading and spreading operations.

3.0 EXPOSURE EVALUATION

This section will identify actual and potential routes of exposure, characterize the populations exposed and determine extent of the exposure to dioxin.

3.1 Routes of Exposure

Potential exposure routes are as follows:

1. Consumption of fish from the Bayou Meto and Rocky Branch Creek.

2. Consumption of groundwater downgradient of the Vertac site.

3. Inhalation of dust-contaminated with dioxin that may become airborne due to implementation of remedial action Alternative IV.

4. Direct contact with waters, sediments or soils adjacent to the site that have been contaminated by surface runoff or erosion processes. Direct contact includes direct dermal exposures as well as direct ingestion exposures (i.e., pica in children).

3.1.1 Fish Consumption

Consumption of contaminated fish from Bayou Meto is an exposure route of primary concern since dioxin readily bioaccumulates in fish. Environmental monitoring data indicate that high concentrations of dioxin are found in fish (<25 to 300 ppt) and sediments (500 ppt) of Bayou Meto (see Table 1-1). Dioxin released from the site via transport on suspended solids in overland runoff or sorbed to airborne dust is of particular concern. Dioxin-bearing particles accumulate in sediments of receiving waters and bioaccumulate in fish. Significant potential human health threats may result from consumption of contaminated fish from Bayou Meto. Arkansas officials have banned fishing on the Bayou Meto; however, the fishing ban is not easily enforced (Falco 1982). Thus, there appears to be a real potential for dioxin exposure.

3.1.2 Groundwater

Concentrations ranging from ND 0.03 ppb (with a mean ± standard deviation of 0.005 ± 0.010 ppb) of dioxin were detected in groundwater monitoring wells downgradient from the Hercules-Transvaal landfill area; however, no existing domestic or industrial wells were reported to be located in areas that are immediately downgradient from the Vertac site (JRB 1983, Schaum and Falco 1982). Potential consumption of contaminated groundwater may result in exposures to dioxin and other contaminants that are both more mobile in the subsurface soils and more soluble in water.

3.1.3 Airborne Dust

Inhalation exposure to dioxin is likely to be via contaminanted dust rather than via vapors since dioxin in soils does not volatilize appreciably.

Potential exposure to dioxin via inhalation of contaminated dust is not expected to be substantial since remedial actions implemented (clay capping of disposal areas and covering the blow-out area) will diminish wind erosion. However, the potential for exposure to dioxin is substantially increased by the proposed remedial action (Alternative IV) which will disturb the soil and create emissions of dioxin-contaminated dust.

3.1.4 Direct Contact with Contaminated Soils/Sediment

Dioxin in contaminated soils may be adsorbed across the skin. The concentration in soils and type of soils are expected to affect dermal adsorption. The direct contact with contaminated soils is dependent upon the degree of outdoor activities such as gardening or playing. The degree of dermal exposure depends upon the amount of skin exposure, duration of contact and soil conditions.

Exposure due to direct ingestion depends on age with children aged two to six years having the greatest exposure potential. Seasonal variation in weather, soil conditions and activity patterns affect the amount of exposure via direct ingestion of contaminated soils/sediments.

3.2 Populations Exposed

3.2.1 Fish Consumption

Populations with high fish consumption from affected water bodies are at an increased risk of dioxin exposure. Data on fish consumption rates and the number of people that consume fish caught from Bayou Meto were not available. Human exposure via consumption of fish should not be occurring since there is a fishing ban for the Bayou Meto; however, there is evidence that the ban is not easily enforced. Complaints of "medicinal" taste and odor problems of fish from Bayou Meto registered with the Arkansas Game and Fish Commission indicate the there has been chronic pollutional problems, and that people may have been exposed to dioxin and other contaminants.

Assuming that most fish from Bayou Meto are likely to be consumed by local residents, the number of exposed people is probably less than the local population. Approximately 476,000 people are in counties that are at least partially drained by Bayou Meto according to census data.

3.2.2 Groundwater

Data on the size (if any) of the population utilizing wells or consuming groundwater from other sources contaminated by the site were unavailable. Walton et al. (1982) state that no domestic or industrial water wells were located in areas that are immediately downgradient from the Vertac site. Contacts with state and local permitting agencies identified only two domestic wells within the vicinity of the site (Walton et al. 1982). One well (50 ft deep) was 1.5 mi west of Vertac and the other well (15 ft deep) was about 1.5 mi southeast of the site. There is insufficient data on groundwater contamination and off-site flows to determine when the plume may reach these

wells, the expected concentrations and the size of the population that may be exposed.

3.2.3 Airborne Dust

Insufficient data are available to determine the no action endangerment level and the size of the exposed population. Monitoring data on ambient concentrations of dioxin-contaminated dust emissions from the site are unavailable.

The population at greatest risk of exposure to dioxin via airborne dust would be workers/observers on-site during the proposed remedial action if an adequate personal protection program was not implemented. It is recommended that an adequate personal protection program will be required under the Remedial Action Plan to eliminate or substantially reduce potential exposures to on-site personnel.

Insufficient data on prevailing wind direction, wind speed and geographical features affecting wind patterns are available to determine which populations are at increased exposure potential for airborne dust. Residents of the subdivision to the south of the site are the nearest potentially exposed off-site population. The proximity of this population to the site subjects this population to an increased risk of exposure to dioxin since airborne dust concentrations are expected to be greatest near the site and to decrease with increasing distance from the site. People that stay at home during the daytime and especially those that are frequently outside for long periods are expected to have higher exposures. This group may include young children, nonworking parents and the elderly. It is assumed that dioxin-contaminated dust concentrations will tend to be higher outdoors relative to inside a house. No quantitative information on the number of residents near the site and specific behavior patterns is available.

3.2.4 Direct Contact

No quantitative data are available on the size of the population potentially exposed to dioxin via direct contact with contaminated soils or sediments on-site or off-site. The fence around the facility limits accessibility and reduces potential accidental direct contact exposures on-site. Detection of dioxin in surface soils in the subdivision south of Vertac (Braden Street, West Lane and Alta Cove) (CH2M Hill 1984) suggests that residents may be at risk for dioxin exposure. People who garden and play outdoors are expected to be at higher risk for direct contact exposures. Since the highest concentrations of dioxin off-site are found in sediments of the Rocky Branch Creek, it is anticipated that people who swim, wade or play in and around the creek may be at increased risk. Likewise, people who use Lake Dupree for recreational activities may have increased exposure.

3.3 Extent of Exposure

3.3.1 Fish Consumption

No estimates of actual fish consumption based on local surveys of the Rocky Branch Creek and Bayou Meto are available. Limited monitoring data on the

dioxin content of fish in the Rocky Branch Creek, Bayou Meto and Lake Dupree are available. Detection of <25 to 300 ppt of dioxin in fish from Bayou Meto and 810 ppt in a fish from Lake Dupree suggest that dioxin exposures may result if such fish were consumed (Schaum and Falco 1982). Estimation of the extent of exposure is difficult because of limited data on dioxin content of fish and consumption rates. This is further complicated by the fact that fishing on Bayou Meto is currently banned.

Using the range of reported dioxin concentrations in Bayou Meto (<25 to 300 ppt), exposures could be estimated as follows:

$$\frac{300 \text{ ng/kg} \times 2.37 \text{ kg/yr}}{70\text{-kg}} = 10.1 \text{ ng/kg/yr}$$

where:

300 ng/kg = maximum content of dioxin detected in fish from Bayou Meto
5.2 lb/yr (2.37 kg/yr or 6.5 g/day) = assumed consumption rate based on the national average consumption rate of freshwater fish
70 kg = assumed body weight of adult

Thus, dioxin exposures from fish consumption may range from <0.85 to 10.1 ng/kg/yr for Bayou Meto to 27.4 ng/kg/yr for Lake Dupree, assuming that a 70-kg adult consumes 5.2 lb/yr of fish and that preliminary monitoring data on fish tissue are representative of the actual content of dioxin in fish. These exposure values are based on limited data and much more extensive data are required to precisely define the magnitude and extent of actual exposures via contaminated fish consumption.

3.3.2 Groundwater

The extent of dioxin exposure via groundwater has not been determined. Due to the apparent lack of water wells and the low solubility of dioxin in water, it is expected that exposure potential will be minimal. Using the highest reported concentration of 0.03 ppb dioxin in groundwater on-site (CH2M Hill 1984a) and assuming a 70-kg adult would consume two liters of water per day, a maximum potential exposure could be calculated as follows:

$$\frac{0.03 \text{ µg/L} \times 2 \text{ L/day}}{(70\text{-kg})} = 0.0009 \text{ µg/kg/day } (0.9 \text{ ng/kg/day})$$

This is a worst case scenario. Insufficient data on groundwater flows, dilution rates and the extent of contamination are available to calculate reasonable conservative exposure estimates. Using the mean concentration of dioxin detected in wells (0.005 ppb) and the above equation, the exposure may be estimated as 0.0001 µg/kg/day. Recent monitoring data have not detected dioxin in any wells on-site and therefore suggests that potential exposure levels may be less.

In addition, actual exposure at this level is unlikely since Walton et al. (1982) and CH2M Hill (1984a) state that data indicate that no existing wells

are located within two miles of the site and there is no contamination in any wells beyond two miles. Future contamination or installation of new drinking water wells downgradient of the site may increase the potential and magnitude of exposures.

3.3.3 Airborne Dust

The extent of the exposure to dioxin via inhalation of contaminated dust from wind erosion is not anticipated to be significant because of remedial actions implemented. No data are available to estimate exposure for no action level or present endangerment level. However, data on the actual content of airborne dioxin contaminated dust are not available to substantiate this conclusion. In addition to air concentrations of dioxin, information on absorption/retention of dioxin dust particulates in the lung, a respiration rate (20 m^3/day usually assumed) and duration of daily exposure would be required to estimate exposure via dioxin dust inhalation.

Prediction of potential exposures for the proposed remedial action will require emission modeling to predict air concentrations. The magnitude of exposure is anticipated to be greatest on-site at locations in closest proximity to the remedial action involving excavation, loading/unloading, transporting and spreading operations. Dust control measures and personnel protection programs may eliminate or reduce worker exposure during remediation. The residents closest to the site are expected to potentially be the off-site population with the greatest extent of exposures.

3.3.4 Direct Contact

No quantitative estimates of the extent of dioxin exposure via direct contact are available. Future exposure assessments should address specific subpopulations suspected of having increased exposures due to their behavior or activities. For example, children playing in contaminated soils or sediments of adjacent waterways are probably exposed to dioxin via direct dermal contact or ingestion. People who garden in residential areas with dioxin-contaminated soils also have increased exposure potential via direct contact. The lack of information on the dermal absorption, amount of direct soil contact, dioxin content of soils/sediments, quantity of soil directly ingested and other factors currently preclude performance of quantitative exposure estimates. Direct contact is an important route that should be addressed in future exposure assessments. The Kimbrough et al. (1977) report on toxicity in six children dermally exposed to dioxin-contaminated soils in horse-arenas in eastern Missouri confirms the potential significance of this route.

4.0 TOXICITY EVALUATION

Exposure to dioxin can cause thymic atrophy, decreased body weight, liver damage, skin lesions (chloracne), renal function impairment, hematologic effects, adrenal atrophy, reproductive system damage, immunosuppression, fetotoxic, teratogenic and mutagenic effects and cancer. Dioxin is an extremely toxic substance, with an LD_{50} value reported as low as 0.6 µg/kg (guinea pig) following oral administration (Schwetz et al. 1973).

4.1 Pharmacokinetics

The available information on the pharmacokinetics of dioxin in several mammalian species of laboratory animals is summarized by Neal et al. (1982), Manara et al. (1982), Gasiewicz et al. (1983), Olson (1983) and USEPA (1984). The absorption of dioxin via oral and dermal exposure routes has been studied but data on absorption via inhalation are not available (USEPA 1984). About 70% to 83% of a single oral (gavage) dose of radiolabeled dioxin (1 µg/kg or 50 µg/kg) was absorbed when administered by gavage to Sprague-Dawley rats (Rose et al. 1976, Piper et al. 1973). With repeated gavage administration of 1 µg/kg/day, absorption was about 80%. Olson (1983) observed about 74% absorption in hamsters receiving a large sublethal dose (650 µg/kg) of radiolabeled dioxin in corn oil. Fries and Marrow (1975) reported about 50% to 60% absorption of dioxin administered to rats in the diet (7 or 20 ppb) for 42 days. Poiger and Schlatter (1980) studied the dermal absorption of dioxin (methanol vehicle) and estimated (based on hepatic content of dioxin) that the amount absorbed from dermal application was about 40% of the amount absorbed from an equivalent oral dose. Application of a soil/water paste decreased hepatic dioxin content to about 2% of the administered dose.

Dioxin is lipophilic and is predominantly distributed to the liver and adipose tissues (USEPA 1984) in most laboratory animal species. Dioxin appears to be distributed throughout the body without metabolic alteration (Olson et al. 1980). However, six metabolites of dioxin in the dog (Poiger et al. 1982) and two metabolites in the rat (Sawahata et al. 1982) have been identified. Excretion and metabolism of dioxin are relatively slow processes in the body resulting in biological half-lives ranging from 10 days in hamsters to 43 days in guinea pigs. Dioxin accumulates in tissues with high adipose content (Nolan et al. 1979, Olson et al. 1980).

4.2 Acute Toxicity

4.2.1 Toxicity in Humans

Acute exposure of humans to dioxin results in nausea and vomiting, headache, and irritation of the eyes, skin and respiratory tract. The initial skin reaction is a cutaneous reaction resembling a chemical burn, followed several days-to-weeks after by chloracne (Taylor 1979). Chloracne, the typical human dermal reaction to dioxin, is a cutaneous eruption of comedones (blackheads), cysts, and in severe cases, pustules. These usually occur on the face and shoulders as a result of squamous metaplasia (transformation of glandular or mucosal epithelium into stratified squamous epithelium) of the dermal glands

(Crow 1978, Passi et al. 1981). Most of the documented acute exposures to dioxin have been the result of chemical industry accidents involving 2,4,5-T, which is contaminated with dioxin (Holmestedt 1980, May 1973, Gianotti 1977, Garattini 1982, Taylor 1979, Crow 1981 and Zack and Suskind 1980).

There are data regarding the health effects of dioxin on children and adults following accidental releases of the chemical from a plant in Seveso, Italy (Pochiari et al. 1979). Reduced peripheral nerve conduction velocities occurred in both adults and children, with a correlation between the incidence and the distance from the plant. Total serum complement activity, lymphocyte blastogenic response and peripheral blood lymphocytes were elevated in children exposed in the accident (Tognoni and Bonaccorsi 1982). The limited number of studies regarding the immunological effects of dioxin in adults have not revealed any reduction in immunocapability (May 1982).

Six children dermally exposed to dioxin-contaminated soil (30 ppm, 30 mg/kg soil) in horse-arenas in eastern Missouri developed headaches, skin lesions and polyarthralgia (pain in joints) (Kimbrough et al. 1977). In the most severe case, epistaxis (nosebleeds) and lethargy were reported.

Numbness of the extremities, skin rashes and irritation, liver dysfunction, weakness, loss of sex drive and psychological changes have been associated with exposure to 2,3,7,8-TCDD and other dioxins, which occur as contaminants in Agent Orange, in veterans and residents of Vietnam. The relationship between exposure to dioxin and the development of these symptoms is unknown (Holden 1979, Bogen 1979).

4.2.2 Toxicity in Laboratory Animals

McConnell et al. (1978 a,b) observed that dioxin induced mortality in a variety of laboratory animals (rat, guinea pig, mouse, rabbit, monkey) at dose (LD_{50}) levels between 0.6 μg/kg and 283.7 μg/kg following oral administration. The dermal LD_{50} value in rabbits was 270 μg/kg (Schwetz et al. 1973).

A summary of studies providing data on the sub-lethal effects of acute exposure to TCDD is presented in Table 4-1. The effects were reported to occur following single exposures ranging from 0.1 to 300 μg/kg in four animal species (rat, guinea pig, chicken, mouse). Liver damage is the most consistently reported effect in most species. Rats receiving a single dose of 100 μg/kg of TCDD showed severe liver damage, thymic atrophy and jaundice (Gupta et al. 1973). In the same study, thymic and liver damage of lesser severity occurred at lower dose levels (25 and 50 μg/kg). In another study (Greig et al. 1973), rats exposed to TCDD (300 μg/kg) exhibited jaundice, multinucleated parenchymal cells of the liver and gastric hemorrhage. Histopathologic liver changes were observed five weeks after single oral doses of TCDD as low as 50 μg/kg were administered to male and female CD rats, and one week after a single dose of 50 μg/kg was administered to female CD-1 mice (Harris et al. 1973). Increased liver weights were found in male Wistar rats seven days after single intraperitoneal doses of 0.1 μg/kg (Cunningham and Williams 1972).

TABLE 4-1 EFFECTS OF DIOXIN IN ANIMALS FOLLOWING ACUTE EXPOSURE

Species	Dose (μg/kg)	Route	Effects	Reference
Rat	25, 50 or 100		Liver damage, thymic atrophy	Gupta et al. (1973)
	100		Jaundice, 43% mortality	
Guinea Pig	3.0		Hemorrhage, adrenal atrophy, cellular depletion of lymphoid organs, 90% mortality	Gupta et al. (1973)
Rat	300		Weight loss, gastric hemorrhage, liver damage (cellular changes), jaundice	Greig et al. (1973)
Chicken	25 - 50		Pericardial edema	Greig et al. (1973)
Rat	10	Oral	Hematologic effects	Weissburg and Zinkl (1973)
Rat	0.1	i.p.	Increased liver weights	Cunningham and Williams (1972)
Rat	50	Oral	Liver damage	Harris et al. (1973)
Mouse	50	Oral	Liver damage	Harris et al. (1973)
Rat	10		Decreased renal function	Anaizi and Cohen (1978)
Rat	10, 25, or 50		Decreased renal function	Hook et al. (1978)

Adapted from NAS (1977), NTP (1982 a,b) and Esposito et al. (1980).

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4.2.3 Toxicity in Aquatic Species

The USEPA (1984) summarizes the available information on the acute toxicity of dioxin to aquatic organisms. The 96-hr lethal concentrations (LC_{50}) reported by Miller et al. (1973) and Norris and Miller (1974) were >0.2 µg/L for Paranais sp. (worm), Physa sp. (snail) and Aedes aegypti (mosquito larvae), >1 µg/L for Oncorhychus kisutch (coho salmon), >10 µg/L for Poecilia reticulata (guppy) and >0.24 µg/L for Ictalurus punctatus (fingerling channel catfish). Helder (1980, 1981 and 1982) observed that the LC_{50} is >0.01 µg/L for Esox lucius (northern pike embryos) and Salmo gairdneri (rainbow trout yolk-sac fry) and >0.1 µg/L for the juvenile rainbow trout.

4.3 Subchronic and Chronic Toxicity

4.3.1 Toxicity in Humans

Several epidemiologic studies and case reports involving dioxin exposure in human subjects have been reported (Esposito et al. 1980). Effects observed include skin lesions (chloracne, prophyria cutanea tarda), liver function impairment and neurological disorders (polyneuropathy, peripheral nerve damage). An International Agency for Research on Cancer (IARC 1982) evaluation of human exposure data concluded that these studies are inadequate since they involve multiple chemical exposures.

4.3.2 Toxicity in Laboratory Animals

Longer exposures to dioxin caused effects similar to those reported following acute exposure including thymic atrophy, liver damage, renal function impairment, hematological effects, hormonal alterations, immunosuppression, nervousness and irritability. Chronic and subchronic studies in many different strains of laboratory mice and rats indicate that the liver is the primary organ affected by long-term exposure (Kociba et al. 1973, 1979, NTP 1980a). A summary of major studies providing dose-response effects is presented in Table 4-2. Studies providing dose-response data indicating the greatest sensitivity to dioxin are described below.

Doses as low as 0.1 µg/kg/day caused a slight degree of liver degeneration in rats in a subchronic 13-wk (5 doses per week) study (Kociba et al. 1976). Dose levels of 1.0 µg/kg/day increased levels of serum bilirubin and alkaline phosphatase and caused pathologic changes in the livers of rats. A no-observed-adverse-effect level (NOAEL) of 0.01 µg/kg dioxin was reported for for noncarcinogenic effects in rats.

Increased mortality was observed in female Sprague-Dawley rats maintained for two years on a diet that provided a dioxin dose of 0.1 µg/kg/day, while no increased mortality was observed in male rats at this dose or in animals receiving doses of 0.01 or 0.001 µg/kg/day (Kociba et al. 1978, 1979). At termination of the study, gross and histologic examination indicated that the liver was the most severely affected organ, with degenerative, necrotic and inflammatory changes observed. Increases in urinary excretion rates of the metabolites, coproporphyrin and uroporphyrin, in the high and middle dose

TABLE 4-2 NOAEL AND LOAEL VALUES OBTAINED FROM SUBCHRONIC AND CHRONIC ORAL TOXICITY STUDIES OF DIOXIN

Species	Duration of Exposure	Endpoints	NOAEL µg/kg/day	LOAEL µg/kg/day	Reference
Rat	13 wk	Decreased body weight, liver pathology	0.01	0.1	Kociba et al. (1976)
Rat	13 wk	Toxic hepatitis	0.07	0.14	NTP (1980a)
Rat	16 wk	Elevated porphyrin levels	0.0014	0.014	Goldstein et al. (1982)
Rat	28 wk	Fatty changes in the liver, decreased body weight	ND[a]	0.014	King and Roesler (1974)
Mouse	13 wk	Toxic hepatitis	ND	0.014	NTP (1980a)
Monkey	36 wk	Pancytopenia	ND	2	Allen et al. (1977)
Rat	104 wk	Degenerative and necrotic changes in the liver	0.001	0.01	Kociba et al. (1978, 1979)
Rat	104 wk	Toxic hepatitis	0.0014	0.007	NTP (1980a)
Mouse	104 wk	Dermatitis and amyloidosis	ND	0.001	NTP (1980a)

(a) ND = Not determined.

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females were consistent with the observed liver damage. Primary liver injury was dose-related with the lowest dose representing a NOAEL for noncarcinogenic effects.

When dioxin was administered by gavage (by stomach tube) in corn oil-acetone (9:1) at dose levels of 0, 0.01, 0.05 or 0.5 µg/kg/wk (0.0, 0.001, 0.007 and 0.07 µg/kg/day), toxic hepatitis was observed in male Osborne-Mendel rats at incidences of none out of 74 tested (0/74), 1/50, 0/50 and 14/50 and in female rats at incidences of 0/75, 0/50, 1/50 and 32/49(NTP 1980a). Other non-neoplastic lesions were not observed, even though extensive histologic examinations were performed. The two preceding studies of noncarcinogenic effects support a NOAEL for rats of ≅0.001 µg/kg/day and a lowest-observed-adverse-effect level (LOAEL) of 0.05 µg/kg/day.

Non-neoplastic effects of chronic dioxin exposures were described in studies investigating the carcinogenic potential of dioxin in mice. In a National Toxicology Program (NTP 1980a) bioassay, histologic examinations were performed on B6C3F1 mice treated biweekly with dioxin by gavage in corn oil-acetone (9:1) for 104 wk followed by an additional 3-wk observation period. The doses for male animals were 0.0, 0.01, 0.05 and 0.5 µg/kg/wk, and for female animals, 0.0, 0.04, 0.2 and 2.0 µg/kg/wk. The only non-neoplastic adverse effect observed was toxic hepatitis, which occurred in males at incidences of 0/73, 5/49, 3/49 and 44/50, and in females at incidences of 0/73, 1/50, 2/48 and 34/47, respectively, in the control, low, medium and high dose groups. In another study, weekly administration of dioxin by gavage at doses of 0.0, 0.007, 0.7 or 7.0 µg/kg/wk for one year resulted in amyloidosis (deposition of amyloid, a complex proteinaceous material) of the kidney, spleen and liver, and dermatitis at the time of death in male Swiss mice (Toth et al. 1978, 1979). The incidences of these effects in the control, low, medium and high dose groups, respectively, were 0/38, 5/44, 10/44 and 17/43. In the high dose group, the amyloidosis was extensive and considered to be the cause of early mortality. Severe toxic effects were observed at doses of 1 µg/kg/day (early mortality) and 0.28 to 0.07 µg/kg/day (toxic hepatitis), while a LOAEL for dermatitis and amyloidosis of 0.001 µg/kg/day was reported.

4.3.3 Toxicity in Aquatic Species

No standard chronic toxicity assays of dioxin in aquatic species were located in the available literature (USEPA 1984) but several studies provide information indicative of chronic toxicity values. In a static bioassay, Miller et al. (1973) indicated that 0.2 µg/L may cause chronic toxicity in *Paranais* sp. (worm). Based on the 55% mortality in coho salmon within 60 days following acute (96-hr) exposures to 0.0056 µg/L (Miller et al. 1979), the USEPA (1984) suggests that 0.0056 µg/L may cause chronic toxicity coho salmon. Similarly the USEPA (1984) concludes that chronic toxicity values such as 0.001 µg/L (rainbow trout) and 0.01 µg/L (northern pike, coho salmon, mosquite fish and channel catfish) can be inferred based on results of acute assays by Helder (1980, 1981, 1982), Yockim et al. (1978) and Branson et al. (1983). A concentration of 1.3 µg/L may not cause chronic toxicity in *Daphnia magna* or *Physa* (USEPA 1984).

Limited data are available on the toxicity of dioxin to aquatic plants. Isensee and Jones (1975) and Isensee (1978) observed no adverse effects in algae (Oedogonium cardiacum) or duckweek (Lemna minor) exposed to 1.3 µg/L and 0.71 µg/L (respectively) for 30 days. Yockim et al. (1978) has also observed no adverse effects on O. cardiacum exposed to 0.0024 to 0.0042 µg/L of dioxin for 32 days.

4.4 Teratogenicity, Reproductive Effects and Fetotoxicity

4.4.1 Effects of Humans

Epidemiological studies have attempted to investigate health effects of dioxin in humans by indirectly evaluating health effects in populations exposed to 2,4,5-T (which commonly contains dioxin as an impurity). A positive association between 2,4,5-T exposures and increases in birth defects or abortions has been reported in human populations in Oregon (USEPA 1979), New Zealand (Hanify et al. 1981) and Australia (Field and Kerr 1979). A lack of any such association has been reported in human populations in Arkansas (Nelson et al. 1979), Hungary (Thomas 1980), New Zealand (Dept. of Health, New Zealand 1980, McQueen et al. 1977) and Australia (Aldred 1978).

4.4.2 Effects in Laboratory Animals

Dioxin has been reported to be fetotoxic and teratogenic when administered alone or in combination with other chemicals. Several studies have been identified in the available literature based on dioxin exposure alone. Effects observed were kidney anomalies, intestinal hemorrhage, general edema, cleft palate and fetal death. Adverse effects on reproduction were also reported.

Intestinal hemorrhage, general edema and a reduction in fetal weights were reported in rats following the administration of 0.125 µg/kg/day in studies by Sparschu et al. (1971). In the same studies, the number of fetuses was reduced and fetal death increased at 0.5 µg/kg/day. No structural malformations were reported at 0.03 µg/kg/day. Courtney and Moore (1971) reported cleft palate and kidney abnormalities in mice borne by dams administered dioxin at doses of 1.0 µg/kg or 3.0 µg/kg. Similarly, kidney malformations were reported by the same authors in offspring from rats which received subcutaneous injections of 0.5 µg/kg/day on day 9, 10, or 13 and 14 of gestation.

Murray et al. (1979) completed a three-generation reproduction study using Sprague-Dawley rats fed dioxin continuously in the diet (at levels of 0, 0.001, 0.01, and 0.1 µg/kg/day). Significant decreases were observed in fertility, litter size, gestation survival, postnatal survival, and postnatal body weight for the 0.01 and 0.1 µg/kg groups. No apparent adverse effect on reproduction was seen at the 0.001 µg/kg dose level.

Although Murray et al. (1979) considered the lowest dose tested, 0.001 µg/kg, to be a NOEL (noncarcinogenic), reevaluation of these data by Nisbet and Paxton (1982) using different statistical methods indicated that there was a

reduction in the gestation index, decreased fetal weight, increased liver-to-body weight ratio, and increased incidence of dilated renal pelvis at the 0.001 µg/kg dose. The reevaluation of data suggests that equivocal adverse effects were seen at the lowest dose (0.001 µg/kg/day) and that this dose should, therefore, represent a LOAEL.

Schantz et al. (1979) found reductions in fertility and various other toxic effects in rhesus monkeys fed 55 ppt dioxin in the diet for 20 mo. This corresponds to a calculated daily dioxin dose of 0.0015 µg dioxin/kg/day. These results suggest that monkeys may be somewhat more sensitive than rats, since the effects in monkeys were more severe and not equivocal.

Luster et al. (1980) examined bone marrow, immunologic parameters, and host susceptibility in B6C3F1 mice following pre- and postnatal exposure to TCDD. Doses of 0, 1.0, 5.0 and 15.0 µg/kg bw of dioxin were given to dams on day 14 of gestation and to offspring on days 1, 7, and 14 following birth. Neonatal body, liver, spleen, and thymus weights were decreased and bone marrow toxicity occurred in the 5.0 and 15.0 µg/kg groups. Red blood cell counts, hematocrits, and hemoglobin were decreased at the highest dose tested.

4.5 Mutagenicity

Studies on the mutagenicity of dioxin have produced conflicting results. Dioxin reportedly produces mutagenic effects in *Escherichia Coli* and *Salmonella typhimurium* TA 1532 (Hussian et al. (1972) but not in *S. typhimurium* test strains TA1535, TA100, TA1538, TA98, and TA1537 with or without metabolic activation (Geiger and Neal 1981). Green et al. (1977) observed an increased incidence of chromosomal breaks in female rats dosed with 4 µg/kg and in males dosed with 2 µg/kg or 4 µg/kg of dioxin twice weekly for 13 weeks.

4.6 Carcinogenicity

4.6.1 Carcinogenicity in Humans

Epidemiologic studies of industrial workers and herbicide applicators suggest that dioxin may be a human carcinogen. However, since dioxin is usually a contaminant of phenoxy acids and/or chlorophenols, human exposure is usually to multiple chemicals. Therefore, the evidence for human carcinogenicity from these studies is only suggestive due to the difficulty of evaluating the risk of dioxin exposure in the presence of the confounding effects of the other chemicals (USEPA 1984).

Hardell (1977) observed an unusual occurrence of relatively rare soft-tissue sarcomas (STS) in 7 of 87 patients seen from 1970 to 1976 at the Department of Oncology, University Hospital, Umea, Sweden. All seven had had occupational exposure to phenoxy acids 10 to 20 yr earlier. The clustering of these rare tumors among these patients prompted the author to suggest that epidemiological studies be designed to determine if exposure to phenoxy acids and their impurities (i.e., dioxins) are related to the occurrence of STS.

A few occurrences of STS have also been reported among chemical industry workers in the United States who were exposed to varying levels of 2,4,5-chlorophenols with dioxin contaminants (Cook et al. 1980, Moes and Selikoff 1981). Honchar and Halperin (1981) reported that 3 of 105 deaths among phenoxy acid workers reported by two chemical companies were from STS.

Zack and Suskind (1980) reported a STS death in a cohort study of workers exposed to dioxin in a trichlorophenol process accident in West Virginia. This tumor, a fibrous histiocytoma, was considered as a rare event.

In a cohort mortality study of 61 male employees of a trichlorophenol manufacturing area who exhibited chloracne following a 1964 exposure incident, Cook et al. (1980) noted four deaths by the end of his study period, one of which was due to a fibrosarcoma.

There are numerous other studies reported regarding STSs. For example, Smith et al. (1982) conducted an initial case-control study of 102 males identified from the New Zealand Cancer Registry as having STSs (ICD 171) between 1976 and 1980. For each case, three controls each with another form of cancer were matched by age and year of registration. The selection of cancer controls from the same registry was done to eliminate recall bias or interviewer bias or both.

The distribution of tumor types differed considerably from the Hardell and Eriksson et al. (1981) study to the Smith et al. (1982) study. Leiomyosarcomas, malignant histocytomas, neurogenic sarcomas and myxosarcoma seem to predominate in the Hardell and Eriksson (1981) study, whereas fibrosarcomas and liposarcomas appear prominently in the Smith et al. (1982) study.

Smith et al. (1983) conducted another case-control study of STSs in males that were reported to the New Zealand Cancer Registry by Public Hospitals between 1976 and 1980. Smith et al. (1983) remarked that it was surprising that he found no STS victim who had ever worked full-time in phenoxyacetic acid herbicide spraying. Perhaps they have not yet been observed for a long enough period. As was pointed out by the author, the findings do not support the hypothesis that exposure to phenoxyacetic acid herbicides causes STS; however, neither do they support a negative finding without better documentation regarding actual exposure and time of actual exposure.

The Michigan Department of Public Health (1983) recently conducted an ecological study of soft and connective tissue cancer mortality rates in Midland and other selected Michigan counties. They found that mortality rates for this cancer were 3.8 to 4.0 times the national average for the periods 1960 to 1969 and 1970 to 1978, respectively, for white females in Midland. These estimates are based upon five deaths and seven deaths, respectively. No excess risk was reported among white males, however. The Michigan Department of Health concluded that because of the occurrence of these two successive elevated rates, it is unlikely to be a chance happening. At the same time the age-adjusted male and female cancer mortality rates for Midland were below that of the State of Michigan for the period 1970 to 1979. Midland County is the home of a major chemical company that produced phenoxyacetic acid herbicides until

recently. The authors stated that a detailed review of death certificates, hospital records, residency and occupational histories of the 20 male and female cases revealed no "commonalities" suggesting a "single causative agent," although a majority of their spouses had worked at this chemical facility. They recommended that a case-control study should be instituted to evaluate possible influences, such as lifestyles, occupation or location of residences, on the risk of STS.

4.6.2 Carcinogenicity in Laboratory Animals

The carcinogenic potential of dioxin has been studied extensively in laboratory animals. A summary of the results of selected comprehensive studies is presented in Table 4-3. The results of these studies show that dioxin-exposed animals exhibited malignant lesions involving multiple organ systems including accessory digestive organs (liver), endocrine (thyroid, adrenal), renal, reproductive (testes), and nasal structures. Representative studies are described below.

Groups of ten male Sprague-Dawley rats were fed a diet containing dioxin for 78 wk at concentrations ranging from 1 ppt to 500 ppt or 1 ppb to 1,000 ppb (Van Miller et al. (1977). These dietary levels represent approximate weekly dose levels of 0.0003 to 0.1 µg/kg or 0.4 to 500 µg/kg. Animals exposed at 5 ppt, 50 ppt, 500 ppt or 5 ppb showed an overall incidence of neoplasms of 38% (23/60). No neoplasms were reported or observed following exposure to 1 ppt dioxin. In the 5 ppt group, 5/10 animals had six neoplasms (earduct carcinoma, lymphocytic leukemia, adenocarcinoma, malignant histiocytoma (with metastases), angiosarcoma and Leydig-cell adenoma). Neoplasms were also observed in the following groups: at 50 ppt, three in 3/10; at 500 ppt, four in 4/10; at 1 ppb, five in 4/10; at 5 ppb, ten in 7/10. Neoplasms were not observed in the controls. Rats administered dioxin at 50, 500 or 1,000 ppb exhibited 100% mortality by the fourth week.

In another study (Kociba et al. 1978), groups of 100 Sprague-Dawley rats (50 males and 50 females) received diets containing dioxin at 0, 22, 210, or 2,220 ppt (equivalent to a daily dose of 0.0, 0.001, 0.01 and 0.1 µg/kg bw) for two years. Administration of 0.01 µg/kg/day increased the incidence of hepatocellular hyperplastic nodules (female: 18/50 versus 8/86 controls) and focal alveolar hyperplasia in the lungs ($P<0.05$). Dietary intake of 0.1 µg/kg/day increased the incidence of hepatocellular carcinomas (female: 11/49 versus 1/86) and squamous cell carcinomas of the lung (female: 7/49 versus 0/86), hard palate/nasal turbinates (male: 4/50 versus 0/85; female: 4/49 versus 0/86), and tongue (male: 3/50 versus 0/85) ($P<0.05$). Also increased in frequency by the 0.1 µg TCDD/kg/day were adenoma of the adrenal cortex (male) and hepatocellular hyperplastic nodules (female).

The NTP (1982a) conducted a study for 104 wk using Osborne-Mendel rats and B6C3F1 mice. The rats and male mice were administered TCDD at 0, 0.01, 0.05 or 0.5 µg/kg/wk by gavage in two divided doses, and the female mice were given 0, 0.04, 0.2, or 2.0 µg/kg/wk. Incidences of follicular cell thyroid adenomas in male rats ($P<0.001$) and of neoplastic nodules in livers of female rats ($P=0.006$) increased significantly. Dioxin increased the numbers of hepato-

TABLE 4-3 SUMMARY OF CARCINOGENIC EFFECTS OF DIOXIN

Species/Sex (Number)	Dose	Duration	Route	Effects	Reference
Rat/M (10)	1 ppt	78 wk	Diet	No neoplasm.	Van Miller et al. (1977)
Rat/M (10)	5-500 ppt			Ear duct carcinoma, benign tumor of the kidney and testes, lymphocytic leukemia, skin carcinomas and benign muscle tumors.	
Rat/M (10)	1-5 ppb			Cholangiocarcinoma of liver, squamous cell tumor of lung, angiosarcoma in skin, glioblastoma in brain, malignant histiocytomas in peritoneum.	
Rat/ M (50) F (50)	0.001 μg/kg	2 yr	Diet	No significant increase in tumors.	Kociba et al. (1978)
	0.01 μg/kg			Liver cancer.	
	0.1 μg/kg			Liver cancer, squamous cell carcinoma of the lung, hard palate/ nasal turbinates, or tongue (P=0.05).	
Mouse/F (30)	0.015 μg/kg/wk	99-104 wk	Dermal	Fibrosarcoma in integumentary system (8/27, P=0.007).	NTP (1982b)
Mouse/M (30)	0.003 μg/kg/wk	99-104 wk	Dermal	Fibrosarcoma in integumentary system (6/28, P=0.08)	
Rat/M (50)	0.5 μg/kg/wk	104 wk	Gavage	Follicular cell adenomas of thyroid (10/50, P=0.001).	NTP (1982a)
Rat/F (50)	0.5 μg/kg/wk	104 wk	Gavage	Neoplastic nodules of the liver (12/49, P=0.006).	

continued-

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Table 4-3 - continued

Species/Sex (Number)	Dose	Duration	Route	Effects	Reference
Mouse/M&F	2.0 µg/kg/wk	104 wk	Gavage	Hepatocellular carcinoma (17/50, P=0.002 in M); (6/47, P=0.14 in F).	NTP (1982a)
Mouse/F	2.0 µg/kg/wk	104 wk	Gavage	Follicular cell adenomas of the thyroid (5/46, P=0.009)	
Mouse/M (39)	0.007 µg/kg/wk	52 wk	Gavage	Liver tumors (13/44, P not specified	Toth et al. (1979)
Mouse/M (44)	0.7 µg/kg/wk	52 wk	Gavage	Liver tumors (21/44, P<0.01)	
Mouse/M (44)	7.0 µg/kg/wk	52 wk	Gavage	Liver tumors (13/43, P=0.11)	

Adapted from Esposito et al. (1980), NTP (1982a,b).

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cellular carcinomas in male mice (P=0.002) and in females (P=0.014). The total liver tumors (carcinomas and adenomas) were increased in males (P<0.001) and females (P=0.002). In addition, female mice had increased incidence of follicular cell thyroid adenomas. These studies indicate that TCDD is an animal carcinogen.

Toth et al. (1979) administered doses of 0, 0.007, 0.7 and 7.0 μg/kg/wk of dioxin to male mice by gavage in a study to determine whether 2,4,5-trichlorophenoxyethanol (2,4,5-TCPE), its contaminant (dioxin) or both were carcinogenic. The incidence of liver tumors was significantly increased in the dose group receiving dioxin at the 0.7 μg/kg/wk level. No significant increased incidence in liver tumors was observed in the 7.0 μg/kg/wk dose group although increased mortality in this group probably precluded detection of tumors with longer latent periods.

The NTP (1982b) conducted a skin painting cancer bioassay of dioxin on Swiss-Webster mice (50 of each sex/dose). A dose of 0.001 μg/application (males) and 0.005 μg/application (females) in acetone suspension was painted on the skin 3 days/wk for 104 wk. The vehicle control group (45 mice/sex) was painted with 0.1 mL acetone 3 times/wk for 104 wk. The incidence of fibrosarcoma in the integumetary system was significantly increased in females (8/27, P=0.007) but not in males (6/28, P=0.08) compared to the incidence respective controls (2/41 and 3/42).

DiGiovanni et al. (1977) reported that dioxin was a tumor initiator in mouse skin. However, ~~the role of dioxin as an~~ initiator needs to be confirmed since appropriate vehicle and promotion-only controls were not included in this assay. Several assays (NTP 1982b, Berry et al. 1978, 1979) demonstrated that dioxin was not a tumor-promoter when applied to mouse skin after unknown initiator (DMBA).

Poland and Knutson (1982) reported that dioxin was a tumor promoter when tested on the skin of mice homozygous for the "hairless" trait but not in mice heterozygous for this recessive trait. Pitot et al. (1980) also reported that dioxin was a promoter for DEN-initiated hepatocarcinogenesis in rats following parenteral administration of the compounds. On mouse skin, dioxin was a complete carcinogen and possibly a tumor initiator, while no tumor-promoting activity could be attributed to dioxin in the assays. In rat liver initiated with DEN, dioxin was a tumor promoter.

In the mouse skin bioassay, initiation with simultaneous administration of dioxin and DMBA, however, did not affect tumor yield (DiGiovanni et al. 1977). Similarly no effect was observed when dioxin was administered either immediately before (five minutes) or one day after DMBA initiation (Berry et al. 1979, DiGiovanni et al. 1977, Cohen et al. 1979). When treatment with dioxin occurred one to ten days before DMBA initiation, dioxin demonstrated a potent anticarcinogenic action. Although one to five days prior exposure to dioxin inhibited tumor initiation by BaP, 3-MC, and BaP-diol-epoxide, the tumor-initiating ability of the latter compound was also inhibited when dioxin exposure occurred either five minutes before or one day after initiation (DiGiovanni et al. 1980). The increased AHH activity resulting from dioxin

exposure may account for the anticarcinogenic activity by altering the metabolism of the initiating compound; however, DiGiovanni et al. (1980) suggests that the initiation of the initiating activity of BaP-diol-epoxide one day after initiation indicates that more than one mechanism participates in the anticarcinogenic activity of dioxin.

4.7 Quantitative Indices of Toxicity

4.7.1 Noncarcinogenic Effects Indices

Recommended exposure limits to dioxin to ensure human safety have been established by several agencies. The National Academy of Sciences (NAS 1977), before TCDD was considered to be a carcinogen, suggested an ADI for dioxin of 0.0001 µg/kg/day based on a 13-wk feeding study in rats (Kociba et al. 1976). The reported NOEL in that study (0.01 µg/kg) was divided by an uncertainty factor of 100 to determine the ADI. The NAS then calculated a suggested-no-adverse-effect-level (SNARL) in drinking water of 0.0007 µg/L, based on the average weight of a human adult (70 kg) and an average daily intake of water of two liters, with water representing 20% of total intake.

The USEPA (1984) has calculated an ADI of 10^{-6} µg/kg/day based on noncarcinogenic toxicity for comparison to the carcinogenic risk assessment value. A LOAEL based on noncarcinogenic toxic effects and reduced fertility of 0.001 µg/kg/day and an uncertainty factor of 1,000 were used in the calculations. Using a bioaccumulation factor of 5,000, and assuming a daily consumption of 6.5 g of fish, a water concentration of 2.0×10^{-6} µg/L was derived. It was noted that this value may not be sufficiently low to protect against the carcinogenic effects of dioxin (USEPA 1984). The USEPA is currently reevaluating the bioconcentration factor for dioxin.

The USEPA (1984) concluded that insufficient data were available concerning adverse effects of dioxin on aquatic life to allow derivation of ambient water quality criterion. Limited information in freshwater species indicate acute values may be >0.1 µg/L and chronic values may be <0.01 µg/L (northern pike, coho salmon, mosquito fish and channel catfish) and <0.001 µg/L (rainbow trout).

4.7.2 Carcinogenic Effects Indices

Since there is no recognized safe concentration for a human carcinogen, and dioxin is a suspected human carcinogen, the recommended concentration of dioxin in water is zero (USEPA 1984). The USEPA calculated a range of concentrations for dioxin corresponding to cancer risk levels of 10^{-5}, 10^{-6} and 10^{-7}. These calculations used a linearized multistage model and were based on animal bioassay data. The recommended criteria which may result in an increased cancer risk of 10^{-5}, 10^{-6} or 10^{-7} are 1.3×10^{-7}, 1.3×10^{-8} and 1.3×10^{-9} µg/L, respectively. These criteria are below the limit of detection of TCDD in water (approximately 3×10^{-5} µg/L) by current analytical methods.

The Food and Drug Administration (FDA) issued a health advisory stating that fish with residues of dioxin ≥50 ppt should not be consumed, but fish with residues of < 25 ppt pose no serious health concern (USEPA 1984). The Centers for Disease Control (CDC) has established 1 ppb as a level of concern for dioxin in residential soils at Times Beach, MO.

5.0 RISK AND IMPACT EVALUATION

5.1 Human Health

Dioxin contamination from the Vertac site presents endangerment to human health. Ingestion of fish from Bayou Meto or Lake Dupree that have bioaccumulated dioxin will substantially increase cancer risks in humans. Limited monitoring data indicate that dioxin has bioaccumulated in fish to levels that are up to 16 times greater than the FDA's health advisory value of $\geq$50 ppt for dioxin residue in fish. Thus, fish are considered unsafe for human consumption. The efficacy of the fishing ban on Bayou Meto is uncertain since it is not easily enforced. Individuals that may consume large quantities of fish from Lake Dupree, Bayou Meto or the Rocky Branch Creek are considered at higher risk.

Groundwater contaminated with dioxin potentially poses an unacceptable cancer risk to humans. The actual risk via the groundwater route is probably minimal due to an apparent lack of exposure potential. However, this route could result in substantial carcinogenic risk if groundwater contaminated at 0.03 ppb dioxin (the highest detected level in groundwater on-site) were consumed. Assuming the 70-kg human would consume two liters of water per day then the dose would be 0.0009 µg/kg/day (0.9 ng/kg/day). Consumption of a dioxin dose of 0.9 ng/kg/day over a lifetime poses unacceptable carcinogenic risk exceeding the 10^{-5} risk associated with consumption of water with a dioxin concentration of 1.3×10^{-7} µg/L (3.7×10^{-9} µg/kg/day or 0.0000037 ng/kg/day). Consumption of drinking water containing 0.005 ppb dioxin (the mean detected concentration) would result in a dose of 0.0001 µg/kg/day (0.1 ng/kg/day) which would also pose unacceptable carcinogenic risk exceeding the 10^{-5} level. The lower bound estimate of induced cancers is zero since consumption may not occur and because recent analyses have not detected dioxin in groundwater monitoring wells.

Other potential risks to human health may result from inhalation exposures to dioxin-contaminated dust from natural wind erosion and/or from the proposed remedial action (Alternative IV) involving excavation, loading/unloading, transporting and spreading dioxin-contaminated soils and materials at the Vertac site. Monitoring data on wind-generated dioxin contaminated dust emissions were not available to estimate exposures and to assess human health risks for a no action alternative or the present endangerment level. The health risk associated with exposures via wind-erosion is anticipated to be minimal relative to that associated with the remedial action (Falco and Schaum 1984). The residents to the south of the site are expected to be at greatest risk due to their proximity to the site (Falco and Schaum 1984). The risk associated with inhalation of dioxin-contaminated dusts will decline with distance from the site.

The potential for direct contact with contaminated soils and sediments poses human health risks. Monitoring data indicate that levels of dioxins in soils and sediments off-site exceed the CDC's 1 ppb level of concern for residential soils established for Times Beach, MO.

5.2 Environmental

There are potential risks to aquatic and terrestrial species related to dioxin releases from the Vertac site. The absence of benthic life, several massive fish kills and reported "medicinal" taste and odor of fish caught from Bayou Meto (receiving waters of the Rocky Branch Creek) reflect the impact of contaminants released from the Vertac site on aquatic life (JRB 1983). The limited environmental monitoring data for sediments in the Rocky Branch Creek, Bayou Meto and Lake Dupree indicate substantial dioxin contamination has occurred. Analyses of fish tissues demonstrates that dioxin has been bio-accumulated to substantial levels (up to 300 ppt in Bayou Meto and 810 ppt in Lake Dupree) but the health significance of such tissue levels and potential impact on survival, growth, development and reproduction of aquatic life remains unknown. The absence of ambient water quality criteria and especially criteria for dioxin levels in sediments impedes performance of a quantitative assessment of potential effects on aquatic organisms.

There is a paucity of monitoring data on the concentration of dioxin in surface waters offsite. The only data available indicate that dioxin was not detected in water from the Rocky Branch Creek. Therefore, it is not possible to compare dioxin concentrations in receiving water to levels causing acute toxicity (>1.0 ppb) in certain freshwater species or chronic toxicity in the rainbow trout (<0.001 ppb) or in several other fish species (<0.01 ppb).

The high content of dioxin in sediments (500 ppt ave) in the Rocky Branch Creek and potential for release to the water column suggests that aquatic organisms may be at risk. No existing guidelines or standards are available to determine risks to avian or terrestrial organisms. The potential impact of contamination on such species is of concern since the Bayou Meto area serves as an important water fowl resting area and contains about 70,000 acres of wetlands. Limited data are available on the avian species and terrestrial species present in the area. Contamination of the Bayou Meto and accumulation of dioxin in the aquatic food chain may endanger predator (avian or terrestrial) species.

5.3 Public Welfare

The major socioeconomic impact of the release of dioxin from the Vertac site has been the loss of adjacent surface waters for fishing and recreation. For example, the release of dioxin to the Rocky Branch Creek and Bayou Meto and transport to Lake Dupree during flooding has caused fish to accumulate (810 ppt) dioxin in excess of the FDA health advisory value of $\geq$50 ppt. Thus, fish from Lake Dupree may be unfit for human consumption. This contamination of fish has required the Arkansas public health officials to issue a fishing ban for the Bayou Meto area. An additional impact on public welfare may be a potential decrease of property values immediately adjacent to the site (i.e., especially residential property values) and the loss of groundwater aquifers as a potential source of drinking water.

6.0 CONCLUSIONS

The most significant endangerment of human health is due to the potential consumption of dioxin-contaminated fish from Bayou Meto. Limited environmental monitoring data indicate that residues of dioxin in fish from Bayou Meto and Lake Dupree may exceed the FDA's health advisory value of $\geq$50 ppt dioxin by about 16 times. Populations that consume large quantities of fish from Bayou Meto, Rocky Branch or Lake Dupree are expected to have increased cancer risk. The fishing ban for Bayou Meto may reduce this threat to human health, but its efficacy is unknown since it is not easily enforced.

The contamination of groundwater represents another substantial potential threat to human health. There is a real potential for offsite migration of contaminants to groundwater. A maximum concentration of 0.03 ppb and a mean of 0.005 ppb of dioxin have been detected in onsite groundwater monitoring wells. Actual exposures to humans via this route is currently considered unlikely since no permitted domestic and industrial wells were located in the area immediately downgradient of the site. Human health may be endangered if water wells are drilled in the future and used for drinking water purposes. Assuming humans may potentially consume groundwater in the future, the resulting dose of dioxin would increase risk of cancer substantially above the 10^{-5} level. Further groundwater monitoring data are necessary to verify and characterize the magnitude and extent of any offsite contamination.

Exposure to dioxin via inhalation of dust-emissions from the proposed remedial action is anticipated to present an increased cancer risk for residents near the Vertac site. Risks associated with inhalation of dioxin-contaminated dust will diminish with distance from the site. Demographic information on the size of this population was unavailable. Risks associated with wind-generated dust emissions are expected to be minimal due to remedial actions already implemented. Detection of dioxin in soils and sediments in excess of the CDC's 1 ppb health concern level for residential soils (established for Times Beach, MO) indicates potential risks associated with direct contact (dermal and ingestion) exposures.

Assessment of risks to aquatic and terrestrial organisms was difficult due to limited environmental monitoring data and the unavailability of established ambient water criteria. Massive fish kills, dioxin bioaccumulated in fish and the absence of benthic life suggest potential impacts on aquatic life.

Loss of fishing in the Bayou Meto area impacts the public welfare. Additionally decrease of property values adjacent to the site or along the bayou may impact the economic stability of the area. Contamination of groundwater may prevent its future use as a drinking water resource.

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Attachment 5

1. Physical Description of the Site and Site History

   a. geographic location
   b. management practices/site use/site modifications
   c. chronological survey
   d. facility description/containment systems
   e. substances brought on site (identity, quantity, form manner of disposal)

2. Site Contamination/Off-Site Contamination

   a. identity of substances detected
   b. concentration of substances detected
   c. analytical methodology and QA/QC
   d. survey of environmental monitoring studies (detailed discussion of environmental media and contamination levels)

3. Environmental Fate and Transport

   a. physical-chemical properties of specified chemicals/ substances (e.g., soil/sediment adsorption coefficients, vapor pressures, solubility, etc.)
   b. photodegradation rates, decomposition rates, hydrolysis rates, chemical transformations, etc.
   c. local topography
   d. description of the hydrological setting and flow system
   e. soil analyses
   f. climatic factors, other factors affecting fate and transport
   g. prediction of fate and transport (where necessary using modeling methods)

4. Toxicological Properties (hazard identification)

   a. metabolism
   b. acute toxicity
   c. subchronic toxicity
   d. chronic toxicity
   e. carcinogenicity
   f. mutagenicity
   g. teratogencity/reproductive effects
   h. other health effects as relevant including neurotoxicity, immuno-depressant activity, allergic reactions, etc.
   i. epidemiological evidence (chemical specific or site specific)
   j. aquatic/non-human terrestrial species toxicity/ environmental quality impairment
   k. human health standards and criteria

5. Exposure Assessment

   a. demographic profile of populations at risk including subpopulation at special risk
   b. background chemical exposures
   c. life style and occupation histories
   d. population macro-and micro-environments
   e. exposure routes
   f. magnitude, source, and probability of exposure to specified substances

6. Risk Evaluation and Impact Evaluation

   a. carcinogenic risk assessment
   b. probability of non-carcinogenic human health effects
   c. non-human species risk assessment
   d. environmental impacts/ecosystem alterations

7. Conclusions

8. Documentation (Appendices)

PART 3 - LEVEL 3 ENDANGERMENT ASSESSMENT

Submitted to:

Office of Waste Programs Enforcement
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Attention: Chief, Health Sciences Section, R. Charles Morgan (2 copies)

VERTAC SITE ENDANGERMENT ASSESSMENT

(Level 3 Example)

Prepared Under

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1.0 INTRODUCTION

Disposal of chemical wastes and discharges of process wastewater over a 30-yr period has resulted in contamination of soils, groundwater and surface waters at the Vertac Chemical Corporation herbicide manufacturing facility in Jacksonville, AR. The release or potential release of contaminants from this site may endanger human health, welfare and the environment. Human health is at risk due to the potential for consumption of contaminated fish, inhalation of airborne contaminants, direct contact with contaminanted soils/sediments and ingestion of contaminated groundwater. Contaminants released to surface waters have been bioaccumulated to substantial levels in fish and other aquatic species.

1.1 Site Description and History

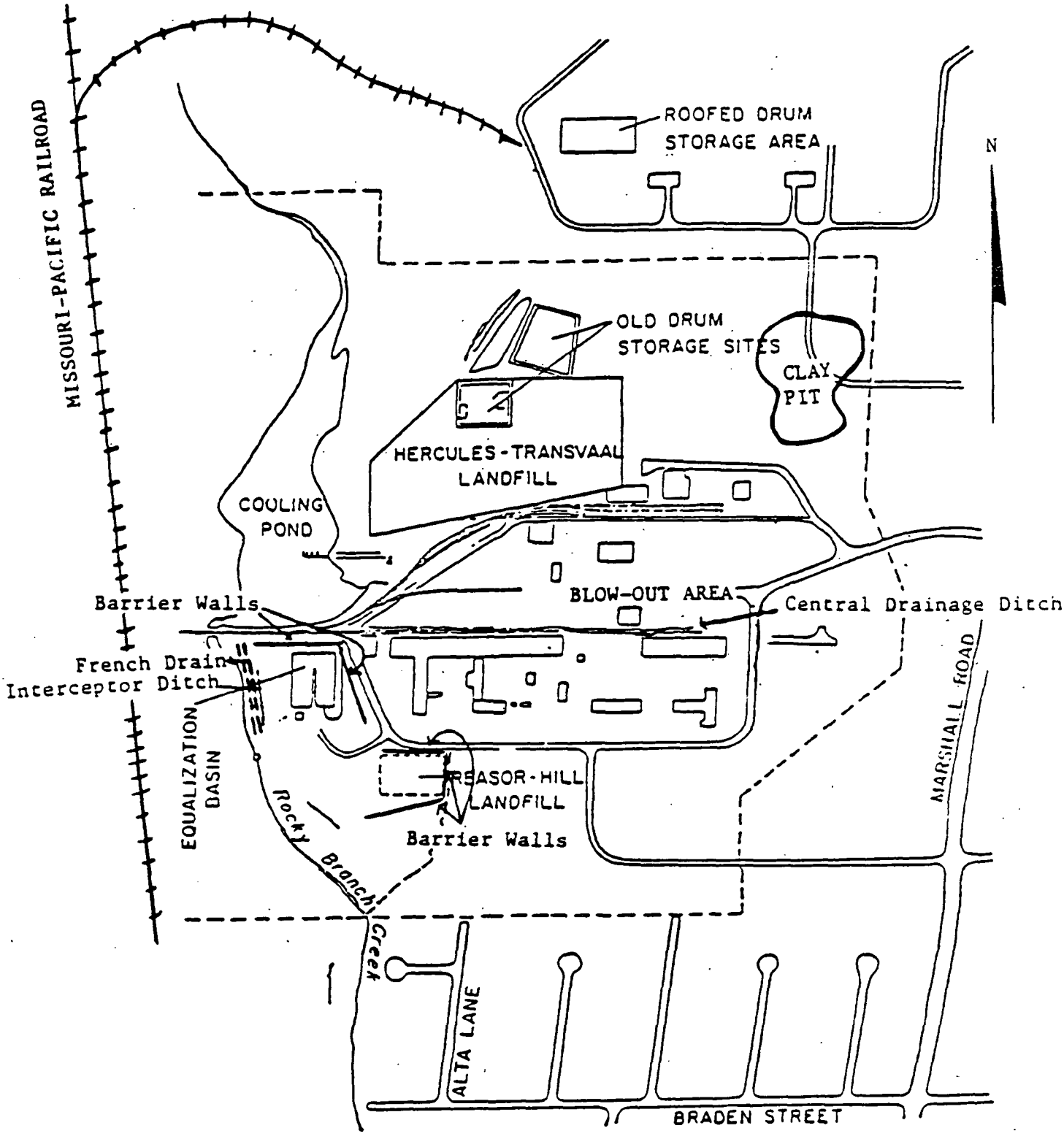
The Vertac hazardous waste site is located in northwest Jacksonville, AR (Pulaski County), approximately 20 mi northeast of Little Rock. The site (about 93 acres in size) is bounded by Marshall Road to the east and the Missouri-Pacific Railroad to the west. The old artillery booster line is on the northern boundary and an adjacent housing development is to the south. The Rocky Branch Creek flows along the western edge of the site and the East Branch of the Rocky Branch Creek flows to the east of the site. The cooling pond located along the western edge of the site was formed by construction of an earthen dam across the Rocky Branch Creek. The Rocky Branch Creek flows into Bayou Meto (a tributary of the Arkansas River) about two miles south of the Vertac site. There is a fence around the entire site with a main gate facing Marshall Road. Figure 1-1 demonstrates the site features and boundaries.

The site is a herbicide manufacturing plant owned by the Vertac Chemical Corporation which currently produces 2,4-dichlorophenoxyacetic acid (2,4-D). The site has been used since the 1930s by a variety of companies for the manufacture of munitions and pesticides including DDT, aldrin, dieldrin, toxaphene, 2,4-D, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 2,4,5-trichlorophenoxypropionic acid (Silvex or 2,4,5-TP) and Agent Orange (a mixture of 2,4-D and 2,4,5-T). The herbicides 2,4,5-T and Agent Orange are known to contain 2,3,7,8-tetrachlorodibenzo-p-dioxin (hereafter referred to as dioxin 2,3,7,8-TCDD or TCDD) as an impurity. Waste disposal, cooling water discharges and other plant operations apparently resulted in on-site and off-site releases of pesticides and herbicides manufactured on site, chemicals used in manufacturing processes and manufacturing impurities/by-products, including TCDD.

Estimates of the quantity and types of contaminated materials at the Vertac site were reported (JRB 1983) as follows:

1. Thirty thousand (30,000) yd^3 (22,800 m^3) of chlorinated phenols, benzene and toluene wastes within the Reasor-Hill landfill.

2. Twenty thousand (20,000) yd^3 (15,200 m^3) of still bottoms, contaminated with 2,3,7,8-TCDD, presently contained in the equalization



Adapted from Walton 1982 as cited in JRB (1983)

FIGURE 1-1 VERTAC SITE MAP

basin wastewater treatment system. This amount includes the clay cap placed on the basin at closure.

3. One hundred thousand (100,000) yd^3 (76,000 m^3) of material, including toluene still bottoms, in the Hercules-Transvaal landfill area.

4. Three thousand (3,000) drums (55 gallons each) of 2,4,5-T still bottoms (repacked in 85 gallon overpack drums) and contaminated soils from the former above-ground storage area, stored in the concrete diked warehouse.

The U.S. Environmental Protection Agency (USEPA) has initiated enforcement actions against the site owners and required a number of remedial actions to be implemented. The major remedial actions completed as of 1984 are summarized below:

1. The Reasor-Hill landfill was capped with clay, covered with soil and seeded with grass. Clay barrier walls were installed on three sides and the downgradient side was left open.

2. The Hercules-Transvaal landfill was capped with clay, covered with soil and seeded with grass. No barrier walls were installed.

3. The former above-ground drum storage area was capped with clay, covered with soil and seeded. The old drums were repacked and placed in the roofed storage warehouse.

4. Two-thirds of the blow-out area (where spills from reactors had occurred) was paved with asphalt and the remainder was capped with clay, covered with soil and seeded.

5. The equalization basin has been subjected to extensive remedial actions including dewatering and lime solidification of sludges, installation of clay barrier walls, installation of a "French drain" on the downgradient side, capping with clay, covering with soil and seeding.

Under the proposed remedial action (Alternative IV), the Reasor-Hill Landfill and North Burial Area (includes old drum storage sites and Hercules-Transvaal Landfill) will be excavated and contaminated materials/soils will be redisposed of in a new on-site secure landfill in an area to the north of and overlapping with the North Burial Area. This proposed remedial action will involve excavation of 50,000 yd^3 of soil from the Reasor-Hill Landfill and 100,000 yd^3 from North Burial Areas.

1.2 Contaminants Found at the Site

Contaminants found at the site include pesticides and herbicides manufactured on site, chemicals used in the manufacture of DDT, aldrin, dieldrin, toxaphene, 2,4-D, 2,4,5-T, 2,4,5-TP (Silvex) and Agent Orange (2,4-D and 2,4,5-T mixture). Dioxin, an impurity resulting from synthesis of 2,4,5-T, is also present at

the Vertac facility. Environmental monitoring surveys from the period of 1978 to 1983 have detected chemical contaminants in groundwater, surface water, soils and sediments. The USEPA Office of Waste Programs Enforcement has identified the following "indicator" chemicals for the Vertac site on the basis of their toxic properties, presence in large quantities or potential and actual releases to the environment:

- 2,3,7,8-TCDD
- 2,4,5-T
- 2,4-D
- 2,4,5-TP
- Chlorophenols
- Chlorobenzenes
- Toluene
- Methanol

This endangerment assessment will focus on dioxin because it is the most highly toxic substance at the facility and is very persistent in soils and aquatic systems. Dioxin has been detected in waste products, groundwater and soils on site and in sediments and fish tissue in adjacent surface waters (see Table 1-1). Refer to CH2M Hill (1984a), JRB (1983) and Walton et al. (1982) for data on individual sampling sites and dates and maps indicating sampling locations and groundwater monitoring wells. A site map showing these locations (which is normally provided in an endangerment assessment) is not included because of the complexity of the several monitoring studies performed at this site. The values presented in Table 1-1 are a composite of the available monitoring data from the period 1979 to 1983.

These data have not been subjected to a comprehensive quality assurance and quality control review but a preliminary review of available data reports indicates that quality control and quality assurance procedures were implemented. These procedures included the chain of custody, split samples, replicate analyses, sample spiking with an internal radiolabelled dioxin standard, routine instrument calibration, methodological (extraction) blanks, adherence to recommended sample holding times and storage temperatures, etc.

TABLE 1-1 RANGES OF DIOXIN CONTAMINATION DETECTED ON-SITE AT THE VERTAC FACILITY AND IN ADJACENT WATER BODIES

Sample Type	Location/Description	Dioxin Concentration, ppb	Total Number of Samples Analyzed	Number with Dioxin Not Detected	Detected Dioxin Concentrations, ppb Mean ± SD(n)[a]	Reference
Sediments	Equalization basin	0.063 to 1,200	5	0	460.2 ± 459.1 (5)	CH2M Hill (1984a)
	Cooling pond	0.236 to 102.0	18	0	18.2 ± 24.2 (18)	CH2M Hill (1984a)
	Drainage ditches, on-site	0.800 to 34.1	6	0	16.1 ± 12.9 (6)	CH2M Hill (1984a)
	On-site groundwater monitoring well	ND[b] to 12.1	4	2	10.0 ± 3.0 (2)	CH2M Hill (1984a)
	Rocky Branch Creek	0.500	NA[c]	NA[c]	NA[c]	Falco (1982)
	Rocky Branch Creek, on-site	0.236 to 17.4	5	0	4.1 ± 7.5 (5)	CH2M Hill (1984a)
	Sewer and interceptors off-site	18.4 to 33.4	3	0	28.3 ± 8.6 (3)	CH2M Hill (1984a)
	Creek bed adjacent to private residences	1	NA	NA	NA	JRB (1983)
	Lake Dupree	0.150	1	0	NA	Schaum and Falco (1982)
Soils	Surface soils on-site	ND[d]	NA	NA	NA	JRB (1983)
	Surface soils on-site	100 to 14,000	NA	NA	NA	Falco and Schaum (1984)
	Hercules-Transvaal area/surface dirt	559	1	0	NA	CH2M Hill (1984a)
	Reasor Hill landfill/dirt	3.42	1	0	NA	CH2M Hill (1984a)
	Reasor Hill landfill/mud	0.505	1	0	NA	CH2M Hill (1984a)
	Reasor Hill landfill area	NR[e]	NA	NA	NA	JRB (1983)
	Blow-out area	0.99 to 45	2	0	22.5 ± 31.7 (2)	CH2M Hill (1984a)
Surface Waters	Rocky Branch Creek, on-site	ND	1	1	NA	CH2M Hill (1984a)
	Discharge in combined sewer at Braden and Alta Lane	0.017	1	0	NA	CH2M Hill (1984a)
Ground Water	Monitoring wells down gradient of Hercules-Transvaal Landfill	"High"	NA	NA	NA	JRB (1983)
	Monitoring wells, on-site	ND to <0.03	35	21	0.005 ± 0.010 (13)	CH2M Hill (1984a)
Wastes	Toluene still bottoms disposed on-site	37,000	NA	NA	NA	JRB (1983)
	Seeps from Reasor Hill	0.045 to 5.5	3	0	2.4 ± 2.7 (3)	CH2M Hill (1984a)
	Equalization basin liquid	445	1	0	NA	CH2M Hill (1984a)
	Equalization basin discharge	<10	1	0	NA	CH2M Hill (1984a)
Fish	Caught in Bayou Meto	<0.025 to 0.300	6	0	0.087 ± 0.110 (6)	Schaum and Falco (1982)
	Caught in Lake Dupree	0.810	1	0	NA	Schaum and Falco (1982)

(a) The mean and standard deviation of samples with detected levels of dioxin were calculated. Samples with "not detected" (ND) levels of dioxin were not used in the calculations. The value in parentheses is the number of samples with detected dioxin levels used in the calculations.
(b) ND = Not detected. Detection limit was not reported.
(c) NA = Not applicable due to insufficient information.
(d) Not detected in measurable quantity. Detection limits 50 to 100 ppt.
(e) NR = detected but concentration not reported.

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2.0 ENVIRONMENTAL FATE AND TRANSPORT

2.1 Factors Affecting Migration

2.1.1 Geology

The Vertac site is situated very near or possibly on the fall line of the Interior Highlands and Coastal Plain physiographic regions. The geologic maps show that the Vertac site is slightly to the west of the fall line suggesting that it is in the Interior Highlands but evidence (the northern part of the site contains clays of the Midway Group which are present in the Coastal Plain) suggests it is also in the Coastal Plain or in the transition zone. The surface soils near the eastern portion of the site are sedimentary. The subsoils are part of the Atoka Formation characteristics of the Interior Highlands.

The site is underlain by the consolidated rock of the Atoka Formation which surfaces in the Interior Highlands and underlies the sediments of the Coastal Plain. The Vertac site is located on the south flank of a westward plunging syncline. The bedrock is alternating gray to black shales and sandstones of the Atoka Formation which dips to the northeast at a rate of about 30 degrees. There are many discrepancies regarding the strike and dip of the rock strata on-site since the site is so close to the fall line. The overlying unweathered bedrock in ascending order is weathered bedrock approximately five feet thick, clays and alluvium.

The soil is classified as a Leadvale-Urban land complex with a 1 to 3% slope. The Leadvale Urban land complex are areas of Leadvale soils that have been modified by urban development. The Leadvale soils are moderately well-drained, nearly level and gentle-sloping soils in valleys. They are formed mainly of loamy sediment washed from uplands composed of sandstone, shale and in some areas from weathered siltstone. The Leadvale soils have moderately low permeability and maintain a medium level of available water capacity. The level of runoff from the Leadvale Urban land complex is medium and the erosion hazard is moderate if the soils are not protected by vegetation. Soil borings indicate the presence of yellowish brown silty sands in the northeast corner of the site and yellowish brown or tan silty clays in the southeast portion of the site (CH2M Hill 1984a).

2.1.2 Hydrology

Surface drainage patterns at the Vertac site are predominantly westerly and easterly. The western 55 acres drain directly to the Rocky Branch Creek. The Rocky Branch Creek enters the Vertac site at the northwest boundary and flows into a man-made cooling pond. About 700,000 gallons/day of process waste-waters enter the cooling pond. Waters from the cooling pond flow out a concrete outlet structure at the southwest extremity of the pond. A central ditch (no longer present) acted as a surface drainage channel from the plant production area and flowed into the cooling pond. The combined flow of surface runoff and process waters enters Rocky Branch Creek and flows south about two miles to Bayou Meto.

The eastern 38 acres of the site drain east to numerous small ditches caused by natural erosion. Along adjacent driveways and roads are a few man-made ditches. The catch basins located on the eastern portion of the site drain to a storm sewer which empties into an open ditch near the main plant entrance. All surface runoff east of the drainage divide eventually flows into the East Branch of the Rocky Branch Creek. Most of this runoff is carried by the "East Ditch" to the East Branch. The East Branch flows into Rocky Branch Creek south of the Vertac Site.

During heavy spring rains it is not uncommon for the Rocky Branch Creek to flood the area south of the Vertac Site. This is important because there is a manmade recreational lake (Lake Dupree) 1.3 mi south of the Vertac site. Lake Dupree and the Rocky Branch Creek are not normally connected but, the low terrain and tendency for flooding in the area potentially enables contaminants discharged into Rocky Branch Creek to be deposited in Lake Dupree (JRB 1983).

2.1.3 Hydrogeology

The Interior Highlands are hilly and underlain by consolidated sediments which dip slightly in a southeasterly direction. The consolidated rock of the Interior Highlands underlies unconsolidated sediments of the Coastal Plain. Above the lowest level of the water table, the consolidated rock of the Highlands has been weathered. Soil and "rotten rock" (i.e., weathered rock) in this region are present to a total depth of about 20 ft (maximum). This weathered rock area is more permeable and porous than unweathered rock. Water is present in intergranular voids of "rotten rocks" and soil while water is only present in joints, fractures and other secondary openings in unweathered rock.

The sediments of the Coastal Plain vary from high plasticity clays to sands and gravels with varying permeabilities. There are three units within the sediments which are major water sources in some areas of Pulaski County. Beds of claystone, calcareous sandstone, sandy limestone, marl and conglomerate (about 7 to 60 ft) comprise one aquifer unit. Fine to medium sand with some interbedded clay lenses (about 320 ft thick) comprise another aquifer unit. Terrace deposits and alluvium (deposited by the Arkansas and Mississippi rivers) composed of fine-grain top stratum and deeper coarser stratum (about 120 ft) is the third aquifer unit. Refer to Walton et al. (1982), CH2M Hill (1984a) and JRB (1983) for further hydrogeologic information and a diagram of the locations of aquifers in the Coastal Plain and Interior Highland regions.

The general horizontal groundwater flow is from north to south (CH2M Hill 1984a). Two groundwater divides are evident on site with one running from the northeast boundary of the site along the east side, across the plant and then due south. The second divide runs from the northwest along the western edge of the cooling pond and south along Rocky Branch. The contaminated water table flows toward the cooling pond and the Rocky Branch Creek at a rate of <1 to 10 in/yr (CH2M Hill 1984a). The vertical groundwater flow rates in bedrock were calculated to range from 2×10^{-2} in/yr to 6.0 in/yr (CH2M Hill 1984a) which indicates potential downward migration of contaminants. Little

is known about the hydrogeology of bedrock deposits at the Vertac site and the structure of bedrock has not been evaluated.

The Rocky Branch Creek received groundwater inflows from the water table from both the east and west. These flows have passed under or through the Reasor-Hill area. Contaminants entering the groundwater east of the divide may eventually enter the Coastal Plain aquifers (off-site) (CH2M Hill 1984a). The recharge and inflow upgradient of contaminant sources flows toward western surface water bodies and are conveyed off-site above ground or in the water table.

2.1.4 Climatology

Precipitation is fairly well distributed throughout the year; however, May is normally the wettest month. The annual precipitation averages about 48 in and about 31% of total precipitation occurs from March through May. August through October are the driest months with a total of 3 in of rain.

Winters are mild with average winter temperatures of 41 F and an average annual snowfall of 5.7 in. The greatest monthly snowfall reported was 12 in in January 1966. The summers are hot with an average daily temperature of 82 F and maximum temperatures of over 100 F occurring frequently in July and August.

2.2 Environmental Fate and Transport of Dioxin

2.2.1 Environmental Fate

2.2.1.1 Biodegradation

Dioxin is not readily biodegraded. Few microbial strains (5/100) capable of degrading persistent pesticides could degrade dioxin slightly (USEPA 1980). Dioxin is persistent in freshwater aquatic environments with a half-life of 550 to 590 days in sediment containing lake waters (Ward and Matsumura 1977). The biodegradation half-life of dioxin was estimated to be greater than one year based on theoretical biotransformation rate values and assumed concentrations of microorganisms (USEPA 1984). The biodegradation half-life of 0.5 yr for dioxin in soils was based on data from a rural Missouri incident involving accidental spraying of dioxin contaminated oils (IARC 1977). Recent data suggest that the half-life may be closer to 10 yr (USEPA 1984).

2.2.1.2 Photodegradation

Dioxin is in the presence of organic solvents (Crosby et al. 1971) or other hydrogen donators is photodegraded (Crosby and Wong 1977). Insufficient information is available on reactions of dioxin in aquatic media under environmental conditions to predict the photodegradation half-life in natural waters. However, photolysis is expected to be an important fate process when hydrogen donating substrates are present (USEPA 1984). Assessment of photodegradation in natural waters is complicated by the tendency for dioxin to be strongly

adsorbed on particles in sediments that are not exposed to ultraviolet (UV) light.

Information on photodegradation of airborne dioxin adsorbed on particulates is conflicting. The importance of photodegradation relative to deposition (dry or wet) in the fate of airborne dioxin is uncertain but may be important. Dioxin sorbed to solid surfaces and exposed to the atmosphere yielded negligible photodegradation (Crosby et al. 1971), while photolysis was evident for dioxin in a condensed phase on glass or silica.

The photodecomposition of dioxin on wet or dry soils under artificial and natural sunlight (UV radiation) was observed to be negligible in soils (Crosby et al. 1971). However, photodecomposition may occur when dioxin and other pesticides (hydrogen donators) are present as a mixture in soils (Crosby and Wong 1977).

2.2.1.3 Oxidation and Hydrolysis

No information on the oxidation of dioxin in aquatic systems was available but its strong electropositive nature suggests it may be more resistant than nonchlorinated or less chlorinated aromatics. The potential for oxidation of dioxin (sorbed on airborne particulates) by atmospheric compounds (NO_x, O_3, etc.) is unknown. Hydrolysis is unlikely to occur under environmental conditions in aquatic systems (USEPA 1984).

2.2.1.4 Volatilization

Quantitative information on volatilization of dioxin from aquatic systems is not available although several references have mentioned volatilization as a possible loss process (Callahan et al. 1979). Matsumura et al. (1983) observed that dioxin may undergo water-mediated evaporation in an aquatic system. Based on theoretical models, the volatilization half-life was predicted to be about 5.5 yr from a pond and 12 yr from a lake. The validity of these estimates has not been assessed with experimental data. Volatilization of dioxin adsorbed on soils is expected to be at a very slow rate due to the extremely low vapor pressure of dioxin (Falco and Schaum 1984).

2.2.1.5 Sorption

Sorption on particles (suspended or sediments) and in microorganisms appears to be an important fate for dioxin in aqueous environments. Isenee and Jones (1975) observed that 85% to 99% of dioxin remained adsorbed on sediments in an aquatic system and the majority of dioxin not on sediments was in aquatic organisms. Ward and Matsumura (1978) observed that more than 90% of dioxin in aquatic medium remained bound to sediments. The low water solubility and high octanol/water partition coefficient of dioxin support these observations.

The half-life of dioxin in soils has been reported to be 1 to 3 yr (Kearney et al. 1972), about 330 days (dry conditions), 190 days (wet conditions) (U.S. Air Forces study cited in USEPA 1984) and 10 yr (Young 1983).

2.2.1.6 Bioaccumulation

Many aquatic species bioaccumulate dioxin. In a static experimental test chamber, the accumulation appeared to be dependent upon initial dioxin concentrations. The bioconcentration factors (determined experimentally in a static system) vary with species and may range from about 2,000 (algae or snail) to 9,000 (catfish) to 26,000 (mosquitofish) (Isenee and Jones 1975, Isenee 1978).

Schaum and Falco (1982) derived a fish-sediment distribution coefficient (K_{FS}) to reflect bioaccumulation of dioxin in fish and enable calculation of potential concentrations in fish from sediment concentrations. Coefficients were derived on the basis of actual monitoring data and on the basis of biota-water and organic matter-water distribution equations from published literature. Limited data on dioxin concentrations in fish (810 ppt in a bass) and in sediments (150 ppt) in Lake Dupree were used to calculate the distribution coefficient as follows:

$$K_{FS} = \frac{810 \text{ ppt}}{150 \text{ ppt}} = 5.4$$

This K_{FS} value probably underestimates the K_{FS} in the catfish population inhabiting the Bayou, since catfish and other benthic feeders tend to bioaccumulate dioxin to a greater extent than nonbenthic feeders. The alternative K_{FS} of 550 was calculated based on an assumed organic carbon content (0.5%) in accordance with the relationships defined by Perwak et al. (1980) and Hamaker (1978). The discrepancy between the K_{FS} values based on monitoring data (5.4) and that derived from biota-water and organic matter-water distribution relationships (550) may be explained by uncertainty in actual organic content of sediments, species differences, insufficient residence time for fish or dioxin to reach equilibrium, or non-equilibrium due to dynamic flow conditions in the Bayou. Thus, the uncertainty regarding the K_{FS} coefficient adds great uncertainty to estimates of human exposure levels.

2.2.2 Environmental Transport

Schaum and Falco (1982) calculated the dioxin load to Bayou Meto based on an environmental transport model. The estimated mean sediment yield rate for the upper Bayou Meto water shed of 0.63/yr/acre was assumed to be constant throughout the watershed and applicable to the Rocky Branch Creek. The assumption was considered valid because factors (rainfall, slope steepness, cover, etc.) affecting erosion appear roughly the same throughout the area. The trapping efficiency of the cooling pond was calculated to range from 0.46 to 0.71. Minimum and maximum sediment loads of 550 tons/yr and 620 tons/yr were calculated. Using the 500 ppt dioxin concentration of sediments near the mouth of Rocky Branch Creek, the minimum and maximum dioxin loads to Bayou Meto were calculated to be 2.7×10^{-7} and 3.1×10^{-7} tons/yr. Nonpoint source pollution data and U.S. Geological Service (USGS) data on the Arkansas River basin sediment loads were used were used to calculate dioxin concentrations at seven different points along Bayou Meto. Calculations assumed steady-state sediment movement since data on the variability of sediment storage and removal rates

in the bayou were unavailable. The uncertainty associated with variations in sediment storage/removal rates were considered insignificant relative to uncertainties associated with the fish-sediment distribution coefficient.

Kearney et al. (1973) examined the mobility of dioxin in five soil types and observed that decreased mobility was associated with increased organic content of soils. Dioxin was relatively immobile in all test soils and Kearney et al. (1973) concluded that leaching to underground water supplies would be unlikely. Matsumura and Benezet (1973) postulated that dioxin transport would be via horizontal transfer of contaminated soils and dust particles. Dioxin does not readily migrate vertically in soils (USEPA 1984). Nash and Beall (1980) observed that 80% of dioxin applied to soils in a microagroecosystem remained in the upper 2 cm of soils and that only trace amounts were detected at 8 to 15 cm. The NRCC (1981) suggested that vertical migration of dioxin may result when the sorption capacity of soils are saturated or as a result of biotic mixing (i.e., action of earthworms or other soil invertebrates). Dioxin solvated by organic solvents may be more readily transported through soils to the groundwater.

Wet and dry deposition of particulate-bound dioxins appear to be an important fate-determining process in the transport of airborne dioxins.

2.3 Contaminant Movement On Site and Off Site

The summary of the Vertac site history indicates that contaminants (dioxin and others) were discharged in untreated wastewaters and process wastes, transported and released to the Rocky Branch Creek possibly as early as 1955 (JRB 1983). Dioxin and other contaminants were also released by seepage from underground burial areas and by erosion of contaminated surface soils.

Contaminants from the Hercules-Transvaal Landfill have migrated to the process cooling pond. The central drainage ditch and surface runoff also transported dioxin to the cooling pond. Contaminants that leaked into the cooling pond and/or settled there probably flowed into the Rocky Branch Creek since the pond is in its steam course. Spills and/or valve ruptures of the trichlorophenol reactor in the "blow-out" area or other areas released dioxin which may have percolated underground or have been transported via surface runoff to the East Branch. Leachates from the equalization basin along the western edge of the site also contributed to contamination of the Rocky Branch Creek. Transport of dioxin to Dupree Lake probably occurred as a result of flooding of the Rocky Branch Creek during periods of heavy spring rains.

Implementation of remedial actions involving disturbance of soils and vehicular movement may have promoted contaminant transport particularly during remediation of the equalization basin. The remedial actions implemented (clay caps, barrier walls, French drain, etc.) may reduce the potential for further contamination by preventing infiltration of surface precipitation, runoff and wind erosion. There is some uncertainty about the vertical migration of contaminants to groundwaters. Unexpectedly, "high" concentrations of dioxin were detected in groundwater monitoring wells downgradient from the Hercules-Transvaal Landfill area (JRB 1983). There is potential for lateral subsurface

movement in this landfill since no barrier walls have been installed. The closure of the equalization basin appears to contain lateral leachate seeps but the effectiveness over time is uncertain since the French drain and barrier walls were constructed over weathered rock (with fissures). Installation of the above-grade neutralization wastewater treatment system and discharge to the local wastewater treatment plant has reduced or eliminated the potential for further release of process waste to the Rocky Branch Creek.

The proposed remedial action (Alternative IV) which involves excavation of contaminated soils/materials and redisposal in a secure landfill on-site) will disturb soils and create the potential release of contaminants as dust emissions. The release and movement of contaminated dust may be reduced by implementation of dust control measures. Falco and Schaum (1984) determined that primary sources of dust emissions would result from vehicle travel over contaminated soils, loading/unloading operations and spreading excavated soil in the new on-site secure landfill. A front-end loader will be used to excavate material and load it into dump trucks. Material will be transported in the trucks on existing roadways where materials will be dumped and spread with a bulldozer in the secure landfill on site. It is assumed that "clean-dirt" will be applied to roadways between the excavation sites and the secure landfill and covered trucks will be used to reduce contaminant releases. The wind-only generated dust emissions were assumed to be negligible compared to mechanically generated dusts occurring during truck travel, loading/unloading and spreading operations. The estimated duration of the proposed excavation/remedial actions and associated dust emissions is 190 days for the Reasor-Hill site and 380 days for the North Burial Area.

3.0 EXPOSURE EVALUATION

This section will identify actual and potential routes of exposure, characterize the populations exposed and determine extent of the exposure to dioxin. The results of exposure assessments for the proposed on-site remedial action and for consumption of fish from off-site contamination of receiving waters are summarized.

3.1 Routes of Exposure

Potential exposure routes are as follows:

1. Consumption of fish from the Bayou Meto and Rocky Branch Creek.

2. Consumption of groundwater downgradient of the Vertac site.

3. Inhalation of dust-contaminated with dioxin that may become airborne due to implementation of remedial action Alternative IV.

4. Direct contact with waters, sediments or soils adjacent to the site that have been contaminated by surface runoff or erosion processes. Direct contact includes direct dermal exposures as well as direct ingestion exposures (i.e. pica in children).

3.1.1 Fish Consumption

Environmental monitoring data indicate that the high concentrations of dioxin are found in fish (<25 to 300 ppt) and sediments (500 ppt) of Bayou Meto (Schaum and Falco 1982). Significant potential human health threats may result from consumption of contaminated fish from Bayou Meto. Arkansas officials have banned fishing on the Bayou Meto; however, the fishing ban is not easily enforced (Falco 1982). Thus, there appears to be a real potential for dioxin exposure. Schaum and Falco (1982) concluded that consumption of dioxin contaminated fish represented the most important potential exposure route and estimated the amount of dioxin bioaccumulating in fish at various distances downstream from the site. This exposure assessment calculated bioaccumulation in fish, estimated potential human consumption rates and derived the resulting exposure levels.

Dioxin released from the site via transport on suspended solids in overland runoff or sorbed to airborne dust is of particular concern. Dioxin-bearing particles accumulate in sediments of receiving waters and bioaccumulate in fish. Monitoring data indicate that 500 ppt of dioxin are present in the Rocky Branch Creek sediments. Schaum and Falco (1982) have calculated the dioxin load to Bayou Meto based on this concentration (500 ppt), modeled sediment redistribution to Bayou Meto and applied the fish-sediment distribution coefficient to calculate dioxin concentrations in fish.

3.1.2 Groundwater

Concentrations ranging from ND to 0.03 ppb (with a mean ± standard deviation of 0.005 ± 0.010 ppb) of dioxin were detected in groundwater monitoring wells

downgradient from the Hercules-Transvaal landfill area; however, no existing domestic or industrial wells were reported to be located in areas that are immediately downgradient from the Vertac site (JRB 1983, Schaum and Falco 1982). The exposure assessment by Schaum and Falco (1982) did not evaluate human exposure via consumption of contaminated groundwater but noted that this route may represent a long-term threat and should be analyzed further. Subsequent groundwater exposure assessments should consider dioxin and other contaminants, that are both more mobile in the subsurface soils and more soluble in water, to characterize the importance of this route.

3.1.3 Airborne Dust

Schaum and Falco (1982) recognized that dioxin would probably be present on dust particles but would be unlikely to volatilize appreciably and be detected as a vapor in ambient air offsite. This potential exposure route was not examined by Schaum and Falco (1982) since remedial actions implemented (clay capping of disposal areas and covering the blow-out area) were expected to diminish releases of dioxin-contaminated dust via wind erosion.

The potential for exposure to dioxin via inhalation of contaminated dust is increased by the proposed remedial action (Alternative IV). Falco and Schaum (1982) assessed the exposure potential associated with remedial actions that disturb the soil and create potential dust emissions.

3.1.4 Direct Contact with Contaminated Soils/Sediment

Dioxin in contaminated soils may be adsorbed across the skin. The concentration in soils and type of soils are expected to affect dermal adsorption. The direct contact with contaminated soils is dependent upon the degree of outdoor activities such as gardening or playing. The degree of dermal exposure depends upon the amount of skin exposure, duration of contact and soil conditions.

Exposure due to direct ingestion depends on age with children aged two to six years having the greatest exposure potential. Seasonal variation in weather, soil conditions and activity patterns affect the amount of exposure via direct ingestion of contaminated soils/sediments.

3.2 Populations Exposed

3.2.1 Fish Consumption

Populations with high fish consumption from affected water bodies are at an increased risk of dioxin exposure. Schaum and Falco (1982) stated that the number of people exposed to dioxin via consumption of fish caught from Bayou Meto cannot be estimated precisely. Exposure via consumption of fish should not be occurring since there is a fishing ban for the Bayou Meto; however, there is evidence that the ban is not easily enforced. Schaum and Falco (1982) estimated the number of people potentially exposed if such a ban was not in effect. The predicted fish catch from the Bayou Meto was divided by an estimate of the individual's consumption rate to estimate the size of

population exposed. Both the fish catch and consumption rates were difficult to assess accurately. The national average consumption of nonmarine fish (5.2 lb/yr) was used in the calculations; however, fish consumption rates may vary by up to threefold between the average and the 95th percentile. The consumption rate of fish from the Bayou Meto (only) is probably less than the amount predicted since the 5.2 lb/yr statistic represents the individual's total consumption which is likely to reflect fish caught from many sources. The mean catch rate (62 lb/acre/yr) was based on the rate from an off-stream reservoir which may differ from that in the Bayou Meto. The total catch (160,000 lb/yr) was estimated by multiplying the mean catch rate by the river surface area (2,600 acres based on an assumed mean width of 150 ft and length of 144 mi). Schaum and Falco (1982) illustrate how the exposed population size may vary according to assumptions made regarding the consumption and catch rates (see Table 3-1).

Assuming that most fish from Bayou Meto are likely to be consumed by local residents, Schaum and Falco (1982) concluded that the number of exposed people is probably less than the local population. Approximately 476,000 people are in counties that are at least partially drained by Bayou Meto according to census data.

3.2.2 Groundwater

Walton et al. (1982) states that no domestic or industrial water wells were located in areas that are immediately downgradient from the Vertac site. Contacts with state and local permitting agencies identified only two domestic wells within the vicinity of the site (Walton et al. 1982).

One well (50 ft deep) was 1.5 mi west of Vertac and the other well (15 ft deep) was about 1.5 mi southeast of the site. Data on the size (if any) of the population utilizing these wells or consuming groundwater from other sources contaminated by the site was unavailable. There are insufficient data on groundwater contamination and off-site flows to determine when the plume may reach these wells and the expected concentrations.

3.2.3 Airborne Dust

The population at greatest risk to exposure to dioxin via airborne dust would be workers/observers on-site during the proposed remedial action if an adequate personal protection program was not implemented. It is assumed that an adequate personal protection program will be required under the Remedial Action Plan to eliminate or substantially reduce potential exposures to on-site personnel.

Insufficient data on prevailing wind direction, wind speed and geographical features affecting wind patterns are available to determine which populations are at an increased exposure potential for airborne dust. Residents of the subdivision to the south of the site are the nearest potentially exposed off-site population (Falco and Schaum 1984). The proximity of this population to the site is assumed to subject this population to an increased risk of exposure to dioxin since airborne dust concentrations are expected to be

TABLE 3-1 ESTIMATES OF POPULATION SIZE EXPOSED AND EFFECTS OF ASSUMPTIONS REGARDING FISH CONSUMPTION RATE AND FISH CATCH RATE

Consumption Rate, lb/individual/year	Population Exposed/Year[a] Catch Rates, lb/acre/year			
	6[b]	30[c]	62[d]	90[e]
2.5	6,240	31,200	64,480	93,600
5.2	3,000	15,000	31,000	45,000
7.5	2,080	10,400	21,493	31,200
10.0	1,560	7,800	16,120	23,400
15.6[f]	1,000	5,000	10,333	15,000
20.0	780	3,900	8,060	11,700
30.0	520	2,600	5,373	7,800

(a) Exposed Population = $\frac{\text{Fish catch rate x stream area}}{\text{consumption rate}}$

Stream area = 2,600 acres.

(b) 10% of estimated mean catch rate.

(c) 50% of estimated mean catch rate.

(d) Estimated mean catch rate.

(e) 150% of estimated mean catch rate.

(f) The expected upper 95% percentile for fish consumption rates.

Adapted from Schaum and Falco (1982).

greatest near the site and to decrease with increasing distance from the site. People that stay at home during the daytime and especially those that are frequently outside for long periods are expected to have higher exposures. This group may include young children, nonworking parents and the elderly. It is assumed that dioxin-contaminated dust concentrations will tend to be higher outdoors relative to inside a house. No quantitative information on the number of residents near the site and specific behavior patterns is available.

3.2.4 Direct Contact

No quantitative data are available on the size of the population potentially exposed to dioxin via direct contact with contaminated soils or sediments on-site or off-site. The fence around the facility limits accessibility and reduces potential accidental direct contact exposures on-site. Detection of dioxin in surface soils in the subdivision south of Vertac (Braden Street, West Lane and Alta Cove) (CH2M Hill 1984) suggests that residents may be at risk for dioxin exposure. People who garden and play outdoors are expected to be at higher risk for direct contact exposures. Since the highest concentrations of dioxin off-site are found in sediments of the Rocky Branch Creek, it is anticipated that people who swim, wade or play in and around the creek may be at increased risk. Likewise, people who use Lake Dupree for recreational activities may have increased exposure.

3.3 Extent of Exposure

3.3.1 Fish Consumption

No estimates of actual fish consumption based on local surveys of the Rocky Branch Creek and Bayou Meto are available. Schaum and Falco (1982) estimated that the annual human exposures to dioxin from consumption of contaminated fish could range from 110 ng/kg of body weight (bw) for fish caught near the confluence of Bayou Meto and the Rocky Branch Creek to as low as 0.09 ng/kg/bw for fish caught from Bayou Meto (mouth). Table 3-2 identifies ranges of predicted dioxin exposures from consuming fish caught at various points along the Bayou Meto as presented by Schaum and Falco (1982). The concentration of dioxin in sediment (C_s) was calculated by dividing dioxin load by total sediment load. The range of values reflects the assumed range of trapping efficiencies (0.41 to 0.71). The concentration of dioxin in fish was calculated by multiplying C_s by the sediment fish distribution coefficient (assumed range of 5.4 to 550). The calculated human exposure assumes a 70-kg human consumes 5.2 lb (6.5 g/day) of fish per year. Estimates of human exposure based on the available monitoring data are in agreement with predictions based on the environmental transport model. There is much uncertainty associated with the predicted exposures. Factors previously discussed (such as utilization of an estimated dioxin sediment load, fish-sediment distribution coefficients, unavailability of actual fish consumption rates, etc.) contribute to the uncertainty. This uncertainty is compounded by the fact that fishing on Bayou Meto is currently banned.

The Schaum and Falco (1982) exposure assessment provides a means to bound the possible range of exposure but the limited data are not sufficient to produce

TABLE 3-2 DIOXIN CONCENTRATION IN SEDIMENT, DIOXIN CONCENTRATION IN FISH, AND HUMAN EXPOSURE BY RIVER MILE

River Mile[a]	Concentration of Dioxin in Sediment (C_S ppt)		Concentration of Dioxin in Fish (C_F ppt)		Estimated Human Exposure, ng/kg/yr	
	Based on Calculations	Based on Monitoring[b]	Based on Calculations	Based on Monitoring[b]	Based on Calculations	Based on Monitoring
132	5.2-6.0	500	28-3,300	300	0.96-110	10.1
100	3.1-3.5	<70	17-1,900	112	0.56-65	3.79
75	2.6-3.0	<85	14-1,600	30	0.48-56	1.0
54	0.83-0.94	<80	4.5-520	<30	0.15-18	NA
34	0.71-0.80	<30	3.8-440	<25	0.13-15	NA
16	0.62-0.70	<20	3.3-390	<25	0.11-13	NA
0	0.49-0.56	NA[c]	2.6-310	NA	0.09-10	NA

(a) River mile defined as the number of miles upstream from the mouth of Bayou Meto.
(b) All C_S and C_F monitoring data were gathered by Arkansas Department of Pollution Control and Ecology in 1981.
(c) NA = No data available.

Adapted from Schaum and Falco (1982).

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a statistically valid estimate of the error range. The predicted exposure values are based on very limited data and much more extensive data are required to precisely define the magnitude and extent of dioxin exposure via contaminated fish consumption.

3.3.2 Groundwater

The extent of dioxin exposure via groundwater has not been determined. Due to the apparent lack of water wells and the low solubility of dioxin in water, it is expected that exposure potential will be minimal. Using the highest reported concentration of 0.03 ppb dioxin in groundwater on-site (CH2M Hill 1984a) and assuming a 70-kg adult would consume two liters of water per day, a maximum potential exposure could be calculated as follows:

$$\frac{0.03\ \mu g/L \times 2\ L/day}{(70\text{-}kg)} = 0.0009\ \mu g/kg/day\ (0.9\ ng/kg/day)$$

This is a worst case scenario. Insufficient data on groundwater flows, dilution rates and the extent of contamination are available to calculate reasonable conservative exposure estimates. Using the mean concentration of dioxin detected in wells (0.005 ppb) and the above equation, the exposure may be estimated as 0.0001 µg/kg/day. Recent monitoring data have not detected dioxin in any wells on-site and therefore suggest that exposure levels may be less.

In addition, actual exposure at this level is unlikely since Walton et al. (1982) and CH2M Hill (1984a) state that data indicate that no existing wells are located within two miles of the site and there is no contamination in any wells beyond two miles. Future contamination or installation of new drinking water wells downgradient of the site may increase the potential and magnitude of exposures.

3.3.3 Airborne Dust

Falco and Schaum (1984) assessed potential exposures to dioxin via inhalation of dust-emissions associated with the proposed remedial action (Alternative IV). The two phased remedial action involves excavation initially at Reasor-Hill Landfill (Phase 1) and finally at the North Burial area (Phase 2). The exposure assessment predicted possible off-site emission rates, used dispersion models to determine resulting off-site air concentrations of dioxin and calculated inhalation exposures. The range of exposure estimates is due to the uncertainty in the concentration of dioxin in the material (soil) to be excavated (assumed to range from 0.1 to 14 ppm). Exposure estimates assume that no dust control measures are implemented during remediation.

Falco and Schaum (1984) used standard equations to predict dust emissions resulting from vehicular travel, loading/unloading and spreading operations. Assumptions regarding the silt content of soils, soil moisture content, particulate size, number of precipitation days, average wind speed and vehicle characteristics were required. The predicted emission rates for dioxin ranged from 1.55×10^{-9} to 2.17×10^{-7} g/sec for Phase 1 and from 2.3×10^{-9} to 3.8 x

10^{-7} for Phase 2. The ambient air concentrations of dioxin were calculated with the method developed by Cowherd et al. (1984) for specific ground-level area sources of particulate emissions. Implementation of the model relied on assumptions of comparability between meteorological conditions at the Vertac site and conditions used to develop the model and comparability between size of the source in the model and the size of the source at Vertac. Falco and Schaum (1984) determined the average air concentrations and plotted isopleths for the site. The average lifetime exposure levels (via inhalation) were calculated for each dioxin-concentration isopleth based on assumed respiration rate, exposure duration, body weight and lifetime expectancy. This assessment also assumed that all inhaled dioxin-particulate inhaled into the body is retained and absorbed. Since the exposure concentrations reflect respirable dust-sized particulates (<10 μ), virtually all inhaled particulates will be retained by the lung. Figure 3-1 illustrates isopleths for the combined phase exposure levels for the area outside the site's southern boundary where the nearest residents are located.

3.3.4 Direct Contact

No quantitative estimates of the extent of dioxin exposure via direct contact are available. Future exposure assessments should address specific subpopulations suspected of having increased exposures due to their behavior or activities. For example, children playing in contaminated soils or sediments of adjacent waterways are probably exposed to dioxin via direct dermal contact or ingestion. People who garden in residential areas with dioxin-contaminated soils also have increased exposure potential via direct contact. The lack of information on the dermal absorption, amount of direct soil contact, dioxin content of soils/sediments, quantity of soil directly ingested and other factors currently preclude performance of quantitative exposure estimates. Direct contact is an important route that should be addressed in future exposure assessments. The Kimbrough et al. (1977) report on toxicity in six children dermally exposed to dioxin-contaminated soils in horse-arenas in eastern Missouri confirms the potential significance of this route.

(Crow 1978, Passi et al. 1981). Most of the documented acute exposures to dioxin have been the result of chemical industry accidents involving 2,4,5-T, which is contaminated with dioxin.

The first cases of chloracne associated with exposure to dioxins occurred following an explosion in a chemical plant producing 2,4,5-T in 1949 (Holmstedt 1980). Zack and Suskind (1980) reported nausea, headaches, fatigue, muscular aches and pains, and chloracne as the frequent complaints among the 228 workers exposed. Chemical tests revealed elevated lipid levels and prolonged prothrombin times. Residual chloracne, peripheral neuropathy, fatigue and severe aches and pains persisted for up to two years. Other reports of adverse effects in humans following acute exposure to dioxin as a result of industrial accidents are provided by Holmestedt (1980), May (1973, Gianotti (1977), Garattini (1982), Taylor (1979) and Crow (1981).

The Lombardy Regional Authority has compiled extensive data regarding the health effects of dioxin on children and adults following accidental releases of the chemical from a plant in Seveso, Italy (Pochiari et al. 1979). Reduced peripheral nerve conduction velocities occurred in both adults and children, with a correlation between the incidence and the distance from the plant. Total serum complement activity, lymphocyte blastogenic response and peripheral blood lymphocytes were elevated in children exposed in the accident (Tognoni and Bonaccorsi 1982). The limited number of studies regarding the immunological effects of dioxin in adults have not revealed any reduction in immunocapability (May 1982).

Caramaschi et al. (1981) reported an increase in the frequency of headaches, eye irritation, gastrointestinal tract symptoms and abnormal g-GT, serum GPT and aminolevulinic acid levels in children living in the Seveso area who developed chloracne. Increased urinary glucaric acid levels, indicative of increased microsomal enzyme activity, were found in children three years after the accident (Ideo et al. 1982).

Six children dermally exposed to dioxin-contaminated soil (30 ppm, 30 mg/kg soil) in horse-arenas in eastern Missouri developed headaches, skin lesions and polyarthralgia (pain in joints) (Kimbrough et al. 1977). In the most severe case, epistaxis (nosebleeds) and lethargy were reported.

Numbness of the extremities, skin rashes and irritation, liver dysfunction, weakness, loss of sex drive and psychological changes have been associated with exposure to 2,3,7,8-TCDD and other dioxins, which occur as contaminants in Agent Orange, in veterans and residents of Vietnam. The relationship between exposure to dioxin and the development of these symptoms is unknown (Holden 1979, Bogen 1979).

4.2.2 Toxicity in Laboratory Animals

McConnell et al. (1978 a,b) observed that dioxin induced mortality in a variety of laboratory animals (rat, guinea pig, mouse, rabbit, monkey) at dose (LD_{50}) levels between 0.6 µg/kg and 283.7 µg/kg following oral administration. The dermal LD_{50} value in rabbits was 270 µg/kg (Schwetz et al. 1973).

A summary of studies providing data on the sub-lethal effects of acute exposure to TCDD is presented in Table 4-1. The effects were reported to occur following single exposures ranging from 0.1 to 300 μg/kg in four animal species (rat, guinea pig, chicken, mouse). Liver damage is the most consistently reported effect in most species. Rats receiving a single dose of 100 μg/kg of TCDD showed severe liver damage, thymic atrophy and jaundice (Gupta et al. 1973). In the same study, thymic and liver damage of lesser severity occurred at lower dose levels (25 and 50 μg/kg). In another study (Greig et al. 1973), rats exposed to TCDD (300 μg/kg) exhibited jaundice, multinucleated parenchymal cells of the liver and gastric hemorrhage. Histopathologic liver changes were observed five weeks after single oral doses of TCDD as low as 50 μg/kg were administered to male and female CD rats, and one week after a single dose of 50 μg/kg was administered to female CD-1 mice (Harris et al. 1973). Increased liver weights were found in male Wistar rats seven days after single intraperitoneal doses of 0.1 μg/kg (Cunningham and Williams 1972).

4.2.3 Toxicity in Aquatic Species

The USEPA (1984) summarizes the available information on the acute toxicity of dioxin to aquatic organisms. The 96-hr lethal concentrations (LC_{50}) reported by Miller et al. (1973) and Norris and Miller (1974) were >0.2 μg/L for *Paranais* sp. (worm), *Physa* sp. (snail) and *Aedes aegypti* (mosquito larvae), >1 μg/L for *Oncorhychus kisutch* (coho salmon), >10 μg/L for *Poecilia reticulata* (guppy) and >0.24 μg/L for *Ictalurus punctatus* (fingerling channel catfish). Helder (1980, 1981 and 1982) observed that the LC_{50} is >0.01 μg/L for *Esox lucius* (northern pike embryos) and *Salmo gairdneri* (rainbow trout yolk-sac fry) and >0.1 μg/L for the juvenile rainbow trout.

4.3 Subchronic and Chronic Toxicity

4.3.1 Toxicity in Humans

Several epidemiologic studies and case reports involving dioxin exposure in human subjects have been reported (Esposito et al. 1980). Effects observed include skin lesions (chloracne, prophyria cutanea tarda), liver function impairment and neurological disorders (polyneuropathy, peripheral nerve damage). An International Agency for Research on Cancer (IARC 1982) evaluation of human exposure data concluded that these studies are inadequate since they involve multiple chemical exposures.

4.3.2 Toxicity in Laboratory Animals

Longer exposures to dioxin caused effects similar to those reported following acute exposure including thymic atrophy, liver damage, renal function impairment, hematological effects, hormonal alterations, immunosuppression, nervousness and irritability. Chronic and subchronic studies in many different strains of laboratory mice and rats indicate that the liver is the primary organ affected by long-term exposure (Kociba et al. 1973, 1979, NTP 1980a). A summary of major studies providing dose-response effects is presented in

TABLE 4-1 EFFECTS OF DIOXIN IN ANIMALS FOLLOWING ACUTE EXPOSURE

Species	Dose (μg/kg)	Route	Effects	Reference
Rat	25, 50 or 100		Liver damage, thymic atrophy	Gupta et al. (1973)
	100		Jaundice, 43% mortality	
Guinea Pig	3.0		Hemorrhage, adrenal atrophy, cellular depletion of lymphoid organs, 90% mortality	Gupta et al. (1973)
Rat	300		Weight loss, gastric hemorrhage, liver damage (cellular changes), jaundice	Greig et al. (1973)
Chicken	25 - 50		Pericardial edema	Greig et al. (1973)
Rat	10	Oral	Hematologic effects	Weissburg and Zinkl (1973)
Rat	0.1	i.p.	Increased liver weights	Cunningham and Williams (1972)
Rat	50	Oral	Liver damage	Harris et al. (1973)
Mouse	50	Oral	Liver damage	Harris et al. (1973)
Rat	10		Decreased renal function	Anaizi and Cohen (1978)
Rat	10, 25, or 50		Decreased renal function	Hook et al. (1978)

Adapted from NAS (1977), NTP (1982 a,b) and Esposito et al. (1980).

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Table 4-2. Studies providing dose-response data indicating the greatest sensitivity to dioxin are described below.

Doses as low as 0.1 μg/kg/day caused a slight degree of liver degeneration in rats in a subchronic 13-wk (5 doses per week) study (Kociba et al. 1976). Dose levels of 1.0 μg/kg/day increased levels of serum bilirubin and alkaline phosphatase and caused pathologic changes in the livers of rats. A no-observed-adverse-effect level (NOAEL) of 0.01 μg/kg dioxin was reported for noncarcinogenic effects in rats.

Increased mortality was observed in female Sprague-Dawley rats maintained for two years on a diet that provided a dioxin dose of 0.1 μg/kg/day, while no increased mortality was observed in male rats at this dose or in animals receiving doses of 0.01 or 0.001 μg/kg/day (Kociba et al. 1978, 1979). At termination of the study, gross and histologic examination indicated that the liver was the most severely affected organ, with degenerative, necrotic and inflammatory changes observed. Increases in urinary excretion rates of the metabolites, coproporphyrin and uroporphyrin, in the high and middle dose females were consistent with the observed liver damage. Primary liver injury was dose-related with the lowest dose representing a NOAEL (noncarcinogenic).

When dioxin was administered by gavage (by stomach tube) in corn oil-acetone (9:1) at dose levels of 0, 0.01, 0.05 or 0.5 μg/kg/wk (0.0, 0.001, 0.007 and 0.07 μg/kg/day), toxic hepatitis was observed in male Osborne-Mendel rats at incidences of none out of 74 tested (0/74), 1/50, 0/50 and 14/50 and in female rats at incidences of 0/75, 0/50, 1/50 and 32/49(NTP 1980a). Other non-neoplastic lesions were not observed, even though extensive histologic examinations were performed. The two preceding studies support a NOAEL for noncarcinogenic effects in rats of ≅0.001 μg/kg/day and a lowest-observed-adverse-effect level (LOAEL) of 0.05 μg/kg/day.

Non-neoplastic effects of chronic dioxin exposures were described in studies investigating the carcinogenic potential of dioxin in mice. In a National Toxicology Program (NTP 1980a) bioassay, histologic examinations were performed on B6C3F1 mice treated biweekly with dioxin by gavage in corn oil-acetone (9:1) for 104 wk followed by an additional 3-wk observation period. The doses for male animals were 0.0, 0.01, 0.05 and 0.5 μg/kg/wk, and for female animals, 0.0, 0.04, 0.2 and 2.0 μg/kg/wk. The only non-neoplastic adverse effect observed was toxic hepatitis, which occurred in males at incidences of 0/73, 5/49, 3/49 and 44/50, and in females at incidences of 0/73, 1/50, 2/48 and 34/47, respectively, in the control, low, medium and high dose groups. In another study, weekly administration of dioxin by gavage at doses of 0.0, 0.007, 0.7 or 7.0 μg/kg/wk for one year resulted in amyloidosis (disposition of amyloid, a complex proteinaceous material) of the kidney, spleen and liver, and dermatitis at the time of death in male Swiss mice (Toth et al. 1978, 1979). The incidences of these effects in the control, low, medium and high dose groups, respectively, were 0/38, 5/44, 10/44 and 17/43. In the high dose group, the amyloidosis was extensive and considered to be the cause of early mortality. Severe toxic effects were observed at doses of 1 μg/kg/day (early mortality) and 0.28 to 0.07 μg/kg/day (toxic hepatitis), while a LOAEL for dermatitis and amyloidosis of 0.001 μg/kg/day was reported.

TABLE 4-2 NOAEL AND LOAEL VALUES OBTAINED FROM SUBCHRONIC AND CHRONIC ORAL TOXICITY STUDIES OF DIOXIN

Species	Duration of Exposure	Endpoints	NOAEL µg/kg/day	LOAEL µg/kg/day	Reference
Rat	13 wk	Decreased body weight, liver pathology	0.01	0.1	Kociba et al. (1976)
Rat	13 wk	Toxic hepatitis	0.07	0.14	NTP (1980a)
Rat	16 wk	Elevated porphyrin levels	0.0014	0.014	Goldstein et al. (1982)
Rat	28 wk	Fatty changes in the liver, decreased body weight	ND[a]	0.014	King and Roesler (1974)
Mouse	13 wk	Toxic hepatitis	ND	0.014	NTP (1980a)
Monkey	36 wk	Pancytopenia	ND	2	Allen et al. (1977)
Rat	104 wk	Degenerative and necrotic changes in the liver	0.001	0.01	Kociba et al. (1978, 1979)
Rat	104 wk	Toxic hepatitis	0.0014	0.007	NTP (1980a)
Mouse	104 wk	Dermatitis and amyloidosis	ND	0.001	NTP (1980a)

(a) ND = Not determined.

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4.3.3 Toxicity in Aquatic Species

No standard chronic toxicity assays of dioxin in aquatic species were located in the available literature (USEPA 1984) but several studies provide information indicative of chronic toxicity values. In a static bioassay, Miller et al. (1973) indicated that 0.2 µg/L may cause chronic toxicity in Paranais sp. (worm). Based on the 55% mortality in coho salmon within 60 days following acute (96-hr) exposures to 0.0056 µg/L (Miller et al. 1979), the USEPA (1984) suggests that 0.0056 µg/L may cause chronic toxicity coho salmon. Similarly the USEPA (1984) concludes that chronic toxicity values such as 0.001 µg/L (rainbow trout) and 0.01 µg/L (northern pike, coho salmon, mosquite fish and channel catfish) can be inferred based on results of acute assays by Helder (1980, 1981, 1982), Yockim et al. (1978) and Branson et al. (1983). A concentration of 1.3 µg/L may not cause chronic toxicity in Daphnia magna or Physa (USEPA 1984).

Limited data are available on the toxicity of dioxin to aquatic plants. Isensee and Jones (1975) and Isensee (1978) observed no adverse effects in algae (Oedogonium cardiacum) or duckweek (Lemna minor) exposed to 1.3 µg/L and 0.71 µg/L (respectively) for 30 days. Yockim et al. (1978) has also observed no adverse effects on O. cardiacum exposed to 0.0024 to 0.0042 µg/L of dioxin for 32 days.

4.4 Teratogenicity, Reproductive Effects and Fetotoxicity

4.4.1 Effects of Humans

Epidemiological studies have attempted to investigate health effects of dioxin in humans by indirectly evaluating health effects in populations exposed to 2,4,5-T (which commonly contains dioxin as an impurity). A positive association between 2,4,5-T exposures and increases in birth defects or abortions has been reported in human populations in Oregon (USEPA 1979), New Zealand (Hanify et al. 1981) and Australia (Field and Kerr 1979). A lack of any such association has been reported in human populations in Arkansas (Nelson et al. 1979), Hungary (Thomas 1980), New Zealand (Dept. of Health, New Zealand 1980, McQueen et al. 1977) and Australia (Aldred 1978).

Thomas (1980) used an approach similar to that of Field and Kerr (1979) for analyzing data from Hungary. One major difference, however, is that Thomas (1980) compared the incidence of stillbirths, cleft lip, cleft palate, spina bifida, anencephalus and cystic kidney disease in all of Hungary between 1976 and 1980 with 2,4,5-T use in all of Hungary in 1975. Because Hungary requires compulsory notification of malformations diagnosed from birth to age one year; because a relatively large percentage (55%) of the Hungarian population lives in rural areas where 2,4,5-T exposure may be expected to be greatest; and because annual use of 2,4,5-T in Hungary had risen from 46,000 kg in 1969 to 1,200,000 kg in 1975, Thomas (1980) considered Hungary to be "...probably the best country in which to examine possible health effects of this herbicide." In any event, all indices of birth defect rates decreased or remained stable over the period of study.

Epidemiologic studies to determine the reproductive effects in individuals exposed to dioxin and 2,4,5-T following the accidental contamination of a populated area around Seveso, Italy, have not been completed.

4.4.2 Effects in Laboratory Animals

Dioxin has been reported to be fetotoxic and teratogenic when administered alone or in combination with other chemicals. Several studies have been identified in the available literature based on dioxin exposure alone. Effects observed were kidney anomalies, intestinal hemorrhage, general edema, cleft palate and fetal death. Adverse effects on reproduction were also reported.

Intestinal hemorrhage, general edema and a reduction in fetal weights were reported in rats following the administration of 0.125 μg/kg/day in studies by Sparschu et al. (1971). In the same studies, the number of fetuses was reduced and fetal death increased at 0.5 μg/kg/day. No structural malformations were reported at 0.03 μg/kg/day. Courtney and Moore (1971) reported cleft palate and kidney abnormalities in mice borne by dams administered dioxin at doses of 1.0 μg/kg or 3.0 μg/kg. Similarly, kidney malformations were reported by the same authors in offspring from rats which received subcutaneous injections of 0.5 μg/kg/day on day 9, 10, or 13 and 14 of gestation.

Murray et al. (1979) completed a three-generation reproduction study using Sprague-Dawley rats fed dioxin continuously in the diet (at levels of 0, 0.001, 0.01, and 0.1 μg/kg/day). Significant decreases were observed in fertility, litter size, gestation survival, postnatal survival, and postnatal body weight for the 0.01 and 0.1 μg/kg groups. No apparent adverse effect on reproduction was seen at the 0.001 μg/kg dose level.

Although Murray et al. (1979) considered the lowest dose tested, 0.001 μg/kg, to be a NOEL (noncarcinogenic), reevaluation of these data by Nisbet and Paxton (1982) using different statistical methods indicated that there was a reduction in the gestation index, decreased fetal weight, increased liver-to-body weight ratio, and increased incidence of dilated renal pelvis at the 0.001 μg/kg dose. The reevaluation of data suggests that equivocal adverse effects were seen at the lowest dose (0.001 μg/kg/day) and that this dose should, therefore, represent a LOAEL.

Schantz et al. (1979) found reductions in fertility and various other toxic effects in rhesus monkeys fed 55 ppt dioxin in the diet for 20 mo. This corresponds to a calculated daily dioxin dose of 0.0015 μg dioxin/kg/day. These results suggest that monkeys may be somewhat more sensitive than rats, since the effects in monkeys were more severe and not equivocal.

Luster et al. (1980) examined bone marrow, immunologic parameters, and host susceptibility in B6C3F1 mice following pre- and postnatal exposure to TCDD. Doses of 0, 1.0, 5.0 and 15.0 μg/kg bw of dioxin were given to dams on day 14 of gestation and to offspring on days 1, 7, and 14 following birth. Neonatal body, liver, spleen, and thymus weights were decreased and bone marrow

toxicity occurred in the 5.0 and 15.0 μg/kg groups. Red blood cell counts, hematocrits, and hemoglobin were decreased at the highest dose tested.

4.5 Mutagenicity

Studies on the mutagenicity of dioxin have produced conflicting results. Dioxin reportedly produces mutagenic effects in various bacterial systems. However, results were negative in tests employing other indicator test systems, including cytogenetic (chromosome analysis) tests and dominant lethal assays. Hussain et al. (1972) reported that dioxin (2 μg/mL) increased the incidence of reverse mutations in *Escherichia coli*. Similarly, dioxin (dose not specified) was reported to be mutagenic without metabolic activation in *Salmonella typhimurium* test strain TA 1532. Green et al. (1977) gave 0.25, 0.5, 1.0, 2.0, or 4.0 μg/kg of dioxin (dissolved in 1 part acetone: 9 parts corn oil) by gavage to male and female Osborne-Mendel rats twice weekly for 13 wk and observed an increased incidence of chromosomal breaks in female rats dosed with 4 μg/kg and in males dosed with 2 μg/kg or 4 μg/kg.

Mutagenic effects (with or without metabolic activation) were not detected when Geiger and Neal (1981) examined the mutagenicity of dioxin (up to 20 μg/plate) using the *S. typhimurium* test strains TA1535, TA100, TA1538, TA98, and TA1537.

4.6 Carcinogenicity

4.6.1 Carcinogenicity in Humans

Epidemiologic studies of industrial workers and herbicide applicators suggest that dioxin may be a human carcinogen. However, since dioxin is usually a contaminant of phenoxy acids and/or chlorophenols, human exposure is usually to multiple chemicals. Therefore, the evidence for human carcinogenicity from these studies is only suggestive due to the difficulty of evaluating the risk of dioxin exposure in the presence of the confounding effects of the other chemicals (USEPA 1984).

Observations of an unusual occurrence of relatively rare soft-tissue sarcomas (STSs) were first made by Hardell (1977). Of some 87 patients seen from 1970 to 1976 at the Department of Oncology, University Hospital, Umea, Sweden, seven individuals with soft-tissue sarcomas were identified. All seven had had occupational exposure to phenoxy acids 10 to 20 yr earlier. The tumors were two leiomyosarcomas; one liposarcoma; one rhabdomyosarcoma; one myxofibrosarcoma; and two additional sarcomas of which the histopathology was uncertain, but one was probably a neurofibrosarcoma and the other a rhabdomyosarcoma. The clustering of this rare tumor type among these patients prompted the author to suggest that epidemiological studies be designed to determine if exposure to phenoxy acids and their impurities (i.e., dioxins) are related to the occurrence of STS.

A few occurrences of soft tissue sarcoma have also been reported among chemical industry workers in the United States who were exposed to varying levels of 2,4,5-chlorophenols with dioxin contaminants (Cook et al. 1980, Moes

and Selikoff 1981). Honchar and Halperin (1981) reported that 3 of 105 deaths among phenoxy acid workers reported by two chemical companies were from STS.

Zack and Suskind (1980) reported a STS death in a cohort study of workers exposed to dioxin in a trichlorophenol process accident in West Virginia. This tumor, a fibrous histiocytoma, was considered as a rare event.

In a cohort mortality study of 61 male employees of a trichlorophenol manufacturing area who exhibited chloracne following a 1964 exposure incident, Cook et al. (1980) noted four deaths by the end of his study period, one of which was due to a fibrosarcoma.

There are numerous other studies reported regarding STSs. For example, Smith et al. (1982) conducted an initial case-control study of 102 males identified from the New Zealand Cancer Registry as having STSs (ICD 171) between 1976 and 1980. For each case, three controls each with another form of cancer were matched by age and year of registration. The selection of cancer controls from the same registry was done to eliminate recall bias or interviewer bias or both.

The distribution of tumor types differed considerably from the Hardell and Eriksson et al. (1981) study to the Smith et al. (1982) study. Leiomyosarcomas, malignant histocytomas, neurogenic sarcomas and myxosarcoma seem to predominate in the Hardell and Eriksson (1981) study, whereas fibrosarcomas and liposarcomas appear prominently in the Smith et al. (1982) study.

Smith et al. (1983) conducted another case-control study of STSs in males that were reported to the New Zealand Cancer Registry by Public Hospitals between 1976 and 1980. Smith et al. (1983) remarked that it was surprising that he found no STS victim who had ever worked full-time in phenoxyacetic acid herbicide spraying. Perhaps they have not yet been observed for a long enough period. As was pointed out by the author, the findings do not support the hypothesis that exposure to phenoxyacetic acid herbicides causes STS; however, neither do they support a negative finding without better documentation regarding actual exposure and time of actual exposure.

The Michigan Department of Public Health (1983) recently conducted an ecological study of soft and connective tissue cancer mortality rates in Midland and other selected Michigan counties. They found that mortality rates for this cancer were 3.8 to 4.0 times the national average for the periods 1960 to 1969 and 1970 to 1978, respectively, for white females in Midland. These estimates are based upon five deaths and seven deaths, respectively. No excess risk was reported among white males, however. The Michigan Department of Health concluded that because of the occurrence of these two successive elevated rates, it is unlikely to be a chance happening. At the same time the age-adjusted male and female cancer mortality rates for Midland were below that of the State of Michigan for the period 1970 to 1979. Midland County is the home of a major chemical company that produced phenoxyacetic acid herbicides until recently. The authors stated that a detailed review of death certificates, hospital records, residency and occupational histories of the 20 male and female cases revealed no "commonalities" suggesting a "single causative

agent," although a majority of their spouses had worked at this chemical facility. They recommended that a case-control study should be instituted to evaluate possible influences, such as lifestyles, occupation or location of residences, on the risk of STS.

4.6.2 Carcinogenicity in Laboratory Animals

The carcinogenic potential of dioxin has been studied extensively in laboratory animals. A summary of the results of selected comprehensive studies is presented in Table 4-3. The results of these studies show that dioxin-exposed animals exhibited malignant lesions involving multiple organ systems including accessory digestive organs (liver), endocrine (thyroid, adrenal), renal, reproductive (testes), and nasal structures. Representative studies are described below.

Groups of ten male Sprague-Dawley rats were fed a diet containing dioxin for 78 wk at concentrations ranging from 1 ppt to 500 ppt or 1 ppb to 1,000 ppb (Van Miller et al. (1977). These dietary levels represent approximate weekly dose levels of 0.0003 to 0.1 μg/kg or 0.4 to 500 μg/kg. Animals exposed at 5 ppt, 50 ppt, 500 ppt or 5 ppb showed an overall incidence of neoplasms of 38% (23/60). No neoplasms were reported or observed following exposure to 1 ppt dioxin. In the 5 ppt group, 5/10 animals had six neoplasms (earduct carcinoma, lymphocytic leukemia, adenocarcinoma, malignant histiocytoma (with metastases), angiosarcoma and Leydig-cell adenoma). Neoplasms were also observed in the following groups: at 50 ppt, three in 3/10; at 500 ppt, four in 4/10; at 1 ppb, five in 4/10; at 5 ppb, ten in 7/10. Neoplasms were not observed in the controls. Rats administered dioxin at 50, 500 or 1,000 ppb exhibited 100% mortality by the fourth week.

In another study (Kociba et al. 1978), groups of 100 Sprague-Dawley rats (50 males and 50 females) received diets containing dioxin at 0, 22, 210, or 2,220 ppt (equivalent to a daily dose of 0.0, 0.001, 0.01 and 0.1 μg/kg bw) for two years. Administration of 0.01 μg/kg/day increased the incidence of hepatocellular hyperplastic nodules (female: 18/50 versus 8/86 controls) and focal alveolar hyperplasia in the lungs ($P<0.05$). Dietary intake of 0.1 μg/kg/day increased the incidence of hepatocellular carcinomas (female: 11/49 versus 1/86) and squamous cell carcinomas of the lung (female: 7/49 versus 0/86), hard palate/nasal turbinates (male: 4/50 versus 0/85; female: 4/49 versus 0/86), and tongue (male: 3/50 versus 0/85) ($P<0.05$). Also increased in frequency by the 0.1 μg TCDD/kg/day were adenoma of the adrenal cortex (male) and hepatocellular hyperplastic nodules (female).

The NTP (1982a) conducted a study for 104 wk using Osborne-Mendel rats and B6C3F1 mice. The rats and male mice were administered TCDD at 0, 0.01, 0.05 or 0.5 μg/kg/wk by gavage in two divided doses, and the female mice were given 0, 0.04, 0.2, or 2.0 μg/kg/wk. Incidences of follicular cell thyroid adenomas in male rats ($P<0.001$) and of neoplastic nodules in livers of female rats ($P=0.006$) increased significantly. Dioxin increased the numbers of hepatocellular carcinomas in male mice ($P=0.002$) and in females ($P=0.014$). The total liver tumors (carcinomas and adenomas) were increased in males ($P<0.001$)

TABLE 4-3 SUMMARY OF CARCINOGENIC EFFECTS OF DIOXIN

Species/Sex (Number)	Dose	Duration	Route	Effects	Reference
Rat/M (10)	1 ppt	78 wk	Diet	No neoplasm.	Van Miller et al. (1977)
Rat/M (10)	5-500 ppt			Ear duct carcinoma, benign tumor of the kidney and testes, lymphocytic leukemia, skin carcinomas and benign muscle tumors.	
Rat/M (10)	1-5 ppb			Cholangiocarcinoma of liver, squamous cell tumor of lung, angiosarcoma in skin, glioblastoma in brain, malignant histiocytomas in peritoneum.	
Rat/ M (50) F (50)	0.001 μg/kg	2 yr	Diet	No significant increase in tumors.	Kociba et al. (1978)
	0.01 μg/kg			Liver cancer.	
	0.1 μg/kg			Liver cancer, squamous cell carcinoma of the lung, hard palate/ nasal turbinates, or tongue (P=0.05).	
Mouse/F (30)	0.015 μg/kg/wk	99-104 wk	Dermal	Fibrosarcoma in integumentary system (8/27, P=0.007).	NTP (1982b)
Mouse/M (30)	0.003 μg/kg/wk	99-104 wk	Dermal	Fibrosarcoma in integumentary system (6/28, P=0.08)	
Rat/M (50)	0.5 μg/kg/wk	104 wk	Gavage	Follicular cell adenomas of thyroid (10/50, P=0.001).	NTP (1982a)
Rat/F (50)	0.5 μg/kg/wk	104 wk	Gavage	Neoplastic nodules of the liver (12/49, P=0.006).	

continued-

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Table 4-3 - continued

Species/Sex (Number)	Dose	Duration	Route	Effects	Reference
Mouse/M&F	2.0 μg/kg/wk	104 wk	Gavage	Hepatocellular carcinoma (17/50, P=0.002 in M); (6/47, P=0.14 in F).	NTP (1982a)
Mouse/F	2.0 μg/kg/wk	104 wk	Gavage	Follicular cell adenomas of the thyroid (5/46, P=0.009)	
Mouse/M (39)	0.007 μg/kg/wk	52 wk	Gavage	Liver tumors (13/44, P not specified	Toth et al. (1979)
Mouse/M (44)	0.7 μg/kg/wk	52 wk	Gavage	Liver tumors (21/44, P<0.01)	
Mouse/M (44)	7.0 μg/kg/wk	52 wk	Gavage	Liver tumors (13/43, P=0.11)	

Adapted from Esposito et al. (1980), NTP (1982a,b).

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and females (P=0.002). In addition, female mice had increased incidence of follicular cell thyroid adenomas. These studies indicate that TCDD is an animal carcinogen.

Toth et al. (1979) administered doses of 0, 0.007, 0.7 and 7.0 μg/kg/wk of dioxin to male mice by gavage in a study to determine whether 2,4,5-trichlorophenoxyethanol (2,4,5-TCPE), its contaminant (dioxin) or both were carcinogenic. The incidence of liver tumors was significantly increased in the dose group receiving dioxin at the 0.7 μg/kg/wk level. No significant increased incidence in liver tumors was observed in the 7.0 μg/kg/wk dose group although increased mortality in this group probably precluded detection of tumors with longer latent periods.

The NTP (1982b) conducted a skin painting cancer bioassay of dioxin on Swiss-Webster mice (50 of each sex/dose). A dose of 0.001 μg/application (males) and 0.005 μg/application (females) in acetone suspension was painted on the skin 3 days/wk for 104 wk. The vehicle control group (45 mice/sex) was painted with 0.1 mL acetone 3 times/wk for 104 wk. The incidence of fibrosarcoma in the integumetary system was significantly increased in females (8/27, P=0.007) but not in males (6/28, P=0.08) compared to the incidence respective controls (2/41 and 3/42).

DiGiovanni et al. (1977) reported that dioxin was a tumor initiator in mouse skin. However, the role of dioxin as an initiator needs to be confirmed since appropriate vehicle and promotion-only controls were not included in this assay. Several assays (NTP 1982b, Berry et al. 1978, 1979) demonstrated that dioxin was not a tumor-promoter when applied to mouse skin after unknown initiator (DMBA).

Poland and Knutson (1982) reported that dioxin was a tumor promoter when tested on the skin of mice homozygous for the "hairless" trait but not in mice heterozygous for this recessive trait. Pitot et al. (1980) also reported that dioxin was a promoter for DEN-initiated hepatocarcinogenesis in rats following parenteral administration of the compounds. On mouse skin, dioxin was a complete carcinogen and possibly a tumor initiator, while no tumor-promoting activity could be attributed to dioxin in the assays. In rat liver initiated with DEN, dioxin was a tumor promoter.

In the mouse skin bioassay, initiation with simultaneous administration of dioxin and DMBA, however, did not affect tumor yield (DiGiovanni et al. 1977). Similarly no effect was observed when dioxin was administered either immediately before (five minutes) or one day after DMBA initiation (Berry et al. 1979, DiGiovanni et al. 1977, Cohen et al. 1979). When treatment with dioxin occurred one to ten days before DMBA initiation, dioxin demonstrated a potent anticarcinogenic action. Although one to five days prior exposure to dioxin inhibited tumor initiation by BaP, 3-MC, and BaP-diol-epoxide, the tumor-initiating ability of the latter compound was also inhibited when dioxin exposure occurred either five minutes before or one day after initiation (DiGiovanni et al. 1980). The increased AHH activity resulting from dioxin exposure may account for the anticarcinogenic activity by altering the metabolism of the initiating compound; however, DiGiovanni et al. (1980)

suggests that the initiation of the initiating activity of BaP-diol-epoxide one day after initiation indicates that more than one mechanism participates in the anticarcinogenic activity of dioxin.

4.7 Quantitative Indices of Toxicity

4.7.1 Noncarcinogenic Effects Indices

Recommended exposure limits to dioxin to ensure human safety have been established by several agencies. The National Academy of Sciences (NAS 1977), before TCDD was considered to be a carcinogen, suggested an ADI for dioxin of 0.0001 µg/kg/day based on a 13-wk feeding study in rats (Kociba et al. 1976). The reported NOEL in that study (0.01 µg/kg) was divided by an uncertainty factor of 100 to determine the ADI. The NAS then calculated a suggested-no-adverse-effect-level (SNARL) in drinking water of 0.0007 µg/L, based on the average weight of a human adult (70 kg) and an average daily intake of water of two liters, with water representing 20% of total intake.

The USEPA (1984) has calculated an ADI of 10^{-6} µg/kg/day based on noncarcinogenic toxicity for comparison to the carcinogenic risk assessment value. A LOAEL based on noncarcinogenic toxic effects and reduced fertility of 0.001 µg/kg/day and an uncertainty factor of 1,000 were used in the calculations. Using a bioaccumulation factor of 5,000, and assuming a daily consumption of 6.5 g of fish, a water concentration of 2.0×10^{-6} µg/L was derived. It was noted that this value may not be sufficiently low to protect against the carcinogenic effects of dioxin (USEPA 1984). The USEPA is currently reevaluating the bioconcentration factor for dioxin.

The USEPA (1984) concluded that insufficient data were available concerning adverse effects of dioxin on aquatic life to allow derivation of ambient water quality criterion. Limited information in freshwater species indicate acute values may be >0.1 µg/L and chronic values may be <0.01 µg/L (northern pike, coho salmon, mosquito fish and channel catfish) and <0.001 µg/L (rainbow trout).

4.7.2 Carcinogenic Effects Indices

Since there is no recognized safe concentration for a human carcinogen, and dioxin is a suspected human carcinogen, the recommended concentration of dioxin in water is zero (USEPA 1984). The USEPA calculated a range of concentrations for dioxin corresponding to cancer risk levels of 10^{-5}, 10^{-6} and 10^{-7}. These calculations used a linearized multistage model and were based on animal bioassay data. The recommended criteria which may result in an increased cancer risk of 10^{-5}, 10^{-6} or 10^{-7} are 1.3×10^{-7}, 1.3×10^{-8} and 1.3×10^{-9} µg/L, respectively. These criteria are below the limit of detection of TCDD in water (approximately 3×10^{-5} µg/L) by current analytical methods.

The Food and Drug Administration (FDA) issued a health advisory stating that fish with residues of dioxin ≥50 ppt should not be consumed, but fish with residues of < 25 ppt pose no serious health concern (USEPA 1984). The Centers

for Disease Control (CDC) has established 1 ppb as a level of concern for dioxin in residential soils at Times Beach, MO.

5.0 RISK AND IMPACT EVALUATION

5.1 Human Health

Quantitative risk assessments (QRA) for exposures to dioxin via consumption of contaminated fish and via inhalation of air-borne dust have focused on carcinogenic effects (Falco 1982, Falco and Schaum 1984). Both risk assessments are based on limited data and required numerous assumptions (previously discussed in Section 3.0) to address data gaps. Falco (1982) emphasizes that the limited data are not sufficient to produce a statistically valid estimate of errors but the assessments provide a means to bound possible exposures and associated risks.

5.1.1 QRA for Consumption of Contaminated Fish

Falco (1982) estimated the upper limit individual cancer risk to range from 10^{-4} to 10^{-1} due to consumption of dioxin contaminated fish from Bayou Meto. These cancer risks are based on potential exposures which were estimated to range from 0.09 ng/kg/yr to 110 ng/kg/yr. The QRA was based on the Kociba et al. (1978) study in which dioxin induced a statistically significant increase in the incidence of tumors in the liver, lung and hard palate or nasal turbinates. The linerized multi-staged model was employed with an assumed continuous exposure during the course of a lifetime (70 yr). The upper lifetime cancer risks were estimated for consumption of fish caught from various distances from the site along the length of Bayou Meto. The upper limit cancer risk estimate is greater than 10^{-4} for consumption of fish from the mouth of Bayou Meto which is approximately 130 mi downstream from the Vertac site. Falco (1982) emphasized that the actual risk may range anywhere between 0 (the lower bound) to upper limit risk estimates presented in Table 5-1. Consumption of fish at a rate greater than the assumed average rate (5.2 lb/yr) increases the upper limit of individual cancer risk. For example, individuals with consumption rates at the expected upper 95th percentile (16 lb/yr) would have cancer risks ranging from 3×10^{-4} to 3.2×10^{-1} corresponding to the range of estimated contamination levels (2.6 to 3,300 ppt dioxin) in fish from Bayou Meto.

Falco and Schaum (1982) estimated that the number of people potentially exposed annually would be 30,000 if one assumes an average consumption rate and average catch rate. Since the upper cancer risk for this group ranges from 10^{-4} to 10^{-1} (depending upon the range of dioxin contamination levels in fish), the corresponding upper bound estimate of induced cancers under this scenario could range from 3 cases (1 case every 25 yr) to 3,000 cases (43 cancers/yr) (assuming continuous exposure for 70 yr).

5.1.2 QRA for Contaminated Groundwater

No QRA for dioxin exposures due to contaminated groundwater has been performed. The actual risk via the groundwater route is probably minimal due to the apparent lack of exposure potential. However, this route may pose unacceptable carcinogenic risk if groundwater contaminated at 0.03 ppb dioxin (the highest detected level in groundwater on-site) were consumed. Assuming the

TABLE 5-1 HUMAN EXPOSURE AND UPPER-LIMIT CANCER RISK ESTIMATES BY RIVER MILE

River Mile	Exposure, ng/kg/yr: Based on Calculations[b]	Exposure, ng/kg/yr: Based on Monitoring[c]	Upper-Limit Lifetime Cancer Risk Estimates[a]: Based on Calculations	Upper-Limit Lifetime Cancer Risk Estimates[a]: Based on Monitoring
132	0.96-110	10.1	0.0012 - 0.122	0.01
100	0.56-65	3.79	0.00065 - 0.073	0.0044
75	0.48-56	1.0	0.00056 - 0.063	0.0012
54	0.15-18	-	0.00017 - 0.021	-
34	0.13-15	-	0.00015 - 0.017	-
16	0.11-13	-	0.00013 - 0.015	-
0	0.09-10	-	0.00010 - 0.012	-

(a) Calculated Exposure = (C_s x K_{FS} x consumption rate)/70 kg body weight where C_s = concentration of TCDD in sediment and K_{FS} = sediment fish distribution coefficient. Consumption rate assumed = 5.2 lb/yr (2.37 kg/yr); low values assume K_{FS} = 5.4; high values assume K_{FS} = 550.

(b) Exposures based on monitoring = (C_F x consumption rate)/70 kg body weight where C_F = measured concentration of TCDD in fish (only available at river miles 132, 100 and 75). Consumption rate assumed = 5.2 lb/yr (2.37 kg/yr).

(c) Upper Limit Risk = $1 - e^{(-4.25 \times 10-1 \times \text{exposure})}$ where exposure is in units of ng/kg/day. The risk could always approach zero as a lower bound.

70-kg human would consume two liters of water per day then the dose would be 0.0009 µg/kg/day (0.9 ng/kg/day). Consumption of a dioxin dose of 0.9 ng/kg/day over a lifetime poses unacceptable carcinogenic risk exceeding the 10^{-5} risk associated with consumption of water with a dioxin concentration of 1.3×10^{-7} µg/L (3.7×10^{-9} µg/kg/day or 0.0000037 ng/kg/day). Consumption of drinking water containing 0.005 ppb dioxin (the mean detected concentration) would result in a dose of 0.0001 µg/kg/day (0.1 ng/kg/day) which would also pose unacceptable carcinogenic risk exceeding the 10^{-5} level. The lower bound estimate is zero since consumption may not occur and because recent analyses have not detected dioxin in groundwater monitoring wells.

5.1.3 QRA for Airborne Dust

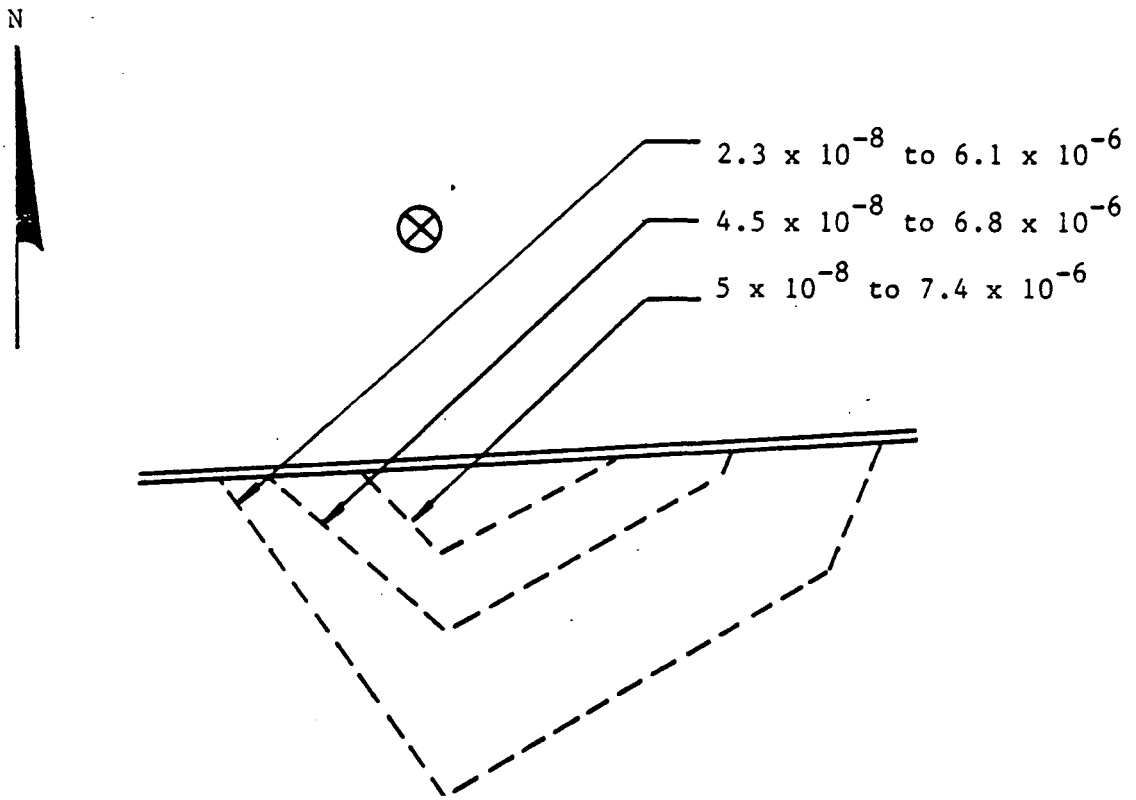
Falco and Schaum (1984) performed a QRA for inhalation exposure to dust (sorbed on dioxin) associated with the proposed remedial action (Alternative IV). The predicted upper bound cancer risk associated with the remedial action ranges from 5×10^{-8} to 7.4×10^{-6} for the nearest residents to the Vertac site. This risk estimate assumes no dust control measures are implemented. The wide range of risk estimates is due to uncertainty in the concentration of dioxin in materials to be excavated (0.1 to 14 ppm). Falco and Schaum (1984) calculated cancer risk with an adjusted cancer potency factor. The cancer potency factor (95% upper limit of the linear coefficient in the dose response model) of 0.156 $(ng/kg/day)^{-1}$ was adjusted to account for differences in absorption via oral exposure versus inhalation exposure routes. Assuming an approximate oral absorption rate of about 50%, the potency factor based on a dose administered in feed was multiplied by a factor of two to yield the potency 0.312 $(ng/kg/day)^{-1}$ based on an absorbed dose. Based on predicted exposure levels, carcinogenic risk levels were calculated and plotted (see Figure 5-1) for the nearest residents of the Vertac site. There is no demographic information available on the number of residents within the isopleths on Figure 5-1. The upperbound estimates of risk associated with inhalation of dioxin-contaminated dust will decline with distance from the site. Sources of uncertainty are associated with parameter value assumptions such as the dioxin concentration in soils, silt content, volume of excavated soil, moisture content of soils, % dioxin absorption in lungs versus gastrointestinal tract and the cancer potency estimates. In addition emission factor equations and dispersion models have associated uncertainties. Thus, information necessary to analyze uncertainty on a statistical basis is unavailable but the estimated range of risks appears representative of these type of calculations (Falco and Schaum 1984).

5.1.4 QRA for Direct Contact

No QRA for dioxin exposures via direct contact with contaminated soils and sediments is available. However, the levels of dioxin in soils and sediments offsite exceed the CDC's 1 ppb level of concern for residential soils established for Times Beach, MO.

5.2 Environmental

No QRA for aquatic or terrestrial life in the environment adjacent to or contaminated by the Vertac site is available. There are potential risks to



Scale: 1 in = 145 meters

⊗ = Center of Dust Emission Source

Property Line

Adapted from Falco and Schaum (1984)

FIGURE 5-1 MINIMUM AND MAXIMUM ACCUMULATIVE UPPER BOUND RISK ESTIMATE IMMEDIATELY SOUTH OF THE VERTAC PROPERTY (RESULTING FROM THE COMBINATION OF PHASE 1 AND 2 ACTIVITIES)

aquatic and terrestrial species related to dioxin releases from the Vertac site. The absence of benthic life, several massive fish kills and reported "medicinal" taste and odor of fish caught from Bayou Meto (receiving waters of the Rocky Branch Creek) reflect the impact of contaminants released from the Vertac site on aquatic life (JRB 1983). The limited environmental monitoring data for sediments in the Rocky Branch Creek, Bayou Meto and Lake Dupree indicate substantial dioxin contamination has occurred. Analyses of fish tissues demonstrates that dioxin has been bioaccumulated to substantial levels (up to 300 ppt in Bayou Meto and 810 ppt in Lake Dupree) but the health significance of such tissue levels and potential impact on survival, growth, development and reproduction of aquatic life remains unknown. The absence of ambient water quality criteria and especially criteria for dioxin levels in sediments impedes performance of a QRA for aquatic organisms.

There is a paucity of monitoring data on the concentration of dioxin in surface waters offsite. The only data available indicate that dioxin was not detected in water from the Rocky Branch Creek. Therefore, it is not possible to compare dioxin concentrations in receiving water to levels causing acute toxicity (>1.0 ppb) in certain freshwater species or chronic toxicity in the rainbow trout (<0.001 ppb) or in several other fish species (<0.01 ppb).

The high content of dioxin in sediments (500 ppt ave) in the Rocky Branch Creek and potential for release to the water column suggests that aquatic organisms may be at risk. No existing guidelines or standards are available to determine risks to avian or terrestrial organisms. The potential impact of contamination on such species is of concern since the Bayou Meto area serves as an important water fowl resting area and contains about 70,000 acres of wetlands. Limited data are available on the avian species and terrestrial species present in the area. Contamination of the Bayou Meto and accumulation of dioxin in the aquatic food chain may endanger predator (avian or terrestrial) species.

5.3 Public Welfare

The major socioeconomic impact of the release of dioxin from the Vertac site has been the loss of adjacent surface waters for fishing and recreation. For example, the release of dioxin to the Rocky Branch Creek and Bayou Meto and transport to Lake Dupree during flooding has caused fish to accumulate (810 ppt) dioxin in excess of the FDA health advisory value of ≥50 ppt. Thus, fish from Lake Dupree may be unfit for human consumption. This contamination of fish has required the Arkansas public health officials to issue a fishing ban for the Bayou Meto area. An additional impact on public welfare may be a potential decrease of property values immediately adjacent to the site (i.e., especially residential property values) and the loss of groundwater aquifers as a potential source of drinking water.

6.0 CONCLUSIONS

The most significant endangerment of human health is due to the potential consumption of dioxin-contaminated fish from Bayou Meto. Falco and Schaum (1982) estimated that chronic (lifetime) consumption of contaminated fish from Bayou Meto may lead to an upper limit individual cancer risk ranging from 1/10,000 to 1/10. Under this scenario (assuming 30,000 people are exposed based on an average catch rate and an average consumption rate) the estimated upper bound of induced cancers may range from 3 cases (1 case/25 yr) to 3,000 cases (43 cases/yr). However, the lower bound estimate of induced cancers is zero regardless of consumption rate and fish catch size. The fishing ban for Bayou Meto may reduce this threat to human health, but its efficacy is unknown since it is not easily enforced.

The contamination of groundwater represents another substantial potential threat to human health. There is a real potential for offsite migration of contaminants to groundwater. A maximum of 0.03 ppb and a mean of 0.005 ppb of dioxin have been detected in on-site groundwater monitoring well. Actual exposures to humans via this route is currently considered unlikely since no permitted domestic and industrial wells were located in the area immediately downgradient of the site. Human health may be endangered if water wells are drilled in the future and used for drinking water purposes. However, assuming humans may potentially consume groundwater in the future, the resulting dose of dioxin would increase risk of cancer substantially above the 10^{-5} level. Further groundwater monitoring data are necessary to verify and characterize the magnitude and extent of any offsite contamination.

Exposure to dioxin via dust-emissions from the proposed remedial action (Alternative IV) was estimated to present an upperbound cancer risk ranging from 5.8×10^{-8} to 7.4×10^{-6} for residents near the Vertac site (within about 300 meters). Demographic information on the size of this population was unavailable and therefore, an estimate of number of excess cancers is not possible.

The potential for direct contact with contaminated soils and sediments poses human health risks. Monitoring data indicate that levels of dioxins in soils and sediments off-site exceed the CDC's 1 ppb level of concern for residential soils (established for Times Beach, MO).

No quantitative assessment of risk to aquatic and terrestrial organisms was available. Limited environmental monitoring data and the unavailability of established ambient water criteria preclude such an assessment. The data demonstrate that dioxin is present in the sediments and bioaccumulates in fish above the FDA's health advisory value of $\geq$50 ppt.

Loss of fishing in the Bayou Meto area impacts the public welfare. Additionally decrease of property values adjacent to the site or along the bayou may impact the economic stability of the area. Contamination of groundwater may prevent its future use as a drinking water resource.

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APPENDIX 3

EPA's PROPOSED ASSESSMENT GUIDELINES

Part 1 - Carcinogen Risk Assessment

Part 2 - Exposure Assessment

Part 3 - Mutagenicity Risk Assessment

Part 4 - Health Assessment of Suspect Developmental Toxicants

Part 5 - Health Risk Assessment Chemical Mixtures

PART 1 - CARCINOGEN RISK ASSESSMENT

federal register

Friday
November 23, 1984

Part VII

Environmental Protection Agency

Proposed Guidelines for Carcinogen Risk Assessment; Request for Comments

ENVIRONMENTAL PROTECTION AGENCY

[FRL-2706-4]

Proposed Guidelines for Carcinogen Risk Assessment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed Guidelines for Carcinogen Risk Assessment and Request for Comments.

SUMMARY: The U.S. Environmental Protection Agency is proposing Guidelines for Carcinogen Risk Assessment (Guidelines). These Guidelines are proposed for use within the policy and procedural framework provided by the various statutes that EPA administers to guide Agency analysis of carcinogenicity data. We solicit public comment and will take public comment into account in revising these Guidelines. These Guidelines will be reviewed by the Science Advisory Board in meetings now tentatively scheduled for April 1985.

These proposed Guidelines were developed as part of a broad guidelines development program under the auspices of the Office of Health and Environmental Assessment (OHEA), located in the Agency's Office of Research and Development. Consonant with the role of OHEA's Carcinogen Assessment Group (CAG) as the Agency's senior health committee for carcinogenicity assessment, the Guidelines were developed by an Agency-wide working group chaired by the Chairman of CAG.

DATE: Comments must be postmarked by January 22, 1985.

ADDRESS: Comments may be mailed or delivered to: Dr. Robert McGaughy, Carcinogen Assessment Group (RD-689), Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, 401 M Street SW., Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT: Dr. Robert McGaughy, Telephone: 202-382-5952.

SUPPLEMENTARY INFORMATION: This is the first proposed revision of the 1976 Interim Procedures and Guidelines for the Health Risk Assessment of Suspected Carcinogens (**Federal Register** 41:21402-21405, 1976). This revision incorporates concepts and approaches to carcinogen assessment that have been developed during the last eight years. These proposed revised Guidelines describe salient principles for evaluating the nature and magnitude of the cancer hazard from suspect carcinogens and general framework to be followed in developing analyses of carcinogenic risk.

These Guidelines were sent to 38 scientists in the field of carcinogenesis from universities, environmental groups, industry, labor, and governmental agencies. We have decided to delay incorporating suggestions from the 26 reviewers who submitted comments into the Guidelines published here until comments submitted during this public comment period are received.

References and supporting documents used in the preparation of these Guidelines as well as comments received are available for inspection and copying at the Public Information Reference Unit (202-382-5926), EPA Headquarters Library, 401 M Street SW., Washington, DC, between the hours of 8:00 and 4:30 p.m.

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I. Introduction

This is the first revision of the 1976 Interim Procedures and Guidelines for Health Risk Assessments of Suspected Carcinogens (U.S. EPA, 1976; Albert et al., 1977). The impetus for this revision is the need to incorporate into these Guidelines the concepts and approaches to carcinogen risk assessment that have been developed during the last eight years. The purpose of these Guidelines is to promote quality and consistency of carcinogen risk assessments within the EPA and to inform those outside the EPA about its approach to carcinogen risk assessment. These Guidelines emphasize the broad but essential aspects of risk assessment that are needed by the experts in the various disciplines required (e.g., toxicology, pathology, pharmacology, and statistics) for carcinogen assessment. Guidance is given in general terms since the science of carcinogenesis is in a state of rapid advancement, and overly specific approaches may rapidly become obsolete.

These Guidelines describe the general framework to be followed in developing an analysis of carcinogenic risk and some salient principles to be used in evaluating the quality of data and in formulating judgments concerning the nature and magnitude of the cancer hazard from suspect carcinogens.

A summary of the current state of knowledge in the field of carcinogenesis and a statement of broad scientific principles of carcinogen risk assessment, which was developed by the Office of Science and Technology Policy (OSTP, 1984), forms an important basis for these Guidelines; the format of these Guidelines is similar to that proposed by the National Research Council (NRC) of the National Academy of Sciences in a report entitled "Risk Assessment in the Federal Government" (NRC, 1983).

These Guidelines are to be used within the policy framework already provided by applicable EPA statutes and do not alter such policies. These Guidelines provide general directions for analyzing and organizing available data. They do not imply that one kind of data or another is a prerequisite for regulatory action to control, prohibit, or allow the use of a carcinogen. The analysis of carcinogenic risks will be carried out independently from considerations of the socioeconomic consequences of regulatory action.

Regulatory decisionmaking involves two components: Risk assessment and risk management. Risk assessment defines the adverse health consequences of exposure to toxic agents; risk management combines the risk assessment with the directives of the enabling regulatory legislation, together with socioeconomic, technical, political, and other considerations, to reach a decision as to whether or how much to control future exposure to the suspected toxic agents.

Risk assessment includes one or more of the following components: hazard identification, dose-response

assessment, exposure assessment, and risk characterization (NRC, 1983).

Hazard identification is a qualitative risk assessment, dealing with the process of determining whether exposure to an agent has the potential to increase the incidence of cancer. For purposes of these Guidelines, malignant and benign tumors are used in the evaluation of the carcinogenic hazard. The hazard identification component qualitatively answers the question of how likely an agent is to be a human carcinogen.

Traditionally, quantitative risk assessment has been used as an inclusive term to describe all or parts of dose-response assessment, exposure assessment, and risk characterization. Quantitative risk assessment can be a useful general term in some circumstances, but the more explicit terminology is usually preferred. The dose-response assessment defines the relationship between the dose of an agent and the probability of induction of a carcinogenic effect. This component usually entails an extrapolation from the generally high doses administered to experimental animals or exposures noted in epidemiologic studies to the exposure levels expected from human contact with the agent in the environment; it also includes considerations of the validity of these extrapolations.

The exposure assessment identifies populations exposed to the agent, describes their composition and size, and presents the types, magnitudes, frequencies, and durations of exposure to the agent.

In risk characterization, the outputs of the exposure assessment and the dose-response assessment are combined to estimate quantitatively some measure of the carcinogenic risk. As part of risk characterization, a summary of the strengths and weaknesses in the hazard identification, dose-response assessment, exposure assessment, and the public health risk estimates are presented. Major assumptions, scientific judgments, and, to the extent possible, estimates of the uncertainties embodied in the assessment are also presented, distinguishing clearly between fact, assumption, and science policy.

II. Hazard Identification (Qualitative Risk Assessment)

A. Overview

The qualitative assessment or hazard identification part of risk assessment contains a review of the relevant biological land chemical information bearing on whether or not an agent may pose a carcinogenic hazard. Since chemical agents seldom occur in a pure state and are often transformed in the body, the review should include information on contaminants, degradation products, and metabolites.

Studies are evaluated according to sound biological and statistical considerations and procedures. These have been described in several publications (Interagency Regulatory Liaison Group, 1979; OSTP, 1984; Peto et al., 1980; Mantel, 1980; Mantel and Haenszel, 1959; Interdisciplinary Panel on Carcinogenicity, 1984; National Center for Toxicological Research, 1981; National Toxicology Program, 1984; U.S. EPA, 1983a; 1983b; 1983c). Results and conclusions concerning the agent, derived from different types of information, whether indicating positive or negative responses, are melded together into a weight-of-evidence determination. The strength of the evidence supporting a potential human carcinogenicity judgment is developed in a weight-of-evidence stratification scheme.

B. Elements of Hazard Identification

1. Physical-Chemical Properties and Routes and Patterns of Exposure

Parameters relevant to carcinogenesis, including physical state, physical-chemical properties, and exposure pathways in the environment should be described.

2. Structure-Activity Relationships

This section should summarize relevant structure-activity correlations that support the prediction of potential carcinogenicity.

3. Metabolic and Pharmacokinetic Properties

This section should summarize relevant metabolic information. Information such as whether the agent is direct-acting or requires conversion to a reactive carcinogenic (e.g., an electrophilic) species, metabolic pathways for such conversions, macromolecular interactions, and transport in, fate in, and excretion from the body as well as species differences in metabolism should be discussed.

4. Toxicologic Effects

Toxicologic effects other than carcinogenicity (e.g., suppression of the immune system, endocrine disturbances, organ damage), which are relevant to the evaluation of carcinogenicity, should be summarized. Prechronic and chronic toxicity evaluations, as well as other test results, may yield information on target organ effects, pathophysiological reactions, and preneoplastic lesions that bear on the evaluation of carcinogenicity. Dose-response and time-to-response analyses of these reactions may also be helpful.

5. Short-Term Tests

Tests for point mutations, numerical and structural chromosome aberrations, DNA damage/repair, and *in vitro* transformation provide supportive evidence of carcinogenicity and may give information on potential carcinogenic mechanisms. A range of tests from each of the above end points helps to characterize an agent's response spectrum.

Short-term *in vivo* and *in vitro* tests that can give indication of initiation and promotion activity may also provide supportive evidence for carcinogenicity.

6. Long-Term Animal Studies

Criteria for the technical adequacy of animal carcinogenicity studies have been published (e.g., U.S. Food and Drug Administration, 1982; Interagency Regulatory Liaison Group, 1979; National Toxicology Program, 1984; OSTP, 1984; U.S. EPA, 1983a; 1983b; 1983c; Feron et al., 1980; Mantel, 1980) and should be used to judge the acceptability of individual studies.

The strength of the evidence that an agent is carcinogenic increases with the increase in number of tissue sites affected by the agent; the increase in number of animal species, strains, and sexes showing a carcinogenic response; the occurrence of clear-cut dose-response relationships as well as a high level of statistical significance of the increased tumor incidence is treated with respect to control groups; the dose-related shortening of the time-to-tumor occurrence or time to death with tumor, and a dose-related increase in the proportion of tumors that are malignant.

Long-term animal studies at or near the maximum tolerated dose level (MTD) are used to ensure an adequate power for the detection of carcinogenic activity. Negative long-term animal studies at exposure levels above the MTD or partial lifetime exposures at the MTD may not be acceptable because of toxicity, or if animal survival is so impaired that the sensitivity of the study is significantly reduced below that of a conventional chronic animal study at the MTD. Positive studies at levels above the MTD should be carefully reviewed to ensure that the responses are not due to factors which do not operate at exposure levels below the MTD. Evidence indicating that high-dose testing produces tumor responses by indirect mechanisms that may be

unrelated to effects at lower does should be dealt with on an individual basis.

The mechanism of the carcinogenic responses under conditions of the experiment should be reviewed carefully as it relates to the relevance of the evidence to human carcinogenic risks (e.g., the occurrence of bladder tumors in the presence of bladder stones and injection site sarcomas). Interpretation of animal studies is aided by the review of target organ toxicity and other effects (e.g., changes in the immune and endocrine systems) that may be noted in prechronic or other toxicological studies. Time and dose-related changes in the incidence of preneoplastic lesions may also be helpful in interpreting animal studies.

Historical control data are often valuable and could be used along with concurrent control data in the evaluation of carcinogenic responses. For the evaluation of rare tumors, even small tumor responses may be significant compared to historical data. In the case of tumors with relatively high spontaneous rates, a response that is significant with respect to the experimental control group becomes questionable if the historical control data indicate that the experimental control group had an unusually low background incidence.

Agents that are positive in long-term animal experiments and also show evidence of promoting or cocarcingenic activity in specialized tests should be considered as complete carcinogens unless there is evidence to the contrary. Agents that show positive results in special tests for initiation, promotion, or cocarcingenicity and no indication of tumor response in well-conducted and well-designed long-term animal studies should be dealt with on an individual basis.

There are widely diverging scientific views (OSTP, 1984; Ward et al. 1979a; 1979b; Tomatis; 1977; Nutrition Foundation, 1983) about the validity of mouse liver tumors when such tumors occur in strains with high spontaneous background incidence and when they constitute the only tumor response to an agent. These Guidelines take the position that the mouse-liver-only tumor response, when other conditions for a classification of "sufficient" evidence in animal studies are met, should be considered as "sufficient" evidence of carcinogenicity with the understanding that this classification could be changed to "limited" if warranted when a number of factors such as the following are observed: The occurrence of tumors only in the highest dose group and/or only at the end of the study; no substantial dose-related increase in the proportion of tumors that are malignant; the occurrence of tumors that are predominately benign, showing no evidence of metastases or invasion; no dose-related shortening of the time to the appearance of tumors; negative or inconclusive results from a spectrum of short-term tests for mutagenic activity; the occurrence of excess tumors only in a single sex.

Positive carcinogenic responses in one species/strain/sex are not generally negated by negative results in other species/strain/sex. Replicate negative studies that are essentially identical in all other respects to a positive study may indicate that the positive results are spurious.

Evidence for carcinogenic action should be based on the observation of statistically significant tumor responses in specific organs or tissues. Appropriate statistical analysis should be performed on data from long-term studies to help determine whether the effects are treatment-related or possibly due to chance. These should at least include a statistical test for trend, including appropriate correction for differences in survival. The weight to be given to the level of statistical significance (the p-value) and to other available pieces of information is a matter of overall scientific judgment. A statistically significant excess of tumors of all types in the aggregate, in the absence of a statistically significant increase of any individual tumor type should be regarded as minimal evidence of carcinogenic action unless there are persuasive reasons to the contrary.

7. Human Studies

Epidemiologic studies provide unique information about the response of humans who have been exposed to suspect carcinogens. Descriptive epidemiologic studies are useful in generating hypotheses and providing supporting data, but can rarely be used to make a causal inference. Analytical epidemiologic studies of the case-control or cohort variety, on the other hand, are especially useful in assessing risks to exposed humans.

Criteria for the adequacy of epidemiologic studies are well recognized and include factors such as the proper selection and characterization of exposed and control groups, the adequacy of duration and quality of follow-up, the proper identification and characterization of confounding factors and bias, the appropriate consideration of latency effects, and the valid ascertainment of the causes of morbidity and death.

The strength of the epidemiologica evidence for carcinogenicity depends on the magnitude, specificity, and statistical significance of the response and increases rapidly with the number of adequate studies which show the same results on populations exposed to the same agent under different conditions.

It should be recognized that epidemiologic studies are inherently capable of detecting only comparatively large increases in the relative risk of cancer. Negative results from such studies cannot prove the absence of carcinogenic action; however, negative results from a well-designed and conducted epidemiologic study that contains usable exposure data can serve to define upper limits of risk which are useful if animal evidence indicates that the agent is potentially carcinogenic.

C. Weight of Evidence

Evidence of possible carcinogenicity in humans comes primarily from two sources: Long-term animal tests and epidemiologic investigations. Results from these studies are supplemented with information from short-term tests, pharmacokinetic studies, comparative metabolism studies, structure-activity relationships, and other relevant toxicologic studies. The question of how likely an agent is to be a human carcinogen should be answered in the framework of a weight-of-evidence judgment. Judgments about the weight of evidence involve considerations of the quality and adequacy of the data and the kinds of responses induced by a suspect carcinogen. There are three major steps to characterizing the weight of evidence for carcinogenicity: (1) Characterization of the evidence from human studies and from animal studies individually, (2) combination of the characterizations of these two types of data into a final indication of the overall weight of evidence for human carcinogenicity, and (3) evaluation of all supportive information to determine if the overall weight of evidence should be modified.

A system for stratifying the weight of evidence is recommended, and EPA has developed a scheme (see the Appendix). The EPA scheme is modeled after the classification system developed by the International Agency for Research on Cancer (IARC, 1982). In the IARC classification method, the evidence that an agent produces cancer in humans is divided into three categories: Sufficient, limited, and inadequate. A similar characterization of evidence is provided for animal data.

The EPA classification system is, in general, an adaptation of the IARC approach for classifying the weight of

evidence for human data and animal data. The EPA classification system for the characterization of the overall weight of evidence for carcinogenicity (animal, human, and other supportive data) includes: Group A—Carcinogenic to Humans; Group B—Probably Carcinogenic to Humans; C—Possibly Carcinogenic to Humans; Group D—Not Classifiable as to Human Carcinogenicity; and Group E—No Evidence of Carcinogenicity for Humans.

In addition, the following modifications of the IARC approach have been made for classifying human and animal studies. For human studies: (1) The observation of a statistically significant association between an agent and life-threatening benign tumors in humans is included in the evaluation of risks to humans. (2) A "no evidence" category is added. This category indicates that no association was found between exposure and increased risk of cancer in well-conducted, well-designed, independent analytical epidemiologic studies. For animal studies: (1) An increased incidence of combined benign and malignant tumors will be considered to provide sufficient evidence of carcinogenicity if the other criteria defining the "sufficient" category of evidence are met. Benign and malignant tumors will be combined unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same morphologic type. (2) An increased incidence of benign tumors alone as "limited" evidence of carcinogenicity is added. (3) Under specific circumstances, such as the production of neoplasms that occur with high spontaneous background incidence, the evidence may be decreased to "limited" if warranted (e.g., there are widely diverging scientific views regarding the validity of the mouse liver tumors as an indic tor of potential human carcinogenicity when this is the only response observed, even in replicated experiments, in the absence of other short-term evidence). (4) A "no evidence" category is also added. This operational category would include substances for which there is no increased incidence of neoplasms in at least two well-designed and well-conducted animal studies of adequate power and dose in different species.

D. Guidance For Quantitative Assessment

The qualitative evidence for carcinogenesis should be discussed for purposes of guiding the dose-response assessment. The guidance should be given in terms of the appropriateness and limitation of specific studies as well as pharmacokinetic considerations that should be factored into the dose-response assessment. The appropriate method of extrapolation should be factored in when the experimental route of exposure differs from that occurring in humans.

Agents that are judged to be in the EPA weight-of-evidence stratification Groups A and B would be regarded as suitable for quantitative risk assessments. The appropriateness of quantifying the risks from agents in Group C, specifically those agents that are at the boundary of Groups C and D, would be judged on a case-by-case basis. Agents that are judged to be in Groups D and E would generally not have quantitative risk assessments.

E. Summary and Conclusion

The summary should present all of the key findings in all of the sections of the qualitative assessment and the interpretive rationale that forms the basis for the conclusion. Uncertainties in the evidence as well as factors that may affect the relevance of the chronic animal study to humans should be discussed. The conclusion should present both the weight-of-evidence rankng and a description that brings out the more subtle aspects of the evidence that may not be evident from the ranking alone.

III. Dose-Response Assessment, Exposure Assessment, and Risk Characterization

After data concerning the carcinogenic properties of a substance have been collected, evaluated, and categorized, it is frequently desirable to estimate the likely range of excess cancer risk associated with given levels and conditions of human exposure. The first step of the analysis needed to make such estimations is the development of the likely relationship between dose and response (cancer incidence) in the region of human exposure. This information on dose-response relationships is coupled with information on the nature and magnitude of human exposure to yield an estimate of human risk. The risk-characterization step also includes an interpretation of these estimates in light of the biological, statistical, and exposure assumptions and uncertainities that have arisen throughout the process of assessing risk.

The elements of dose-response assessment are described in section III.A. Guidance on human exposure assessment is provided in another EPA document (U.S. EPA, 1984); however, section III.B. of these Guidelines includes a brief description of the specific type of exposure information that is necessary for use in carcinogenic risk assessment. Finally, in section III.C. there is a description of the type of information and its interpretation necessary for accurately characterizing risk and the degree to which it can be known.

It should be emphasized that calculation of quantitative estimates of cancer risk does not require that an agent be a human carcinogen. The likelihood that an agent is a human carcinogen is a function of the weight of evidence, as this has been described in the hazard identification section of these Guidelines. It is nevertheless important to present quantitative estimates, appropriately qualified and interpreted, in those circumstances in which there is likelihood that the agent is a human carcinogen. Appropriately qualified quantitative estimates of risk, together with estimates of their uncertainty, are useful in cost-benefit analyses, in setting regulatory priorities, and for evaluating residual risks associated with the application of regulatory controls.

It should be emphasized in every quantitative risk estimation that the results are uncertain. The uncertainties due to experimental and epidemiologic variability as well as uncertainty in the exposure assessment can be important. There are major uncertainties in extrapolating both from animals to humans and from high to low doses. There are important species differnces in uptake, metabolism, and organ distribution of carcinogens, as well as species and strain differences in target site susceptibilty. Human populations are variable with respect to genetic constitution, diet, occupational and home environment, activity patterns, and other cultural factors. Risk estimates should be presented together with the associated hazard assessment (section III.C.3.) to ensure that there is an appreciation of the weight of evidence for carcinogenicity that underlies the quantitative risk estimates.

A. Dose-Response Assessment

1. Selection of Data

As indicated in section II.D. guidance needs to be given by the individuals doing the qualitative assessment (toxicologists, pathologists, pharmacologists, etc.) to the statisticans doing the quantitative assessment as to the appropriate data to be used in the dose-response assessment. This is determined by the quality of the data, its relevance to human modes of exposure, and other technical details.

If available, estimates based upon human epidemiologic data are preferred. If adequate exposure data exist in a well-designed and conducted negative epidemiologic study, an upper-bound estimate of risk should be used in preference to higher risks estimated from animal data. In the absence of human data, data from a species that responds most like humans should be used, if information to this effect exists. Where, for a given agent, several studies are available which may involve different animal species, strains, and sexes, at several doses and by different routes of exposure, the following approach to selecting the data sets is used. The tumor incidence data are separated according to organ site and tumor type. All biologically and statistically acceptable data sets are presented. The range of the risk estimates is identified with due regard to biological relevance (particularly in the case of animal studies) and appropriateness of route of exposure. Because it is possible that human sensitivity is as high as the most sensitive responding animal species, in the absence of evidence to the contrary, the biologically acceptable data set from long-term animal studies showing the greatest sensitivity should generally be given the greatest emphasis, again with due regard to biological and statistical considerations.

When the exposure route in the species from which the dose-response information is obtained differs from the route occurring in environmental exposures, uncertainties about the dose delivered to the target organs from different exposure media should be explicitly considered, and the assumptions should be carefully stated.

Where two or more significantly elevated tumor sites or types are observed in the same study, extrapolations may be conducted on selected sites or types. These selections will be made on biological grounds. To obtain a total estimate of carcinogenic risk, animals with one or more tumor sites or types showing significantly elevated tumor incidence should be pooled and used for extrapolation; if the tumor sites or types are occurring independently, this procedure is the same as summing the risks from the several kinds of statistically significant tumors. The pooled estimates will generally be used in preference to risk estimates based on single sites or types.

Benign tumors should generally be combined with malignant tumors for risk estimates unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same morphologic type. However, the contribution of the benign tumors to the total risk should be indicated.

2. Choice of Mathematical Extrapolation Model

Since risks at low exposure levels cannot be measured directly either by animal experiments or by epidemiologic studies, a number of mathematical models have been developed to extrapolate from high to low dose. However, different extrapolation models may fit the observed data reasonably well but may lead to large differences in the projected risk at low doses.

No single mathematical procedure is recognized as the most appropriate for low-dose extrapolation in carcinogenesis. When relevant biological evidence on mechanism of action exists, the models or procedures employed should be consistent with the evidence. However, when data and information are limited, as is the usual case given the high degree of uncertainty associated with the selection of a low-dose extrapolation model, specific guidance on model selection is necessary to provide a desirable degree of consistency in risk assessments. The choice of low-dose extrapolation models should be consistent with current understanding of the mechanisms of carcinogenesis and not solely on goodness of fit to the observed tumor data. Although mechanisms of the carcinogenesis process are largely unknown, at least some elements of the process have been elucidated, e.g., linearity of tumor initiation. In further support of a linear model, it has been shown that, if a carcinogenic agent acts by accelerating the same stages of the carcinogenic process that lead to the background occurrence of cancer, the added effect of the carcinogen at low dose is virtually linear. Thus, a model that is linear at low dose is plausible.

The linearized multistage model procedure for low-dose extrapolation (U.S. EPA, 1980) is therefore recommended in most cases unless there is evidence on carcinogenesis mechanisms or other biological evidence that indicates the greater suitability of an alternative extrapolation model, or there is statistical or biological evidence that excludes the use of the linearized multistage model.

It should be emphasized that the linearized multistage model leads to a plausible upper limit to the risk which is consistent with some mechanisms of carcinogenesis. However, such an estimate does not necessarily give a realistic prediction of the risk. In certain cases, the linearized multistage model cannot be used successfully with the observed data as, for example, when the data are nonmonotonic or flatten out at high doses. In these cases it may be necessary to make adjustments to the procedure to achieve low-dose linearity.

When pharmacokinetic or metabolism data are available, or when other substantial evidence on the mechanistic aspects of the carcinogenesis process exists, a different low-dose extrapolation model might be considered more appropriate on biological grounds. When a different model is chosen, the risk assessment should clearly discuss the nature and strength of the evidence that lead to the choice. In most cases, considerable uncertainty will remain concerning response at low doses; therefore, an upper-limit risk estimate using the linearized multistage model should also be presented.

3. Equivalent Exposure Units Among Species

Low-dose risk estimates derived from laboratory animal data extrapolated to humans are complicated by a variety of factors that differ among species and potentially affect the response to carcinogens. Included among these factors are differences between humans and experimental test animals with respect to life span, body size, genetic variability, population homogeneity, existence of concurrent disease, pharmacokinetic effects such as metabolism and excretion patterns, and the exposure regimen.

The usual approach for making interspecies comparisons has been to use standardized scaling factors. Commonly employed standardized dosage scales include mg per kg body weight per day, ppm in the diet or water, mg per m^2 body surface area per day, and mg per kg body weight per lifetime. In the absence of comparative toxicological, physiological, metabolic, and pharmacokinetic data for a given suspect carcinogen, the extrapolation of body weight to the 0.67 power is considered to be appropriate.

B. Exposure Assessment

In order to obtain a quantitative estimate of the risk, the results of the dose-response assessment must be combined with an estimate of the exposures to which the populations of interest are likely to be subject. While the reader is referred to the Proposed Guidelines for Exposure Assessment (U.S. EPA, 1984) for specific details, it is important that the cancer risk assessor and the decision-maker have an appreciation of the impact of the

strengths and weaknesses of exposure assessment on the overall cancer risk assessment process.

At present there is no single approach to exposure assessment that is appropriate for all cases. On a case-by-case basis, appropriate methods are selected to match the data on hand and the level of sophistication required (e.g., preliminary assessment using crude data and worst case assumptions versus a final assessment using extensive monitoring data). The assumptions, approximations, and uncertainties need to be clearly stated because, in some instances, these will have a major effect on the risk assessment.

In general, the magnitude, duration, and frequency of exposure provide fundamental information for estimating the concentration of the carcinogen to which the organism is exposed. These data are generated from monitoring information, modeling results, and/or reasoned estimates. An appropriate treatment of exposure should consider the potential for exposure via ingestion, inhalation, and dermal penetration from relevant sources of exposures. Where feasible, an attempt should be made to assess the dose to the target organ, either through experimental evidence or reasonable assumptions and modeling.

Special problems arise when the human exposure situation of concern suggests exposure regimens, e.g., route and dosing schedule, which are substantially different from those used in the relevant animal studies. Unless there is evidence to the contrary in a particular case, the cumulative dose received over a lifetime, expressed as average daily exposure prorated over a lifetime, is recommended as the appropriate measure of exposure to a carcinogen. That is, the assumption is made that a high dose of a carcinogen received over a short period of time is equivalent to a coresponding low dose spread over a lifetime. This approach becomes more problematical as the exposures in question become more intense but less frequent, especially when there is evidence that the agent has shown dose-rate effects.

An attempt should be made to assess the level of uncertainty associated with the exposure assessment which is to be used in a cancer risk assessment. This measure of uncertainty should be included in the risk characterization (section III.C.) in order to provide the decision-maker with a clear understanding of the impact of this uncertainty on any final quantitative risk estimate.

C. Risk Characterization

1. Options for Numerical Risk Estimates

Depending on the needs of the individual program offices, numerical estimates can be presented in one or more of the following three ways.

a. Unit Risk—Under an assumption of low-dose linearity, the unit cancer risk is the excess lifetime risk due to a continuous constant lifetime exposure of one unit of carcinogen concentration. Typical exposure units include ppm or ppb in food or water, mg/kg/day by ingestion, or ppm or ug/m ^{3} in air.

b. The Dose Corresponding to a Given Level of Risk—This approach can be useful, particularly when using nonlinear extrapolation models where the unit risk would differ at different dose levels.

c. Individual and Population Risks—Risk may be characterized either in terms of the excess individual lifetime risks or the excess number of cancers produced per year in the exposed population or both.

Irespective of the options chosen, the degree of precision and accuracy in the numerical risk estimates currently do not permit more than one significant figure to be presented.

2. Concurrent Exposure

In characterizing the risk due to concurrent exposure to several carcinogens, the risks are combined on the basis of additivity unless there is specific information to the contrary. Interactions of cocarcinogens, promoters, and inititators with known carcinogens should be considered on a case-by-case basis.

3. Summary of Risk Characterization

Whichever method of presentation is chosen, it is critical that the numerical estimates not be allowed to stand alone, separated from the various assumptions and uncertainties upon which they are based. The risk characterization should contain a discussion and interpretation of the numerical estimates that affords the risk manager some insight into the degree to which the quantitative estimates are likely to reflect the true magnitude of human risk, which generally cannot be known with the degree of quantitative accuracy reflected in the numerical estimates. The final risk estimate will be generally rounded to one significant figure and will be coupled with the EPA classification of the qualitative weight of evidence. For example, a lifetime individual risk of 2×10^{-4} resulting from exposure to a "possible human carcinogen" (Group C) should be designated as:

2×10^{-4} [C]

This bracketed designation of the qualitative evidence should be included with all numerical risk estimates (i.e., unit risks, which are risks at a specified concentration, or concentrations corresponding to a given risk). Agency statements, such as Federal Register notices, briefings, and action memoranda, frequently include numerical estimates of carcinogenic risk. It is recommended that whenever these numerical estimates are used, the qualitative weight-of-evidence classification should also be included.

IV. Appendix—EPA Classification System for Evidence of Carcinogenicity From Human Studies and From Animal Studies (Adapted From IARC)

A. Assessment of Evidence for Carcinogenicity From Studies in Humans

Evidence of carcinogenicity from human studies comes from three main sources:

1. Case reports of individual cancer patients who were exposed to the agent(s).

2. Descriptive epidemiologic studies in which the incidence of cancer in human populations was found to vary in space or time with exposure to the agent(s).

3. Analytical epidemiologic (case-control and cohort) studies in which individual exposure to the agent(s) was found to be associated with an increased risk of cancer.

Three criteria must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias which could explain the association.

2. The possibility of confounding has been considered and ruled out as explaining the association.

3. The association is unlikely to be due to chance.

In general, although a single study may be indicative of a cause-effect relationship, confidence in inferring a causal association is increased when several independent studies are concordant in showing the association, when the association is strong, when there is a dose-response relationship, or when a reduction in exposure is followed by a reduction in the incidence of cancer.

The degrees of evidence for carcinogenicity* from studies in humans are categorized as:

1. Sufficient evidence of

*For purpose of public health protection, agents associated with life-threatening benign tumors in humans are included in the evaluation.

carcinogenicity, which indicates that there is a causal relationship between the agent and human cancer.

2. Limited evidence of carcinogenicity, which indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be excluded.

3. Inadequate evidence, which indicates that one of two conditions prevailed: (a) There were few pertinent data, or (b) the available studies, while showing evidence of association, did not exclude chance, bias, or confounding.

4. No evidence, which indicates that no association was found between exposure and an increased risk of cancer in well-designed and well-conducted independent analytical epidemiologic studies.

5. No data, which indicates that data are not available.

B. Assessment of Evidence for Carcinogenicity From Studies in Experimental Animals

These assessments are classified into five groups:

1. Sufficient evidence+ of carcinogenicity, which indicates that there is an increased incidence of malignant tumors or combined malignant and benign tumors§: (a) In multiple species or strains; or (b) in multiple experiments (preferably with different routes of administration or using different dose levels); or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset. Additional evidence may be provided by data on dose-response effects, as well as information from short-term tests or on chemical structure.

2. Limited evidence of carcinogenicity, which means that the data suggest a carcinogenic effect but are limited because: (a) The studies involve a single species, strain, or experiment; or (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) an increase in the incidence of benign turmors only.

3. Inadequate evidence, which indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect.

4. No evidence, which indicates that there is no increased incidence of neoplasms in at least two well-designed and well-conducted animal studies in different species.

5. No data, which indicates that data are not available.

The categories "sufficient evidence" and "limited evidence" refer only to the strength of the experimental evidence that these agents(s) are carcinogenic and not to the power of their carcinogenic action.

C. Categorization of Overall Evidence

Group A—Human Carcinogen

This category is used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agent(s) and cancer.

Group B—Probable Human Carcinogen

This category includes agents for which the evidence of human carcinogenicity from epidemiologic studies ranges from almost "sufficient" to "inadequate." To reflect this range, the category is divided into higher (Group B1) and lower (Group B2) degrees of evidence. Usually, category B1 is reserved for agents for which there is at least limited evidence of carcinogenicity to humans from epidemiologic studies. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard agents for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans. Therefore, agents for which there is inadequate evidence from human studies and sufficient evidence form animal studies would usually result in a classification of B2.

In some cases, the known chemical or physical properties of an agent and the results from short-term tests allow its transfer from Group B2 to B1.

Group C—Possible Human Carcinogen

This category is used for agents with limited evidence of carcinogenicity in animals in the absence of human data. It includes a wide variety of evidence: (a) Definitive malignant tumor response in a single well-conducted experiment, (b) marginal tumor response in studies having inadequate design or reporting, (c) benign but not malignant tumors with an agent showing no response in a variety of short-term tests for mutagenicity, and (d) marginal responses in a tissue known to have a high and variable background rate.

In some cases, the known physical or cehmical properties of an agent and results from short-term tests allow a transfer from Group C to B2 or from Group D to C.

Group D—Not Classified

This category is used for agent(s) with inadequate animal evidence of carcinogenicity.

Group E—No Evidence of Carcinogenicity for Humans

This category is used for agent(s) that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both epidemiologic and animal studies.

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+Under specific circumstances, such as the production of neoplasms that occur with high spontaneous background incidence, the evidence may be decreased to "limited" if warranted (e.g., there are widely diverging scientific views regarding the validity of the mouse liver tumor as an indicator of potential human carcinogenicity when this is the only response observed, even in replicated experiments in the absence of short-term or other evidence).

§Benign and malignant tumors will be combined unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same morphologic type.

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PART 2 - EXPOSURE ASSESSMENT

federal register

Friday
November 23, 1984

Part VIII

Environmental Protection Agency

Proposed Guidelines for Exposure Assessment; Request for Comments

ENVIRONMENTAL PROTECTION AGENCY

[FRL-2706-5]

Proposed Guidelines for Exposure Assessment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed Guidelines for Exposure Assessment and Request for Comments.

SUMMARY: The U.S. Environmental Protection Agency is proposing Guidelines for Exposure Assessment (Guidelines). These Guidelines are proposed for use within the policy and procedural framework provided by the various statutes which EPA administers to guide Agency analysis of exposure data. We solicit public comment and will take public comment into account in revising these Guidelines. These Guidelines will be reviewed by the Science Advisory Board in meetings now tentatively scheduled for April 1985.

These proposed Guidelines were developed as part of a broad guidelines development program under the auspices of the Office of Health and Environmental Assessment (OHEA), located in the Agency's Office of Research and Development. Consonant with the role of OHEA's Exposure Assessment Group (EAG) as the Agency's senior health committee for exposure assessment, the Guidelines were developed by an Agency-wide working group chaired by the Director of EAG.

DATE: Comments must be postmarked by January 22, 1985.

ADDRESSES: Comments may be mailed or delivered to: Dr. James W. Falco, Exposure Assessment Group (RD-689), Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, 401 M Street S.W., Washington, DC 20460.

FOR FURTHER INFORMATION CONTACT: Dr. James W. Falco, Telephone: 202-475-8909.

SUPPLEMENTARY INFORMATION: Preliminary drafts of these Guidelines were sent out for review to 15 scientists and engineers in the field of exposure assessment within government, universities in the United States and abroad, and the private sector. Comments received from these reviews, generally favorable, were taken into account in developing the Guidelines proposed here.

In addition, as a result of the reviews, four areas requiring further research were identified as follows:

(1) Development of Mathematical Model Selection Criteria.

A large number of mathematical models are used to estimate a wide variety of parameters needed for estimating exposures. Guidance in the form of selection criteria are needed to ensure that the most appropriate mathematical model is used for each exposure parameter estimate.

(2) Development of Guidance for Analysis of Metabolism Data.

Guidance is needed to provide appropriate consideration of metabolism data in the calculation of whole body dose and in the extrapolation of whole organism dose from one species to another.

(3) Definition of the Relationship Between Exposure Assessment and Epidemiology.

Guidance is needed to ensure that pertinent parameters of exposure are measured in prospective epidemiologic studies. Methods providing the best estimates of exposure for retrospective and historical epidemiologic studies must be defined.

(4) Development of Methods to Relate Exposures Measured by Personal Monitoring to Source Contributions.

Guidance is needed to establish methods to relate exposures as measured by personal monitoring to controllable sources and to discriminate among possible sources and between background and anthropogenic sources.

It is the Agency's intent to revise the Guidelines periodically to incorporate the results obtained in the four research areas defined above as they become available.

In addition to the publication of the Guidelines, the Agency also will provide technical support documents that contain detailed technical information needed to implement the Guidelines. Two of these technical reports entitled "Development of Statistical Distribution or Ranges of Standard Factors Used in Exposure Assessments" and "Methodology for Characterization of Uncertainty in Exposure Assessments" are currently available. Technical reports for the four new guideline areas described above will be available at the time of publication of the corresponding guideline section. These technical support documents will be revised periodically to reflect improvements in exposure assessment methods and new information or experience.

Support documents used in the preparation of these Guidelines as well as comments received are available for inspection and copying at the Public Information Reference Unit (202-382-5926), EPA Headquarters Library, 401 M Street S.W., Washington, DC, between the hours of 8:00 a.m. and 4:30 p.m.

Dated: November 9, 1984.

William D. Ruckelshaus,

Administrator.

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I. Introduction

These Guidelines provide the Agency with a general approach and framework for carrying out human or nonhuman exposure assessments for specified pollutants. ~~The Guidelines have been~~ developed to assist future assessment activities and encourage improvement in those EPA programs that require, or could benefit from the use of exposure assessments. The Guidelines are procedural. They should be followed to the extent possible in instances where exposure assessment is a required element in the regulatory process or where exposure assessments are carried out on a discretionary basis by EPA management to support regulatory or programmatic decisions.

This document, by laying out a set of questions to be considered in carrying out an exposure assessment, should help avoid inadvertent mistakes of omission. EPA recognizes that gaps in data will be common, but the Guidelines will nevertheless serve to assist in organizing the data that are available, including any new data developed as part of the exposure assessment. It is understood that exposure assessments may be performed at many different levels of detail depending on the scope of the assessment.

These Guidelines should also promote consistency among various exposure assessment activities that are carried out by the Agency. Consistency with respect to common physical, chemical, and biological parameters, with respect to assumptions about typical exposure

situations, and with respect to the characterization of uncertainty of estimates, will enhance the comparability of results and enable the Agency to improve the state-of-the-art of exposure assessment over time through the sharing of common data and experiences.

It is recognized that the main objective of an exposure assessment is to provide reliable data and/or estimates for a risk assessment. Since a risk assessment requires the coupling of exposure information and toxicity or effects information, the exposure assessment process should be coordinated with the toxicity/effects assessment. This document provides a common approach to format, which should simplify the process of reading and evaluating exposure assessments and thereby increase their utility in assessing risk.

As the Agency performs more exposure assessments, the Guidelines will be revised to reflect the benefit of experience.

II. General Guidelines and Principles

A. Exposure and Dose

Exposure has been defined by Committee E-47, Biological Effects and Environmental Fate, of the American Society for Testing and Materials, as the contact with a chemical or physical agent. The magnitude of the exposure is determined by measuring or estimating the amount of an agent available at the exchange boundaries, i.e., lungs, gut, skin, during some specified time. Exposure assessment is the determination or estimation (qualitative or quantitative) of the magnitude, frequency, duration, and route of exposure. Exposure assessments may consider past, present, and future exposures with varying techniques for each phase, i.e., modeling of future exposures, measurements of existing exposure, and biological accumulation for past exposures. Exposure assessments are generally combined with environmental and health effects data in performing risk assessments.

In considering the exposure of a subject to a hazardous agent, there are several related processes. The contact between the subject of concern and the agent may lead to the intake of some of the agent. If absorption occurs, this constitutes an uptake (or an absorbed dose) which then may lead to health effects. When biological tissue or fluid measurements indicate the presence of a chemical, exposures can be estimated from these data. Presence of a chemical in such biological samples is the most direct indication that an exposure has occurred. The route of exposure generally impacts the overall exposure and should be considered in performing risk assessments.

B. Decision Path to Determine Scope of the Assessment

The first step in preparing an exposure assessment should be the circumscription of the problem at hand to minimize effort by use of a narrowing process. A decision logic path that describes this process is shown in Figure 1. As illustrated in Figure 1, the preliminary assessment and the in-depth assessment are two major phases in this logic path.

The preliminary assessment phase should commence by considering what risk is under study and what law might regulate the exposure to the agent. Within this framework, a preliminary data base should be compiled from readily available scientific data and exposure information based on manufacturer, processor, and user practices. Next, the most likely areas of exposure (manufacuring, processing, consumer, distribution, disposal, ambient, water and food, etc.) should be identified. Since a complete data search has not been conducted, well-identified assumptions and order of magnitude estimates are used to further narrow the exposure areas of concern.

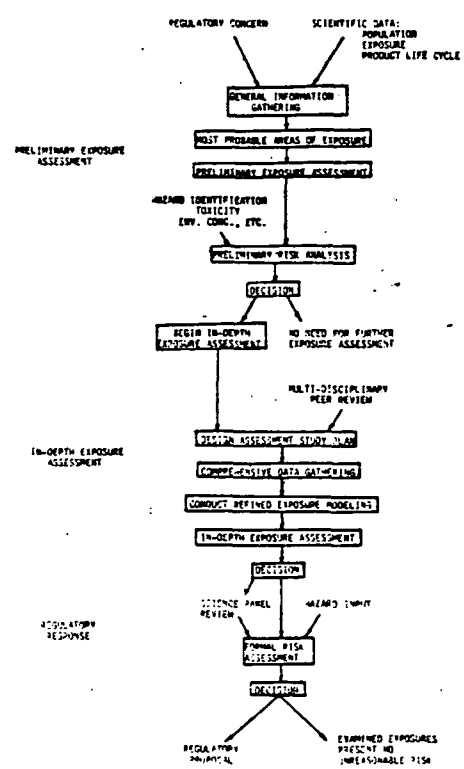

FIGURE 1. DECISION PATH FOR EXPOSURE ASSESSMENT

Data from this preliminary exposure assessment can then be coupled with toxicity information to perform a preliminary risk analysis. As a result of this analysis, a decision will be made that either an in-depth exposure assessment is necessary or that there is no need for further exposure information. The organization and contents of an in-depth exposure assessment are given in the following section.

In assembling the information base for either a preliminary assessment or a more detailed assessment, its adequacy should be ascertained by addressing the following considerations:

—Availability of information in every area needed for an adequate assessment;
—Quantitative and qualitative nature of the data;
—Reliability of information;
—Limitations on the ability to assess exposure.

C. Uncertainty

Exposure assessments are based on monitoring data, simulation model estimates, and assumptions about parameters used in approximating actual exposure conditions. Both data and assumptions contain varying degrees of uncertainty which influence the accuracy of exposure assessments. An evaluation of these uncertainties is important when the assessment is the basis for regulatory action.

The uncertainty analyses performed will vary depending on the scope of the assessment, the quantity and quality of monitoring data collected, and the type and complexity of mathematical models used. A discussion of the types of analysis used for quantifying uncertainties in exposures is presented in the next section.

III. Organization and Contents of an Exposure Assessment

A. Overview

A suggested outline for an exposure assessment document is given in Exhibit 1. The five major topics to be addressed within most exposure assessments are as follows: Source(s); Exposure Pathways; Monitored or Estimated Concentration Levels and Duration; Exposed Population(s); and Integrated Exposure Analysis. These five topics are appropriate for exposure assessments in general, whether the assessments are of global, national, regional, local, site-specific, workplace-related, or other scope. The topics are appropriate for exposure assessments on new or existing chemicals and radionuclides.

They are also applicable to both single media and multimedia assessments. Since exposure assessments are performed at different levels of detail, the extent to which any assessment contains items listed in Exhibit 1 depends upon its scope. The outline is a guide to organize the data whenever they are available.

B. Detailed Explanation of Outline

1. Executive Summary

The "Executive Summary" should be written so that it can stand on its own as a miniature report. Its main focus should be on a succinct description of the procedures used, assumptions employed, and summary tables or charts of the results. A brief discussion of the uncertainties associated with the results should be included.

2. Introduction (Purpose and Scope)

This section should state the intended purpose of the exposure assessment and identify the agent being investigated, the types of sources and exposure routes included, and the populations of concern.

Exhibit 1.—Suggested Outline for an Exposure Assessment

1. EXECUTIVE SUMMARY
2. INTRODUCTION
   a. Purpose
   b. Scope
3. GENERAL INFORMATION
   a. Identity
      (1) Molecular formula and structure, CAS number, TSL number
      (2) Description of technical grades, contaminants, additives
      (3) Other identifying characteristics
   b. Chemical and Physical Properties
4. SOURCES
   a. Characterization of Production and Distribution
      (1) Production and processing
      (2) Distribution in commerce
   b. Uses
   c. Disposal
   d. Summary of Environmental Releases
5. EXPOSURE PATHWAYS AND ENVIRONMENTAL FATE
   a. Transport and Transformation
   b. Identification of Principal Pathways of Exposure
   c. Predicting Environmental Distribution
6. MONITORED OR ESTIMATED CONCENTRATION LEVELS
   a. Summary of Monitoring Data
   b. Estimation of Environmental Concentrations
   c. Comparison of Concentration Estimates with Monitoring Data
7. EXPOSED POPULATIONS
   a. Human Populations (Size, Location, and Habits)
      (1) Population size and characteristics
      (2) Population location
      (3) Population habits
   b. Nonhuman Populations (where appropriate)
      (1) Population size and characteristics
      (2) Population location
      (3) Population habits
8. INTEGRATED EXPOSURE ANALYSIS
   a. Calculation of Exposure
      (1) Identification and characterization of the exposed populations and critical elements of the ecosystem
      (2) Pathways of exposure
   b. Human Dosimetry and Monitoring
   c. Development of Exposure Scenarios and Profiles
   d. Evaluation of Uncertainty
9. REFERENCES
10. APPENDICES

3. General Information

a. *Identity.* (1) Molecular formula and structure, synonyms, Chemical Abstract Service number, Toxic Substance List number.

(2) Description of technical grades, contaminants, additives.

(3) Other identifying characteristics.

b. *Chemical and Physical Properties.* This subsection should provide a summary description of the chemical and physical properties of the agent. Particular attention should be paid to the features that would affect its behavior in the environment. Examples of factors to be included are molecular weight, density, boiling point, melting point, vapor pressure, solubility, pK_a, partition coefficients, and half-lives.

4. Sources

The points at which a hazardous substance is believed to enter the environment should be described, along with any known rates of entry. Points of entry may be indoors as well as outdoors, and environments include indoor settings such as offices as well as outdoor environments. A detailed exposure assessment should include a study of sources, production, uses, destruction/disposal, and environmental release of a substance. The studies should include a description of human activities with respect to the substance and the environmental releases resulting from those activities. It should account for the controlled mass flow of the substance from creation to destruction and provide estimates of environmental releases at each step in this flow. Seasonal variations in environmental releases should also be examined. All sources of the substances should be accounted for with the sum of the uses, destruction, and the environmental releases. The environmental releases can be described in terms of geographic and temporal distribution and the receiving environmental media, with the form identified at the various release points.

a. *Characterization of Production and Distribution.* All sources of the substance's release to the environment, consistent with the scope of the assessment, should be included, such as production, extraction, processing, imports, stockpiles, transportation, accidental/incidental production as a side reaction, and natural sources. The sources should be located, and activities involving exposure to the substance should be identified.

b. *Uses.* The substance should be traced from its sources through various uses (with further follow-up on the products made to determine the presence of the original material as an impurtiy), exports, stockpile increases, etc.

c. *Disposal.* This subsection should contain an evaluation of disposal sites and destruction processes, such as incineration of industrial chemical wastes, incineration of the substance as part of an end-use item in municipal waste, landfilling of wastes, biological destruction in a secondary wastewater treatment plant, or destruction in the process of using the end product. Hazardous contaminants of the substance may be included, and products containing the substance as a contaminant may be followed from production through destruction/disposal.

d. *Summary of Environmental Releases.* Estimates should be made of the quantities of the substances released to the various environmental media. Sources of release to the environment include production, use, distribution/transport, natural sources, disposal, and contamination of other products. Environmental releases should be presented at a reasonable level of detail. Extremely detailed exposure estimates would attempt to specify the following information for each significant emission source: Location, amount of the substances being released as a function of time to each environmental medium, physical characteristics of the emission source, and the physical and chemical form of the substance being released. Evaluation of the uncertainties associated,with the emission estimates should be given. A detailed discussion of procedures for estimating uncertainty is presented in section 8.d.

5. Exposure Pathways and Environmental Fate

The exposure pathways section should address how a hazardous agent moves from the source to the exposed population or subject. For a less detailed assessment, broad generalizations on environmental pathways and fate may be made. In the absence of data, e.g., for new substances, fate estimates may

have to be predicted by analogy with data from other substances. Fate estimates may also be made by using models and/or monitoring data and laboratory-derived process rate coefficients. At any level of detail, certain pathways may be judged insignficiant and not pursued further.

For more detailed assessments involving environmental fate, the sources analysis described previously should provide the amount and rate of emissions to the environment, and possibly the locations and form of the emissions. The environmental pathways and fate analysis follows the substance from its point of initial environmental release, through the environment, to its ultimate fate. It may result in an estimation of the geographic and temporal distribution of concentrations of the substance in the various contaminated environmental media.

a. *Transport and transformation.* The substance, once released to the environment, may be transported (e.g., convected downstream in water or on suspended sediment, through the atmosphere, etc.) or physically transformed (e.g., volatilized, melted, absorbed/desorbed, etc.); may undergo chemical transformation such as photoysis, hydrolysis, oxidation, reduction; may undergo biotransformation such as biodegradation; or may accumulate in one or more media. Thus, the environmental behavior of a substance should be evaluated before exposures are assessed. Factors that should be addressed include:

- How does the agent behave in air, water, soil, and biological media? Does it bioaccumulate or biodegrade? Is it absorbed or taken up by plants?
- What are the principal mechanisms for change or removal in each of the environmental media.
- Does the agent react with other compounds in the environment?
- Is there intermedia transfer? What are the mechanisms for intermedia transfer? What are the rates of the intermedia transfer or reaction mechanisms?
- How long might the agent remain in each environmental medium? How does its concentration change with time in each medium?
- What are the products into which the agent might degrade or change in the environment? Are any of these degradation products ecologically or biologically harmful? What is the environmental behavior of the harmful products?
- Is a steady-state concentration distribution in the environment, or in specific segments of the environment, achieved? If not, can the nonsteady-state distribution be described?
- What is the resultant distribution in the environment—for different media, different types or forms of the agent, for different geographical areas, at different times or seasons?

b. *Identification of Principal Pathways of Exposure.* The principal pathway analysis should evaluate the sources, locations, and types of environmental releases, together with environmental behavioral factors, to determine the significant routes of human and environmental exposure to the substance. Thus, by listing the important characteristics of the environmental release (entering media, emission rates, etc.) and the agent's behavior (intermedia transfer, persistence, etc.) after release to each of the entering media, it should be possible to follow the movement of the agent from its initial release to its subsequent fate in the environment. At any point in the environment, human or environmental exposure may occur. Pathways that result in major concentrations of the agent and high potential for human or environmental contact are the principal exposure pathways.

c. *Predicting Environmental Distribution.* Models may be used to predict environmental distributions of chemicals. Many modeling estimates of environmental distribution of chemicals are based in part on monitoring data. In predicting environmental distributions of chemicals, available monitoring data should be considered.

In this section an estimation is made, using appropriate models, of representative concentrations of the agent in different environmental media, and its time-dependence in specific geographical locations (e.g., river basins, streams, etc.).

6. Monitored or Estimated Concentration Levels

a. *Summary of Monitoring Data.* Monitoring data are used to identify releases (source terms) and, in the exposure pathways and fate assessments, to quantitatively estimate both release rates and environmental concentrations. Some examples of uses of monitoring data are: Sampling of stacks of discharge pipes for emissions to the environment; testing of products for chemical or radionuclide content: testing of products for chemical or radioactive releases; sampling of appropriate points within a manufacturing plant to determine releases from industrial processes or practices; and sampling of solid waste for chemical or radionuclide content. These data should be characterized as to accuracy, precision, and representativeness. If actual environmental monitoring data are unavailable, concentrations can be estimated by various means, including the use of fate models (see previous section) or, in the case of new chemicals, by analogy with existing chemicals.

The analysis of monitoring data should be considered a complement to environmental pathway and fate analysis for the following reasons: For most pollutants, particularly organic and new chemicals, monitoring data are limited; analysis of monitoring data does not often yield relationships between environmental releases and environmental concentration distribution in media or geographic locations that have not been monitored; analysis of monitoring data does not provide information on how and where biota influence the environmental distribution of a pollutant; and monitored concentrations may not be traceable to individual sources that EPA can regulate. Monitoring data are, however, a direct source of information for exposure analysis and, furthermore, they can be used to calibrate or extrapolate models or calculations to assess environmental distribution.

b. *Estimation of Environmental Concentrations.* Concentrations of agents should be estimated for all environmental media that might contribute to significant exposures. Generally, the environmental concentrations are estimated from monitoring data, mathematical models, or a combination of the two.

The concentrations must be estimated and presented in a format consistent with available dose-response information. In some cases an estimate of annual average concentration will be sufficient, while in other cases the temporal distribution of concentrations may be required. Future environmental concentrations resulting from current or past releases may also be projected. In some cases, both the temporal and geographic distributions of the concentration may be assessed. Moreover, if the agent has natural sources, the contribution of these to environmental concentrations may be relevant. These "background" concentrations may be particularly important when the results of tests of toxic effects show a threshold or distinctly nonlinear dose-response.

The uncertainties associated with the estimated concentrations should be evaluated by an analysis of the

uncertainties of the model parameters and input variables. When the estimates of the environmental concentrations are based on mathematical models, the model results should be compared to available monitoring data, and any significant discrepancies should be discussed. Reliable, analytically-determined values should be given precedence over estimated values whenever significant discrepancies are found.

7. Exposed Populations

Populations selected for study may be done *a priori*, but frequently the populations will be identified as a result of the sources and fate studies. From an analysis of the distribution of the agent, populations convected and subpopulations (i.e., collections of subjects) at potentially high explosure can be identified, which will then form the basis for the populations studied. Subpopulations of high sensitivity, such as pregnant women, infants, chronically ill, etc., may be studied separately.

In many cases, exposed populations can be described only generally. In some cases, however, more specific information may be available on matters such as the following:

a. *Human Populations. (1) Population size and characteristics (e.g., trends, sex/age distribution)*

(2) Population location

(3) Population habits—transportation habits, eating habits, recreational habits, workplace habits, product use habits, etc.

b. *Nonhuman Populations (where appropriate).* (1) Population size and characteristics (e.g., species, trends)

(2) Population location

(3) Population habits

Census and other survey data may be used to identify and describe the population exposed to various contaminated environmental media. Depending on the characteristics of available toxicological data, it may be appropriate to describe the exposed population by other characteristics such as species, race-age-sex distribution, and health status.

8. Integrated Exposure Analysis

The integrated exposure analysis combines the estimation of environmental concentrations (sources and fate information) with the description of the exposed population to yield exposure profiles. Data should be provided on the size of the exposed populations; duration, frequency, and intensity of exposure; and routes of exposure. Exposures should be related to sources.

For more detailed assessments, the estimated environmental concentrations should be considered in conjunction with the geographic distribution of the human and environmental populations. The behavioral and biological characteristics of the exposed populations should be considered and the exposures of populations to various concentration profiles should be estimated.The results can be presented in tabular or graphic form, and an estimate of the uncertainty associated with them should be provided.

a. *Calculations of Exposure. The calculation of exposure involves two major aspects:*

(1) Identification of the Exposed Population and Critical Elements of the Ecosystem.

The estimate of environmental concentrations also should give the geograhical areas and environmental media contaminated. The stated purpose of the assessment should have prescribed the human and environmental subjects for which exposures are to be calculated. If the subjects are not listed, the contaminated geographical areas and environmental media can be evaluated to determine subject populations. The degree of detail to be used in defining the exposed population distribution depends on the concentration gradient over geographic areas.

(2) Identification of pathways of exposure.

(a) Identification and description of the routes by which the substances travel from production site, through uses, through environmental releases/sources, through transport and fate processes, to the target population.

(b) Quantitative estimates of the amounts of the chemical following each exposure pathway. Such estimates allow the various pathways to be put in the perspective of relative importance.

From the geogrpahic and tempral distribution of environmental concentrations, the exposed population, the behavioral characteristics, and the critical elements of the ecosystem, exposure distributions can be estimated. The results of exposure calculation should be presented in a format that is consistent with the requirements of the dose-response functions which may later be used in a risk assessment. For example, when health risks caused by exposure over extended durations are considered, average daily exposure over the duration of exposure usually is calculated. When lifetime risks are considered, average daily exposure over a lifetime usually is calculated. In contrast, when health risks caused by exposures over short durations are considered, exposure rates are calculated over short time intervals to ensure that peak risks are defined. Many exposure assessments are based on the average exposure occurring over the exposure period. The range of possible exposures is usually divided into intervals, and the exposures within each interval are counted. The reuslts can be presented in a tabular form or as a histogram.

The population residing in a specific geographic area may be exposed to a substance from several exposure routes. For each exposure route, exposure of individuals in these populations may be determined by summing the contribution of all sources to the exposure route. When exposures involve more than one exposure route, the relative amounts of a substance absorbed is usually route dependent. Consequently, total absorbed dose estimates must account for these differences. Because EPA regulates sources of releases, the contribution to exposures from each type of source being considered should be displayed. Exposure estimates should be presented for each significant exposure route (i.e., those routes consistent with the regulatory purpose), and the results should be tabulated in such a way that total externally applied and absorbed dose can be determined.

b. *Human Dosimetry and Monitoring.* Biological monitoring of human body fluids and tissues for substances or their metabolites can be used to estimate current or past exposure to chemicals. When analytical methods are available, chemicals that have been absorbed into the body can be measured in body tissue and fluid. Such measurements can be used to estimate exposure. However, the substances to which humans are exposed are highly variable in the degree to which they leave in the body reliable indicators of exposure. Furthermore, although a compound may be relatively easy to detect in body tissue, for some compounds, attributing body burdens to specific environmental releases may be difficult because of limited ability to obtain environmental monitoring data.

c. *Development of Exposure Scenarios and Profiles.* Depending on the scope of the exposure assessment, the total exposure may be fractionated into one or more "exposure scenarios" to facilitate quantification. As an example, Table 1 lists seven very broad scenarios: Occupational, Consumer, Transportation, Disposal, Food, Drinking Water, and Ambient. For each of the scenarios, the major topics necessary to quantify exposure include sources, pathways, monitoring, and population

characteristics. Investigation of only one scenario may be necessary for the scope of some assessments. For example, a pesticide application exposure assessment may consider the occupational scenario which would address the exposure to applicators and populations in the vicinity of the site. An exposure assessment around a hazardous waste site may focus on the disposal scenario. The exposure assessment also may consider other scenarios. The more extensive and comprehensive the scope, the more scenarios are usually involved.

TABLE 1. EXPOSURE ASSESSMENT NEEDS FOR VARIOUS EXPOSURE SCENARIOS

Exposure scenario	Source needs	Fate needs	Population characteristics needs	Monitoring needs
Occupational (chemical production)	Site/plant locations in-plant/on-site materials balance.	Physical and chemical properties models.	Workers, families, population around sites/plants.	In-plant/on-site releases, ambient levels surrounding site/plants. human monitoring.
Consumer (direct use of chemical or inadvertant use).	Consumption rates, distribution pattern amounts in products.	Physical and chemical properties, shelf life release rates, models.	Consumers	Levels in products releases.
Transportation/storage/spills	Patterns of distribution and transportation; models for spills.	Physical and chemical properties, environmental fate models.	Storage, transportation workers, general population in area.	Releases, ambient levels.
Disposal (include incineration, landfill).	Materials balance around disposal method, efficiency, releases to environment.	Fate within disposal process; environmental fate of releases; models.	Workers at site of disposal, general population around site.	Releases, levels at various points within process, ambient levels.
Food	Food chain, packaging, additives	Food chain models, fate during preparation or processing of food.	General population, nonhuman population.	Levels in food, feedstuff; food chain sampling.
Drinking water	Groundwater, surface water, distribution system.	Leach rates from pipes, chlorination processes, fate in water; models.	General population	Levels in drinking water, groundwater, surface water, treatment plants.
Ambient	Releases to environment; air, land, water.	Environmental fate models	General population, nonhuman population.	Ambient Air, water, soil, etc.; human monitoring.

It will usually be advantageous in performing an exposure assessment to identify exposure scenarios, quantify the exposure in each scenario, and then integrate the scenarios to estimate total exposure. In this "integrated exposure analysis," summation of independent exposures from different scenarios (keeping exposure routes separate) often will result in a breakout of exposure by subpopulations, since the individual scenarios usually treat exposure by subpopulation. Therefore, the integration of the scenarios, or integrated exposure analysis, will often result in an exposure profile.

For each exposed subpopulation, exposure profiles should include the size of the group, the make-up of the group (age, sex, etc.), the source of the agent, the exposure pathways, the frequency and the intensity of exposure by each route (dermal, inhalation, etc.), duration of exposure, and the form of the agent when exposure occurs. Assumptions and uncertainties associated with each scenario and profile should be clearly discussed.

d. *Evaluation of Uncertainty.* (1) *Introduction.* Often an exposure assessment progresses through several stages of refinement. The purpose of these Guidelines is to present methods appropriate for characterization of uncertainty for assessments at various stages of refinement, from assessments based upon limited initial data to those based upon extensive data.

The appropriate method for characterizing uncertainty for an exposure assessment depends upon the underlying parameters being estimated, the type and extent of data available, and the estimation procedures utilized. The uncertainty of interest is always with regard to the population characteristic being estimated. For example, when the population distribution of exposures is being estimated, characterization of uncertainty addresses the possible differences between the estimated distribution of exposure and the true population distribution of exposure.

An exposure assessment quantifies contact of a substance with affected population members (human or nonhuman subjects). The measure of contact (e.g., environmental level of absorbed dose) depends upon what is needed to predict risk. An integrated exposure assessment quantifies this contact via all routes of exposure (inhalation, ingestion, and dermal) and all exposure pathways (e.g., occupational exposure, exposure from consumption of manufactured goods, etc.). The exposed population generally is partitioned into subpopulations such that the likely exposure of all members of a subpopulation is attributable to the same sources. The exposure for each member of a subpopulation is then the sum of exposures over a fixed set of sources and pathways. The measured or estimated exposures for members of a subpopulation are ideally used to estimate the subpopulation distribution of exposure or characteristics thereof. However, a lack of sufficient information sometimes precludes estimation of the subpopulation distributions of exposure and only summary measures of this distribution, such as the mean, minimum, maximum, etc., are estimated. In each case characterization of uncertainty for the exposure assessment primarily addresses limitations of the data and the estimation procedures. The proportions of the population members in the individual subpopulations are usually estimated and can be used (by combining estimated distributions for the subpopulations) to estimate the distribution of exposure for the total population. Uncertainty concerning the sizes of the subpopulations should be addressed by discussing limitations of the data and estimation methods as well as by tabulating confidence interval estimates for the population sizes whenever possible.

(2) *Assessments Based Upon Limited Initial Data.* The initial exposure assessment for a substance may be based upon limited data for exposure and/or input variables for an exposure prediction model (i.e., an equation that expresses exposure as a function of one or more input variables). These data might be either extant data or data produced by an initial small-scale study. The initial limited data frequently are insufficient to permit estimation of the entire distribution of exposure. Instead, summary measures of this distribution, such as the mean, minimum, and maximum, are usually estimated.

If the assessment is based upon measured exposures, the methods used to characterize uncertainty depend mainly upon whether or not the data result from a probability sample for which the probability of inclusion is known for each sample member. Characterization of uncertainty for an assessment based upon a probability sample of exposures is discussed later in section 8. d. (5). If the measured exposures are not based upon a probability sample, acknowledgement

that no strictly valid statistical inferences can be made beyond the units actually in the sample is one aspect of the characterization of uncertainty. If inference procedures are implemented, the assumptions upon which these inferences are based (e.g., treatment of the sample as if it was a simple random sample, or assumption of an underlying model) should be explicitly stated and justified. The data collection methods and inherent limitations of the data should also be discussed.

An initial exposure assessment also may be based upon limited data, such as estimated ranges, for input variables for an exposure prediction model. The exposure prediction model would be derived from a postulated exposure scenario that describes the pathways from sources to contact with population members. If the data were only sufficient to support estimates of the ranges of the input variables, the exposure assessment might be limited to a sensitivity analysis. The purpose of the sensitivity analysis would be to identify influential model input variables and develop bounds on the distribution of exposure. A sensitivity analysis would estimate the range of exposures that would result as individual model input variables were varied from their minimum to their maximum possible values with the other input variables held at fixed values, e.g., their midranges. The overall minimum and maximum possible exposures usually would be estimated also. For an exposure assessment of this type, the uncertainty would be characterized by describing the limitations of the data used to estimate plausible ranges of model input variables and by discussing justification for the model. Justification of the model should include a description of the exposure scenario, choice of model input variables, and the functional form of the model. Sensitivity to the model formulation also can be investigated by replicating the sensitivity analysis for plausible alternative models.

If the maximum possible exposure estimated by the sensitivity analysis presented no significant health risk, there might be no need to refine the assessment. If both the minimum and maximum exposures presented a potentially significant health risk, it would be known that the exposure scenario represented a significant health problem without refining the assessment. When the minimum exposure estimate does not present a potentially significant health risk and maximum dose, then greater importance is placed on choosing a summary parameter of the exposure distribution (e.g., the mean or percentile) as the basis for a regulatory decision. Refining the exposure assessment to estimate the distribution of exposure permits selection of any summary parameter (minimum, maximum, mean, or percentile, etc.) as the basis for regulatory decision.

The sensitivity analysis can be enhanced by computing the predicted exposures that result from all possible input variable combinations. If each input variable has only a finite set of possible values, the set of all possible combinations of the input variables can be formed, and the predicted exposure can be computed for each combination. These exposure predictions can be used to form a distribution of exposures by counting the number of occurrences of each exposure level or interval of exposures. This is equivalent to estimating the distribution of exposures that results from treating all input variable combinations as equally likely. This procedure can also be applied by discretizing continuous input variables and representing them by equally-spaced points. In the limit, as the equal spaces become small and the number of points becomes large, the distribution of exposure that results from counting occurrences of exposure levels is equivalent to estimating the distribution of exposures that results from statistically-independent, continuous input variables with uniform distributions on the estimated ranges. This estimated distribution of exposure values can be produced by the methods of mathematical statistics or Monte Carlo simulation. The Monte Carlo method consists of randomly generating input variate values and using these to compute corresponding exposure levels, generating an exposure distribution via many iterations. Interpretation of statistics based upon this exposure distribution would be in terms of the equally likely input variable combinations. For example, the 95th percentile of this distribution would be the exposure level exceeded by only 5% of the exposures resulting from treating all combinations of input variable values as equally likely. Although this distribution of exposures cannot be interpreted as an estimate of the population distribution (unless the input variables actually are statistically independent and uniformly distributed), it provides additional information for making regulatory decisions. Characterization of uncertainty would include a discussion of limitations of the data and justification for the model as discussed above. Sensitivity to model formulation could also be investigated by estimating the distribution of exposure that results from using the same uniform input variable distributions with plausible alternative models and comparing the estimated percentiles.

(3) *Assessments Based Upon Subjective Estimates of Input Variable Distributions.* If a model has been formulated that expresses exposure as a function of one or more input variables, the methods of mathematical statistics or Monte Carlo simulation can be used to estimate the population distribution of exposure from an estimate of the joint distribution of the model input variables. Ideally model input variables should be represented by empirically validated probability distributions. In some cases, it may be possible to formulate an estimate of the joint distribution of model input variables from discussions with subject-matter experts (e.g., via histograms for statistically-independent input variables). The estimated population distribution of exposure will be equivalent to the distribution discussed in section 6. d. (2) for equally likely combinations of input variable values only when the input variable distributions supported are independent uniform distributions. When qualitative knowledge of input variable distributions is ued to estimate the population distribution of exposure, uncertainty is characterized by discussing justification for the presumed model and input variable distributions. Alternative models and/or alternative input variable distributions also should be discussed. Sensitivity to these alternatives can be investigated by estimating the distributions of exposure that result from plausible alternatives and comparing the percentiles of the estimated exposure distributions. All available data, even if data are limited, should be used to validate the presumed input variable distributions and the predicted distribution of exposure.

(4) *Assessments Based Upon Data for Model Input Variables.* The exposure assessment based upon an estimate of the joint probability distribution for model input variables can be refined by collecting sample survey data for model input variables for a sample of population members. The population distribution of exposure can then be estimated by computing the expected exposure for each sample member based upon the model. These expected exposures can be used to directly compute confidence interval estimates for percentiles of the exposure

distribution. Alternatively, the sample survey data can be used to compute joint confidence interval estimates for percentiles of the input variable distribution, which can then be used to generate confidence interval estimates for percentiles of the exposure distribution. In either case, the interval estimates for percentiles of the exposure distribution are a useful quantitative characterization of uncertainty.

Characterization of uncertainty for the exposure assessment would contain a thorough discussion of limitations of the data and justification for the model used to compute expected exposures. The design of the sample survey used to produce the data base should also be discussed. If a probability sample were not used, the lack of a probability sample would be an additional source of uncertainty. Any assumptions used in computing the confidence interval estimates, such as independence of model input variables, should be explicitly stated and justified. Sensitivity to model formulation can be investigated by estimating the distribution of exposure for plausible alternative models and comparing the estimated percentiles, if sample survey data have been collected for the input variables of the alternative models. Appropriate available data for exposure should be used to validate the predicted distribution of exposure. If specific probability distributions have been presumed for any model input variables, the data for these variables should be used to test for goodness of fit for these distributions.

(5) *Assessments Based Upon Data for Exposure.* A major reduction in the uncertainty associated with an exposure assessment can be achieved by directly measuring the exposure for a sufficiently large sample of members of the affected population. This reduction in uncertainty is achieved by eliminating the use of a model to predict exposure. The measured exposure levels can be used to directly estimate the population distribution of exposure and confidence interval estimates for percentiles of the exposure distribution. Direct confidence interval estimates also can be computed for other characteristics of the exposure distribution, such as the mean exposure.

These confidence interval estimates are then the primary characterization of uncertainty for the exposure assessment. Limitations of the data and design of the sample survey used to collect the data also should be discussed. If the sample was not a probability sample, this would again be an additional source of uncertainty.

(6) *Summary.* A summary of the primary methods recommended for characterizing uncertainty in exposure assessments is presented in Table 2. Virtually all exposure assessments, except those based upon measured exposure levels for a probability sample of population members, rely upon a model to predict exposure. The model may be any mathematical function, simple or complex, that expresses an individual's exposure as a function of one or more input variables. Whenever a model that has not been validated is used as the basis for an exposure assessment, the uncertainty associated with the exposure assessment may be substantial. The primary characterization of uncertainty is at least partly qualitative in this case, i.e., it includes a description of the assumptions inherent in the model and their justification. Plausible alternative models should be discussed. Sensitivity of the exposure assessment to model formulation can be investigated by replicating the assessment for plausible alternative models.

TABLE 2.—SUMMARY OF PRIMARY METHODS FOR CHARACTERIZING UNCERTAINTY FOR EXPOSURE ASSESSMENTS

Type and extent of data	Population characteristic being estimated	Primary methods for characterizing uncertainty	
		Qualitative methods	Quantitative methods
Measured exposures for a large sample of population members.	Distribution of exposure	1. Limitations of the survey design and measurement techniques.	1. Confidence interval estimates for percentiles of the exposure distribution. 2. Goodness of fit for exposure models, if any have been postulated.
Measured exposures for a small sample of population members.	Summary parameter(s) of the exposure distribution, e.g., mean or a percentile.	1. Limitations of the survey design and measurement techniques.	1. Confidence interval estimates for the summary parameter(s). 2. Goodness of fit for exposure models, if any have been postulated.
Measured model input variables for a large sample of population members.	Distribution of exposure	1. Limitations of the survey design and measurement techniques. 2. Validity of the exposure model	1. Confidence interval estimates for percentiles of the exposure distribution. 2. Goodness of fit for input variable distribution functions, if any have been postulated. 3. Estimated distribution of exposure based upon alternative models.
Estimated distributions of model input variables.	Distribution of exposure	1. Validity of the exposure model 2. Limitations of the data or other basis for the input variable distributions.	1. Confidence interval estimates for percentiles of the exposure distribution. 2. Goodness of fit for input variable distributions, if input variable data are available. 3. Estimated distribution of exposure based upon alternative models.
Limited data for model input variables	Minimum, maximum, and range of the exposure distribution.	1. Limitations of the data 2. Validity of the exposure model	If input variable data are very limited, e.g., some extant data collected for other purposes, quantitative characterization of uncertainty may not be possible.

When an exposure assessment is based upon directly measured exposure levels for a probability sample of population members, uncertainly can be greatly reduced and described quantitatively. In this case, the primary sources of uncertainty are measurement errors and sampling errors. The effects of these sources of error are measured quantitatively by confidence interval estimates of percentiles of the exposure distribution. Moreover, the sampling errors can be limited by taking a large sample.

Whenever the latter is not feasible, it is sometimes possible to obtain at least some data for exposure and model input variables. These data should be used to assess goodness of fit of the model and/or presumed distributions of input variables. This substantially reduces the amount of quantitative uncertainty for estimation of the distribution of exposure and is strongly recommended. It is recognized, however, that it may not be feasible to collect such data.

9. References

The references should contain a listing of all reports, documents, articles, memoranda, contacts, etc. that have been cited in the report.

10. Appendices

The appendices may contain such items as memoranda and letters that are not readily accessible, other tables of monitoring data, detailed lists of emission sources, detailed tables of exposures, process flow diagrams, mathematical model formulations, or any other item that may be needed to describe or document the exposure assessment.

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PART 3 - MUTAGENICITY RISK ASSESSMENT

federal register

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Part IX

Environmental Protection Agency

Proposed Guidelines for Mutagenicity Risk Assessment; Request for Comments

ENVIRONMENTAL PROTECTION AGENCY

[FRL-2706-6]

Proposed Guidelines for Mutagenicity Risk Assessment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed Guidelines for Mutagenicity Risk Assessment and Request for Comments.

SUMMARY: The U.S. Environmental Protection Agency is proposing Guidelines for Mutagenicity Risk Assessment (Guidelines). These Guidelines are proposed for use within the policy and procedural framework provided by the various statutes that EPA administers to guide Agency analysis of mutagenicity data. We solicit public comment and will take public comment into account in revising these Guidelines. These Guidelines will be reviewed by the Science Advisory Board in meetings now tentatively scheduled for April 1985.

These proposed Guidelines were developed as part of a broad guidelines development program under the auspices of the Office of Health and Environmental Assessment (OHEA), located in the Agency's Office of Research and Development. Consonant with the role of OHEA's Reproductive Effects Assessment Group (REAG) as the Agency's senior health committee for mutagenicity assessment, the Guidelines were developed by an Agency-wide working group chaired by the REAG.

DATES: Comments must be postmarked by January 22, 1985.

ADDRESSES: Comments may be mailed or delivered to: Dr. David Jacobson-Kram, Reproductive Effects Assessment Group (RD-689), Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, 401 M Street SW., Washington, DC 20460.

FOR FURTHER INFORMATION CONTACT: Dr. David Jacobson-Kram, Telephone: 202-382-7336.

SUPPLEMENTARY INFORMATION: Public comments received as a result of the proposed guidelines for Mutagenicity Risk Assessment, which was published in the **Federal Register** [45(221):74984-74988) on November 13, 1980, have been addressed. The guidelines published here reflect the suggestions that were provided during that initial comment period. A new draft of these Guidelines, taking into account the earlier public comments, was recently sent for review to approximately 14 scientists in the field of chemical mutagenesis within government, universities in the United States, and the private sector. Comments received from these reviews, generally favorable, were also taken into account in developing the Guidelines proposed here.

References and supporting documents used in the preparation of these Guidelines as well as comments received are available for inspection and copying at the Public Information Reference Unit (202-382-5926), EPA Headquarters Library, 401 M Street, SW, Washington, DC, between the hours of 8:00 a.m. and 4:30 p.m.

Dated: November 9, 1984.

William D. Ruckelshaus,

Administrator.

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I. Introduction

On November 13, 1980, the U.S. Environmental Protection Agency (EPA) published purposed guidelines for Mutagenicity Risk Assessment (*1*) and solicited comments on those guidelines. The proposed guidelines of 1980 described the procedures that the Agency would follow to evaluate the genetic risks associated with the exposure of humans to chemical mutagens. These procedures incorporated a weight-of-evidence approach that considered the quality and adequacy of all the available data on a chemical substance in order to make qualitative, and, where possible, quantitative evaluations of mutagenic potential. The Agency stated that mutagenicity risk assessments prepared pursuant to the proposed guidelines would be utilized within the requirements and constraints of the applicable statutes that the Agency administers to arrive at regulatory decisions concerning mutagenicity.

The current proposed Guidelines address the comments received in response to the Agency's proposed mutagenicity risk assessment guidelines and provide the basis for the Agency's risk assessments for mutagenicity. These Guidelines, which adopt the general approach set forth in the 1980 proposal, reflect additional changes made in response to the comments and to new scientific information generated since the time of the proposal.

The current proposed Guidelines reflect changes made in response to the public comments to the proposed guidelines of 1980. These changes dealt primarily with the section addressing the weight-of-evidence approach. This section has been expanded to define "sufficient," "suggestive," and "limited" evidence for potential human germ-cell mutagenicity and to include two categories of evidence, "sufficient" and "suggestive" for chemical interaction with the gonads. Also, in the quantitative assessment section, the dominant skeletal and dominant cataract tests have been added to the list of systems for possible use in estimating the magnitude of genetic risks. Other minor changes have been made in the text for clarification.

A draft of the current proposed Guidelines was submitted for review to individuals from industry, educational institutions, enivornmental groups, and other government agencies. These reviews were useful in revising the Guidelines.

The Agency has not attempted to provide in the current proposed Guidelines a detailed discussion of the mechanisms of mutagenicity or of the various test systems that are currently in use to detect mutagenic potential. Background information on mutagenicity and mutagenic test systems is available in "Identifying and Estimating the Genetic Impact of Chemical Environmental Mutagens," National Academy of Sciences (NAS) Committee on Chemical Environmental Mutagens (*2*), as well as in other recent publications(*3, 4*).

For the information of the reviewer, Chapter II discusses the comments that were received in response to the proposed guidelines of 1980 and the Agency's responses to those comments. The current proposed Guidelines for Mutagenicity Risk Assessment, for which comments are currently invited, are described in Chapter III. The Agency anticipates that, as methods for mutagenicity risk assessment are

refined, and more information becomes available in the area of mutagenicity, revisions to these Guidelines may be desirable or necessary.

II. Comments Received From the Federal Register Publication of the Proposed 1980 Guidelines and Agency Responses to These Comments

As stated in the Introduction, the current Guidelines are being proposed to encourage further public comment. For the information of the reviewer, a summary of the public comments received in response to the proposed guidelines of 1980 and the Agency responses to those comments are presented here.

A total of 34 comments were received, 17 from manufacturers of regulated products, eight from associations, four from individuals, three from educational institutions, and one each from a private consulting laboratory and a government agency. Many responses noted that the proposed guidelines of 1980 were timely and appropriate and praised the Agency for initiating procedures for scientific evaluation of mutagenicity data. Other commenters felt that the proposed guidelines were "premature." Various reasons were given for this position: (1) The mechanisms by which mutations occur are not understood; (2) the data bases for many mutagenicity tests are limited, and hence the tests have not been validated; (3) the Agency should wait until the EPA Gene-Tox Program is completed; and (4) epidemiologic studies have failed to document chemically-induced mutations in humans.

It is the opinion of the Agency that there is a need for mutagenicity guidelines because various statutes administered by the Agency provide the authority to regulate chemicals on the basis of mutagenicity. The purpose of the current proposed Guidelines is to promote Agency-wide consistency in the evaluation of mutagenicity data. In response to the specific concerns enumerated above relating to the issue of prematurity, the Agency has concluded that the comments do not provide an adequate basis for delaying the development of mutagenicity guidelines. Specifically, with regard to the first comment that the mechanisms by which mutations occur are not understood, the Agency does not believe that a full understanding of all aspects of these mechanisms is necessary to evaluate the mutagenic potential of chemicals in the environment. Additionally, the comment ignores the extensive body of data on specific chemical DNA adducts, repair processes, and mutational expression that enable description of the mutational process in specific physiochemical terms (*2*).

With regard to the second comment, the Agency agrees that the data bases for many mutagenicity tests are limited; however, the Agency does not agree that the validity of a test is a function of the size of the data base. Validity is the extent to which a test measures the particular biological end point of interest and should not be confused with sensitivity, the proportion of known mutagens that are positive in a system, or specificity, the proportion of nonmutagens that are negative. Hence, a mutagenesis assay is validated when its ability to detect a heritable genetic change is demonstrated.

In response to the third comment, the Agency does not believe it is necessary to wait for completion of the Gene-Tox Program before issuing guidelines for evaluating mutagenicity data. The Agency acknowledges that future scientific developments can be expected to affect the methods for the evaluation of mutagenicity data. Such developments may stem from phase II of the Gene-Tox Program (which focuses on test applications) as well as from other collaborative activities in basic and applied research. However, the Agency believes that the current Guidelines, as written, can accommodate new information.

With respect to the fourth comment, the Agency does not agree that the failure to identify a chemical as a known human mutagen is justification for not proposing guidelines to evaluate mutagenicity data. Despite the difficulty in translating changes in mutation rate to alterations in disease frequency, the NAS Committee on Chemical Environmental Mutagens has concluded that the net effect of an increase in mutation rate is harmful because almost all mutants with any detectable effect are deleterious (*2*).

A. Comments on the Introduction

Many commenters on the proposed guidelines of 1980 were critical of the statement, "Since the prospect of curing most heritable diseases caused by mutagens in the near future is unlikely, minimizing exposure to mutagens is among the best available means to protect against further deterioration of the human gene pool." At the present time there is no direct evidence in humans that heritable diseases are being caused by chemical mutagens, and there is no evidence of deterioration of the gene pool. This sentence has been deleted.

Several commenters objected to the statement, "Mutations are largely recognized as being deleterious," and pointed out that many mutations are silent or have no effect. In the current proposed Guidelines, this sentence has been changed to read, "It is generally recognized that most mutations that are phenotypically expressed are in some ways deleterious to the organism carrying them."

One commenter requested an explanation of how mutagenicity guidelines would be administered and requested a statement indicating requirements for genetic toxicology testing in premarket manufacturing notices. The Agency believes that the language in the current proposed Guidelines clearly states that they will be used to assess risks associated with human exposure to chemical mutagens. Requirements for genetic toxicology testing are the responsibility of the appropriate Agency office.

B. Concepts Relating to Heritable Genetic Risk

One commenter objected to the definition of a mutagen because it was not limited to stable and heritable alternations in the DNA. The Agency agrees that the ultimate end point of concern for the purpose of the current proposed Guidelines is heritable and stable mutation. For gene mutations, heritability is an obvious and necessary component, since all tests used to detect gene mutations actually detect mutant cells or organisms that are descendants of the treated cells. The same is not always true for certain cytogenetic end points, such as chromatid breaks, etc., which may be detected in the same cell generation in which they occur. Since these latter end points provide information relevant to heritable mutation, they will be considered in any mutagenicity assessment. As a result, the Agency feels that the general definition of a mutagen as used in these Guidelines is appropriate.

C. Testing Systems

One commenter felt that most cytogenetic end points that are routinely evaluated (e.g., chromosome breaks, micronuclei) are not transmitted, and therefore, are not germane to the issue of heritable mutation. The Agency disagrees. Although it is clear that cells that carry such aberrations generally do not reproduce, other related aberrations (i.e., balanced translocations, inversions, small duplications, and deficiencies) are compatible with cell survival in germ cells and can be transmitted. Additionally, there is no evidence indicating that the non-transmissible aberrations occur by

mechanisms different from transmissible aberrations.

Several commenters requested that the Agency establish minimal criteria by which assays are to be judged for use in risk assessment determinations. The Agency believes that to list a specific set of criteria that must be met for each assay before the Agency evaluates data would be overly restrictive and inappropriate. Data generated in any system that measures or correlates with a true genetic end point may provide some useful information. The Agency believes that the general protocols and criteria for data evaluation established by the expert committees of the Phase-I Gene-Tox Program as well as other sources provide sufficient guidance for those planning to conduct mutagenicity tests.

D. Weight-of-Evidence Approach

Several commentes suggested that the weight-of-evidence section required clarification of the phrase, "positive response in any two different point mutation test systems," because this phrase may be subject to various interpretations. The Agency agrees that the section as proposed may have been subject to misinterpretation. Therefore, the current proposed Guidelines define sufficient evidence of potential human mutagenicity to include positive responses in any two different gene mutation test systems (one of which utilized mammalian cells) or positive responses in two different somatic cytogenetic tests (one of which utilizes mammalian cells), coupled with sufficient evidence of germ-cell interaction in both caes. Alternatively, the combination of a positive finding in one mammalian gene mutation assay and one mammalian cytogenetics test and sufficient evidence of germ-cell interaction also provides sufficient evidence of potential human mutagenicity. The demostration of heritable effects induced in mammalian germ cells is by itself sufficient evidence for mutagenicity.

Many commenters objected to the criterion that considers a chemical mutagen a potential human germ-cell mutagen if there is "evidence for the presence of the test substance and/or its matabolites in mammalian gonadal organs." First, they pointed out that the presence of a chemical in the testis or ovary does not necessarily mean it has reacted with germ-cell DNA. Such studies are generally performed with radiolabeled chemicals, and it is possible that metabolism of the compound could result in incorporation of the radiolabel into normal cellular macromolecules. The Agency recognizes the shortcomings in the various criteria used to determine whether a mutagen interacts with germ-cell DNA. As a result, in the current Guidelines, two categories of such evidence have been adopted. Sufficient evidence that a mutagen interacts in the mammalian gonad will be the demonstration that an agent interacts with germ-cell DNA or other chromatin constituents, or that it induces such end points as unscheduled DNA synthesis, sister chromatid exchange (SCE), or chromosomal aberrations in germinal cells. Suggestive evidence will include advese gonadal effects following acute, subchronic, or chronic toxicity testing or adverse reproductive effects, such as decreased fertilization index, reduced sperm count, or abnormal sperm morphology.

One commenter suggested that the Agency develop a scale of weighting tests which would place more emphasis on test systems more relevant to human beings. The Agency has explored the possibility of developing such a scale and has concluded that the assignment of fixed values for each test system could be overly simplistic and might not allow for the consideration of such variables as dose range, route of exposure, and magnitude of respone. The Agency believes that the scheme in the current proposed Guidelines, which generally gives greater weight to mammalian rather than submammalian assays and to germ cell rather than somatic cell data, is currently the most appropriate way to evaluate the information from a variety of systems.

E. Quantitative Assessment of Results

Several commenters expressed the opinion that it is not possible to quantitatively express the risk of genetic disease from exposure to a chemical, and therefore no attempt should be made to do so. The Agency does not suggest that it is necessarily possible to generate a numerical estimate of the genetic risk that will result from exposure to any particular chemical. It is well-recognized and documented that the mutational component of certain categories of human genetic disease is not known. However, mutagenicity data have been used to generate semi-quantitative estimates of the impact of ionizing radiation on genetic disease(*5, 6*). The current proposed Guidelines state the Agency's commitment to utilize existing relevant mutagenicity data to give some estimate of potential human mutagenicity. All such estimates will include a careful delineation of the assumptions and uncertainties associated with the assessment.

Many commenters objected to the use of "linear or nonthreshold models" for low-dose extrapolation on point mutation rates. The Agency acknowledges that linearity and the presence or absence of a threshold are separate issues. The Agency will strive to use the most appropriate extrapolation model for risk analysis and will be guided by the available data in this selection. However, it is anticipated that for whole-animal germ-cell assays, few dose points will be available to define a dose-response function. In these situations there is a theoretical basis for a linear, nonthreshold extrapolation provided that no major germ-cell killing (and thus possible cell selection) has occurred(*2, 7*).

One commenter suggested that for quantitative risk it is more appropriate to rely on tests for structural chromosomal aberrations than on gene mutations, particularly since many diseases can be more readily associated with an identifiable chromosome abnormality. The Agency agrees that associations between diseases and specific chromosomal changes can be estimated. This concept is well documented and has been discussed at length in the NAS report(*2*). However, similar estimates can be made for gene mutations, and such techniques have been used for some time for effects of ionizing radiation(*5, 6*). Because the spectrum of mutational effects induced by different chemicals is known to be variable, the Agency believes that it is necessary to perform estimates on all end points.

One commenter objected to the omission of the dominant skeletal and cataract mutation systems for quantitative risk assessment. The Agency recognizes that these dominant mutation systems do have relevance in the preparation of quantitative risk assessment along with specific-locus test systems. The current proposed Guidelines have been modified to include both types of tests.

III. Proposed Guidelines

A. Introduction

This section describes the procedures that the U.S. Environmental Protection Agency will follow in evaluating the potential genetic risk associated with human exposure to existing industrial chemicals and to pesticides. The central purpose of the health risk assessment is to provide a judgment concerning the weight of evidence that an agent is a potential human mutagen with respect to transmitted genetic changes, and, if so, how great an impact it is likely to have on public health. Regulatory

decision making involves two components: Risk assessment and risk management. Risk assessment estimates the potential adverse health consequences of exposure to toxic chemicals; risk management combines the risk assessment with the directives of the enabling regulatory legislation—together with socioeconomic, technical, political, and other considerations—to reach a decision as to whether or how much to control future exposure to the chemnicals. The issue of risk management will not be dealt with in these Guidelines.

Risk assessment is comprised of the following components: Hazard identification, dose-response assessment, exposure assessment, and risk characterization(*8*). Hazard identification is the qualitative risk assessment, dealing with the inherent toxicity of a chemical substance. The qualitative mutagenicity assessment answers the question of how likely an agent is to be a human mutagen. The three remaining components comprise quantitative risk assessment, which provides a numerical estimate of the public health consequences of exposure to an agent. The quantiative mutagenicity risk assessment deals with the question of how much mutational damage is likely to be produced by exposure to a given agent under particular exposure scenarios.

In a dose-response assessment, the relationship between the dose of a chemical and the probability of induction of an adverse effect is defined. The component generally entails an extrapolation from the high goses administered to experimental animals or noted in some epidemiologic studies to the low exposure levels expected from human contact with the chemical in the environment.

The exposure assessment identifies populations exposed to toxic chemicals, describes their composition and size, and presents the types, magnitudes, frequencies, and durations of exposure to the chemcials. This component is developed independently of the other components of the mutagenicity assessment and is addressed in separate Agency guidelines(*9*).

In risk characterization, the outputs of the exposure assessment and the dose-response assessment are combined to estimate quantitatively the mutation risk, which is expressed as either esimated increase of generic disease per generation or per lifetime, or the fractional increase in the assumed background mutation rate of humans. In each step of the assessment, the strengths and weaknesses of the major assumptions need to be presented, and the nature and magnitude of uncertainties need to be characterized.

The procedures set forth in these Guidelines will ensure consistency in the Agency's scientific risk assessments for mutagenci effects. The necessity for a consistent approach to the evaulation of mutagenic risk from chemical substances arises from the authority conferred upon the Agency by a number of statutes to regulate potential mutagens. As appropriate, these Guidelines will apply to statutes administered by the Agency, including the Federal Insecticide, Fungicide, and Rodenticide Act; the Toxic Substances Control Act; the Clean Air Act; the Federal Water Pollution Control Act; the Safe Drinking Water Act; the Resource Conservation and Recovery Act; and the Comprehensive Environmental Response, Compensation, and Liability Act. Because each statute is administered by separate offices, a consistent Agency-wide approach for performing risk assessments is desirable.

The mutagencity risk assessments prepared pursuant to these Guidelines will be utilized within the requirements and constraints of the applicable statutes to arrive at regulatory decisions concerning mutagenicity. The standards of the applicable statutes and regulations may dictate that additional considerations (e.g., the economic and social benefits associated with use of the chemical substance) will come into play in reaching appropriate regulatory decisions.

The Agency is concerned with the risk associated with both germ-cell mutations and somatic cell mutations. Mutations carried in germ cells are inherited by future generations and may contribute to genetic disease, whereas mutations occurring in somatic cells may be implicated in the etiology of several disease states, including cancer. These Guidelines, however, are only concerned with genetic damage as it relates to germ-cell mutations. The use of mutagenicity test results in the assessment of carcinogenic risk is described in the proposed Guidelines for Carcinogen Risk Assessment(*10*).

As a result of the progress in the control of infectious diseases, increases in average human life span, and better procedures for identifying genetic disorders, a considerable heritable genetic disease burden has been recognized in the human population. It is estimated that at least 10% of all human disease is related to specific genetic states, such as abnormal composition, arrangement, or dosage of genes and chromosomes(*2, 6, 11*). Such genetic diseases can lead to structural or functional health impairments. These conditions may be expressed *in utero*; at the time of birth; or during infancy, childhood, adolescence, or adult life; they may be chronic or acute in nature. As a result, they often have a severe impact upon the affected individuals and their families in terms of physical and mental suffering and economic losses, and upon society in general, which often becomes responsible for institutional care of severely affected individuals. Some examples of genetic conditions are Down's and Klinefelter's syndromes, cystic fibrosis, hemophilia, sickle cell anemia, and achondroplastic dwarfism. Other commonly recognized conditions that are likely to have a genetic component include hypercholesterolemia, hypertension, pyloric stenosis, glaucoma, allergies, several types of cancer, and mental retardation. These disorders are only a few of the thousands that are at least partially genetically determined(*12*).

Estimation of the fraction of human genetic disease that results from new mutation is difficult, although in certain specific cases insights are available(*13*). It is clear that recurring mutation is important in determining the incidence of certain genetic conditions, such as some chromosomal aberration syndromes (e.g., Down's) and rare dominant and X-linked recessive diseases (e.g., achondroplasia and hemophilia A). For other single-factor conditions (e.g., sickle-cell anemia and color blindness) and certain multifactorial conditions (e.g., pyloric stenosis), the contribution of new mutations to disease frequency is probably very small. However, it is generally recognized that most mutations that are phenotypically expressed are in some ways deleterious to the organism receiving them. Adverse effects may be manifested at the biochemical, cellular, or physiological levels of organization. Although mutations are the building blocks for further evolutionary change of species, it is believed that increases in the mutation rate above the spontaneous level could lead to an accumulation of deleterious mutations in the human population and, to a varying extent, an increased frequency of expressed genetic disease.

Life in our technological society results in exposure to many natural and synthetic chemicals. Some have been shown to have mutagenic activity in mammalian and submammalian test systems, and thus may have the potential to increase genetic damage in the human population. Chemicals exhibiting mutagenic activity in various

test systems have been found distributed among foods, tobacco, drugs, food additives, cosmetics, industrial compounds, pesticides, and consumer products. As our knowledge of genetics and disease etiology increases, and techniques for detecting mutations in human beings improve, we may become aware of chemically-induced human genetic effects. The extent to which exposure to natural and synthetic environmental agents may have increased the amount of genetic damage in the present human population and contributed to the mutational "load" that will be transmitted to future generations is unknown at this time. However, for the reasons cited above, it seems prudent to limit exposures to potential human mutagens.

1. Concepts Relating to Heritable Mutagenic Risk

For the purposes of these Guidelines, a mutagen is considered a chemical substance or mixture of substances that can induce alterations in the DNA of either somatic or germinal cells. The mutagenicity of physical agents (e.g., radiations) is not addressed here. There are several mutagenic end points of concern to the Agency. These include point mutations (i.e., submicroscopic changes in the base sequence of DNA) and structural or numerical chromosome aberrations. Structural aberrations include deficiencies, duplications, inversions, and translocations, whereas numerical aberrations are gains or losses of whole chromosomes (e.g., trisomy, monosomy) or sets of chromosomes (haploidy, polyploidy).

It is conceivable that only one or a few molecules of an active compound may be sufficient to cause certain types of heritable changes in DNA. Mutagenic effects may also come about through mechanisms other than chemical alterations of DNA. Among these are interference with normal DNA synthesis, or induction of DNA misrepair, DNA methylation, abnormal nuclear division processes, or lesions in non-DNA targets (e.g., protamine, tubulin).

The best evidence that an agent induces heritable mutations in human beings would be epidemiologic data indicating a strong association between chemical exposure and a heritable response. Such data do not exist at this time because any specific mutation is a rare event, and only a small fraction of the estimated thousands of human genes and conditions are currently useful as markers in estimating mutation rates. Human genetic variability, small numbers of offspring per individual, and long generation times further complicates such studies. In addition, only dominant mutations, some sex-linked recessive mutations, and certain chromosome aberrations can be detected in the first generation after their occurrence. Conditions caused by autosomal recessive mutations (which appear to occur more frequently than dominants) or by interaction of multiple factors may go unrecognized for many generations. Therefore, in the absence of human germ-cell data, it is appropriate to rely on data from experimental animal systems.

Despite species differences in metabolism, DNA repair, and other physiological processes affecting chemical mutagenesis, the virtual universality of DNA as the genetic material and of the genetic code provides a rationale for using various nonhuman test systems to predict the intrinsic mutagenicity of test chemicals. Additional support for the use of nonhuman systems is provided by the observation that chemicals causing genetic effects in one species or test system frequently cause similar effects in other species or systems. There also exists evidence that chemicals can induce genetic damage in somatic cells of exposed humans. For example, high doses of mutagenic chemotherapeutic agents have been shown to cause chromosomal abnormalities(*14*), sister chromatid exchange(*14*), and, quite probably, point mutations in human lymphocytes exposed *in vivo*(*15*). While these results are not in germ cells, they do indicate that it is possible to induce mutagenic events in human cells *in vivo*. Furthermore, a wide variety of different types of mutations have been observed in humans including numerical chromosome aberrations, translocations, base-pair substitutions, and frameshift mutations. Although the cause of these mutations is uncertain, it is clear from these observations that the human germ-cell DNA is subject to the same types of mutational events that are observed in other species and test systems.

Certain test systems offer notable advantages: Cost; anatomical, histological, and/or metabolic similarities to humans; suitability for handling large numbers of test organisms; a large data base; and a basis for characterizing genetic events(*10*).

2. Test Systems

Many test systems are currently available that can contribute information about the mutagenic potential of a test compound with respect to various genetic end points. These tests have recently been evaluated through the EPA Gene-Tox Programs and the results of Phase I have been published(*4*). The Agency's Office of Pesticides and Toxic Substances has published various testing guidelines for the detection of mutagenic effects(*16, 17*).

Test systems for detecting point mutations include those in bacteria, eukaryotic microorganisms, higher plants, insects, mammalian somatic cells in culture, and germinal cells of intact mammals (e.g., the mouse specific-locus test). Positive results in a mouse germinal gene-mutation test argue strongly that a chemical is a potential human mutagen because such tests demonstrate that the mutations occur in mammalian germinal cells and are transmitted to the next generaton. However, because large numbers of offspring must usually be generated, it is not expected that many chemicals will be tested using these systems. To obtain data on a large number of environmental chemicals, it will be necessary to rely on other tests to identify and characterize hazards from gene mutations.

Test systems for detecting structural chromosome aberrations have been developed in a variety of organisms including higher plants, insects, fish, birds, and several mammalian species. Many of these assays can be performed *in vitro* or *in vivo*, and in either germ or somatic cells. Procedures available for detecting structural chromosome aberrations in mammalian germ cells include measurement of heritable translocations or dominant lethality, as well as direct cytogenetic analyses of germ cells and early embryos in rodents.

Some chemicals may cause numerical chromosome changes (i.e., aneuploidy) as their sole mutagenic effect. These agents may not be detected as mutagens if evaluated only in tests for DNA damage, gene mutations, or chromosome breakage and rearrangement. Therefore, it is important to consider tests for changes in chromosome number in the total assessment of mutagenic hazards. Although tests for the detection of variation in the chromosome number are still at an early stage of development, systems exist in such diverse organisms as fungi, Drosophila, mammalian cells in culture, and intact mammals (e.g., mouse X-chromosome loss assay). Nondisjunction and chromosome lagging are recognized sources of numerical aberrations. Aneuploidy can also arise from chromosome breakage and reunion followed by segregation(*18*). The mechanmisms by which nondisjunction occurs are not well understood. However, proteins (e.g., spindle apparatus), rather than DNA, may be

the target molecules for at least some mechanisms of induced nondisjunction.

Other end points that provide information bearing on the mutagenicity of a chemical can be detected by a variety of test systems. Such tests measure DNA damage in eukaryotic or prokaryotic cells, unscheduled DNA synthesis in mammalian somatic and germ cells, mitotic recombination and gene conversion in yeast, and sister-chromatid exchange in mammalian somatic and germ cells. Results in these assays are useful because the induction of these end points often correlates positively with the potential of a chemical to induce mutations.

In general, for all three end points (i.e., point mutations and numerical and structural aberrations) the Agency will place greater weight on tests conducted in germ cells than in somatic cells, on tests performed *in vivo* rather than *in vitro*, in eukaryotes rather than prokaryotes, and in mammalian species rather than in submammalian species. Formal numerical weighting systems have been developed(*19*); however, the Agency has concluded that these do not readily accommodate such variables as dose range, route of exposure, and magnitude of response.

The Agency anticipates that from time to time data from chemically-exposed human beings will be available (e.g., cytogenetic markers in peripheral lymphocytes). When posssible, the Agency will use such data in conjunction with other studies for the purpose of performing risk assessments.

The test systems mentioned previously are not the only ones that will provide evidence of mutagenicity or related DNA effects. These systems are enumerated merely to demonstrate the breadth of the available techniques for characterizing mutagenic hazards, and to indicate the types of data that the Agency will consider in its evaluation of mutagenic potential of a chemical agent. Most systems possess certain limitations that must be taken into account. The selection and performance of appropriate tests for evaluating the risks associated with human exposure to any suspected mutagen will depend on sound scientific judgment and experience, and may necessitate consultation with geneticists familiar with the sensitivity and experimental design of the test system in question. In view of the rapid advances in test methodology, the Agency expects that both the number and quality of the tools for assessing genetic risk to human beings will increase with time. The Agency will closely monitor developments in mutagenicity evaluation and will refine its risk assessment scheme as better test systems become available.

B. Qualitative Assessment (Hazard Identification)

The assessment of potential human germ-cell mutagenic risk is a multistep process. The first step is an analysis of the evidence bearing on a chemical's ability to induce mutagenic events, while the second step involves an analysis of its ability to produce these events in the mammalian gonad. All relevant information is then integrated into a weight-of-evidence scheme which presents the strength of the information bearing on the chemical's potential ability to produce mutations in human germ cells. For chemicals demonstrating this potential, one may decide to proceed with an evaluation of the quantitative consequences of mutation following expected human exposure.

For hazard identification, it is clearly desirable to have data from mammalian germ-cell tests, such as the mouse specific-locus test for point mutations and the heritable translocation or germ-cell cytogenetic tests for structural chromosome aberrations. It is recognized, however, that in most instances such data will not be available, and alternative means of evaluation will be required. In such cases the Agency will evaluate the evidence bearing on the agent's mutagenic activity and the agent's ability to reach and interact with or affect the mammalian gonadal target. When evidence exists that an agent possesses both these attributes, it is reasonable to deduce that the agent is a potential human germ-cell mutagen.

1. Mutagenic Activity

In evaluating chemicals for mutagenic activity, a number of factors will be considered: (1) Genetic end points (e.g., gene mutations, structural or numerical chromosomal aberrations) detected by the test systems, (2) sensitivity and predictive value of the test systems for various classes of chemical compounds, (3) number of different test systems used for detecting each genetic end point, (4) consistency of the results obtained in different test systems and different species, (5) aspects of the dose-response relationship, and (6) whether the tests are conducted in accordance with appropriate test protocols agreed upon by experts in the field.

The array of mutagenicity tests available will be reviewed within the following qualitative perspective: greater weight will be attributed to tests conducted in germ cells than in somatic cells, to studies in mammalian cells than in submammalian cells, and to studies in eukaryotic cells than in prokaryotic cells.

2. Chemical Interactions in the Mammalian Gonad

Evidence for chemical interaction in the mammalian gonad spans a range of different types of findings. Each chemical under consideration needs to be extensively reviewed since this type of evidence may be part of testing exclusive of mutagenicity per se (e.g., reproduction, metabolism, and mechanistic investigations). Although it is not possible to classify clearly each type of information that may be available on a chemical, two possible groups are illustrated.

Sufficient evidence of chemical interaction is given by the demonstration that an agent interacts with germ-cell DNA or other chromatin constituents, or that it induces such end points as unscheduled DNA synthesis, sister-chromatid exchange, or chromosomal aberrations in germinal cells. Positive results in a mammalian germ-cell mutation study also demonstrate the action of the chemical in the gonadal target cells.

b. *Suggestive evidence* will include the finding of adverse gonadal effects following acute, subchronic, or chronic toxicity testing, or findings of adverse reproductive effects, which are consistent with interaction with germ cells.

3. Weight-of-Evidence Determination

The evidence for a chemical's ability to produce mutations and to interact with the germinal target are integrated into a weight-of-evidence judgment that the agent may pose a hazard as a potential human germ-cell mutagen. All information bearing on the subject, whether indicative of potential concern or not, must be evaluated. Whatever evidence may exist from humans must also be factored into the assessment.

Information available will vary greatly from chemical to chemical because there are many mutagenicity test systems, and there has been no systematic attempt to develop information on all chemicals of concern. The responses noted for different tests may also vary from chemical to chemical since often one does not find consistent positive or negative results across all tests. Chemicals may show positive effects for some end points in some test systems, but negative responses in others. Each review must take into account the limitations in the testing and in the types of responses that may exist.

To provide guidance as to the categorization of the weight of evidence, a classification scheme is presented to illustrate, in a simplified sense, the strength of the information bearing on the potential for human germ-cell mutagenicity (Table 1). It is not possible to illustrate all potential combinations of evidence, and considerable judgment must be exercised in reaching conclusions. The factors illustrated in Table 1 and discussed previously in sections 1, 2, and 3 must all be considered in making an assessment of mutagenicity. In addition, certain responses in tests that do not measure well-defined mutagenic end points (e.g., SCE induction in mammalian germ cells) or germ-cell tests in higher eukaryotes (e.g., Drosophila tests) may provide a basis for raising the weight of evidence from one category to another:

Sufficient evidence for potential human germ-cell mutagenicity would include cases in which positive responses are demonstrated in a mammalian germ-cell test. Also, in general, sufficient evidence exists when there is confirmed mutagenic activity in other test systems (positive responses in at least two different test systems, at least one of which is in mammalian cells), and there is sufficient evidence for germ-cell interaction as defined above.

Suggestive evidence encompasses a weight-of-evidence category between sufficient and limited that includes cases in which there is some evidence for mutagenic activity and for interaction with germ cells.

Limited evidence for potential human germ-cell mutagenicity exists when evidence is available only for mutagenicity tests (other than mammalian germ cells) or only for chemical interactions in the gonad.

Table 1.—Classification of Weight of Evidence for Potential Human Germ-Cell Mutagenicity [a]

1. *Sufficient* evidence exists when positive responses are demonstrated in:
   a. at least one *in vivo* mammalian germ-cell mutation test, or
   b. at least two point mutation tests (at least one in mammalian cells) plus sufficient evidence that the chemical interacts with mammalian germ cells, or
   c. least two structural chromosome aberration tests (at least one in mammalian cells) plus sufficient evidence that the chemical interacts with mammalian germ cells, or
   d. one gene mutation assay in mammalian cells and one structural chromosome aberration test in mammalian cells and sufficient evidence for chemical interaction with mammalian germ cells.
2. *Suggestive* evidence exists in those cases in which there are positive data for both mutagenic activity and evidence for chemical interactions in the gonad, but the evidence is less than sufficient. This category is potentially large and heterogeneous in nature and ranges from almost sufficient to essentially limited.
3. *Limited* evidence denotes a situation in which the evidence is limited to information on mutagenic activity or to evidence of chemical reactivity in the target.

[a] Takes into consideration the extent, quality, and consistency of responses bearing on an agent's ability to product mutagenic events and to interact with the mammalian gonadal target. Nonmutagenic test responses (e.g., SCE in germ cells) may help to elevate evidence of mutagenicity from one category to another.

Designation of evidence as limited does not preclude the use of such information to set priorities for further testing or to support a case for potential carcinogenicity.

Although definitive proof of nonmutagenicity is not possible, it seems appropriate that a chemical could be classified operationally as not a human germ-cell mutagen, if it gives negative responses in those test systems that together fulfill the criteria (i.e., all relevant end points) for sufficient evidence of a potential human germ-cell mutagen, providing that all assays have been properly performed. Test systems used to define a negative should be capable of detecting weak responses (adequate statistical power) and should be appropriate for the chemical or class of chemicals under investigation.

Negative evidence of chemical interaction in the gonad in the presence of evidence of mutagenic activity may still signal some concern in regard to somatic effects(*10*). Other combinations of relevant information will most likely require case-by-case evaluation. It may also be possible to operationally define a chemical as not being a human germ-cell mutagen based on negative results from other assays which provide information about mutagenicity and/or interaction with germ-cell chromatin.

C. Quantitative Assessment

The preceding section addressed primarily the processes of hazard identification, i.e., the determination of whether a substance is a potential germ-cell mutagen. Often, no further data will be available, and judgments will need to be based on mainly qualitative criteria. For quantitative risk assessment, further information is required, namely, determination of the heritable effect per unit of exposure (dose-response) and the relationship between mutation rate and disease incidence. Dose-response information is combined with anticipated levels and patterns of human exposure in order to derive a quantitative assessment (risk characterization).

1. Dose-Response

Two approaches to obtaining dose-response data are available. One approach requires experimental data on germinal mutations induced in intact mammals. Several test systems may provide such information, e.g., the mouse heritable translocation, dominant skeletal, dominant cataract, and specific-locus tests. Although the dominant skeletal and cataract assays have the advantage of measuring dominant mutations, the heritability of observed effects has not been clearly demonstrated. The experimental data on induced mutation frequency are usually obtained at exposure levels much higher than those that will be experienced by human beings. An assessment of human risk is obtained by extrapolating the induced mutation frequency or the observed phenotypic effect downward to the approximate level of anticipated human exposure.

The Agency will strive to use the most appropriate extrapolation models for risk analysis and will be guided by the available data and mechanistic considerations in this selection. However, it is anticipated that for tests involving germ cells of whole mammals, few dose points will be available to define dose-response functions. In these situations certain theoretical considerations will apply(*20*). For point mutations, linear extrapolations with no threshold may be used as a conservative approximation, provided the results allow one to rule out major germ-cell selection. For structural chromosome rearrangements such as heritable translocations, linear extrapolation of the experimental data is thought to overestimate the risks at low levels of exposure and use of a multiple-hit model is more appropriate.

The second experimental approach for quantitative assessment of genetic risk uses molecular dosimetry data from intact mammals in conjunction with mutagenicity and dosimetry data from other validated test systems(*21*). The intact mammal is used primarily for relating the exposure level for a given route of administration of a chemical to germ-cell dose, i.e., the level of mutagen-DNA interactions. This information is then used in conjunction with results obtained from mutagenicity test systems in which the relationship between the induction of mutations and chemical interactions with DNA can be derived.

Using mutagen-DNA interactions as the common denominator, a relationship can be constructed between mammalian exposure and the induced mutation frequency. The amount of DNA binding induced by a particular chemical agent may often be determined at levels of anticipated human exposure. This approach is still experimental and its application involves many unknowns, such as possible differences between mammalian germ cells and cells of the reference system with regard to types of genetic damage induced and magnitude of repair.

For some mutagenic events, DNA may not necessarily be the critical target. Interaction of chemicals with other macromolecules, such as tubulin, which is involved in the separation of chromosomes during nuclear division, can lead to chromosomal nondisjunction. At present, general approaches are not available for dose-response assessments for these types of mutations. Ongoing research should provide the means to make future assessments on chemicals causing aneuploidy.

2. Exposure Assessment

The exposure assessment identifies populations exposed to toxic chemicals, describes their composition and size, and presents the types, magnitudes, frequencies, and durations of exposure to the chemicals. This component is developed independently of the other components of the mutagenicity assessment(*9*).

3. Risk Characterization

In performing mutagenicity risk assessments, it is important to consider each genetic end point individually. For example, although certain chemical substances that interact with DNA may cause both point and chromosomal mutations, it is expected that the ratio of these events may differ for individual chemicals and between doses for a given chemical. Furthermore, transmissible chromosomal aberrations appear to be inducible with higher frequencies in meiotic and postmeiotic germ-cell stages, which have a brief life span, than in spermatogonial stem cells, which can accumulate genetic damage throughout the reproductive life of an individual. For these reasons, when data are available, the Agency, to the best extent possible, will assess risks associated with all genetic end points.

Any risk assessment should clearly delineate the strengths and weaknesses of the data, the assumptions made, the uncertainties in the methodology, and the rationale used in reaching the conclusions, e.g., similar or different routes of exposure and metabolic differences between humans and test animals. When possible, quantitative risk assessments should be expressed in terms of the estimated increase of genetic disease per generation or per lifetime, or the fractional increase in the assumed background spontaneous mutation rate of humans(*5*). Examples of quantitative risk estimates have been published (*6, 22*); these examples may be of use in performing quantitative risk assessments for mutagens.

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PART 4 - HEALTH ASSESSMENT OF SUSPECT DEVELOPMENTAL TOXICANTS

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Part X

Environmental Protection Agency

Proposed Guidelines for the Health Assessment of Suspect Developmental Toxicants and Request for Comments

ENVIRONMENTAL PROTECTION AGENCY

[FRL-2706-7]

Proposed Guidelines for the Health Assessment of Suspect Developmental Toxicants

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed Guidelines for the Health Assessment of Suspect Developmental Toxicants and Request for Comments.

SUMMARY: The U.S. Environmental Protection Agency is proposing Guidelines for the Health Assessment of Suspect Developmental Toxicants (Guidelines). These Guidelines are proposed for use within the policy and procedural framework provided by the various statutes that EPA administers to guide Agency analysis of developmental toxicity data. We solicit public comment and will take public comment into account in revising these Guidelines. The Guidelines will be reviewed by the Science Advisory Board in meetings now tentatively scheduled for April 1985.

These proposed Guidelines were developed as part of a broad guidelines development program under the auspices of the Office of Health and Environmental Assessment (OHEA), located inthe Agency's Office of Research and Development. Consonant with the role of OHEA's Reproductive Effects Assessment Group (REAG) as the Agency's senior health committee for developmental toxicity assessment, the Guidelines were developed by an Agency-wide working group chaired by the REAG.

DATE: Comments must be postmarked by January 22, 1985.

ADDRESSES: Comments may be mailed or delivered to: Dr. Carole A. Kimmel, Reproductive Effects Assessment Group (RD-689), Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, 401 M Street, SW., Washington, DC 20460.

FOR FURTHER INFORMATION CONTACT: Dr. Carole A. Kimmel, telephone: 202-382-7331.

SUPPLEMENTARY INFORMATION: A preliminary draft of the Guidelines was sent for review to approximately 20 scientists in the field of developmental toxicology within government, universities in the United States, and the private sector. Comments received from these reviewers, generally favorable, were taken into account in developing the Guidelines proposed here.

References and supporting documents used in the preparation of these Guidelines as well as comments received are available for inspection and copying at the Public Information Reference Unit (202-382-5926), EPA Headquarters Library, 401 M Street, SW., Washington, DC, between the hours of 8:00 a.m. and 4:30 p.m.

Dated: November 9, 1984.

William D. Ruckelshaus,

Administrator.

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I. Introduction

These Guidelines describe the procedures that the U.S. Environmental Protection Agency will follow in evaluating potential developmental toxicity associated with human exposure to environmental toxicants. In the past, the Agency has sponsored conferences and issued publications which addressed issues related to such evaluations(*1, 2, 3*). These publications provided some of the scientific basis for these risk assessment Guidelines, and testing guidelines have provided protocols designed to determine the potential of a test substance to induce structural and/or other abnormalities in the developing conceptus. The Agency's authority to regulate substances that have the potential to interfere adversely with human development is derived from a number of statutes which are implemented through multiple offices within the Agency. Because many different offices evaluate developmental toxicity, there is a need for intra-agency consistency in the approach to assess these types of effects. The procedures described here will promote consistency in the Agency's assessment of developmental toxic effects.

Approximately 50% of human conceptuses fail to reach term(*3, 4*); approximately 3% of newborn children are found to have one or more significant congenital malformations at birth, and, by the end of the first postnatal year, about 3% more are found to have serious developmental defects (*5, 6*). It is estimated that 20% of human congenital malformations are caused by mutations, 10% are attributable to known environmental factors, and the remainder result from unknown causes (*7*).

Numerous agents have been shown to be developmental toxicants in animal test systems(*8*). Several of them have also been shown to be the cause of adverse developmental effects in humans, including alcohol, aminopterin, busulfan, chlorobiphenyls, diethylstilbestrol, isotretinoin, organic mercury, thalidomide, and valproic acid (*9, 10, 11, 12*). Exposure to agents affecting development generally results in multiple manifestations (malformation, functional impairment, altered growth, and/or lethality). Therefore, assessment efforts should encompass a wide array of adverse developmental end points such as spontaneous abortions, stillbirths, malformations, and other adverse functional physical changes that occur postnatally.

The developmental toxicity assessments prepared pursuant to these Guidelines will be utilized within the requirements and constraints of the applicable statutes to arrive at regulatory decisions concerning developmental toxicity. These Guidelines provide a general format for analyzing and organizing the available data for conducting risk assessments. The Guidelines do not change any statutory or regulatory prescribed standards for the type of data necessary for regulatory action. Moreover, risk assessment is just one component of the regulatory process and defines the adverse health consequences of exposure to a toxic agent. The other component, risk management, combines risk assessment with the directives of the enabling regulatory legislation together with socio-economic, technical, political, and other considerations to reach a decision as to whether or how much to control future exposure to the suspected toxic agent. The issue of risk management will not be addressed in these Guidelines.

The National Research Council(*13*) has defined risk assessment as being comprised of some or all of the following

components: hazard identification, dose-response assessment, exposure assessment, and risk characterization. In general, the process of assessing the risk of human developmental toxicity may be adapted to this format. However, due to special considerations in assessing developmental toxicity, which will be discussed later in these Guidelines, it is not always appropriate to follow the exact standards as defined for each component.

Hazard identification is the qualitative risk assessment in which all available experimental animal and human data are used to determine if an agent is likely to cause developmental toxicity. In considering developmental toxicity, these Guidelines will address not only malformations, but also fetal wastage, growth alteration, and functional abnormalities that may result from developmental exposure to environmental agents.

The dose-response assessment defines the relationship of the dose of an agent and the occurrence of developmental toxic effects. According to the National Research Council(*13*), this component would usually include the results of an extrapolation from high doses administered to experimental animals or noted in epidemiologic studies to the low exposure levels expected for human contact with the agent in the environment. However, since at present there is no mathematical extrapolation model that is generally accepted for developmental toxicity, the Agency, for the most part, continues to use safety factors and margins of safety, which will be discussed in these Guidelines.

The exposure assessment identifies populations exposed to the agents, describes their composition and size, and presents the types, magnitudes, frequencies, and durations of exposure to the agent.

In risk characterization, the exposure assessment and the dose-response assessment are combined to estimate some measure of the risk of developmental toxicity. As part of risk characterization, a summary of the strengths and weaknesses in each component of the assessment are presented along with major assumptions, scientific judgments, and, to the extent possible, estimates of the uncertainties.

II. Definitions and Terminology

The Agency recognizes that there are differences in the use of terms in the field of developmental toxicology. For the purposes of these Guidelines the following definitions and terminology will be used.

Developmental Toxicology—The field dealing with the induction of adverse effects on the developing organism occurring up to the time of puberty. The manifestations of developmental toxicity include: (1) Death of the developing organism, (2) structural abnormality (teratogenicity), (3) altered growth, and (4) functional deficiency.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure; the distinguishing feature between the terms is the period during which the insult occurred. The terms, as used here, include malformation, altered growth, and *in utero* death.

Altered Growth—A significant alteration in fetal or neonatal organ or body weight. Body weight may or may not be accompanied by a change in crown-rump length and/or in skeletal ossification. Altered growth can be induced at any stage of development, may be reversible, or may result in a permanent change.

Functional Teratology—The field dealing with the causes, mechanisms, and manifestations of alterations or delays in functional competence of the organism or organ system following exposure to an agent during critical periods of development either pre- or postnatally.

Malformations and Variations—A malfunction is usually defined as a permanent structural deviation which generally is incompatible with or severely detrimental to normal postnatal survival or development. A variation is usually defined as a divergence beyond the usual range of structural constitution but which may not have as severe an effect on survival or health as a malformation. Distinguishing between variations and malformations is difficult since there exists a continuum of responses from the normal to the extreme deviant. There is no generally accepted classification of malformations and variations. Other terminology that is often used but no better defined, includes anomalies, deformations, and aberrations.

III. Qualitative Assessment (Hazard Identification of Developmental Toxicants)

Developmental toxicity studies provide a number of end points that are useful for evaluating the potential of an agent to produce adverse outcomes of pregnancy. The four types of effects on the conceptus that may be produced by *in utero* exposure to toxicants include death, structural abnormality, altered growth, and functional deficits. Of these, the first three effects are measured in the conventional developmental toxicity (teratogenicity) protocol (discussed below), while functional deficits are seldom evaluated in routine assessments of environmental agents. This section will discuss the format and analysis of conventional studies as well as the use of data from other types of studies, including functional studies, short-term tests, and pharmacokinetics.

A. Conventional Developmental Toxicology Protocols: End Points and Their Interpretation

The most commonly used protocol for assessing developmental toxicity involves the administration of a test substance to pregnant animals (usually mice, rats, or rabbits) during the period of major organogenesis, evaluation of maternal responses throughout pregnancy, and examination of the dam and the uterine contents just prior to term(*2, 3, 14, 15*). Other protocols may use exposure periods of one to a few days to investigate periods of particular sensitivity for induction of anomalies in specific organs or organ systems(*16*). Fetuses alive at maternal sacrifice are thoroughly evaluated for alterations in morphological development. Because the relationship of maternal and fetal toxicity is important in assessing the developmental toxicity of an agent, dose-response data are important. Ideally, study designs should include a high dose, which produces some maternal toxicity (i.e., a level that produces marginal but significantly reduced body weight or weight gain during pregnancy up to a level that produces no more than 10% maternal mortality), a low dose, which demonstrates a no observed effect level (NOEL) for maternal and/or fetal effects, and at least one intermediate dose level. Test animals should be selected based on considerations of species, strain, age, weight, and health status, and should be randomized to dose groups in order to reduce bias and provide a basis for performing valid statistical tests. Replication of the study is desirable and strengthens the confidence of data interpretation.

The next two sections discuss individual end points of maternal and developmental toxicity, respectively, as measured in the conventional developmental toxicity study. The third section deals with the integrated evaluation of all data including the relative effects of exposure on maternal animals and their offspring.

1. End Points of Maternal Toxicity

A number of end points that may be observed as indicators of maternal toxicity are listed in Table 1. Maternal

mortality is an obvious end point of maternal toxicity; however, a number of other end points can be observed which may give an indication of the subtle effects of the agent. For example, in well-conducted studies the end point, percent pregnant, indicates the general fertility rate of the animal stock used and is an important indicator of toxic effects if treatment begins prior to implantation.

Table 1.—End Points of Maternal Toxicity

Mortality
Percent Pregnant (includes all litters with implants)
Body Weight
  Treatment days (at least first, middle, and last treatment days) Sacrifice day
Body Weight Change
  Throughout Gestation
  During treatment (including increments of time within treatment period)
  Post-treatment to sacrifice
  Corrected maternal (body weight change throughout gestation minus gravid uterine weight or litter weight at sacrifice)
Organ Weights (in cases of suspected specific organ toxicity)
  Absolute
  Relative to body weight
Food and Water Consumption (where relevant)
Clinical Signs (on days of treatment and at sacrifice)
  Daily weight changes during treatment
  Types and incidence of clinical signs

Body weight and the change in body weight are viewed collectively as indicators of maternal toxicity for most species, although these end points may not be as useful in rabbits, because body weight changes in rabbits are not good indicators of pregnancy status. Body weight changes may provide more information than a daily body weight measured during treatment or during gestation. Changes in weight during treatment could occur that would not be reflected in the overall weight change throughout gestation, because of compensatory weight gain that may occur following treatment but before sacrifice. For this reason, changes in weight during treatment can be examined as another indicator of maternal toxicity.

Changes in maternal body weight corrected for gravid uterine weight at sacrifice may indicate whether the effect is primarily maternal or fetal. For example, there may be a signficant reduction in weight gain throughout gestation and in gravid uterine weight, but no change in corrected maternal weight gain which would indicate primarily an intrauterine effect. Conversely, a change in corrected weight gain and no change in gravid uterine weight suggests primarily maternal toxicity and little or no intrauterine effect. An alternate estimate of maternal weight change during gestation can be obtained by subtracting the sum of the weights of the fetuses. However, this weight does not include the uterine tissue, placental tissue, or the amniotic fluid.

Changes in other end points should also be determined. For example, changes in relative and absolute organ weights may be signs of maternal effect when an agent is suspected of causing specific organ toxicity. Food and water consumption data are useful, especially if the agent is administered in the diet or drinking water. The amount ingested (total and relative to body weight) and the dose of the agent (relative to body weight) can then be calculated, and changes in food and water consumption with treatment can be evaluated along with changes in body weight and body weight gain. Consumatory data are also useful when an agent is suspected of affecting appetite, water intake, or excretory function. Clinical signs of toxicity may also be used as indicators of maternal toxicity. Daily body weight changes during treatment along with clinical observations may be useful in describing the profile of maternal toxicity.

2. End Points of Developmental Toxicity

Because the maternal animal and not the conceptus is the individual treated during gestation, statistical analysis of the data should consider both the individual fetus and the litter. Table 2 indicates the way in which fetal and litter end points can be expressed.

Table 2.—End Points of Developmental Toxicity

All litters

No. implantation sites/dam
No. corpora lutea (CL)/dam*
Percent Preimplantation loss
No. and percent live fetuses/litter
No. and percent resorptions/litter
No. and percent litters with resorptions
No. and percent late fetal deaths/litter
No. and percent nonlive (late fetal deaths + resorptions) implants/litter
No. and percent litters with nonlife implants
No. and percent affected (nonlive + malformed) implants/litter
No. and percent with affected implants
No. and percent litters with total resorptions

Litters with live fetuses

No. and percent litters with live fetuses
No. and percent live fetuses/litter
No. males/litter
No. females/litter
No. ratio/litter
Mean ($\bar{x}$) fetal body weight/litter
Mean ($\bar{x}$) male body weight/litter
Mean ($\bar{x}$) female body weight/litter
No. and percent externally malformed fetuses/litter
No. and percent viscerally malformed fetuses/litter
No. and percent skeletally malformed fetuses/litter
No. and percent malformed fetuses/litter
No. and percent litters with malformed fetuses
No. and percent malformed males/litter
No. and percent malformed females/litter
No. and percent fetuses with variations/litter
No. and percent litters having fetuses with variations
Types and incidence of individual malformations
Types and incidence of individual variations
Individual fetuses and their malformations and variations (grouped according to litter and dose)

* Only when treatment begins prior to implantation. May be difficult in mice.

When treatment begins prior to implantation, an increase in preimplatation loss could indicate an adverse effect either on the developing blastocyst or on the process of implantation itself. Further studies would be necessary to determine the cause and extent of this type of effect.

The number of live fetuses per litter, based on all litters, includes any litters that have no live implants. On the other hand, total nonlive implants (postimplantation loss), is a combination of the end points, resorptions, and late fetal deaths. An increased incidence per litter for any of the end points indicating postimplantation loss would be considered a significant toxic effect to the conceptus. The number of litters showing an increased incidence for these end points is less useful than incidence per litter, because a litter is counted whether it has one or all resorbed, dead, or nonlive implants.

A statistically significant increase in postimplantation loss following exposure to an agent is a severe form of developmental toxicity, but there is considerable interlitter variability in the incidence of postimplantation loss(*17*). If a statistically significant increase is found after exposure to an agent, the data may be compared not only with concurrent controls, but also with recent historical control data. If a given study control group exhibits an unusually high or low incidence of postimplantation loss compared to historical controls, then scientific judgment would have to be used to determine the adequacy of the studies for risk assessment purposes.

The end point for affected implants (i.e., the combination of nonlive and

malformed conceptuses) given an indication of the total intrauterine response to an agent and sometimes reflects a better dose-response relationship than each taken individually. This is especially true at the high end of the dose-response curve in cases where most implants die *in utero*. In such cases, the malformation rate may appear to decrease because only unaffected fetuses have survived to term. If the incidence of prenatal death or malformation is unchanged, then the incidence of affected implants will not provide any additional information.

The number of live fetuses per litter, based on those litters that have one or more live fetuses, may be unchanged even though the incidence of nonlive in all litters is increased. This could occur either by an increase in the number of litters with no live fetuses or by an increase in the number of implants per litter. A decrease in the number of live fetuses per litter should be accompanied by an increase in the incidence of nonlive implants per litter, unless the implant numbers differ among dose groups.

The sex ratio per litter, as well as the body weights of males and females, can be examined to determine whether or not one sex is preferentially affected by the agent. However, this is an unusual occurrence.

A change in fetal body weight is a sensitive indicator of developmental toxicity, in part because it is a continuous variable. In some cases, fetal weight reduction may be the only indicator of developmental toxicity; if so, there is always a question remaining as to whether weight reduction is a permanent or transitory effect. When fetal weight reduction is the only indicator of developmental toxicity, data from the two-generation reproduction study(*3*) may be useful for evaluating these parameters. Ideally, follow-up studies to evaluate postnatal viability, growth, and survival through weaning should be conducted. There are other factors that should be considered in the evaluation of fetal weight changes. For example, in polytocous animals, fetal weight is usually inversely correlated with litter size, and the upper end of the dose-response curve may be confounded by smaller litters and increased fetal weight. Additionally, the average body weight of male fetuses is greater than that of female fetuses in the more commonly used laboratory animals.

Live fetuses should be examined for external, visceral, and skelatal malformations. If only a portion of the litter is examined, then it is preferable that those to be examined be selected on a random basis from each litter. The incidence of individual types of malformations and variations gives an indication of the types of developmental deviations produced by a particular agent. A listing of individual malformations and variations by fetus gives an indication of the pattern of developmental deviations. The incidence of external, visceral, and skeletal malformations gives an indication of which systems may be specifically affected. A significant increase in the incidence of particular malformations or of the total number of fetuses malformed per treated litter as compared with controls indicates a teratogenic effect. If variations are significantly increased in a dose-related manner, these should also be evaluated as a possible indication of developmental toxicity. The Interagency Regulatory Liaison Group noted that dose-related increases in spontaneously occurring defects are as relevant as dose-related increases in any other developmental toxicity end points(*18*). The number and percentage of litters with malformed fetuses are more reliable indicators of developmental toxicity than the number of litters with resorptions, since malformations do not occur frequently in controls. The data on the incidence of individual types of malformations and variations should be examined for significant changes which may be masked if the data on all malformations and variations are pooled. This information can also be used for comparison with historical control data. Appropriate historical control data are helpful in interpretation of major malformations, especially those that normally occur at a low incidence when seen in an individual study apparently unrelated to dose.

3. Overall Evaluation of Maternal and Developmental Toxicity

As discussed previously, individual end points are evaluated in developmental toxicity studies, but an integrated evaluation must be done considering all maternal and developmental end points in order to interpret the data fully. The overall interpretation usually consists of the evaluation of maternal toxicity and the dose levels at which it occurs, then the evaluation of developmental toxicity and the levels at which these end points occur. In general, an agent that produces changes in any of the four major classes of developmental toxicity at a dose that is minimally toxic or not toxic to the maternal animal is considered to have selective developmental effects. However, when effects are produced at maternally toxic doses by agents to which adult human exposure may occur at toxic levels (e.g., smoking, alcohol, solvents), these developmental effects should no be ignored.

Approaches for ranking agents for their selective developmental toxicity are being developed; Schardein(*9*) has reviewed several of these. Of current interest are approaches that develop ratios relating an adult toxic dose to a developmental toxic dose(*19, 20, 21*). Ratios near unity indicate that developmental toxicity occurs only at doses producing maternal toxicity; as the ratio increases, there is a greater likelihood of developmental effects occurring without maternal manifestations. Although further exploration and validation are necessary, such approaches may ultimately help in identifying those agents that pose the greatest threat and should be given priority for further testing(*22*).

B. Functional teratology

Developmental effects, which are inducible by exogenous agents, are not limited to death, structural abnormalities, and altered growth. Rather, it has been demonstrated in a number of instances that subtle alterations in the functional competence of an organ or a variety of organ systems may result from exposure during critical developmental periods that may occur between conception and puberty. Often, these functional defects are observed at dose levels below those at which gross malformations are evident(*23*). Much of the early work in this field was related to behavioral evaluations, and the term "behavioral teratology" became prominent in the mid 1970s. Less work has been done on other functional systems, but sufficient data have accumulated to indicate that the cardiopulmonary, immune, endocrine, digestive, urinary, and reproductive systems are subject to alterations in functional competence. Hence the term "functional teratology" has been applied to this general area.

The variety of systems and end points that may be evaluated is too extensive to discuss here(*24*), (*25*). At present no standard testing procedures are routinely used, and this has led to apparent discrepancies in the outcome of certain studies. Some attempts to standardize and evaluate procedures are being made(*26*). The determination of functional competence often involves highly specialized training and equipment and is not generally practical for routine test procedures. Therefore, these approaches may have their greatest application in determining the nature of a suspected alteration in term

of its biological significance and dose-response relationship.

The means for appropriate interpretation of data from functional teratology studies is not always clear due to the lack of knowledge about the toxicological significance of specific functional alterations. However, several general concepts have arisen from the research to date which may be useful in designing studies and evaluating data.

1. Several aspects of study design are similar to those used in standard developmental toxicity studies (e.g., a dose-response approach with the highest dose producing minimal overt maternal or fetal toxicity, number of litters large enough for adequate statistical power, randomization of animals to dose groups, litter generally considered the statistical unit, etc.).

2. Replication of a study strengthens the confidence of data interpretation.

3. Use of a pharmacological challenge may aid in evaluating function and "unmasking" effects not otherwise detectable, particularly in the case of organ systems that are endowed with a reasonable degree of functional reserve capacity.

4. Choice of functional tests with a moderate degree of background variability may be more useful in detecting effects of agent exposure than tests based on functional systems with low variability that may be impossible to disrupt without being life-threatening. Butcher et al.(*27*) have discussed this with relation to behavioral end points.

5. A battery of functional tests is often necessary to evaluate fully the functional competence of any given system; these tests may need to be conducted at several ages to account for maturational changes.

6. Critical periods for the disruption of functional competence may include both the prenatal period to the time of puberty, and the effect is likely to vary depending on the time of exposure.

Although interpretation of functional data may be difficult at present, there are at least two days in which the data from these studies may be useful for risk assessment purposes. First, these studies can be used to indicate whether or not an agent has the potential to cause functional alterations, and whether these effects occur at doses lower than those that produce other forms of toxicity. Second, if the agent in question is already in the environment, the functional data may be used for focusing on organ systems to evaluate in exposed human populations.

C. Short-Term Testing in Development Toxicity

The need for developmental toxicity screens has arisen from the large number of agents in or entering the environment and the increased interest in reducing the number of animals used in and the expense of testing. Currently, two approaches are being considered for their applicability in the overall testing process: an *in vivo* mammalian screen and a variety of *in vitro* systems. Neither approach is seen at this time as replacing current *in vivo* developmental toxicity testing. Rather, they are being considered for their usefulness in assigning priorities for further, more extensive testing.

1. *In Vivo* Mammalian Teratology Screen

An *in vivo* approach developed by Chernoff and Kavlock(*28*) uses the pregnant mouse and it designed to reduce the resources required for precliminary indication of developmental toxicity. This approach is based on the hypothesis that a prenatal insult, which results in altered development, will be manifested postnatally as reduced viability and/or impaired growth. In general, the test substance is administered over the period of major organogenesis at a single dose level that will elicit some degree of maternal toxicity. After birth, the pups are counted and weighed on days 1 and 3. End points that are considered in the evaluation include: general maternal toxicity (including survival and weight gain), litter size, viability and weight of the offspring, and gross malformations. Basic priority categories for further testing have also been suggested: (1) Agents that induce perinatal death should receive highest priority, (2) agents inducing perinatal weight changes should be ranked lower in priority, and (3) agents inducing no effect should receive the lowest priority(*28*). The major goal of this test is to predict the potential for developmental toxicity of an agent in the species utilized. It does not increase the ability to extrapolate risk to other species, including humans. Additional studies to evaluate the validity of this approach as a screen for developmental toxicity are currently being carried out, and a system for giving a numerical ranking to the results has been suggested to prioritize agents for further testing(*29, 30*).

2. *In Vitro* Teratology Screens

Test systems that fall under the general heading of "*in vitro*" include any system that employs a test subject other than the intact pregnant mammal. These systems have long been used to assess events associated with normal and abnormal development, but only recently have they been considered for their potential as screens in testing (*31, 32, 33*). Many of these systems are now being evaluated for their ability to predict the developmental toxicity of various agents. This validation process requires certain considerations in study design, including defined end points for toxicity and an understanding of the system's ability to handle various test agents(*32, 34*). A list of agents for use in these validation studies has been developed(*35*).

3. Application

When the validity of a screening system is established, it may be used to set priorities for further, more comprehensive *in vivo* testing. In many cases, a battery of two or more screening systems may be needed, employing tests with end points that collectively represent several embryologic processes. In addition, many of these systems can be applied in an attempt to answer specific questions of a dose-response, target-organ, or mechanistic nature. *In vitro* approaches may aid in establishing the effective dose that reaches the target tissue. Either the *in vivo* or *in vitro* short-term approaches may be useful in addressing structure-activity relationships and the synergistic-antagonistic potential of chemical interactions. Thus, pertinent information can be derived from these approaches and may be useful in the assessment of potential risk.

D. Pharmacokinetics

Extrapolation of data between species can be aided considerably by the availability of data on the pharmacokinetics of a particular agent in the species tested and, if possible, in humans. Information on half-lives, placental metabolism and transfer, and concentrations of the parent compound and metabolites in the maternal animal and conceptus may be useful in predicting risk for developmental toxicity. Such data may also be helpful in defining the dose-response curve, developing a more accurate comparison of species sensitivity including that of humans (*36, 37*), determining dosimetry at target sites, and comparing pharmacokinetic profiles for various dosing regimens or routes of exposure.

Pharmacokinetic studies in developmental toxicology are most useful once a developmental toxic effect has been produced in a give species with a particular agent. Pharmacokinetic

data for risk assessment in developmental toxicology ideally should be derived from pregnant females at the stage when developmental insults occur. Often the only data available are from males, nonpregnant females, or from pregnant females at a time unrelated to the event of interest (e.g., pharmacokinetic analyses done during the fetal period when malformations were induced early in organogenesis). The correlation of pharmacokinetic and developmental toxicity data may be useful in determining the contribution of specific pharmacokinetic parameters to the effects observed (*38*).

E. Human Studies

Because of the ethical considerations involved, little human testing has been or is likely to be done. Therefore, dose-effect developmental toxicity data from humans are generally not available. Human epidemiologic studies may provide the best information for assessing human risk and would reduce the problems in species-to-species extrapolation. However, interpretation of epidemiologic data must account for confounding factors, such as maternal age, parity, multiple exposures to environmental agents, difficulty in obtaining accurate estimates of exposure levels in the environment, insufficient data on background incidence of certain developmental end points, etc. When human data are available, they can be used with other supporting animal data to assess human risk.

F. Comparisons of Molecular Structure

Comparisons of the chemical or physical properties of an agent with those of known developmental toxicants may provide some indication of a potential for developmental toxicity. Such information may be useful in priority-setting of Agents for testing or for further evaluation when only minimal data are available.

G. Weight-of-Evidence Determination

Information available from studies discussed previously, whether indicative of potential concern or not, must be evaluated and factored into the assessment. The types of data may vary from chemical to chemical, and certain types of data may be more relevant than other types of data in performing developmental toxicity assessments. Therefore, all data pertinent to developmental toxicity should be examined in the determination of a chemical's potential to cause developmental toxicity in humans. Whatever evidence may exist from humans must also be factored into the assessment.

IV. Quantitative Assessment

Risk assessment involves the description of the nature and often the magnitude of potential human risk, including a description of any attendant uncertainty. In the final phase of the risk assessment, the outputs of the qualitative evaluation, the dose-response, and the exposure data are combined to give qualitative and/or quantitative estimates of the developmental toxicity risk. As part of the risk assessment, a summary of the strengths and weaknesses of the hazard identification, dose-response assessment, exposure assessment, and the risk characterization are presented. Major assumptions, scientific judgments, and, to the extent possible, estimates of the uncertainties in the assessment are also presented.

A. Dose-Response Assessment

Because human dose-effect data usually are not available, other methods have been used in developmental toxicology for estimating exposure levels that are unlikely to produce adverse effects in humans. The dose-response assessment ~~is usually based~~ upon the evaluation of tests performed in laboratory animals. Two approaches frequently employed involve the use of safety factors and margins of safety, which in some respects are conceptually similar. However, they are computed differently and are often used in different regulatory situations. The choice of approach is dependent upon many factors, including the statute involved, the situation being addressed, the data base used, and the needs of the decision-maker.

The safety factor approach is intended to derive a calculated exposure level that is unlikely to cause any developmental toxic responses in humans. The size of the safety factor will vary from agent to agent and will require the exercise of scientific judgment(*3, 39*), taking into account interspecies differences, the nature and extent of human exposure, the slope of the dose-response curve, and the severity of the developmental effects observed at exposure levels below maternal toxicity in the test species. The safety factor selected is then divided into the NOEL obtained from the most appropriate and/or sensitive mammalian species examined to obtain an acceptable exposure level. Currently, there is no one laboratory animal species that can be considered most appropriate for predicting risk to humans(*9*). Each agent should be considered on a case-by-case basis.

The margin of safety approach derives a ratio of the NOEL from the most sensitive species to the estimated human exposure level from all potential sources(*40*). The adequacy of the margin of safety is then considered, based upon the weight of evidence, including quality of data, number of species affected, dose-response relationships, and other factors such as benefits of the agent.

As discussed earlier, the preferred study design for a developmental toxicity study includes a minimum of three doses: a high dose that produces minimal maternal toxicity, at least one intermediate dose, and a low dose that demonstrates a NOEL. Nevertheless, there may be circumstances in that there is a need to perform a risk assessment based on the results of a study in which a NOEL could not be identified, but, rather, in which the lowest dose administered caused some marginally significant effect(s). This lowest dose could be identified as the lowest observed effect level (LOEL). In circumstances where a LOEL can be identified, it may be appropriate to apply an additional safety factor. The magnitude of this additional factor is ~~dependent upon~~ scientific judgment. In some instances, additional studies may be needed to strengthen the confidence in this additional safety factor.

B. Exposure Assessment

The results of the dose-response assessment are combined with an estimate of human exposure in order to obtain a quantitative estimate of risk. The proposed Guidelines for Exposure assessment are being developed separately and will not be discussed in any detail here. In general, the exposure assessment describes the magnitude, duration, schedule, and route of exposure. This information is developed from monitoring data and from estimates based on modeling of environmental exposures. Unique considerations relevant to developmental toxicity are duration and period of exposure as related to stage of gestation (i.e., critical periods), and the fact that a single exposure may be sufficient to produce adverse developmental effects (i.e., chronic exposure is not necessary for developmental toxicity to be manifested).

C. Risk Characterization

There are numerous uncertainties associated with the toxicological and exposure components of risk assessment that in the past have often not been

readily apparent or consistently presented. The presentation of any qualitative or quantitative risk assessment for developmental toxicity should be accompanied by statements concerning the quality of the data, resolving power of the studies, number of end points examined, selection of doses, replication of the data, the number of species examined, pharmacokinetic considerations, and any other factors that affect the quality and precision of the assessment. The presentation of any numerical estimate should be sufficiently qualified as to the assumptions used and the accuracy of the estimates.

In the assessment of developmental toxicity, statistical considerations require special attention. For example, the power of a study (i.e., the ability to demonstrate an effect), is limited by the sample size used in the study, the background incidence of the end point observed, and the variability in the incidence of the end point. As an example, Nelson and Holson(*41*) have shown that the number of litters needed to detect a 5 or 10 percent change was dramatically lower for fetal weight (a continuous variable with low variability) than for resorptions (a binomial response with high variability). With the current recommendation in testing protocol being 20 rodents per dose group(*1, 3*), it is possible to detect an increased incidence of malformations in the range of 5 to 12 times above control levels, an increase of 3 to 6 times the *in utero* death rate, and a decrease of 0.15 to 0.25 times the fetal weight. Thus, even within the same study, the ability to detect a change in fetal weight is much greater than for the other end points measured. Consequently, for statistical reasons only, changes in fetal weight are often observable at doses below those producing other signs of developmental toxicity.

At present, there is no mathematical model that is generally used for estimating developmental toxicity responses below the applied dose range. This is due primarily to the lack of understanding of the biological mechanisms underlying developmental toxicity, intra/interspecies differences in the types of developmental events, the influence of maternal effects on the dose-response curve, and whether or not a threshold exists below which no effect will be produced by an agent. The assumption of a threshold is based largely on the biological rationale that the embryo is known to have some capacity for repair of the damage or insult(*42*), and that most developmental deviations are probably multifactorial in nature(*43*). However, the existence of a no effect level cannot be proven statistically.

Discussions of risk extrapolation procedures have noted that further work is needed to improve mathematical tools for developing estimates of potential human developmental risk(*39, 44*). Gaylor(*45*) has suggested an approach for controlling risk that combines the use of mathematical models for low-dose estimation of risk with the application of a safety factor based on a preselected level of allowable risk. This approach is similar to approaches proposed for carcinogenesis, but does not preclude the possibility of a threshold, and may provide a more quantitative approach to controlling risk. For the present, the Agency will continue to use safety factors and margins of safety as described above, where applicable. However, more appropriate models will be sought and applied if considered acceptable.

These Guidelines summarize the procedures that the U.S. Environmental Protection Agency will follow in evaluating the potential for agents to cause developmental toxicity. These Guidelines will be reviewed and updated as advances are made in the field, since it is evident that our ability to evaluate and predict human developmental toxicity is imprecise. Further studies that delineate the mechanisms of developmental toxicity and pathogenesis, provide comparative pharmacokinetic data, and elucidate the functional modalities that may be altered by exposure to toxic agents will aid in the interpretation of data and interspecies extrapolation. These types of studies, along with further evaluation of the relationship between maternal and fetal toxicity and the concept of a threshold in developmental toxicity, will provide for the development of improved mathematical models to more precisely assess risk.

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PART 5 - HEALTH RISK ASSESSMENT
CHEMICAL MIXTURES

federal register

Wednesday
January 9, 1985

Part III

Environmental Protection Agency

Proposed Guidelines for the Health Risk Assessment of Chemical Mixtures and Request for Comments; Notice

ENVIRONMENTAL PROTECTION AGENCY

[FRL-2742-8]

Proposed Guidelines for the Health Risk Assessment of Chemical Mixtures

AGENCY: Environmental Protection Agency (EPA.

ACTION: Proposed guidelines for the Health Risk Assessment of Chemical Mixtures and request for comments.

SUMMARY: The U.S. Environmental Protection Agency is proposing Guidelines for the Health Risk Assessment of Chemical Mixtures (Guidelines). These Guidelines are proposed for use within the policy and procedural framework provided by the various statutes that EPA administers to guide Agency analysis of health effects data. We solicit public comment and will take public comment into account in revising these Guidelines. These Guidelines will be reviewed by the Science Advisory Board in meetings now tentatively scheduled for April 1985.

These proposed Guidelines were developed as part of a board guidelines development program under the auspices of the Office of Health and Environmental Assessment (OHEA), located in the Agency's Office of Research and Development. Consonant with the role of OHEA's Environmental Criteria and Assessment Office in Cincinnati (ECAO–Cin) as the Agency's senior health committee for health risk assessment of chemical mixtures, the Guidelines were developed by an Agency-wide working group chaired by the Director of ECAO–Cin.

DATE: Comments must be postmarked by March 11, 1985.

ADDRESS: Comments may be mailed or delivered to: Dr. Jerry Stara, Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency, 26 West St. Clair, Cincinnati, OH 45268.

FOR FURTHER INFORMATION CONTACT: Dr. Richard Hertzber, Telephone: 513–684–7531.

SUPPLEMENTARY INFORMATION: Preliminary drafts of these Guidelines were sent for review to approximately 20 scientists in the fields of toxicology, pharmacokinetics and statistics within the Agency and a later draft was sent for external review to 12 scientists within government, academia and the private sector. Comments received from these reviewers, generally favorable, were considered in developing the Guidelines proposed here.

References and supporting documents used in the preparation of these guidelines as well as comments received are available for inspection and copying at the Public Information Reference Unit (202–382–5926), EPA Headquarters Library, 401 M Street, SW., Washington, DC, between the hours of 8:00 a.m. and 4:30 p.m.

Dated: January 2, 1985.

William D. Ruckelshaus,

Administrator.

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I. Introduction

The primary purpose of this document is to generate a consistent Agency approach for evaluating data on the chronic and subchronic effects of chemical mixtures. It is a procedural guide which emphasizes broad underlying principles of the various science disciplines (toxicology, pharmacology, statistics) necessary for assessing health risk from chemical mixture exposure. Approaches to be used with respect to the analysis and evaluation of the various data are also discussed.

It is not the intent of these Guidelines to regulate any social or economic aspects concerning risk of injury to human health or the environment caused by exposure to a chemical agents(s). All such action is addressed in specific statutes and federal legislation and is independent of these Guidelines.

While some potential environmental hazards involve significant exposure to only a single compound, most instances of environmental contamination involve concurrent or sequential exposures to a variety of compounds that my induce similar or dissimilar effects over exposure periods ranging from short-term to lifetime. In some instances, the mixtures are highly complex consisting of scores of compounds that are generated simultaneously as by-products from a single source or process (e.g., coke oven emissions and diesel exhaust). In other cases, complex mixtures of related compounds are produced as commercial products (e.g., PCBs, gasoline and pesticide formulations) and eventually released to the environment. Another class of mixtures consists of compounds, often unrelated chemically or commercially, which are placed in the same area for disposal or storage, eventually come into contact with each other, and are released as a mixture to the environment. The quality and quantity of pertinent information available for risk assessment varies considerably for different mixtures. Occasionally, the chemical compositions of a mixture is well characterized, levels of exposure to the population are known, and detailed toxicologic data on the mixture are available. Most frequently, not all components of the mixture are known, exposure data are uncertain, and toxicologic data on the known components of the mixture are limited. Nonetheless, the Agency may be required to take action because of the number of individual at potential risk or because of the known toxicologic effects of these compounds that have been identified in the mixture.

Guidelines for single compound risk assessments have been developed for subchronic and chronic exposures to both systemic toxicants and carcinogens. In the current document, these approaches are extended to provide compatible guidelines for assessing the effects of multiple toxicant or multiple carcinogen exposures.

The ability to predict how specific mixtures of toxicants will interact must be based on an understanding of the mechanisms of such interactions. Most reviews and texts that discuss toxicant interactions make some attempt to discuss the biological or chemical bases of the interactions (e.g., Klaassen and Doull, 1980; Levine, 1973; Goldstein et al., 1974; NRC, 1980a; Veldstra, 1956; Withey, 1981). Although different authors use somewhat different classification schemes for discussing the ways in which toxicants interact, it generally is recognized that toxicant interactions may occur during any of the toxicologic processes that take place with a single compound-absorption, distribution, metabolism, excretion, and activity at the receptor site(s). In addition, compounds may interact chemically, causing a change in the biological effect or they may interact by causing different effects at different receptor sites.

Because of the uncertainties inherent in any approach to predicting the magnitude and nature of toxicant interactions, any assessment of health risk from chemical mixture must include a thorough discussion of all assumptions. No single approach is recommended in these Guidelines. Instead, guidance is given for modifying a few simple approaches involving risk addition or dose addition. The mathematical details are presented in Section IV.

III. Proposed Approach

No single approach can be recommended to risk assessments for multiple chemical exposures. Nonetheless, general guidelines can be recommended depending on the type of mixture, the known toxic effects of the components in the mixture, the availability of toxicity data on the mixture or similar mixtures, the known or anticipated interactions among components in the mixture, and the quality of the exposure data. Given the complexity of this issue and the relative paucity of empirical data from which sound generalizations can be constructed, emphasis must be placed on flexibility, judgment, and a clear articulation of the assumption and limitations in any risk assessment that is developed. The proposed approach is summarized in Table I and detailed below.

A. Data Available on Similar Mixtures

For predicting the effects of subchronic or chronic exposure to mixtures, the preferred approach is to use subchronic or chronic health effects data on the mixture of concern and adopt the same procedures as those used for single compounds, either systemic toxicants or carcinogens. Such data are most likely to be available on highly complex mixtures, such as coke oven emission or diesel exhaust, which are generated in large quantities and associated with or suspected of having adverse health effects. Even if such data are available, attention should be given to the persistence of the mixture in the environment as well as the variability of composition of the mixture over time or from different sources of emissions. If the components in the mixture are known to partition into different environmental compartments or to degrade or transform at different rates in the environment, then those factors must also be taken into account, or the confidence in and applicability of the risk assessment is diminished.

TABLE 1.—OUTLINE OF THE RISK ASSESSMENT APPROACH FOR CHEMICAL MIXTURES

1. Health effects information is available on the chemical mixture of concern.
   a. If yes, proceed to Step 5.
   b. If no, proceed to Step 2.
2. Assess the similarity of the mixture on which health effects data are available to the mixture of concern, with emphasis on any differences in components, proportions of components, and environmental partitioning.
   a. If sufficiently similar, proceed to Step 5.
   b. If not sufficiently similar or if no such data exist, proceed to Step 3.
3. Derive appropriate indices of acceptable exposure and/or potency factors for carcinogenicity on the individual components in the mixture and proceed to Step 4.
4. Assess data on interactions of components in the mixture.
   a. If sufficient quantitative information is available on the interactions (including mechanisms) of two or more toxicants from subchronic or chronic studies, proceed to Step 6.
   b. If qualitative information is available on acute interactions, attempt to qualitatively indicate the nature of potential interactions and proceed to Step 7.
5. Conduct risk assessment on the mixture of concern based on health effects data on the mixture, using the same procedures as those for single compounds. Proceed to Step 8.
6. Use an appropriate interaction model to combine risk assessment on compounds for which the data are adequate and use assumption of dose addition for remaining toxicants. Proceed to Step 8.
7. Use an additivity assumption for all compounds in the mixture. Proceed to Step 8.
8. Develop an integrated summary of the qualitative and quantitative assessments with special emphasis on uncertainties and assumptions.

Similarly, if the risk assessment is conducted based on data from a single mixture which is known to be generated with varying compositions depending on time or different emission sources, then the confidence in the applicability of the data to a risk assessment also is diminished. This can be offset to some degree if data are available on several mixtures of the same components but having different ratios of the components which encompass the differences in composition seen with time or from different emission sources. If such data are available, an attempt should be made to determine if significant and systematic differences exist among the chemical mixtures. If significant differences are noted, ranges of risk can be estimated based on toxicologic data from the various mixtures. If no significant differences are noted, then a single risk assessment may be adequate, although some statement should be made giving the range of ratios of the components in the mixtures to which the risk assessment applies.

If no data are available on the mixtures of concern but health effects data are available on a similar mixture (i.e., a mixture having the same components but at slightly different ratios, or having several common components but lacking one or more components, or having one or more additional components) a decision must be made whether the mixture on which health effects data are available is or is not "sufficiently similar" to the mixture of concern to permit a risk assessment. The determination of "sufficient similarity" must be made on a case-by-case basis, considering not only the uncertainties associated with using data on a dissimilar mixture but also the uncertainties of using approaches based on additivity, which are detailed later. In determining reasonable similarity, consideration should be given to any information on the components which differ or are contained in markedly different proportions between the mixture on which health effects data are available and the mixture of concern.

B. Data Available Only on Mixture Components

If data are not available on an identical or reasonably similar mixture, the risk assessment may be used on the toxic or carcinogenic properties of the components in the mixture. When little or no quantitative information is available on the potential interaction among the conponents, dose additive models are recommended for systemic toxicants (defined later). Several studies have demonstrated that dose additive models often predict reasonably well the toxicities of mixtures composed of a substantial variety of both similar and dissimilar compounds (Pozzani et al., 1959; Smyth et al., 1969, 1970; Murphy, 1980). The problem of multiple toxicant exposure has been addressed by the American Conference of Governmental Industrial Hygienists (ACGIH, 1983), the Occupational Safety and Health Administration (OSHA, 1983), the World Health Organization (WHO, 1981), and the National Research Council (NRC, 1980a,b). Although the focus and purpose of each group was somewhat different, all groups that recommended an approach elected to adopt some type of dose additive model. Nonetheless, as discussed in Section IV, dose additive models are not the most biologically plausible approach if the compounds do not have the same mode of toxicologic action. Consequently, depending on the nature of the risk assessment and the available information or modes of action and patterns of joint action, the most reasonable additive model should be used.

1. Systemic Toxicants

For systemic toxicants, the current risk assessment methodology used by the agency for single compounds most often results in the derivation of an exposure level which is considered acceptable or which is not anticipated to cause adverse effects. Depending on the route of exposure, media of concern, and the legislative mandate guiding the risk

assessments, the exposure levels may be expressed in a variety of ways such as Acceptable Daily Intakes (ADIs), levels associated with various Margins Of Safety (MOS), or Ambient Air Standards. For the purpose of this discussion, the term "Acceptable Level" (AL) will be used to indicate any of the criteria, standards, or advisories derived by the Agency. For such estimates, the "hazard index" (HI) of a mixture based on the assumption of dose additivity may be defined as:

$$HI = E_1/AL_1 + E_2/AL_2 + \cdots + E_i/AL_i \quad \text{(II-1)}$$

where:

E_i = exposure level to the ith toxicant, and
AL_i = maximum acceptable level for the ith toxicant

Since the inverse of the acceptable level can be used as an estimate of toxic potency, Equation II-1 can be interpreted as a normalized weighted-average dose, with each component dose scaled by its potency. As this index approaches unity, concern for the potential hazard of the mixture increases. If $HI > 1$, the concern for the potential hazard is the same as if an acceptable level were exceeded for an individual compound, i.e., if E_i/AL_i exceeded 1. If the variabilities of the acceptable levels are known, or if the acceptable levels are given as ranges (e.g., associated with different margins of safety), then HI should be presented with estimates of variation or as a range.

The hazard index is not a mathematical prediction of incidence of effects or severity. Statistical properties of this index and its dependence on the shape of the dose-response curves for the components are not yet known. Much additional research is required to determine the accuracy of the hazard index as a numerical prediction of toxic severity. The hazard index is only a numerical indicator of the transition between acceptable and unacceptable exposure levels and should not be overinterpreted.

As discussed in Section IV, the assumption of additivity is most properly applied to compounds that induce the same effect by the same mechanism. Consequently, the application of Equation II-1 to a mixture of compounds that does not interact and is not expected to induce the same types of effects could overestimate hazard. Thus, if the application of Equation II-1 results in an index near to or greater than unity, it may be desirable to segregate the compounds in the mixture by critical effect and derive separate indices for each effect. Conversely, if the dissimilar effects influence one another (e.g., liver failure diminishing the function of another organ), then simple dose addition could underestimate the total hazard; this is discussed more fully in Section III.

The Agency has developed methods for estimating dose-response curves for single chemicals, e.g. carcinogens (U.S. EPA, 1984). In attempting to assess the response to mixtures using dose-response curves for the components of the mixture, dose-additive or response-additive assumptions can be used, with preference given to the most biologically plausible assumption.

2. Carcinogens

For carcinogens, whenever linearity of the dose-response curve can be assumed (usually restricted to low doses), the increase in incremental risk P, caused by exposure d, is related to carcinogenic potency B, as:

$$P = d\,B. \quad \text{(II-2)}$$

For multiple compounds, this equation may be generalized to:

$$P = \Sigma\, d_i B_i. \quad \text{(II-3)}$$

This equation assumes independence of action by the several carcinogens and is equivalent to the assumption of dose addition as well as to response addition with completely negative correlation of tolerance (see Section IV). Analogous to the procedure used in Equation II-1 for systemic toxicants, an index could be developed by dividing exposure levels (E) by doses (DR) associated with varying levels of risk:

$$HI = E_1/DR_1 + E_2/DR_2 + \ldots = E_i/DR_i \quad \text{(II-4)}$$

It should be emphasized that because of the uncertainties in estimating dose response relationships for single compounds and the additional uncertainties in combining the individual estimate to assess response from exposure to mixtures, response rates and hazard indices may have merit in comparing risks but should not be regarded as measures of absolute risk.

3. Interactions

None of the above equations incorporates any form of synergistic or antagonistic interaction. Some types of information, however, may be available that suggest that two or more components in the mixture may interact. Such information must be assessed in terms of both its relevance to subchronic or chronic hazard and its suitability for quantitatively altering the risk assessment.

For example, if chronic or subchronic toxicity or carcinogenicity studies have been conducted that permit a quantitative estimation of interaction for two chemicals, then it may be desirable to consider using equations detailed in Section IV, or modifications of these equations, to treat the two compounds as a single toxicant with greater or lesser potency than would be predicted from additivity. Other compounds in the mixture, on which no such interaction data are available, could then be treated in an additive manner. Before such a procedure is adopted, however, a discussion should be presented of the likelihood that other compounds in the mixture may interfere with the interaction of the two toxicants on which quantitative interaction data are available. If the weight of evidence suggests that interference is likely, then an attempt to quantitatively alter the risk assessment may not be justified. In such cases, the discussion of the risk assessment may only indicate the likely nature of interactions, either synergistic or antagonistic, but not attempt to quantify the magnitude of this interaction.

Other types of available information, such as those relating to mechanisms of toxicant interaction, or quantitative estimates of interaction between two chemicals derived from acute studies, are even less likely to be of quantitative use in the assessment of long-term health risks. Usually it will be appropriate only to discuss these types of information. Indicate the relevance of the information to subchronic or chronic exposure, and, as above, indicate, if possible, the nature of any potential interaction, without attempting to quantify the magnitude of the interaction.

4. Uncertainties

In addition to uncertainties on the nature and magnitude of toxicant interactions in the mixture, data may be inadequate to assess exposure to human populations or the potential health effects of one or more components of the mixture. In such a case, the less studied chemicals must not be assumed to be harmless. Instead the uncertainty is increased. Confidence in the risk assessment is reduced because the contribution of these components to the toxicity of the mixture and, consequently, the toxicity of the mixture itself are not known.

a. *Health Effects.* In some cases, when health effects data are incomplete, it may be possible to argue by analogy or quantitative structure-activity relationships that the compounds on which no health effects data are available are not likely to significantly affect the toxicity of the mixture. If a risk assessment is conducted based on such an argument, the limitations of the approach must be clearly articulated.

Since a methodology has not been adopted for estimating an acceptable level (e.g., ADI) or carcinogenic potency for single compounds based either on quantitative structure-activity relationships or on the results of short-term screening tests, such methods are not presently recommended as the sole basis of a risk assessment on chemical mixtures.

b. *Exposure Uncertainties.* If levels of exposure to certain compounds known to be in the mixture are not available, but information on health effects and environmental persistence and transport suggest that these compounds are not likely to be significant in affecting the toxicity of the mixture, then a risk assessment can be conducted based on the remaining compounds in the mixture, with appropriate caveats. If such an argument cannot be supported, no final risk assessment can be performed until adequate monitoring data are available. As an interim procedure, a risk assessment may be conducted for those components in the mixture for which adequate exposure and health effects data are available. If the results of the interim risk assessment suggest that a hazard already exists, resources might be better expended on remedial action as part of the a risk management decision rather than on further assessment. Concern is not reduced if the interim risk assessment does not suggest a hazard because not all components in the mixture have been considered.

c. *Uncertainties Regarding Composition of the Mixture.* As a worst case scenario, information may be lacking not only on health effects and levels of exposure, but also on the identity of some components in the mixture. Analogous to the procedure described in the previous paragraph, an interim risk assessment can be conducted on the components of the mixture for which adequate health effects and exposure information are available. If a hazard is indicated, then the resulting partial assessment should be carefully qualified to avoid over interpretation of the accuracy of the assessment. If no hazard is indicated, the risk assessment should not be quantified until better health effects and monitoring data are available.

III. Assumptions and Limitations

Most of the data available on toxicant interactions are derived from acute toxicity studies using experimental animals in which mixtures of two compounds were tested, often in only a single combination. Major areas of uncertainty with such data involve the appropriateness of interaction data from an acute toxicity study to quantitatively alter a risk assessment for subchronic or chronic exposure, the appropriateness of interaction data on two component mixtures to quantitatively alter a risk assessment on a mixture of several compounds, and the predictability of interaction data on experimental animals to quantitatively assess interactions in humans.

The use of interaction data from acute toxicity studies to assess the potential interactions on chronic exposure would be highly questionable unless the mechanism(s) of the interaction on acute exposure were known to apply to low dose chronic exposure. However, most known biological mechanisms for toxicant interactions involve some form of competition between the chemicals or phenomena involving saturation of a receptor site or metabolic pathway. As the doses of the toxicants are decreased, it is likely that these mechanisms either no longer will exert a significant effect or will be decreased to an extent which cannot be measured or approximated.

The use of information from two component mixtures to assess the interactions in a mixture containing more than two compounds also is questionable from a mechanistic perspective. For example, if two compounds are known to interact, either synergistically or antagonistically, because of the effects of one compound on the metabolism or excretion of the other, the addition of a third compound which either chemically alters or affects the absorption of one of the first two compounds could substantially alter the degree of the toxicologic interaction. Usually, detailed studies quantifying toxicant interactions are not available on multicomponent mixtures, and the few studies that are available on such mixtures (e.g., Gullino et al., 1956) do not provide sufficient information to assess the effects of interactive interference.

Concerns with the use of interaction data on experimental mammals to assess interactions in humans is based on the increasing appreciation for systematic differences among species in their response to individual chemicals. If systematic differences in interspecies sensitivity exist among species, then it seems reasonable to suggest that the magnitude of toxicant interactions among species also may vary in a systematic manner. Consequently, even if excellant chronic data are available on the magnitude of toxicant interactions in a species of experimental mammal, there is uncertainty that the magnitude of the interaction will be the same in humans. Again, data are not available to properly assess the significance of this uncertainty.

Last, it should be emphasized that none of the models for toxicant interaction can predict the magnitude of toxicant interactions in the absence of extensive data. If sufficient data are available to estimate interactive coefficients as described in Section IV, then the magnitude of the toxicant interactions for various proportions of the same components can be predicted. The availability of an interaction ratio (observed response divided by predicted response) is useful only in assessing the magnitude of the toxicant interaction for the specific proportions of the mixture which were used to generate the interaction ratio.

The basic assumption in the recommended approach is the risk assessments on chemical mixtures are best conducted using toxicologic data on the mixture of concern or a reasonably similar mixture. While such risk assessments do not formally consider toxicologic interactions as part of a mathematic model, it is assumed that responses in experimental mammals or human populations noted after exposure to the chemical mixture can be used to conduct risk assessments on human populations. In bioassays of chemical mixtures using experimental mammals, the same limitations inherent in species-to-species extrapolation for single compounds apply to mixtures. When using health effects data on chemical mixtures from studies on exposed human populations, the limitations of epidemiologic studies in the risk assessment of single compounds also apply to mixtures. Additional limitations may be involved when using health effects data on chemical mixtures if the components in the mixture are not constant or if the components partition in the environment.

If sufficient data are not available on the effects of the chemical mixture of concern or a reasonably similar mixture, the proposed approach is to assume additivity. Dose additivity is based on the assumption that the components in the mixture have the same mode of action and elicit the same effects. This assumption will not hold true in most cases, at least for mixtures of systemic toxicants. For systemic toxicants, however, most single compound risk assessments will result in the derivation of acceptable levels, which, as currently defined, cannot be adapted to the different forms of response additivity as described in Section IV.

Additivity models can be modified to incorporate quantitative data on toxicant interactions from subchronic or

hronic studies using the models given 1 Section IV or modifications of these 1odels. If this approach is taken, owever, it will be under the assumption 1at other components in the mixture do ot interfere with the measured 1teraction. In practice, such subchronic r chronic interactions data seldom will e available, and most risk assessments, n the absence of health effects data on he mixture of concern, will be based on n assumption additivity.

Dose-additive and response-additive ssumptions can lead to substantial rrors in risk estimates if synergistic or ntagonistic interactions occur. Although dose additivity has been hown to predict the acute toxicities of nany mixtures of similar and dissimilar ompounds (e.g., Pozzani et al., 1959; Smyth et al., 1969, 1970; Murphy, 1980), ome marked exceptions have been oted. For example, Smyth et al. (1970) ested the interaction of 53 pairs of ndustrial chemicals based on acute ethality in rats. For most pairs of ompounds, the ratio of the predicted LD_{50} to observed LD_{50} did not vary by nore than a factor of 2. The greatest variation was seen with an equivolume mixture of morpholine and toluene, in which the observed LD_{50} was about five times less than the LD_{50} predicted by dose addition. In a study by Hammond et al. (1979), the relative risk of lung cancer attributable to smoking was 11, while the relative risk associated with asbestos exposure was 5. The relative risk of lung cancer from both smoking and asbestos exposure was 53, indicating a substantial synergistic effect. Consequently, in some cases, additivity assumptions may substantially underestimate risk. In other cases, risk may be overestimated. While this is certainly an unsatisfactory limitation, it is a limitation associated more with the nature and quality of the available data on toxicant interaction than with the proposed approach itself.

IV. Mathematical Models and the Measurement of Joint Action

The simplest mathematical models for joint action assume no interaction in any mathematical sense. They describe either dose addition or response addition and are motivated by data on acute lethal effects of mixtures of two compounds.

A. Dose Addition

Dose addition assumes that the toxicants in a mixture behave as if they were dilutions or concentrations of each other, thus the slopes of the dose-response curves for the individual compounds are identical, and the response elicited by the mixture can be predicted by summing the individual doses after adjusting for differences in potency; this is defined as the ratio of equitoxic doses. Probit transformation typically makes this ratio constant at all doses when parallel straight lines are obtained. Although this assumption can be applied to any model (e.g., the one-hit model in NRC, 1980b), it has been most often used in toxicology with the log-dose probit-response model, which will be used to illustrate the assumption of dose additivity. Suppose that two toxicants show the following log-dose probit-response equations:

$$Y_1 = 0.3 + 3 \log Z_1 \qquad \text{(IV-1)}$$

$$Y_2 = 1.2 + 3 \log Z_2 \qquad \text{(IV-2)}$$

where Y_i is the probit response associated with a dose of Z_i $(i=1,2)$.

The potency, p, of toxicant-2 with respect to toxicant-1 is defined by the quantity Z_1/Z_2 when $Y_1 = Y_2$ (that is what is meant by equitoxic doses). In this example, the potency, p, is approximately 2. Dose addition assumes that the response, Y, to any mixture of these two toxicants can be predicted by:

$$Y = 0.3 + 3 \log (Z_1 + pZ_2) \qquad \text{(IV-3)}$$

Thus, since p is defined as Z_1/Z_2, Equation IV-3 essentially converts Z_2 into an equivalent dose of Z_1 by adjusting for the difference in potency. A more generalized form of this equation for any member of toxicants is:

$$Y = a_1 + b \log (f_1 + \Sigma f_i p_i) + b \log Z \qquad \text{(IV-4)}$$

where a_1 is the y-intercept of the dose-response equation for toxicant-1, b is the slope of the dose-response lines for the toxicants, f_i is the proportion of the ith toxicant in the mixture, p_i is the potency of the ith-toxicant with respect to toxicant-1 (Z_1/Z_i), and Z is the sum of the individual doses in the mixture. A more detailed discussion of the derivation of the equations for dose addition is presented by Finney (1971).

B. Response Addition

The other form of additivity is referred to as response addition. As detailed by Bliss (1939), this type of joint action assumes that the two toxicants act on different receptor systems and that the correlation of individual tolerances may range from completely negative $(r=-1)$ to completely positive $(r=+1)$ correlation. Response addition assumes that the response to a given concentration of a mixture of toxicants is completely determined by the responses to the components and the correlation coefficient. Taking P as the proportion of organisms responding to a mixture of two toxicants which evoke individual responses of P_1 and P_2, then

$$P = P_1 \text{ if } r=1 \text{ and } P_1 > P_2 \qquad \text{(IV-5)}$$

$$P = P_2 \text{ if } r=1 \text{ and } P_1 < P_2 \qquad \text{(IV-6)}$$

$$P = P_1 + P_2 (1 - P_1) \text{ if } r=0 \qquad \text{(IV-7)}$$

$$P = P_1 + P_2 \text{ if } r=-1 \text{ and } P < \qquad \text{(IV-8)}$$

More generalized mathematical models for this form of joint action have been given by Plackett and Hewlett (1948).

C. Interactions

All of the above models are noninteractive and do not allow for the measurements of synergistic or antagonistic effects. For measuring toxicant interactions for mixtures of two compounds, Finney (1942) proposed the following modification of Equation IV-4 for dose addition:

$$Y = a_1 + b \log (f_1 + pf_2 + K [pf_1 f_2]^{0.5}) + b \log Z \qquad \text{(IV-9)}$$

where a_1, b, f_2, p and Z are defined as before and K is the coefficient of interaction. A positive value of K indicates synergism, a negative value indicates antagonism, and a value of zero corresponds to dose addition as in Equation IV-4. Like other proposed modifications of dose addition (Hewlett, 1969), the equation assumes a consistent interaction throughout the entire range of proportions of individual components. To account for such asymmetric patterns of interaction as those observed by Alstott et al. (1973), Durkin (1981) proposed the following modification to Equation IV-9:

$$Y = a_1 + b \log (f_1 + pf_2 + K_1 f_1 [pf_1 f_2]^{0.5} + K_2 f_2 [pf_1 f_2]^{0.5}) + b \log Z \qquad \text{(IV-10)}$$

in which $K(pf_1 f_2)^{0.5}$ is divided into two components, $K_1 f_1 (pf_1 f_2)^{0.5}$ and $K_2 f_2 (pf_1 f_2)^{0.5}$. Since K_1 and K_2 need not have the same sign, apparent instances of antagonism at one receptor site and synergism at another receptor site can be estimated. When K_1 and K_2 are equal, Equation IV-10 reduces to Equation IV-9.

It should be noted that to obtain a reasonable number of degrees of freedom in the estimation of K in Equation IV-9 or K_1 and K_2 in Equation IV-10 requires that the toxicity of several different combinations of the two components must be assayed along with assays of the toxicity of the individual components. Since this requires experiments with large numbers of animals, such analyses have been restricted for the most part to data from acute bioassays using insects (e.g., Finney, 1971) or aquatic organisms (Durkin, 1979). Also, because of the complexity of experimental design and the need for large numbers of animals, neither Equation IV-9 nor Equation IV-10 has been generalized or applied to mixtures of more than two toxicants. Modifications of response-additive models to include interactive terms have

also been proposed, along with appropriate statistical tests for the assumption of additivity (Korn and Liu, 1983; Wahrendorf et al., 1981).

In the epidemiologic literature, measurements of the extent of toxicant interactions (S) can be expressed as the ratio of observed relative risk to relative risk predicted by some form of additivity assumption. Analogous to the ratio of interaction in classical toxicology studies, $S=1$ indicates no interaction, $S<1$ indicates synergism, $S<1$ indicates antagonism. Several models for both additive and multiplicative risks have been proposed (e.g., Hogan et al., 1978; NRC, 1980b; Walter, 1976). For instance, Rothman (1976) has discussed the use of the following measurement of toxicant interaction based on the assumption of risk additivity:

$$S=(R_{11}-1)/(R_{10}+R_{01}-2) \qquad \text{(IV-11)}$$

where R_{10} is the relative risk from compound-1 in the absence of compound-2, R_{01} is the relative risk from compound-2 in the absence of compound-1, and R_{11} is the relative risk from exposure to both compounds. A multiplicative risk model adapted from Walter and Holford (1978, Eq. 4) can be stated as:

$$S=R_{11}/(R_{10}R_{01}) \qquad \text{(IV-12)}$$

As discussed by both Walter and Holford (1978) and Rothman (1976), the risk-additive model is generally applied to agents causing diseases while the multiplicative model is more appropriate to agents that prevent disease. The relative merits of these and other indices have been the subject of considerable discussion in the epidemiologic literature (Hogan et al., 1978; Kupper and Hogan, 1978; Rothman, 1978; Rothman et al., 1980; Walter and Holford, 1978) which has not yet been resolved.

Both the additive and multiplicative models assume statistical independence in that the risk associated with exposure to both compounds in combination can be predicted by the risks associated with separate exposure to the individual compounds. As illustrated by Siemiatycki and Thomas (1981) for multistage carcinogenesis, the better fitting statistical model will depend not only upon actual biological interactions but also upon the stages of the disease process which the compounds affect. Consequently, there is no *a priori* basis for selecting either type of model in a risk assessment. As discussed by Stara et al. (1983), the concepts of multistage carcinogenesis and the effects of promoters and cocarcinogens on risk are extremely complex issues. Although risk models for promoters have been proposed (e.g., Burns et al., 1983) no single approach can be recommended at this time.

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APPENDIX 4

TEST PROTOCOL CRITERIA FOR ANIMAL ASSAYS

Several test systems have been devised to determine the potential for development of various toxicologic endpoints following exposure to various chemical substances. These assays share in common certain fundamental features with respect to design and conduct. These are discussed below:

1. Dose

In acute studies, a single administration of the test substance at four or five varying dose levels should be sufficient for determining ranges of mortality and toxic effects. Doses are selected to provide data sufficient to estimate the LD_{50} (the dose at which 50% of the test organisms die) and to produce a dose-response curve.

For subchronic and chronic studies, at least three dose levels should be used in addition to a concurrent control group. The highest dose level should elicit some signs of toxicity without causing excessive lethality. The lowest dose level should not produce toxicity. To obtain maximum information on the dose-response characteristics of the test chemical, at least one intermediate dose is generally used.

2. Route of Exposure and Duration of Treatment

The most common routes of compound administration for chronic and subchronic testing are inhalation, oral and dermal. Corresponding routes, in addition to ocular exposure, are employed in acute toxicity studies.

In subchronic testing, oral and inhalation studies are accomplished in three months. In most inhalation studies, comparable results will be obtained from either the 5- or 7-day/week exposure. The inhalation exposure schedule is usually 5 days/week, 6 hours/day. For repeated dermal route studies, a maximum of 21 applications to rabbits on a 5-day/week basis is considered to be practical and of sufficient duration.

In chronic toxicity testing, the oral route of administration is usually preferred if the test substance is known to be absorbed from the gastrointestinal tract. If the test substance is administered in the drinking water or mixed in the diet, exposure is continuous. If the test substance is administered by gavage or capsule, the animals are dosed seven days per week. For cutaneous exposure, dosing schedules should be selected to simulate human exposure. For inhalation exposures, the choice of intermittent or continuous dosing depends on the objectives of the study and on the expected human exposure conditions. Long-term inhalation studies are patterned on expected occupational exposures of 6 to 8 hours/day for 5 days/week or possible environmental exposures of 22 to 24 hours/day for 7 days/week.

3. Selection of Species

The selection of species should take into account, whenever possible, whether the test species' metabolism of the chemical, or its analogues, is similar to that of humans.

Historically, it has generally been recommended that chronic and subchronic testing be performed with two mammalian species, one a rodent and the other a nonrodent. The rat has normally been the rodent of choice. Dogs are the species of choice for the nonrodents. The strains of test species used should be well characterized, commonly used, disease resistant, and free from interfering congenital defects. In special circumstances with a small number of chemicals, other species have been shown to be more sensitive than either the rat or the dog. However, the use of additional species would often not appreciably affect the determination of a safe exposure level for man.

4. Number of Animals

The number of animals to be employed in chronic tests varies depending on the goals and needs of the investigation. A sufficient number of animals should be used so that reliable statistical analysis can be performed to evaluate the test results. At the end of the study, enough animals should be alive in each group for a thorough clinical and morphological examination. With respect to species tested, a minimum of 50 rodents/sex/dose level and 8 dogs/sex/dose level should be utilized in chronic toxicity tests. At least 20 rats/sex/dose level and 4 dogs/sex/dose level are considered to be sufficient for subchronic testing. For repeated skin application studies, 20 rabbits/sex/dose are usually required.

5. Age of Animals

The age at which animals are started on a test is an important consideration in toxicity testing. In routine subchronic testing it is generally recommended that rodents be started on treatment as young as practically possible. The earliest practical age to start rodents on test is 5 to 8 weeks. For nonrodents, especially the dog, starting the exposure at 4 to 10 months is preferable to using older animals.

In chronic testing, exposure of rodents and dogs should be no later than six weeks and four months of age, respectively.

APPENDIX 5

DEFINITION OF TOXICOLOGIC ENDPOINTS

A wide range of chemicals have been reported to produce adverse health effects. The effects manifested have been characterized as toxicologic endpoints which include primarily neurotoxicity, behavioral toxicity, hepatotoxicity, renal toxicity, blood toxicity, teratogenicity, reproductive toxicity, mutagenicity, or carcinogenicity. These endpoints can be characterized as follows:

- Neurotoxicity refers to effects of toxic substances on various structures comprising the nervous system. The effects exerted may involve direct damage to structures including axons of peripheral neurons, myelin, synaptic junctions, etc. Manifestations of neurotoxicity include acute toxic effects such as muscular twitching, weakness, convulsions, and respiratory paralysis. Delayed neurotoxicity may result from direct action of the toxic substance through axon degeneration followed by demyelination of tracts in the spinal cord or peripheral nerves with resultant paralysis.

- Behavioral toxicity refers to changes in adaptive behavioral capacity that result from the effect of toxic substances on the neural system. Changes may occur in behavioral functions such as acquisition of skills, learning, short- and long-term memory, decision-making, and psychomotor functioning.

- Hepatotoxicity is the elicitation of adverse effects in the morphology and/or function of the liver. Some common endpoints of chemical injury include the following:

  - Accumulation of abnormal amounts of hepatic lipid, especially triglycerides
  - Inhibition of protein synthesis
  - Lipid peroxidation of hepatic microsomes
  - Necrosis
  - Cholestasis
  - Cirrhosis
  - Carcinogenesis

- Renal toxicity is the elicitation of adverse effects in the morphology and/or functions of the kidney. Some manifestations of renal toxicity include depression of creatinine clearance and phosphate reabsorption to severe tubular degeneration.

- Blood toxicity refers to chemical-induced alteration in components of the blood by influencing their production, rate of peripheral destruction or distribution.

- Teratology may be defined as the study of permanent structural or functional abnormalities arising during embryogenesis and that are generally incompatible with, or severely detrimental to, normal post-natal survival or development.

- Reproductive toxicity refers to detrimental effects on reproduction and on the offspring following parental exposure. Manifestations of reproductive toxicity include impaired fertility, fetal death and birth or developmental defects.

- Mutagenicity is the capacity to cause heritable changes in the genetic make-up of a cell. Manifestation of mutagenic effects include point mutations, numerical aberrations, and structural aberrations.

- Carcinogenicity refers to the ability of a chemical to significantly increase the incidence of malignant lesions in animals or humans, to induce rarely occurring tumors, or significantly decrease the latency period for tumor development relative to an appropriate background or control group.