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Checklist for Camera-Ready Copies

Toxicological Profile for _____

Contractor	**ATSDR**	
	[]	Contractor Checklist Verified
Title Page		
[]	[]	Spacing is Correct
[]	[]	Contract Number is Correct
[]	[]	Month and Year of Release are Correct
[]	[]	Draft for Public Comment – No Data in Running Footer on any Page
[]	[]	Final – No Footer on any Page
[]	[]	Final – "Draft" Removed From Title
Pagination		
[]	[]	Disclaimer is on Page ii
		The Following Parts Start on Odd-Numbered Pages:
[]	[]	- Foreword
[]	[]	- Quick Reference for Health Care Providers
[]	[]	- Contributors
[]	[]	- Peer Review
[]	[]	- Contents
[]	[]	- List of Figures
[]	[]	- List of Tables
[]	[]	- Each Chapter
[]	[]	- Appendices
[]	[]	Blank Pages (without numbers) have Been Inserted for Even- Numbered Pages, Where Necessary
[]	[]	Page Numbers are in Sequence
[]	[]	There are no Pages Missing
[]	[]	There are no Duplicate Pages
[]	[]	There is a Blank Page at the End
Other		
[]	[]	Contents, List of Figures, List of Tables – Words and Page Numbers Match the Words and Page Numbers in the Text
[]	[]	Copies of all Tables and Figures are Sharp and Clear
[]	[]	MRLs are Expressed to One Significant Figure
[]	[]	In References, the Asterisk (*) is Defined on the First Page of the Chapter
[]	[]	Names and Titles of Peer Reviewers have been Verified

_____ _____
Contractor/Author Date

_____ _____
ATSDR Chemical Manager Date

EXHIBIT 3
(Page 1 of 1)

DRAFT
TOXICOLOGICAL PROFILE FOR
[SUBSTANCE X]

Prepared by:
[Contractor Name]
Under Contract No. [_____]

Prepared for:
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

[DATE]

TOXICOLOGICAL PROFILE FOR
[SUBSTANCE X]

Prepared by:
[Sub-Contractor Name]
Under Contract No. [_____]

Prepared for:
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

[DATE]

DISCLAIMER

The use of company or product name(s) is for identification purposes only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

[*Use the following boilerplate text for the Draft for Public Comment versions. Delete for the Final versions]*. This information is distributed solely for the purpose of pre dissemination public comment under applicable information quality guidelines. It has not been formally disseminated by the Agency for Toxic Substances and Disease Registry. It does not represent and should not be construed to represent any agency determination or policy.

UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary, but no less than one every three years. A Toxicological Profile for [Substance X] was released in [year]. This edition supersedes any previously released draft or final profile.

For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
1600 Clifton Road NE, F-32
Atlanta, Georgia 30333

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QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure*, by *type of health effect* (death, systemic, immunologic, reproductive), and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

Section 3.8 Biomarkers of Exposure and Effect
Section 3.11 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110 ***Fax:*** (404) 498-0057
E-mail: atsdric@cdc.gov ***Internet:*** http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity;* and numerous chemical-specific case studies.*Managing Hazardous Materials Incidents*

is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact:* NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. *Contact:* NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

*The National Institute of Environmental Health Sciences (*NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: aoec@dgs.dgsys.com • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (A TSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in non-technical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes. the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, sub-acute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, sub-acute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road, N.E.
Mail Stop F-32
Atlanta, Georgia 30333

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (public Law 99-499), which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on October 25, 2001 (66 FR 54014). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); and October 21, 1999 (64 FR 56792). Section 104(i) (3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Julie Louise Gerberding, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

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Legislative Background

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[Contractor], [Address]

[Name], [Credentials}
[Contractor], [Address]

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying endpoints.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies and significant problems in format or content, and establishes that guidance has been followed.

PEER REVIEW

A peer review panel was assembled for [Substance X]. The panel consisted of the following members:

- [Name, Title, Affiliation, City, State]
- [Name, Title, Affiliation, City, State]
- [Name, Title, Affiliation, City, State]
- [Name, Title, Affiliation, City, State]

These experts collectively have knowledge of [Substance X's] physical and chemical properties, toxicokinetic, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this [Substance X].

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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LIST OF TABLES

Table 3-1 Levels of Significant Exposure to Copper – Inhalation

Key to[a] Figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	(mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
ACUTE EXPOSURE							
Systemic							
1	Mouse	3 hr	Resp	3.3			Drummond et al. 1986
2	Mouse	1-2 wk 5d/wk 3hr/d NOAEL	Resp		0.12 (alveoli thickening)		Drummond et al. 1986
3	Hamster	3 hr	Resp	1.21	3.3 (decr cilia beating frequency)		Drummond et al. 1986
	Hamster	1-2 wk 5d/wk 3hr/d	Resp	0.13			Drummond et al. 1986
Immuno/Lymphoret							
5	Mouse	1-2 wk 5d/wk 3hr/d			0.12 (decr bactericidal activity)	0.13 (decr mean survival time)	Drummond et al. 1986
6	Mouse	3 hr			3.3 (decr bactericidal activity)	0.56 (decr mean survival time)	Drummond et al. 1986
INTERMEDIATE EXPOSURE							
Systemic							
7	Rabbit (NS)	1 mo 5d/wk 6hr/d	Resp	0.6M			Johansson et al. 1983 Copper Chloride
	Rabbit (NS)	4-6 wk 5d/wk 6hr/d	Resp	0.6M			Johansson et al. 1984 Copper Chloride

Table 3-1 Levels of Significant Exposure to Copper – Inhalation (continued)

Key to[a] Figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	(mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
CHRONIC EXPOSURE							
Systemic							
9	Human	8hr/d 5d/wk	Hemato		0.64 (decr hemoglobin and erythrocyte levels)		Finelli et al 1981 NS
		NOAEL					

Table 3-2 Levels of Significant Exposure to Copper – Oral

Key to[a] Figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	(mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Wistar)	2-15 wk (F)				550 M (increased mortality)	Haywood 1985 NS
	Rat	NOAEL				31 F (100% mortality)	NTP 1993 Copper Sulfate
2	Mouse (B6C3F1) Systemic	14d (W) 14d				62 M (increased mortality)	NTP 1993 Copper Sulfate
	Human	(W)	Gastro	0.011	0.017 (nausea, vomiting, diarrhea or abdominal pain)		Auraya et al. 2001 copper sulfate
3	Human	once (W) once	Gastro		0.03 (nausea, vomiting)		Gotteland et al 2001 copper sulfate
4	Human	(W)	Gastro		6 (vomiting)		Karlsson and Noren 1965 copper sulfate
7	Human once	once (W)	Gastro		0.08 M (vomiting, diarrhea)		Nicholas and Brist 1968 NS
6	Human	(W)	Gastro	0.0057	0.011 (nausea)		Olivares et al 2001 copper sulfate
8	Human (W)	2 wks once	Gastro	0.272[b] F	0.0731 F (abdominal pain, nausea, and/or vomiting)		Pizamo et al 1999 copper sulfate

9

Table 3-2 Levels of Significant Exposure to Copper – Oral (continued)

	Key to[a] Figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	(mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
		Systemic						
		Human	1 wk (W)	Gastro		0.1 F (nausea, vomiting, and/or abdominal pain)		Picarro et al 2001 Copper sulfate and copper oxide
		Rat (NS)	1-2 wk (F) NOAEL			300 M (parenchymal cell hypertrophy)		Haywood 1980 Copper Sulfate
					300 M			
			Hepatic					
10		Rat	1-2 wk (F)			300 M (increased alanine aminotransferase activity)		Haywood and Comerford 1980 copper sulfate
11		Rat	1-2 wk	Hepatic		450 M (hepatocellular necrosis)		Haywood et al 1985a
	12	(Wistar)	(F) Hepatic			450 M (copper-containing droplets and Granules in proximal tubule Cells)		NS
	14	Rat (Wistar)	2 wk (F)	Renal		200 M (Droplets in proximal tubule) lumen)		Haywood et al. 1985b NS
13								

Renal

Renal

Table 3-2 Levels of Significant Exposure to Copper – Oral (continued)

	Key to[a] Figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)		System	(mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
		Systemic							
		Rat (Fischer – 344)	(W)		Resp	29 M			NTP 1993 Copper Sulfate
			14d	NOAEL	Cardio	29 M			
					Gastro	29 M			
					Hepatic	29 M			
15					Bd Wt	26 F	10 M (protein droplets in epithelial Cells of proximal tubule)		
		Rat (Fischer - 344	14 d (F)			285 F			NTP 1993 copper sulfate
					Cardio	285 F			
16				Resp	Gastro	23 F	44 F (hyperplasia of forestomach Mucosa)		
					Hemato	93 F	196 F (depletion of hematopoietic Cells in bone marrow)		
						92 M	198 M (inflammation)		
					Renal	46 M	92 M (increased protein droplets in Cortical tubules)		
					Bd Wt	93 F	196 F (19% decrease in body weight Gain)		

Renal

Table 3-2 Levels of Significant Exposure to Copper – Oral (continued)

	Key to[a] Figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)		System	(mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
		Systemic							
		Mouse (B6C3F1)	14d (W)		Resp	24 M			NTP 1993 Copper Sulfate
				NOAEL	Cardio	24 M			
					Gastro	24 M			
					Hepatic	24 M			
					Renal	24 M			
17					Bd Wt	24 M			
		Mouse (B6C3F1)	14 d (F)			717 M			NTP 1993 copper sulfate
					Cardio	717 M			
18				Resp	Gastro	92 M	197 M (hyperplasia of forestomach Mucosa)		
						717 M			
					Renal	717 M			
					Bd Wt	717 M			
	INTERMEDIATE EXPOSURE								
	Systemic								
		Human	9 mo (W)		Gastro	0.319			Olivares et al. 1998 copper sulfate
						0.319			
19					Bd Wt	0.379			

Hepatic

Table 3-2 Levels of Significant Exposure to Copper – Oral (continued)

	Key to[a] Figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)		System	(mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
		Systemic							
		Human	12 wks (C)		Gastro	0.14			Pratt et al 1985 Copper gluconate
				NOAEL	Heamto	0.14			
					Hepatic	0.14			
		Rat (Sprague-Dawley)	30 – 58 d (F)		Hepatic	20 F			Cristofori et al 1992 NS
20									
					Renal	20 F			
	21								
		Rat (Sprague-Dawley)	99 d (W)				8 M (increased aspartate aminotransferase activity)		Epstein et al 1982 copper sulfate
					Bd Wt	8 M			
	22			Hepatic					
		Rat (Fischer – 344)	18 wks (F)				150 M (inflammation and increased serum enzyme activity in adult rats)		Fuentealba et al 2000 Copper sulfate
				Hepatic					
							120 M (inflammation, necrosis, and increases serum enzyme levels in young rats)		
23									
		Rat (NS)	3-15 wk (F)				180 M (necrosis)		Haywood 1980 copper sulfate
							180 M (cytoplasmic droplets and Desquamation of epithelial cells In proximal tubules)		
	24			Hepatic					

Table 3-2 Levels of Significant Exposure to Copper – Oral (continued)

Key to[a] Figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	(mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
	Systemic						
25	Rat (Wistar)	2-15 wks (F)	Hepatic		280 M (inflammation, necrosis)	550 M (chronic hepatitis)	Haywood 1985 NS
		NOAEL			280 M (degeneration of proximal Tubule cells)		
			Bd Wt			550 M (weight loss) 280 M 50% decrease in body weight gain)	
26	Rat (NS)	3 – 15 wk (F)	Hepatic		180 M (increased alanine aminotransferase activity)		Haywood and Comerford 1980 copper sulfate
	Rat (Wistar)	15 wk (W)			320 M (necrosis)	640 M (chronic hepatitis)	Haywood and Loughran 1985 copper sulfate
		Hepatic	Bd Wt			640 M (weight loss) 320 M (50% decrease in body weight gain)	
27	Rat (Wistar)	4-14 wks (F)	Hepatic		280 M (hepatocellular necrosis)		Haywood et al 1985a NS
					280 M (tubular cell necrosis)		
28	Rat	4-15 wk			200 M (reversible degeneration and necrosis of tubule cells)		Haywood et al. 1985b
29	Renal	Renal					

NS

Table 3-2 Levels of Significant Exposure to Copper – Oral (continued)

Key to[a] Figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
	Systemic						
	Rat (NS)	30 d (G)	Hemato		100 M (decreased erythrocyte and hemoglobin levels)		Kumar and Sharma 1987 copper sulfate
				NOAEL	100 M (increased glucose, cholesterol, Bilirubin, serum enzymes, and Decreased total protein levels)		
30					100 M (increased BUN levels) Tubule cells)		
31	Rat (Wistar)	15 wk (F)	Cardio		14 M (increased blood pressure)		Lui and Mederios 1986 copper carbonate
	Rat (Holtzman)	21 wks (F)	Musc/skel	120 M			Liewellyn 1985 copper acetate
			Bd Wt		120 (23% decrease in body weight gain)		
32							
Hepatic							
Renal							

Table 3-2 Levels of Significant Exposure to Copper – Oral (continued)

Key to[a] Figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
	Systemic						
	Rat (Fischer – 344)	13 wk (F)		134 F			NTP 1993 copper sulfate
			NOAEL Resp	134 F			
			Gastro	16 M	33 M		
			Hemato	33 M	66 M		
33			Hepatic	8 M	66 M (chronic active inflammation With focal necrosis)		
					16 M		
			Renal	9 F	17 F (increased BUN)	134 F (tubular degeneration)	
			Bd Wt	65 M	140 M (24% decrease in body weight gain)		
34	Rat (NS)	20 d (G)	Hemato		100 M (hdecreases in erythrocyte, hemoglobin, and hematocrit levels)		Rana and Kumar 1980 copper sulfate
					100 M (hepatocelular necrosis)		
					100 M (tubular cell necrosis)		

Table 3-2 Levels of Significant Exposure to Copper – Oral (continued)

	Key to[a] Figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	(mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
		Systemic						
		Mouse (B6C3F1)	13 wk (F)		814 M			NTP 1993 copper sulfate
				NOAEL Resp	Cardio 814 M			
					Gastro 126 F	267 F (hyperplasia of forestomach mucosa)		
35					814 M			
					814 M			
					Bd Wt 187 M	398 M (12% decrease in body weight gain)		
		Pig (Hampshire)	54 d (F)	Hemato	11	24		Kline et al 1971 copper sulfate
				Bd Wt	11	24 (decreased body weight gain)		
	36	Pig (NS)	49 d (F)	Hemato Hepatic		36 F (decreased hemoglobin levels) 36 F (increased aspirate aminotransferase activity)		Suttle and Mills 1966a
	37	Pig (NS)	6 wks (F)	Hemato		35 F (decreased hemoglobin level) 35 F (increased asparatate aminotransferase activity)		Suttle and Mills 1966a copper carbonate
	39	Immuna/Lymphoret Mouse (C57BL/6N)	8 wks (W)			24 (impaired immune function)		Pocion et al 1990 copper sulfate
38	Hepatic							
Renal								

Table 3-2 Levels of Significant Exposure to Copper – Oral (continued)

Key to[a] Figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	(mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
	Immuno/Lymphoret						
40	Mouse (C57BL/6N)	3-5 or 8-10 wks (W)			13 (altered cell-mediated and humoral immunity)		Pocino et al. 1991 copper sulfate
	Neurological						
	Rat Dawley)	11 mo (W NOAEL			36 F (decreased 3,4-dihydroxyphenylacetic acid levels in corpus striatum)		DeVries et al 1986 copper sulfate
	Rat (NS)	30 d (F)					Murthy et al 1981 copper sulfate
	Reproductive						
41	Rat (Fischer - 344)	13 wks (F)		66 M			NTP 1993 copper sulfate
42 (Sprague-)	Mouse (B6C3F1)	13 wks (F) 23	68F	398 M 536 F			NTP 1993 copper sulfate
	Mink (dark mink)	153 or 157 d (F)					Aulerich et al 1983 Copper sulfate
43	**Developmental**						
44	Rat (Wistar)	60 – 73 d (W)	12		130 (delayed growth and development)		Haddad et al 1991 copper acetate
47	Mouse	1 mo + gd 0-19		138 F	208 (decreased mean litter size and fetal fetal body weights)		Lecyk et al 1980 copper sulfate
45							
46							

Table 3-2 Levels of Significant Exposure to Copper – Oral (continued)

Key to[a] Figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL Less Serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
	Developmental						
	Other (dark mink)	153 or 367d (F)					Aulerich et al 1982 copper sulfate
	CHRONIC EXPOSURE						
	Death		NOAEL	13			
	Mouse (C567BL/6N)	(W)				4.2 (14.7% decrease in lifespan)	Massie and Aiello 1984 copper gluconate
48	Mouse	850d	Bd WT	4.2 M			Massie and Aiello 1984 copper gluconate
50		850d					

49 a The number corresponds to entries in Figure 3-2.

b Used to derive an acute-duration oral minimal risk level (MRL) of 0.02 mg Cu/kg/day. To estimate total copper exposure, the concentration of copper in the drinking water (o.0272 mg Cu/kg/day) was added to the reported average dietary copper intake (0.0266 mg Cu/kg/day). The total copper intake (0.0538 mg Cu/kg/day) was divided by an uncertainty factor of 3 to account for human

The acute-duration oral MRL of 0.02 mg Cu/kg/day was also adopted for use as an intermediate-duration oral MRL.

variability. Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; G = gavage; Gastro = gastrointestinal; gd = gestational day; Gn pig = guinea pig; hemato = hematological; hr = hour(s); LOAEL = lowest observed adverse effect level; M = male; min = minute(s); mo = mounth(s); Musc/Skel = musculoskeletal; NOAEL = no observed adverse effect level; occup = occupational; NS = not specified; Resp = respiratory; (W) = drinking water; wk = week(s)

EXHIBIT 11
(Page 1 of 2)

Table 3-3 Levels of Significant Exposure to Beryllium – Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
Immuno/Lymphoret						
Human	48 hr			0.19 (allergic dermatitis) Mg/ml		Curtis 1951 BeSO4
Human	48 hr			0.19 (allergic dermatitis) Mg/ml		Curtis 1951 BeC12
Human	48 hr			0.019 (allergic dermatitis) Mg/ml		Curtis 1951 BeF2
Human	48 hr			0.19 (allergic dermatitis) Mg/ml		Curtis 1951 Be(NO3)2
Gn Pig (albino)	1 x			0.1 (delayed type hypertensive reaction)		Belman 1969
Gn Pig (albino)	1 x			0.02 (delayed type hypertensive reaction)		Belman 1969
Gn Pig (Hartley)	1 d			0.25 (delayed hypertensive reaction) splenic hyperplasia. Lung inflammation)		Marx and Burrell 1973
Gn Pig (Dunkin Hartley)	24 hr			3 (delayed type hypersensitivity)		Zissu et al 1996 beryllium sulfate

BeC12

BeF2

BeSO4

Table 3-3 Levels of Significant Exposure to Beryllium – Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
INTERMEDIATE EXPOSURE						
Immuno/Lymphoret						
Gn Pig (Hartley)	24 wk 1x2/wk			0.0005 (increased macrophage inhibition factor and T-cell activity)		Marx and Burrell 1973

BeC12 = beryllium chloride; BeF2 = beryllium fluoride; Be(NO3)3 = beryllium nitrate; BeSO4 = beryllium sulfate; Gn pig = guinea pig; hr = hour(s); LOAEL = lowest observed adverse effect level; NOEL = no observed adverse effect level; wk = week(s); x = timesp

BeSO4

ug

Figure 3-1. Levels of Significant Exposure to Beryllium - Inhalation

Acute (≤14 days)

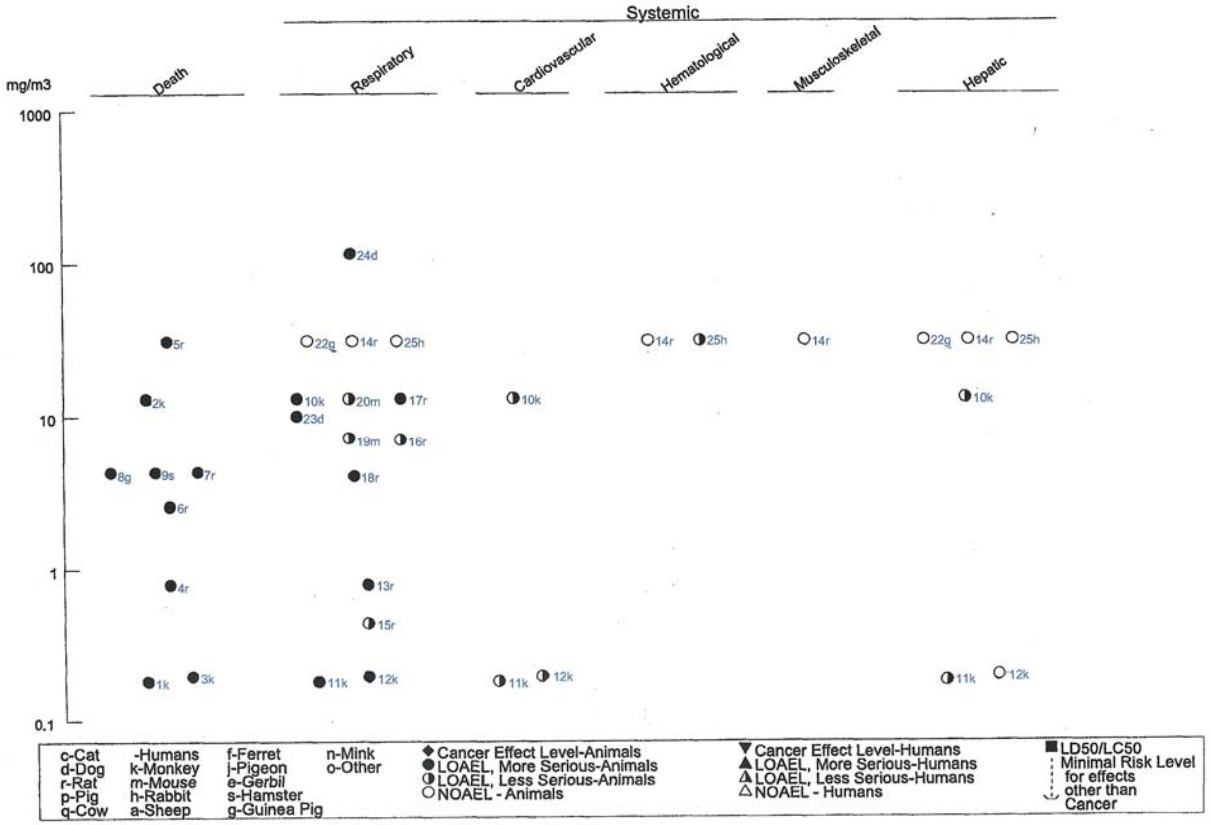


Figure 3-1. Levels of Significant Exposure to Beryllium - Inhalation (*Continued*)

Acute (≤14 days)

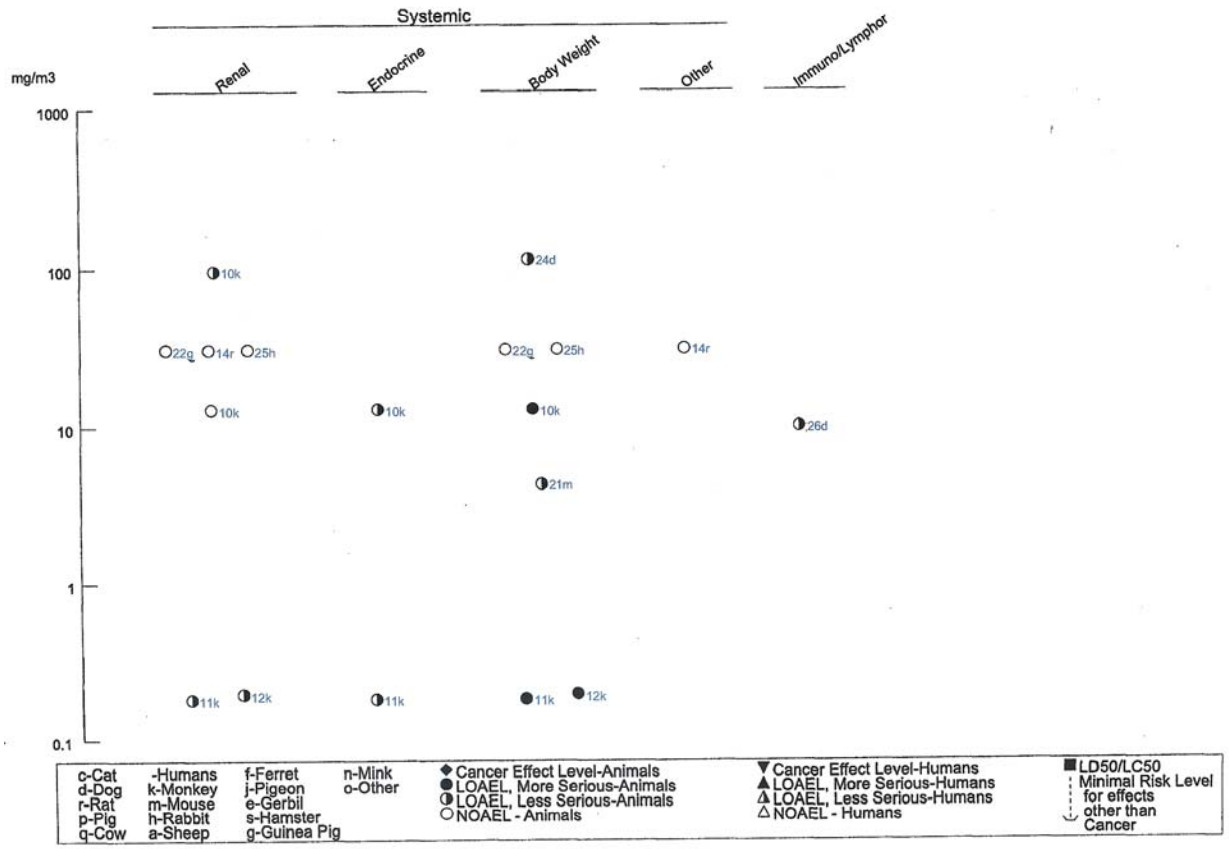


Figure 3-1. Levels of Significant Exposure to Beryllium - Inhalation (*Continued*)

Intermediate (15-364 days)

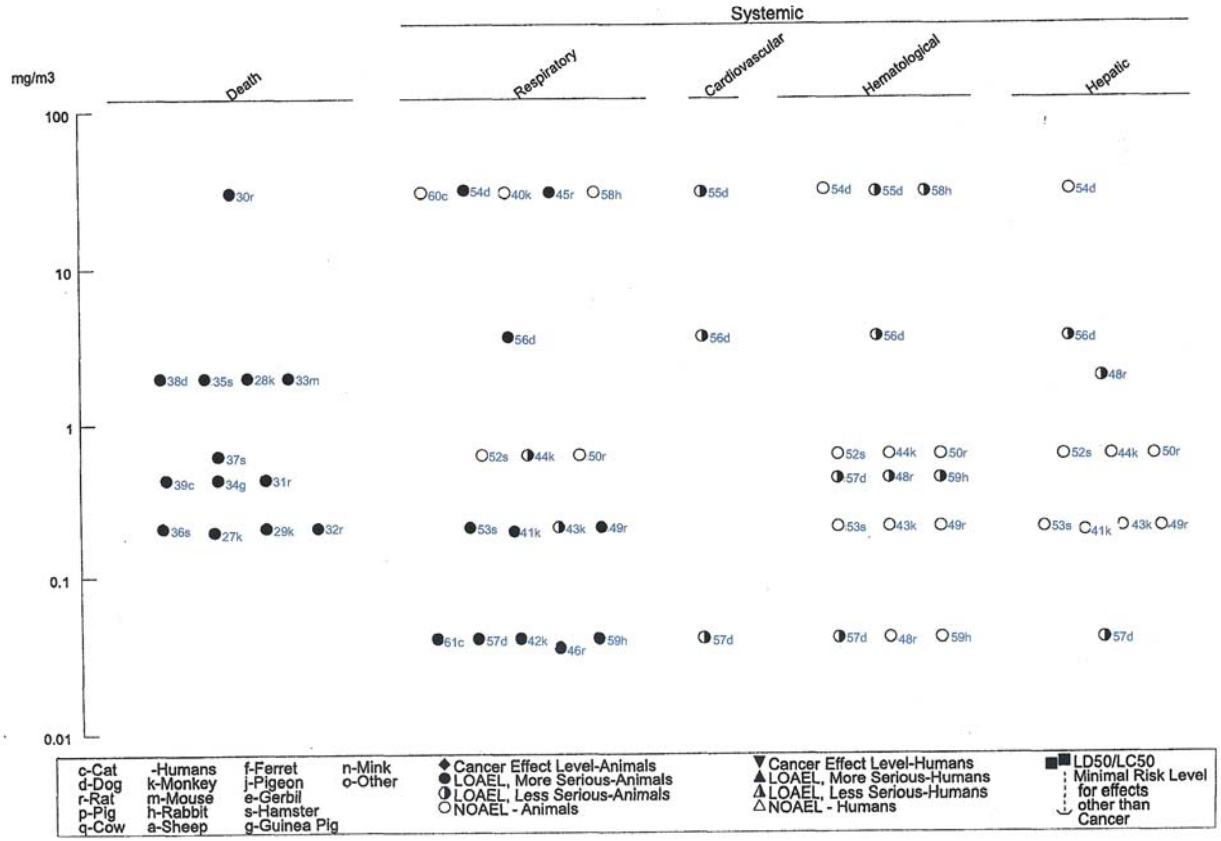


Figure 3-1. Levels of Significant Exposure to Beryllium - Inhalation (*Continued*)

Intermediate (15-364 days)

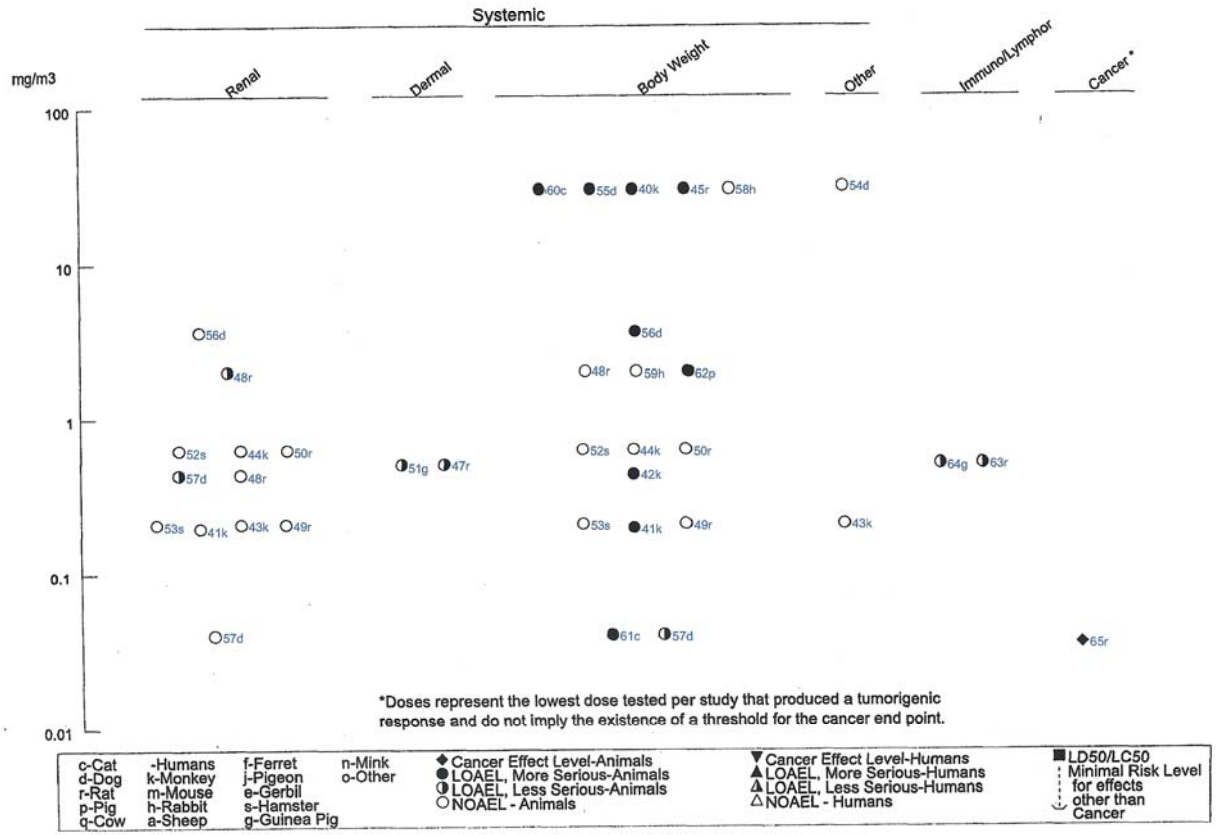
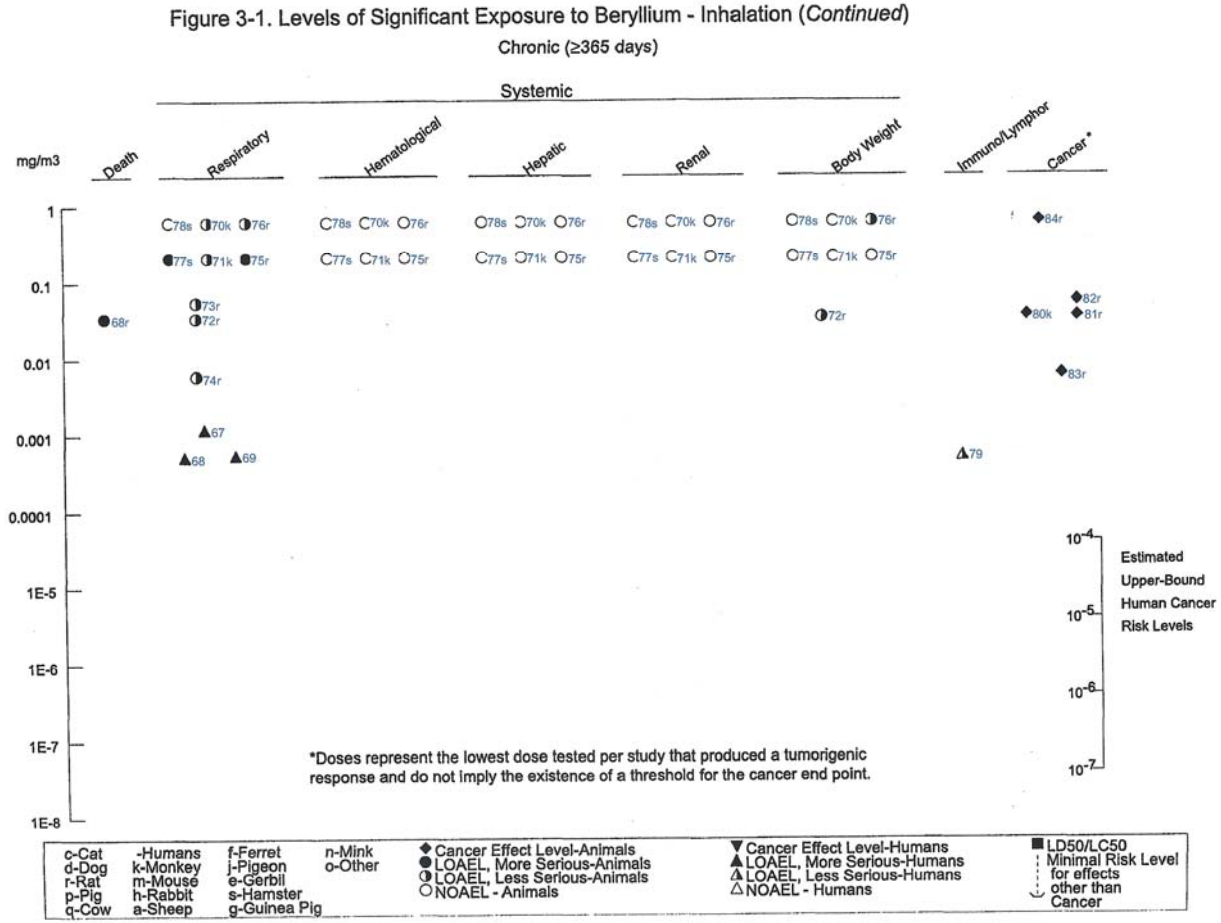


Figure 3-1. Levels of Significant Exposure to Beryllium - Inhalation (*Continued*)

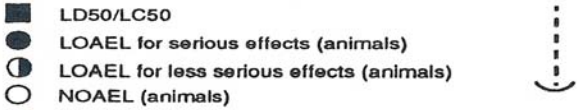


SAMPLE LSE FIGURE KEY

Select appropriate symbols and abbreviations from the set illustrated below when preparing keys for the LSE figures.

Key

r	Rat
m	Mouse
h	Rabbit
s	Hamster
g	Guinea pig
d	Dog
c	Cat
k	Monkey
p	Pig
f	Ferret
a	Sheep
n	Mink
j	Pigeon
e	Gerbil
q	Cow



Minimal risk level for effects other than cancer

The number next to each point corresponds to entries in Table 2-__.

APPENDIX B
USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical. The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around
   hazardous waste sites?

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for non-cancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for non-cancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 3-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).

(5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in Chapter 9 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 →

Table 3-1 Levels of Significant Exposure to [Chemical X] – Inhalation

Key to Figure [a]	Species	Exposure Duration	System	NOAEL (ppm)	LOAEL (effect) Less Serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5 Frequency ↓	6 ↓	7 ↓	8 ↓	9 ↓		10 ↓
3 → Systemic							
4 → 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 [b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
						11 ↓	
Cancer							
38	Rat	18 mo 5 d/wk 7 hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89 – 104 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors nasal tumors)	NTP 1982
40	Mouse	79 – 103 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 3-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^3 ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability)

SAMPLE

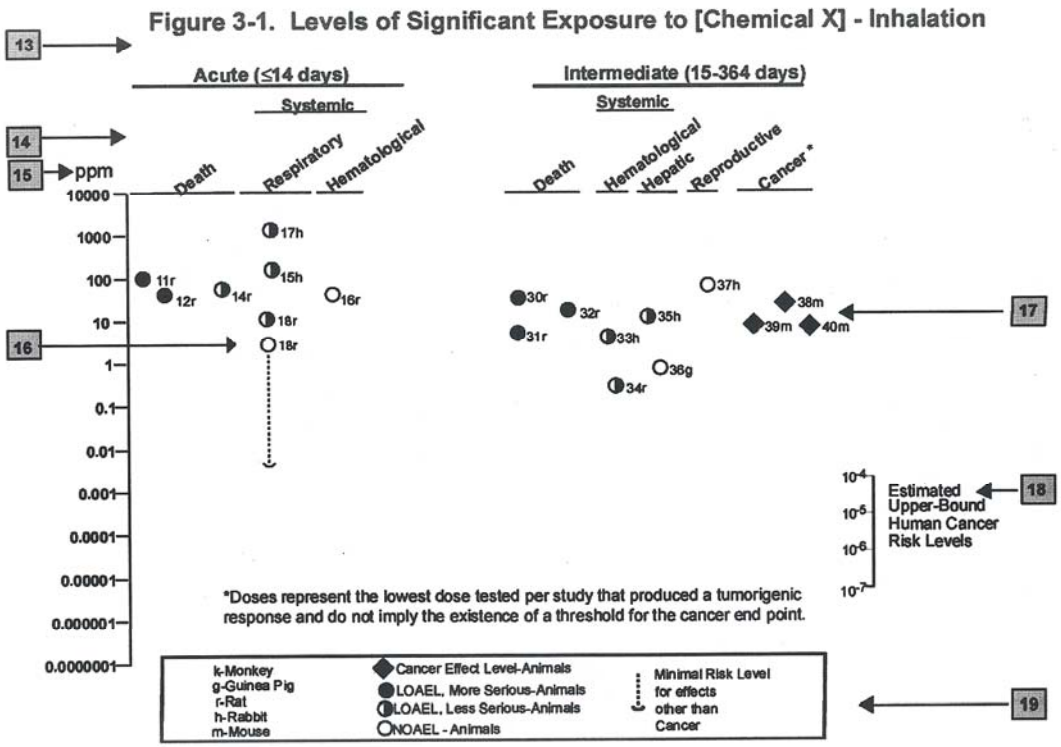


Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation
13
Acute (≤14 days)
Systemic
Intermediate (15-364 days)
Systemic
14
15
ppm
Death
Respiratory
Hematological
Death
Hematological
Hepatic
Reproductive
Cancer*
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
0.0000001
16
11r
12r
14r
15h
17h
16r
18r
18r
30r
31r
32r
33h
34r
35h
36g
37h
38m
39m
40m
17
10-4
10-5
10-6
10-7
Estimated Upper-Bound Human Cancer Risk Levels
18
*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.
k-Monkey
g-Guinea Pig
r-Rat
h-Rabbit
m-Mouse
Cancer Effect Level-Animals
LOAEL, More Serious-Animals
LOAEL, Less Serious-Animals
NOAEL - Animals
Minimal Risk Level for effects other than Cancer
19

APPENDIX A

ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure. MRLs are based on non-cancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

APPENDIX A

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mail stop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Copper and Compounds
CAS Number: [Number]
Date: July 3, 2002
Profile Status: Third Draft
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to Figure: 9
Species: Humans

Minimal Risk Level: 0.02 [X] mg copper/kg/day [ ] ppm

Reference: Pizarro F, Olivasred M, Uauy R, et al. 1999. Acute gastrointestinal effects of graded levels of copper in drinking water. Environ Health Perspect 107:117-121.

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details):

A group of 60 healthy women (mean ages of 32.9–36.3 years) were divided into four groups. Each group consumed water containing 0, 1, 3, or 5 mg ionic copper as copper sulfate (0, 0.0272, 0.0731, and 0.124 mg Cu/kg/day) for a 2-week period with a 1-week rest between copper exposures. Every week the subjects received a bottle containing copper sulfate solution and were asked to mix this solution bottle with 3 L water; this water was then used for drinking and cooking. The subjects recorded daily water consumption and any symptoms. Blood samples were collected 1 week before the study, at the end of the first 2-week exposure period, and at the end of the study; the blood was analyzed for serum copper, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase activities, and hemoglobin levels. The average copper dietary intake, based on a 24-hour dietary recall, was 1.7 mg Cu/day (0.0266 mg u/kg/day using an average body weight of 64 kg).

Effects noted in study and corresponding doses: No significant alterations in serum copper, ceruloplasmin, hemoglobin, or liver enzymes were observed. Twenty-one subjects reported gastrointestinal symptoms, predominantly nausea. Nine subjects reported diarrhea with or without abdominal pain, no association between copper level and diarrhea was found. Six of these episodes of diarrhea occurred during the first week of the study independent of copper concentration. Twelve subjects reported abdominal pain, nausea, or vomiting; the incidences were 3/60, 1/60, 10/60, and 9/60 in the control, 0.0272, 0.0731, and 0.124 mg/kg/day groups, respectively. There was a significant difference between in the incidences at concentrations of #1 mg/L (0.0272 mg/kg/day) versus ∃3 mg/L (0.0731 mg/kg/day). No other differences between groups were found.

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Dose and end point used for MRL derivation:

The MRL is based on the NOAEL of 0.0272 mg Cu/kg/day for gastrointestinal effects in women ingesting copper sulfate in drinking water (Pizarro et al. 1999). To estimate total copper exposure, the concentration of copper in the drinking water (0.0272 mg Cu/kg/day) was added to average dietary copper intake (0.0266 mg Cu/kg/day). The total copper exposure level of 0.0538 mg Cu/kg/day was considered a no-observed-adverse-effect-level (NOAEL) for gastrointestinal effects.

[ ] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a extrapolation from animals to humans
[ ] 3 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

Yes. Daily doses were calculated using reported daily copper intakes (0.04, 1.74, 4.68, and 7.94 mg) and the average of the mean reported body weights (64 kg).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

NA

Was a conversion used from intermittent to continuous exposure?

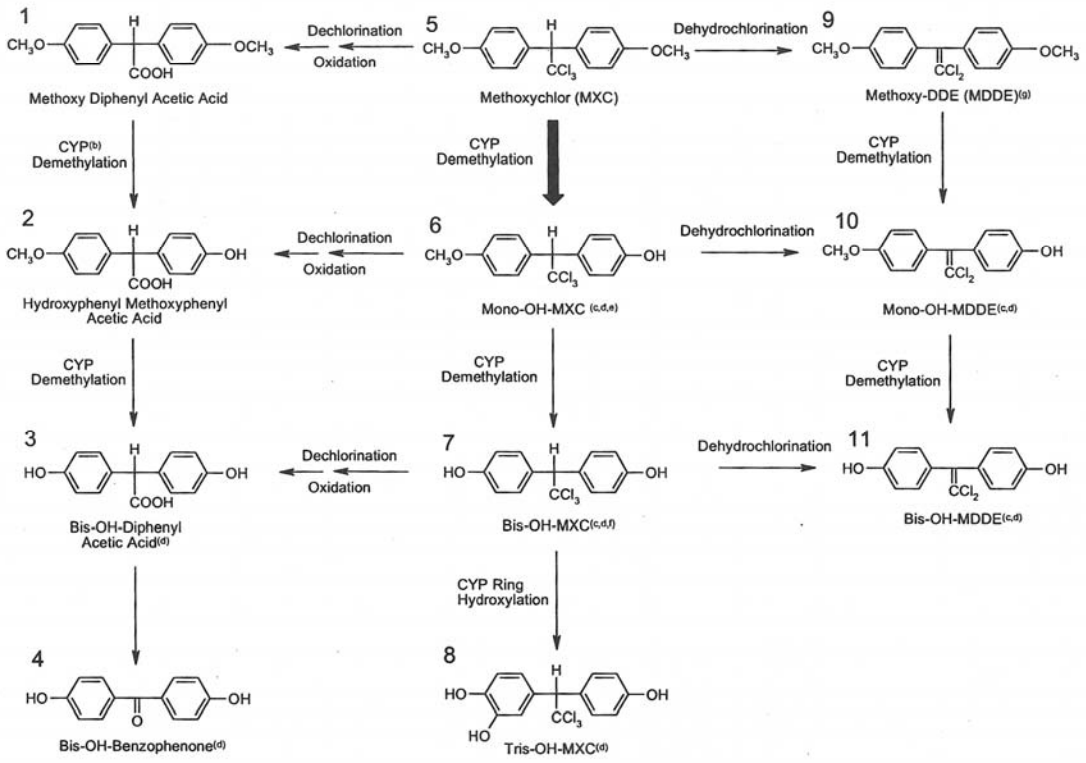
No

Other additional studies or pertinent information that lend support to this MRL:

Several other studies conducted by this group and by other investigators support the identification of the gastrointestinal tract as a sensitive target of copper toxicity. Nausea and/or vomiting was reported by adults ingesting a single dose of 0.011 to 0.08 mg Cu/kg/day as copper sulfate (Araya et al. 2001; Gotteland et al. 2001; Nicholas and Brist 1968; Olivares et al. 2001); no gastrointestinal effects were reported after ingesting 0.0057 mg Cu/kg/day as copper sulfate (Olivares et al. 2001). Daily exposure to 0.1 mg Cu/kg/day for 1 week also resulted in an increased occurrence of nausea, vomiting, and/or abdominal pain (Pizarro et al. 2001). An intermediate-duration study in infants receiving 2 mg/L copper sulfate (0.3 mg Cu/kg/day) in drinking water for 9 months (starting at 3 months of age) did not find an increased occurrence of gastrointestinal effects or alterations in biomarkers of liver toxicity (Olivares et al. 1998). Although the LOAEL identified in the Olivares et al. (2001) study is lower than the NOAEL
identified in the Pizarro et al. (1999) study, the Pizarro et al. (1999) study was selected as the critical study because it is a longer-duration study and it more closely mimics an exposure scenario of a
population drinking copper-contaminated drinking water. Animal studies support the identification of the gastrointestinal tract as the most sensitive target of toxicity. Hyperplasia of the forestomach mucosa was observed in rats exposed to 44 mg Cu/kg/day as copper sulfate in the diet (NTP 1993) and in mice exposed to 197 mg Cu/kg/day as copper sulfate in the diet (NTP 1993). At higher doses, liver and kidney damage have been observed (Haywood 1980; Haywood and Comerford 1980; Haywood et al. 1985b; NTP 1993).

Agency Contact (Chemical Manager): Alfred Dorsey

Figure 3-2. Proposed Metabolic Pathways of Methoxychlor[a]



(a) Adapted from Kapoor et al. 1970; Kupfer and Bulger 1987b; Kupfer et al. 1990
(b) CYP = cytochrome P-450
(c) Estrogenic compound
(d) Metabolite identified in excreta
(e) Mono-OH-MXC = 2-(p-Methoxyphenyl)-2-(p-hydroxyphenyl)-1,1,1-trichloroethane
(f) Bis-OH-MXC = 2,2-Bis(p-hydroxyphenyl)-1,1,1-trichloroethanol (HPTE)
(g) MDDE = Methoxydiphenyldichloroethylene

Figure 3-2 Proposed Metabolic Pathways of [Substance X]
Key to Metabolite Chemical Names

1. Bis(4-methoxyphenyl)acetic acid
   Methoxy Diphenyl Acetic Acid

2. á-(4-hydroxyphenyl)-á-(4-methoxyphenyl)acetic acid
   Hydroxyphenyl Methoxyphenyl acetic acid

3. Bis(4-hydroxyphenyl)acetic acid
   Bis-OH-Diphenyl acetic acid
   CASRN: 40232-93-7

4. 4,4-Dihydroxybenzophenone
   Bis-OH-Benzophenone
   CASRN: 611-99-4

5. 1,1,1-Trichloro-2,2-bis(4-methoxyphenyl)ethane
   Methoxychlor (MXC)
   CASRN: 72-43-5

6. 1,1,1-Trichloro-2-(4-hydroxyphenyl)-2-(4-methoxyphenyl)ethane
   Mono-OH-MXC
   2-(p-Methoxyphenyl)-2-(p-hydroxyphenyl)-1,1,1-trichloroethane

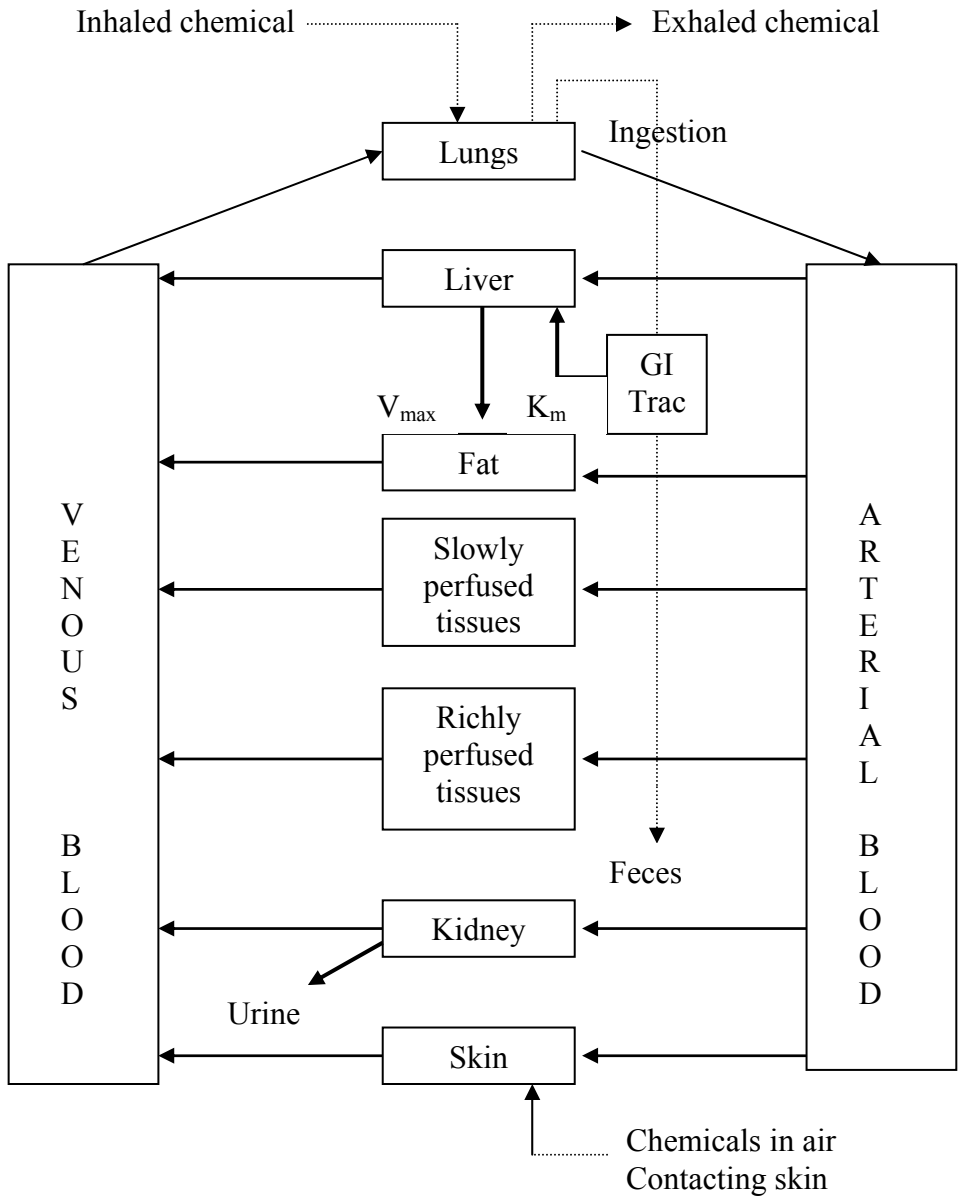
7. 1,1,1-Trichloro-2,2-bis(4-hydroxyphenyl)ethane
   Bis-OH-MXC
   2,2-Bis(p-hydroxyphenyl)-1,1,1-trichloroethanol (HPTE)
   CASRN: 2971-36-0

8. 1,1,1-Trichloro-2-(3,4-dihydroxyphenyl)-2-(4-hydroxyphenyl)ethane
   Tris-OH-MXC
9. 1,1-Dichloro-2,2-bis(4-methoxyphenyl)ethene
   Methoxy-DDE (MDDE)
   Methoxydiphenyldichloroethylene
   CASRN: 2132-70-9

10. 1,1-Dichloro-2-(4-hydroxyphenyl)-2-(4-methoxyphenyl)ethene
    Mono-OH-MDDE

11. 1,1-Dichloro-2,2-bis(4-hydroxyphenyl)ethene
    Bis-OH-MDDE
    CASRN: 14868-03-2

Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, Metabolized in the liver, and excreted in the urine or by exhalation.

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Table 3-3. Genotoxicity of Copper *In Vivo*

Species (test system)	End point	Results	Reference	Compound
Drosophila melanogaster (injection into larvae)	Recessive lethals	+	Law 1938	Copper sulfate
White Leghorn chick bone marrow cells (intraperitoneal injection and oral exposure)	Chromosomal aberrations	+	Bhunya and Jena 1996	Copper sulfate
White Leghorn chick bone marrow cells (intraperitoneal injection and oral exposure)	Micronuclei	+	Bhunya and Jena 1996	Copper sulfate
White Leghorn chick erythrocytes (intraperitoneal injection and oral exposure)	Micronuclei	+	Bhunya and Jena 1996	Copper sulfate
Inbred Swiss mice bone marrow cells (intraperitoneal and/or subcutanous injection)	Chromosomal aberrations	+	Bhunya and Pati 1987	Copper sulfate
Inbred Swiss mice bone marrow cells (intraperitoneal and/or subcutanous injection)	Micronuclei	+	Bhunya and Pati 1987	Copper sulfate
Inbred Swiss mice (intraperitoneal injection)	Sperm abnormalities	+	Bhunya and Pati 1987	Copper sulfate
CBA mice bone marrow Cells (intraperitoneal injection)	Micronuclei	–	Tinwell and Ashby 1990	Copper sulfate
Swiss mice (intraperitoneal injection)	Chromosomal aberrations	+	Agarwal et al. 1990	Copper sulfate

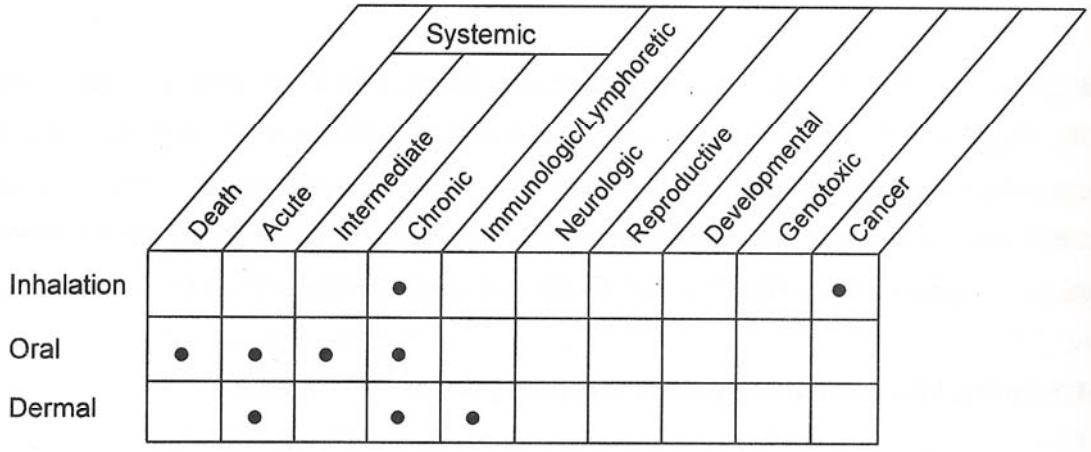
+ = positive results; – = negative results

Table 3-4. Genotoxicity of Copper *In Vitro*

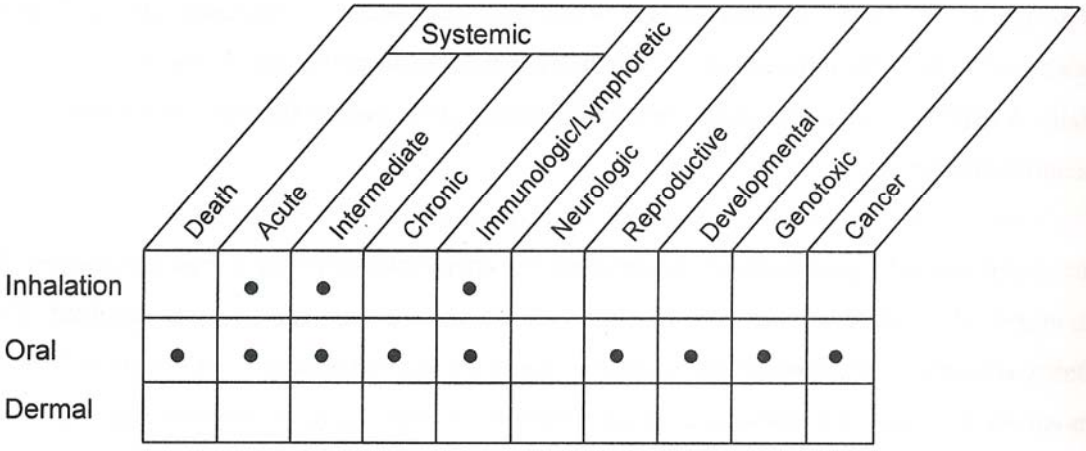
Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Compound
Prokaryotic organisms:					
Salmonella Typhimurium TA 102	Reverse mutation	NT	–	Marzin and Phi 1985	Copper sulfate
S. typhimurium TA98, TA102, TA1535, TA1537	Reverse mutation	–	–	Wong 1988	Copper chloride
S. typhimurium TA 100	Reverse Mutation	NT	–	Tso and FungTA100 1981	Copper chloride
Escherichia coli	Reverse Mutation	NT	+	Demerec et al 1951	Copper sulfate
Avian Myeloblastosis virus, DNA polymerase	Errors in DNA synthesis	NT	+	Sirover and Loeb 1976	Copper chloride
Bacillus subtilis	*rec* assay	NT	–	Nishioka 1975	Copper chloride
Eukaryotic organisms:					
Fungi: *Saccharomyces Cerevisiae*	Reverse mutation	NT	–	Singh 1983	Copper sulfate
S. cerevisiae	Recombination	NT	–	Sora et al. 1986	
Insects:					
Drosophila Melanogaster	Recessive lethals	NT	+	Law 1938	Copper sulfate
Mammalian cells:					
Chinese hamster ovary cells	DNA synthesis	NT	+	Garrett and Lewtas 1983	Copper chloride
Rat hepatocytes Breaks	DNA strand	NT	+	Sina et al. 1983	Copper sulfate
Chinese hamster V79 cells	DNA strand breaks	NT	+	Sideris et al. 1988	Copper nitrate
Chinese hamster V79 cells	Sister chromatid exchange	NT	+	Sideris et al 1988	Copper nitrate

– = negative result; + = positive result; DNA = deoxyribonucleic acid; NT = not tested

Figure 3-4. Existing Information on Health Effects of Copper



Human



Animal

● Existing Studies

Table 4-1. Chemical Identity of Copper

Characteristic	Information	Reference
Chemical Name	Copper	
Synonym(s)	Not Reported	
Registered Trade Name(s)	Not Reported	
Chemical Formula	Cu	HSDB 2002
Chemical Structure	Face-centered Cubic	Budavani 2001
Identification Numbers:		
CAS Registry	7440-50-8	HSDB 2002
NIOSH RTECS	GL5324000	HSDB 2002
EPA Hazardous Waste	Not Reported	
OHM/TADS		
DOT/UN/NA/IMCO Shipping	Not Reported	
HSDB	1622	HSDB 2002
NCI	Not Reported	

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation United Nations North America/International Mantime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; CHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-1. Chemical Identity of Beryllium and Beryllium Compounds[a]

Characteristic		Beryllium Chloride	Beryllium Fluoride	Beryllium Hydroxide	Beryllium Oxide
Synonym(s)	Beryllium-9; glucinium; Glucinum; beryllium	Beryllium dichloride	Beryllium difluoride	Beryllium hydrate; beryllium dihydroxide	Beryllia; beryllium monoxide
Registered trade name(s)	No data	No data	No data	No data	Thermalox 995
Chemical formula	Be	$_2$	BeF_2	$Be(OH_2)$	BeO
Identification numbers:					
CAS registry	7440-41-7	7787-47-5	7787-49-7	13327-32-7	1304-56-9
NIOSH RTECS	DS1750000	DS2525000	DS2800000	DS3150000	DS4025000
EPA hazardous waste	P015[b] BeC1	No data	No data	No data	No data
OHM/TADS	72116604[c]	7217359[c]	7800049[c]	No data	No data
DOT/UN/NA/IMCO shipping	UN1567/IM06.1	NA1566/IM06.1	NA1566/IM06.1	UN1566/IM06.1	UN1566/IM06.1
HSDB					
NCI	No data	No data	No data	No data	No data

Metallic

357 355 350

512 1607

Table 4-3. Physical and Chemical Properties of Copper and Copper Sulfate

Property	Copper	Copper Sulfate
Molecular weight	63.546[a]	159.61[a]
Color	Reddish[b]	Blue crystals, white dehydrated[b]
Physical State	Solid[b]	Solid[b]
Melting Point	1,083[c]	Decomposes at 560[a]
Boiling point	2,595[c]	No data
Specific gravity (20/4 °C)	8.94 [c]	3.60 [a]
		2.286 (pentahydrate)[a]
Odor	No data	None[d]
Odor threshold:		
Air	No data	No data
Water	No data	No data
Taste	No data	No data
Taste threshold	No data	No data
pK_a		
Solubility:		32.0 g/100g (20 °C)[f]
Water	Insoluble[e]	Soluble in methanol, slightly
Organic		Soluble in ethanol[b]
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{oc}	No data	No data
Vapor pressure:	1 (1,628 °C)[g]	No data
Henry's law constant at 25 °C	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors at 25 °C	h	h
ppm to mg/m^3		
Explosive limits	No data	No data

[a]Lide 2000
[b]Lewis 1997
[c]Budavari et al, 2001
[d]Meister et al. 2001
[e]Stewart and Lassister 2001
[f]Dean 1985
[g]Lewis 2000
[h]Since these substances exist in the atmosphere in the particulate state, the concentration is expressed as mg/m^3.

pK_a = The dissociation constant of the conjugate acid

Table 4- 2. Physical and Chemical Properties of Beryllium and Beryllium Compounds[a]

Property	Beryllium metal	Fluoride	Beryllium Hydroxide	Beryllium Oxide	Beryllium carbonate (basic)
Molecular weight	9.012	47.01	43.03[b]	25.01	112.05
Color	Gray	Colorless	White[c]		
Physical state	Solid; hexagonal structured	Glassy, hygroscopic	Amorphous powder or Crystalline solid[d]	Light, amorphous powder[d]	Powder
Melting point	1,287 – 1,292 °C[c]	555 °C[b]	Decomposes (loses water) When heated[f]	2,508-2,547 °C[b]	No data
Boiling point	2,970 °C[c]	1,175 °C[b]	Not applicable	3,787 °C[b]	No data
Density	1,846 g/cm^3 [c]	1.986 g/cm^3 (25 °C)[b]	1.92 g/cm ^{3} [b]	3.016 g/cm ^{3} [c]	No data
Odor	Odor threshold: None	Not applicable	Not applicable	Not applicable	Not applicable
Solubility: Beryllium	Water Insoluble	Very soluble	0.8x10^{-4} mol/L[g](3.44 mg/L)	Very sparingly	Insoluble (cold) Decomposes(hot)
Flashpoint	Other solvent(s) Soluble in dilute acid and alkali	Slightly soluble in alcohol[d]	Soluble in hot concentrated acid and alkali[d]	Soluble in concentrated acids[d]	Soluble in acid, alkali
	Partition coefficients:				
	Log K_{ow} No data	No data	No data	No data	No data
	Log K_{oc} No data	No data	No data	No data	No data
	Vapor pressure 1 mmHg (1,520 °C)	No data	No data	No data	No data
	Henry's law constant No data	No data	No data	No data	No data
	Autoignition temperature No data	No data	No data	No data	No data
	No data	No data	No data	No data	No data
	Flammability limits No data	No data	No data	No data	No data
	Conversion factors[h]				
	Explosive limits No data	No data	No data	No data	No data

Table 5-1. Facilities That Produce, Process, or Use 1,2-Dibromoethane

Facility	Location[b]	Range of maximum amounts on site in pounds	Activities and Uses
Shell Chemical Company	Belpre, OH	10,000-99,999	As a reactant
Sun Refinery and Marketing Co.	Oregon, OH	10,000-99,999	As a formulation component
Sun Refinery and Marketing Co.	Tulsa, OK	1,000-9,999	As a formulation component
Kerr-Mcgee Refining Corp.	Wynnewood, OK	1,000-9,999	Import; as a formulation component
Chevron U.S.A. Inc.	Philadelphia, PA	10,000-99,999	As a formulation component
Exxon Baytown Refinery	Baytown, TX	10,000-99,999	As a formulation component
De Pont Beaumont Works	Beaumont, TX	10,000-99,999	In re-packaging
Chevron U.S.A. Inc. El Paso Refinery	El Paso, TX	0-99	As an impurity
La Porte Chemical Corporation	La Porte, TX	No Data	Produce ; for on-site use/processing
Ethyl Corporation Houston Plant	Pasadena, TX	100,000 – 999,999	As a formulation component; in repackaging
Chevron U.S.A. Inc. Port Arthur	Port Arthur, TX	10,000 – 99,999	As a formulation component
Diamond Shamrock Refining & Marketing Co.	Sunray, TX	10,000 – 99,999	As a formulation component
Phillips 66 Company Sweeny Refinery And Petrochemical	Sweeney, TX	10,000 – 99,999	As a formulation component
Marathon Petroleum Company	Texas City, TX	10,000 – 99,999	As a formulation component
Diamond Shamrock Refining & Marketing Company	Three Rivers, TX	10,000 – 99,999	As a formulation component

Refinery

[a]Derived from TRI 1989
[b]Post Oiifce state abbreviations used

Table 5-1. Facilities That Produce, Process, or Use Copper

State[a]	Number of Facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities & Uses[c]
AL	45	100	49,999,999	1,2,3,5,7,8,9,11,12,13
AR	44	100	9,999,999	1,4,7,8,9,11,12,13,14
AZ	27	100	999,999,999	1,2,3,4,5,7,8,9,11,12
CA	153	0	49,999,999	14
CO	15	1,000	9,999,999	2,3,4,7,8,11,12,14
CT	50	100	499,999,999	1,2,3,4,5,6,7,8,9,11,12,13,14
DE	1	10,000	99,999	8
FL	20	1,000	9,999,999	7,8,10,11
GA	48	100	499,999,999	1,2,3,4,5,6,7,8,9,11,12,13,14
IA	32	100	99,999,999	1,2,3,4,5,7,8,9,12
ID	4	10,000	999,999	1,5,8,9,12
IL	151	0	99,999,999	1,2,3,4,5,6,7,8,9,11,12
IN	158	100	499,999,999	1,2,3,4,5,6,7,8,9,11,12,13,14
KS	26	100	9,999,999	1,2,3,4,6,7,8,11,12,14
KY	69	100	49,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13
LA	7	100	9,999,999	6,7,8,10
MA	63	1,000	9,999,999	1,2,3,4,5,6,7,8,9,11,12
MD	7	1,000	999,999	1,2,4,5,7,8,9,13
ME	9	10,000	9,999,999	2,3,8
MI	130	0	49,999,999	1,2,3,4,5,6,7,8,9,10,11,12
MN	49	100	999,999	1,2,3,4,5,7,8,9,10,11,12,14
MO	77	1,000	99,999,999	1,2,3,4,5,7,8,9,11,12,13
MS	29	1,000	49,999,999	2,3,4,7,8,9,12
MT	2	1,000	99,999	1,5,6,11
NC	67	0	49,999,999	1,2,3,4,5,6,7,8,9,10,12
ND	2	10,000	99,999	8
NE	19	1,000	9,999,999	1,2,3,4,7,8,9,11,12,13
NH	20	1,000	49,999,999	2,3,4,8,9
NJ	40	1,000	49,999,999	1,2,3,4,6,7,8,9,11,12
NM	6	1,000	9,999,999	2,3,8,12
NV	5	1,000	99,999	8,11,12
NY	91	0	49,999,999	1,2,3,4,5,6,7,8,9,10,11,12,14
OH	223	100	49,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13
OK	48	0	9,999,999	1,2,3,4,5,7,8,9,11,12,13
OR	18	0	999,999	2,3,4,7,8,9,10,12
PA	215	0	99,999,999	1,2,3,4,5,6,7,8,9,11,12,13,14
PR	22	10,000	9,999,999	2,3,6,7,8,11
RI	29	1,000	9,999,999	2,3,4,6,7,8,9,10,11,12
SC	51	100	49,999,999	1,2,3,5,6,7,8,9,10,11,12

Table 5-1. Facilities That Produce, Process, or Use Copper (continued)

State[a]	Number of Facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities & Uses[c]
SD	8	1,000	999,999	1,5,7,8
				1,2,3,4,5,6,7,8,9,10,11,12,13
TN	87	0	499,999,999	14
TX	95	0	99,999,999	1,2,3,4,5,6,7,8,9,10,11,12,14
UT	10	1,000	9,999,999	1,3,4,5,6,7,8,11,12
				1,2,3,4,5,6,7,8,10,11,12,13
VA	44	100	9,999,999	14
VT	3	1,000	999,999	2,3,4,6,8,9
WA	28	0	9,999,999	1,2,5,6,7,8,9,10,11,12,14
WI	126	0	9,999,999	1,2,3,4,5,6,7,8,9,10,11,12
WV	14	0	9,999,999	2,3,6,7,8,12
WY	3	10,000	999,999	1,4,9,10,12

Source TRI00
[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Imported
3. Used Processed
4. Safe Distribution
5. By Product
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary/Other Uses
13. Manufacture Impunity
14. Process Impunity

Figure 6-1. Frequency of NPL Sites with Copper Contamination

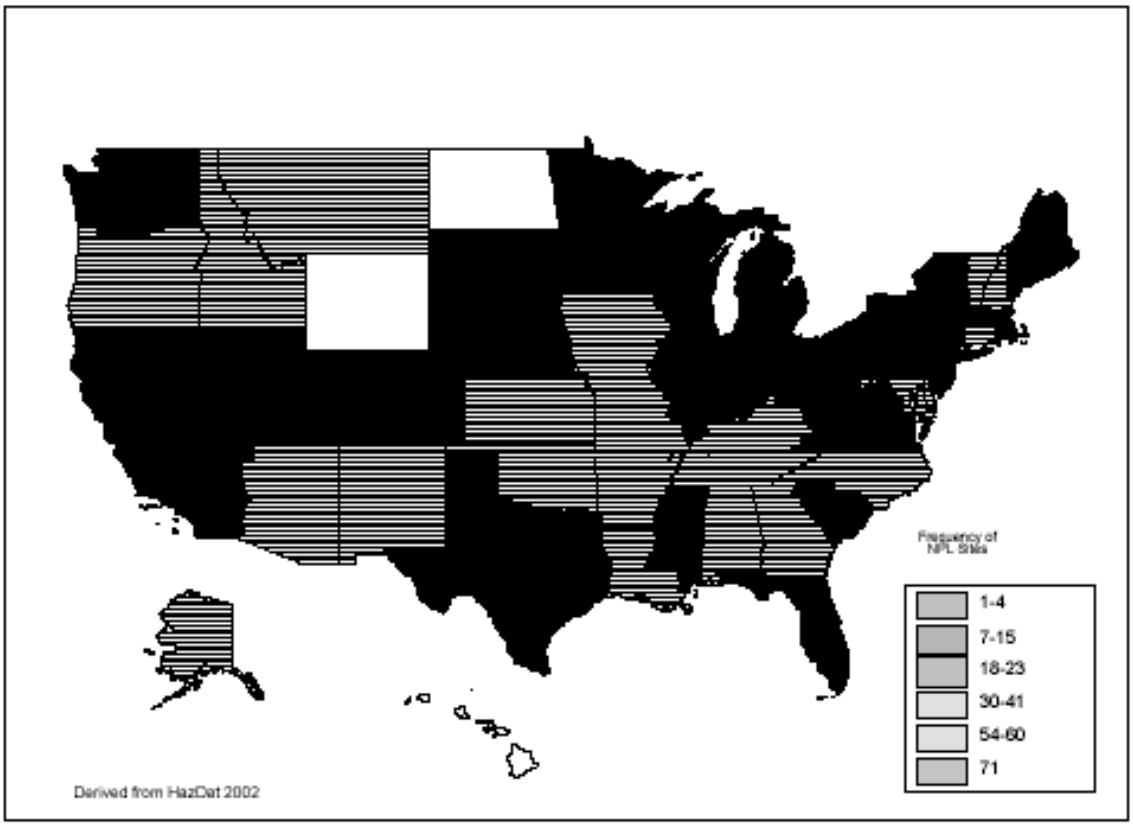


Table 6-1. Releases to the Environment from Facilities That Manufacture or Process 1,2-Dibromoethane[a]

Facility	Location[b]	Reported amounts released in pounds						
		Air	Underground Injection	Water	Land	Total environment[c]	POTW transfer	waste transfer
Great Lakes Chemical Co. El Dorado-Main Plant	El Dorado, AR	9,700	0	0	0	9,700	0	14,000
Great Lakes Chemical Corp. South Plant	El Dorado, AR	3,700	44	0	0	3,744	0	0
Ethyl Corporation	Magnolia, AR	18,100	0	0	0	18,100	0	23,300
Texaco Ref. 7 Mktg, Inc.	Bakersfield, CA	150	0	0	0	150	0	0
Exxon Co. Usa. Benicia	Benicia, CA	0	0	0	0	0	0	0
Arco Products Company Los Angeles Refinery	Carson, CA	60	0	0	0	60	0	0
Shell Oil Company	Carson, CA	145	0	0	0	145	0	0
Shell Oil Company	Carson, CA	71	0	0	0	71	0	0
Chevron U.S.A. Inc.	El Segundo, CA	13	0	90	250	353	1	1
Tosco Corporation	Martinez, CA	500	No Data	250	0	1,000	No Data	0
Chevron Research Co Richmond Research Ctr	Richmond, CA	0	0	0	0	0	0	0
Chevron U.S.A. Inc. Richmond Refinery	Richmond, CA	500	0	0	0	500	No Data	0
Mobil Oil Corporation Torrence Refinery	Torrance, CA	500	0	0	0	500	250	0
Texaco Ref. & Mktg. Inc	Wilmington, CA	50	0	2	0	52	2	0
Chevron USA Inc Hawaiian Refinery	Ewa Beach, HI	500	No Data	250	0	750	0	0
Shell Oil Company	Roxana IL	0	0	0	0	0	0	0
Rock Island Refining Corp	Indianapolis, MN	250	0	0	250	500	0	250
Ethyl Process Development Ctr	Baton Rouge, LA	5,500	0	250	0	5,750	0	0
Exxon Baton Rouge Refinery	Baton Rouge, LA	18	0	0	0	18	0	0

Table 6-1. Releases to the Environment from Facilities
That Produce, Process or Use Copper

State[b]	Number of Facilities	Reported amounts released in pounds per year[a]						
		Air[c]	Water	Underground Injection	Land	Total on-site release[d]	Total off-site release[d]	Total on and off-site release
AL	45	15,983	1,820	No data	454	18,257	348,257	366,982
AR	44	5,932	1,727	No Data	186,925	194,584	333,088	527,672
AZ	27	1,812	537	No Data	81,842	84,191	41,647	125,838
CA	153	35,838	1,320	No Data	309,783	346,941	57,669	404,611
CO	15	1,097	21	No Data	55,556	56,674	25,937	82,611
CT	50	12,357	1,646	No Data	1,503	15,506	106,385	121,891
DE	1	No Data	No Data	No Data	No Data	No Data	No Data	0
FL	20	2,381	1,455	67,858	631	72,325	56,440	128,765
GA	48	3,498	807	No Data	31,670	35,975	389,388	425,363
IA	32	3,623	261	No Data	4,603	8,487	127,744	136,231
ID	4	297	No Data	No Data	544,000	544,297	5,780	550,077
IL	151	63,734	5,537	No Data	1,645,215	1,714,486	845,173	2,559,659
IN	158	51,990	1,417	No Data	147,739	201,146	2,421,974	2,623,120
KS	26	5,890	251	No Data	63,005	69,146	61,547	130,693
KY	69	25,029	485	No Data	62,455	87,969	245,453	333,422
LA	7	22	738	2,100	205	3,065	15,927	18,992
MA	63	5,338	68	No Data	No Data	5,406	78,600	84,005
MD	7	253	10	No Data	250	513	85,596	86,109
ME	9	114	31	No Data	5	150	9,139	9,289
MI	130	115,647	670	17	167	116,501	616,441	732,942
MN	49	20,778	8	No Data	5	20,791	939,660	960,451
MO	77	22,823	612	No Data	9,826	33,261	178,639	211,900
MS	29	2,685	129	No Data	505	3,319	66,681	70,000
MT	2	417	No Data	No Data	2,940,000	2,940,417	No Data	2,940,417
NC	67	8,575	1,563	0	272	10,410	1,471,083	1,481,493

Table 6-1. Releases to the Environment from Facilities That Produce, Process or Use Copper (continued)

State[b]	Number of Facilities	Reported amounts released in pounds per year[a]						
		Air[c]	Water	Underground Injection	Land	Total on-site release[d]	Total off-site release[d]	Total on and off-site release
ND	2	18	15	No Data	No Data	33	707	740
NE	19	4,185	31	No Data	36,000	40,216	14,260	54,476
NH	20	1,057	25	No Data	0	1,082	141,099	142,181
NJ	40	19,383	171	1	No Data	19,555	11,202	30,757
NM	6	500	No Data	No Data	48,117	48,617	27,837	76,454
NV	5	502	No Data	No Data	21,000	21,502	93	21,595
NY	91	15,456	3,752	No Data	63	19,271	643,566	662,837
OH	223	49,464	6,083	0	1,180,213	1,235,760	635,915	1,971,675
OK	46	15,14	307	No Data	52,882	68,331	69,013	137,344
OR	18	784	6	No Data	14,754	15,544	1,765	17,309
PA	215	107,564	2,668	No Data	45,649	155,881	2,504,799	2,660,680
PR	22	15,251	35	No Data	5	15,291	1,155	16,446
RI	29	6,569	5	No Data	0	6,574	39,076	45,650
SC	51	13,643	685	No Data	4,425	18,753	185,338	204,091
SD	8	19	No Data	No Data	No Data	19	10,818	10,837
TN	87	421,476	868	No Data	461	422,805	316,473	739,278
TX	95	18,694	1,187	596	155,144	175,621	251,209	426,830
UT	10	192	17	No Data	10,767	10,976	40,103	51,079
VA	44	39,599	1,095	No Data	160,092	200,786	157,407	358,193
VT	3	No Data	No Data	No Data	250	250	760	1,010
WA	28	1,987	695	No Data	12,463	15,145	87,031	102,176
WI	126	39,480	873	No Data	2,058	42,411	427,058	469,469

Table 6-1. Releases to the Environment from Facilities That Produce, Process or Use Copper (continued)

State[b]	Number of Facilities	Reported amounts released in pounds per year[a]						
		Air[c]	Water	Underground Injection	Land	Total on-site release[d]	Total off-site release[d]	Total on and off-site release
WV	14	1,951	27	5	30,158	32,141	35,481	67,622
WY	3	392	1	No Data	57,046	57,439	93	57,532
Total	2,487	1,179,421	39,659	70,577	7,918,163	9,207,819	14,130,974	23,338,793

Source TRI 2002
[a]Data in TRI are maximum amounts released by each facility
[b]Post Office state abbreviations are used
[c]The sum of fugitive and stack releases of the chemical to air, land, water, and underground injection wells
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells
[e]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW)

Table 7-1. Analytical Methods for Determining Copper in Biological Materials

Sample Matrix	Preparation Method	Analytical Method	Sample Detection Limit	Percent Recovery	Reference
Blood or Tissue	Acid Digestion	Method 8005[a]; ICP-AES	1µ/100 ML blood; 0.2 µg/g tissue	Not Available	NIOSH 1987
Urine	Filter and Polydityiocarbamate Resin collection followed By low temperature Plasma ashing or acid Digestion	Method 8310[a] ICP-AES	0.1 µg	Not Available	NIOSH 1987
Tissue	HNO_3 Digestion	AAS/graphite Furnace	0.25 µg/g wet weight	103.1±7.7% Mean Recovery; 8.2±6.9% Mean Difference in duplicates[b]	Lowe et al. 1985
Toenails	HNO_3 Digestion	AAS/graphite Furnace	0.6 µg/g	0.01% accuracy <5% within run precision; 3.5% day-to-day precision	Wilhelm et al. 1991

[a]Simultaneous, multielemental analysis, not compound specific
[b]Mean±1 standard deviation

AAS = atomic absorption spectrometry; ICP-AES = inductively coupled plasma-atomic emission spoectroscopy

Table 7-2. Analytical Methods for Determining Copper in Environmental Samples

Sample Matrix	Preparation Method	Analytical Method	Sample Detection Limit	Percent Recovery	Reference
Air	Filter collection on 0.8 mμ membrane filter and acid digestion	Method 730, ICP-AES	1 μg	No bias Identified	NIOSH 1987
Air	Filter collection on 0.8 mμ membrane filter and acid digestion	Method 7029, AAS	0.05 μg	No significant Bias	NIOSH 1987
Water, waste Water	Acidify with 1:1 HNO_3 To a pH<2	Method 220.1, AAS/direct Aspiration	20 μg /L	0.9-29.7% Bias Between 7.5 and 332 μg /L	EPA 1983
Water, waste Water	Sample solutions should contain 0.5% HNO_3	Method 220.2, AAS/furnace technique	1 μg /L	Not available	EPA 1983
Water, waste Water	Filter and acidify sample	Method 220.7, CLP-m ICP-AES	6 μg /L	Not available	EMMI 1997
Water, waste Water	Digestion with H_2SO_4 And HNO_3	Neocuproine, Spectrometric	120 μg /L in 1 cm cell	Not available	Greenberg et al. 1985
Waste water	Adjust pH to 1.65-1.85, mix, filter	Method 200.1, Flame atomic Absorption	4 mg /L	Not available	EMMI 1997
Water, waste Water	Filter and acidify	Method 200.7_M, ICP-AES	25 μg /L	Not available	EMMI 1997
Groundwater, Surface water, And drinking water	Filter and acidify	Method 200.8, ICP-MS	20 μg /L	Not available	EMMI 1997
Marine waters	Digest in HNO_3, Concentrate on Iminodiacetate Chelating resin, elute With 1.25 M HNO_3	Method 200.10, ICP-MS	7 μg /L	Not available	EMMI 1997

Table 7-2. Analytical Methods for Determining Copper in Environmental Samples (continued)

Sample Matrix	Preparation Method	Analytical Method	Sample Detection Limit	Percent Recovery	Reference
Marine waters, Estuarine waters, seawaters, and brines	Digest in HNO_3, concentrate on iminodiacetate chelating resin, elute with 1.25 M HNO_3	Method 200.13, GFAA	5 µg/L	Not available	EMMI 1997
Soil, sediment, sludge, and solid waste	Digestion with HNO_3, and H_2O_2, reflux with dilute HCI	Method 7210, AAS	20 µg/L	As in Method 220.1	EPA 1986
Food	Closed-system Digestion	AAS or ASV	0.32 µg/g (ASV), not reported (AAS)	94-100	Holak 1983
Biological tissues	HNO_3 Digestion , reaction with H_2O_2	Method 200.3, ICP-MS	18 µg/L	Not Available	EMMI 1997
Fish tissue	Dissociate tissue in tetraammonium hydroxide, acidify with HNO_3	Method 200.11, ICP-AES	18 µg/L	Not Available	EMMI 1997

AAS = atomic absorption spectrometry; ASV = anodic stripping voltammetry; GFAA = graphite furnace atomic absorption; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; ICP-MS = inductively coupled plasma-mass spectrometry

Table 8-1. Regulations and Guidelines Applicable to Copper

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification Copper 8-hydroxyquinoline	Group 3[a]	IARC 2002
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	0.2 mg/m^3	ACGIH 2001
	Fume (Cu)	1.0 mg/m^3	
	Dusts and mists (as Cu)		
EPA	Serious health effects from Ambient air exposure (Cu)		EPA 2002b 40CFR61.01(b)
NIOSH	REL (10-hour TWA)		
	Fume (as Cu)	0.1 mg/m^3	
	Dusts and mists (as Cu)	1.0 mg/m^3	
	IDLH		
	Fume, dusts, and mists (as Cu)	100 mg/m^3	
OSHA	PEL (8-hour TWA) for general industry		
	Fume (as CU)	0.1 mg/m^3	
	Dusts and mists (as Cu)	1.0 mg/m^3	
	PEL (8-hour TWA) for construction industry		OSHA 2002b
	Fume (as CU)	0.1 mg/m^3	29CFR1926.55
	Dusts and mists (as Cu)	1.0 mg/m^3	
	PEL (8-hour TWA) for shipyard		OSHA 2002a
	Fume (as CU)	0.1 mg/m^3	29CFR1915.1000
	Dusts and mists (as Cu)	1.0 mg/m^3	
b. Water			
DOT	Marine pollutant (Cu metal powder and cupric sulfate)		DOT 2002 49CFR172.101, Appendix B
EPA	Drinking water standard Action level (Cu)	1.3 mg/L	EPA 2002C
	MCLG (Cu)	1.3 mg/L	EPA 2002d 40CFR141.51(b)

Table 8-1. Regulations and Guidelines Applicable to Copper (continued)

Agency	Description	Information	Reference
NATIONAL (cont)			
EPA	Groundwater monitoring (Cu)		EPA 2002g
	Suggested Method	PQL	40DFR264,
	6010	60 µg/L	Appendix IX
	7210	200 µg/L	
	Hazardous substance in accordance with Section 311 (b)(2)(A) of the Clean Water Act (cupric sulfate and cupric sulfate, ammoniated)		EPA 2002j 40CFR116.4
	Reportable quantity of hazardous substance designated pursuant to Section 311 of the Clean Water Act		EPA 2002k 40CFR117.3
	Cupric sulfate	10 pounds	
	Cupric sulfate, ammoniated	100 pounds	
	Secondary MCL for public water systems (Cu)	1.0 mg/L	EPA 2002e 40CFR143.3
	Toxic pollutant designated pursuant to Section 307(a)(1) of the Federal Water Pollution Control Act and is subject to effluent limitations (Cu and compounds)		EPA 2002a 40CFR401.15
	Water quality criteria (Cu)		EPA 1999
	Freshwater		
	CMC	13.0 µg/L	
	CCC	9.0 µg/L	
	Saltwater		
	CMC	4.8 µg/L	
	CCC	3.1 µg/L	
	Human health for consumption of water and organism Organoleptic effect criteria	1,300 µg/L	
c. Food and Drugs			
EPA	Exemption from requirement of a tolerance in meat, milk, poultry, eggs, fish, shellfish, and irrigated crops when it results from the use as an algaecide, herbicide, and fungicide when used in accordance with good agricultural practices (CU)		EPA 2002f 40CFR180.1021

Table 8-1. Regulations and Guidelines Applicable to Copper (continued)

Agency	Description	Information	Reference
NATIONAL (cont)			
FDA	Bottled water; allowable level (Cu)	1.0 mg/L	FDA 2001a 21CFR165.110
	Clinical chemistry test system; copper test system measures copper levels in plasma, serum, and urine	Exempt from premarket notification procedures in Subpart E of Part 807	FDA 2001b 21CFR862.1190
	Color additives exempt from certification – copper powder for use in externally applied drugs	Cu no less than 95%	FDA 2001e 21CFR73.1647
	Color additives exempt from certification – copper powder for use in cosmetics		FDA 2001c 21CFR73.2647
	Direct food substance affirmed as generally recognized as safe when used as a nutrient supplement or as a processing aid (cupric sulfate)		FDA 2001c 21CFR184.1261
	Drug products containing certain active ingredients offered over-the-counter; inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses (Cu)	Weight control drug product	FDA 2001g 21CFR310.545 (a)(20)
	Trace minerals added to animal feeds as nutritional dietary supplements are generally recognized as safe when added at levels consistent with good feeding practices (Cu compounds)		FDA 2001i 21CFR582.80
IOM	Recommended dietary allowance (RDA)	0.9 mg/day	IOM 2001
d. Other	Carcinogenicity classification (Cu)	Group D[b]	IRIS 2002
EPA	RfC	No data	
	RfD	No Data	

Table 8-1. Regulations and Guidelines Applicable to Copper (continued)

Agency	Description	Information	Reference
NATIONAL (cont)			
EPA	Reportable quantity designated as a CERCLA hazardous substance under Section 307(a) of the Clean Water Act (Cu)	5,000 pounds	EPA 2002h 40CFR 302.4
	Reportable quantity designated as a CERCLA hazardous substance under Section 311(b) (4) of the Clean Water Act (cupric sulfate)	10 pounds	EPA 2002h 40CFR302.4
	Toxic chemical release reporting; community right-to-know; effective date of reporting (Cu)	01/01/87	EPA 2002i 40CFR372.65(a)
STATE			
Regulations and Guidelines:			
a. Air			
Illinois	Toxic air contaminant (Cu)		BNA 2001
Louisiana	Toxic air pollutant[c]	25 pounds/year	BNA 2001
	Minimum emission rate (Cu and compounds)		
New Mexico	Toxic air pollutant		BNA 2001
	Fume (Cu)		
	OEL	0.2 mg/m^3	
	Emissions	0.0133 pounds/hour	
	Dusts and mists (as Cu)		
	OEL	1.0 mg/m^3	
	Emissions	0.0667 pounds/hour	
Vermont	Cu compounds		BNA 2001
	Hazardous ambient air standard	100 $\mu g/m^3$	
	Averaging time	8 hours	
	Action level	4 pounds/hour	
b. Water			
Arizona	Drinking water guideline (Cu)	1,3000 µg/L	HSDB 2002
North Carolina	Groundwater quality standard (Cu)	1.0 mg/L	BNA 2001
c. Food	No data		

Table 8-1. Regulations and Guidelines Applicable to Copper (continued)

Agency	Description	Information	Reference
STATE (cont)			
d. Other			
Arizona	Soil remediation levels (Cu and compounds)		BNA 2001
	Residential	2,800 mg/kg	
	Non-residential	63,000 mg/kg	
Florida	Toxic substance in the workplace (Cu fume, dust, and mist)	25 pounds/year	BNA 2001

[a]Group 3: unclassifiable as to carcinogenicity to humans
[b]Group D: not classifiable as to human carcinogenicity
[c]Class II: suspected human carcinogen and known or suspected human reproductive toxin

ACGIH = American Conference of Governmental Industrial Hygienists; BNA = Bureau of National Affairs; CERCLA = Comprehensive Environmental Response Compensation and Liability Act; CFR – Code of Federal Regulations; CCC = criterion continuous concentration; CMC = criteria maximum concentration; Cu = copper; DOT = Department of Transportation; EPA = Environmental Protection Agency; FDA = Food and Drug Administration;
HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life and health; IOM = Institute of Occupational Medicine; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; OEL = occupational exposure limit; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantitation limits; RDAS = recommended dietary allowance: REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit value; TWA = time-weighted average

Appendix C
ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotranferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid

DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/ON/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	*Federal Register*
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{5o}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{5o}	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	luteinizing hormone
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans-muconic* acid
MAL	maximum allowable level

mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon

PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmilcokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short- Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{5o}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to

<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
$\dot{q}_1$	cancer slope factor
-	negative
+	positive
(+)	weakly positive result
(-)	weakly negative result

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GLOSSARY

Absorption -- The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption -- The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) -- is usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model -- is a statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers -- are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Case-Control Study -- A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report -- describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series -- describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study -- A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study -- A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs -- substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship – the quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurrs. The terms, as used here, include malformations and variations, altered growth, and inutero death.

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

Epidemiology-- refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity -- a specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life -- a measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence -- The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunological Effects -- are functional changes in the immune response.

Immunologic Toxicity – The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

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

In Vivo **--** Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO}) -- The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

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

Lymphoreticular Effects -- represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL) -- An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF) -- A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity -- State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality -- Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen -- A substance that causes mutations. A mutation is a change in the DNA sequence of a cell=s DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy -- The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to a chemical.

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

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio-- a means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound -- a phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL) -- An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40 hour workweek.

Pesticide -- general classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics -- is the science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model -- is a set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model -- is a type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model -- is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence -- The number of cases of a disease or condition in a population at one point in time.

Prospective Study--a type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Recommended Exposure Limit (REL) -- A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the No-Observed-Adverse-Effect Level (NOAEL- from animal and human studies) by a consistent application of

uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

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

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study -- A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to casual factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk -- the possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor -- An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio-- The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL) -- The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic -- The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF) -- A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating fromdata obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using Lowest-Observed-Adverse-Effect Level (LOAEL) data rather than No-Observed-Adverse-Effect Level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic -- any chemical that is foreign to the biological system.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of beryllium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of beryllium.

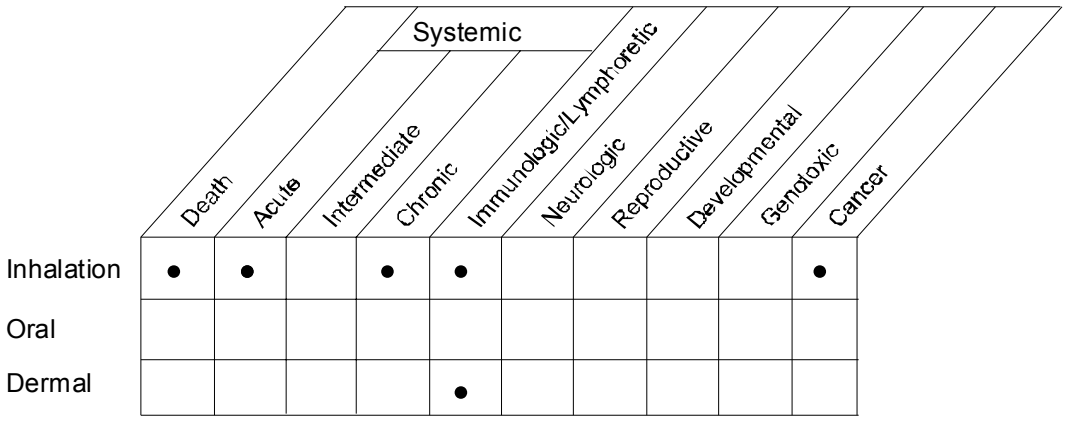
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Beryllium

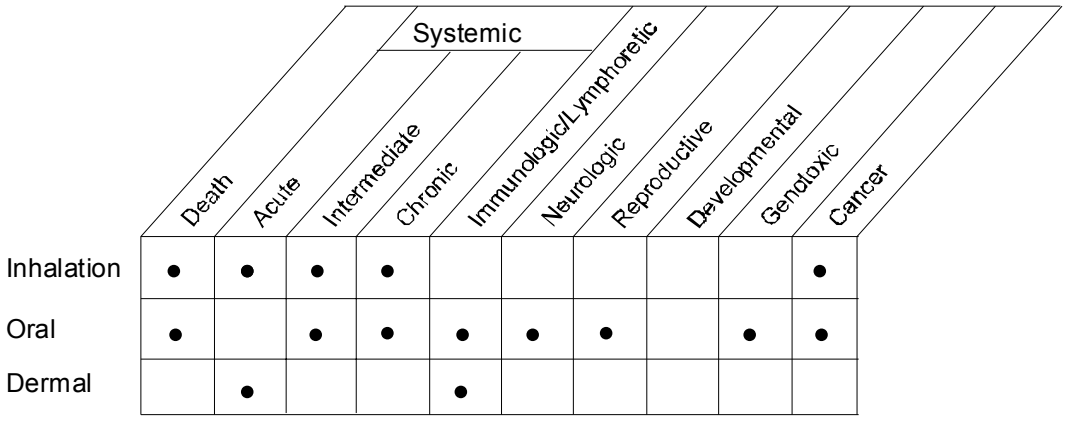
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to beryllium are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of beryllium. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Studies regarding adverse health effects in humans after exposure to beryllium or its compounds are limited (Figure 3-5). No studies were located regarding neurological, developmental, reproductive, or genotoxic effects in humans following inhalation exposure to beryllium or its compounds. Studies regarding death were limited to chronic inhalation exposure. An accidental leakage of beryllium did not cause respiratory, hepatic, or immunological effects. Most of the human data concerns respiratory effects

Figure 3-5. Existing Information on Health Effects of Beryllium



Human



Animal

● Existing Studies

and lung cancer as a result of occupational exposure to beryllium or its compounds. Immunological data indicate that beryllium induces a T-cell lymphocyte-mediated immune response in the lung and skin. No studies were located regarding any effects in humans following oral exposure to beryllium. Since beryllium is poorly absorbed through the gastrointestinal wall, effects from this route of exposure are unlikely. For dermal exposure, only skin effects (ulcerations) were reported.

The database for animals is more complete. LC_{50} values have been reported for a number of beryllium compounds. Systemic effects of acute, intermediate, and chronic exposure via inhalation include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular effects. Immunological and carcinogenic effects were observed in various species after inhalation exposure to beryllium. No studies were located regarding neurological, developmental, reproductive, or genotoxic effects in animals after inhalation exposure to beryllium or its compounds. Oral LD_{50} values were reported for many of the beryllium compounds. No other oral exposure studies were located regarding acute effects in animals exposed to beryllium or its compounds. Immunological, neurological, reproductive, genotoxic, and carcinogenic effects due to ingestion of beryllium are reported in the available literature.

No dermal studies were located regarding death, neurological, developmental, reproductive, genotoxic, or carcinogenic effects in animals. Acute dermal studies report dermatological effects of beryllium on sensitized animals. Since beryllium is a T-cell activator, exposure can cause immunological effects on the skin.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. The lung is the main target organ of inhaled beryllium and its compounds in humans (Eisenbud et al. 1948a; Van Ordstrand et al. 1945) and animals (Haley et al. 1989; Hart et al. 1984; Robinson et al. 1968; Sanders et al. 1975; Schepers 1964; Sendebach and Witschi 1987b; Sendebach et al. 1980, 1989); however, the heart, liver, kidney, adrenal (Schepers 1965), skin (Stiefel et al. 1980), and the hematopoietic tissue (Hall et al. 1950) in animals have also been identified as target organs of beryllium exposure. The effects of occupational exposure to beryllium or its compounds include acute pneumonitis as a result of inhalation exposure to more soluble beryllium compounds or chronic beryllium disease as a result of inhalation of soluble and less soluble beryllium compounds (e.g., beryllium oxide) (Cullen et al. 1987; Eisenbud and Lisson 1983; Eisenbud et al. 1948a; Rossman et al. 1988). Because an animal model that mimics all aspects of chronic beryllium disease has not been identified, it is inappropriate to use animal data to derive an acute-duration inhalation MRL. No human acute-duration studies were identified; thus, an acute-duration inhalation MRL was not identified. No data were located regarding effects in humans after acute oral exposure to beryllium. No acute oral MRL can be derived because the only acute oral data in animals involves lethality (Ashby et al. 1990; Kimmerie 1966; Lanchow University 1978; Venugopal and Luckey 1977). The target organs of acute oral exposure of animals to low levels of beryllium are not known, but beryllium compounds are poorly absorbed from the gastrointestinal tract (Furchner et al. 1973; Le Fevre and Joel 1986; Morgareidge et al. 1975; Reeves 1965). In humans and animals sensitized to beryllium, contact with beryllium and its soluble and insoluble compounds can cause dermatitis and skin granulomas (Belman 1969; Curtis 1951; Marx and Burrell 1973; Williams et al. 1987). In general, the more soluble the compound the greater the sensitizing potential. Dermal effects usually occur on abraded skin. Dermal absorption of beryllium is assumed to be poor and would not likely cause further systemic effects. Dermal studies would be helpful to determine the amount and duration of exposure necessary for human sensitization. Additional human exposure studies that examine the potential of beryllium to cause beryllium sensitization and chronic beryllium disease after a <2 weeks of exposure would be useful for establishing an acute-duration

inhalation MRL. The information regarding beryllium toxicity is useful to the general population and to populations residing at or near hazardous waste sites, who might be subject to acute exposure.

Intermediate-Duration Exposure. No studies were located regarding effects in humans after intermediate-duration inhalation exposure to beryllium or its compounds. The available occupational exposure studies provide sufficient evidence that beryllium sensitization and chronic beryllium disease would be the most sensitive end points following intermediate-duration inhalation exposure to beryllium; however, no intermediate-duration studies were identified. Several studies indicate that the lung is the main target organ in animals for intermediate exposure to soluble and insoluble beryllium compounds via inhalation (Hall et al. 1950; Schepers 1964; Schepers et al. 1957; Stokinger et al. 1950; Wagner et al. 1969). Other target organs in animals include the heart, liver, kidney, skin, and hematopoietic tissue (Hall et al. 1950; Stiefel et al. 1980; Stokinger et al. 1950). Derivation of an intermediate-duration inhalation MRL is precluded because there are no human intermediate-duration studies and an animal model that mimics all aspects of chronic beryllium disease has not been identified, thus making it inappropriate to derive an MRL from animal data. There are limited data on the toxicity of ingested beryllium following intermediate-duration exposure. The available animal data suggest that rickets is a critical end point following ingestion of beryllium carbonate (Guyatt et al. 1933; Jacobson 1933; Kay and Skill 1934). The rickets do not appear to be due to a direct effect of beryllium on the bone. Rather, the rickets are due to a phosphorus deficiency, which results from the binding of beryllium to dietary phosphorus in the gut. Thus, the available data are insufficient for derivation of an intermediate-duration oral MRL. Additional studies involving exposure to low concentrations of several beryllium compounds would be useful for identifying critical targets of toxicity and establishing dose-response relationships. According to one study, guinea pigs were sensitized to beryllium via intradermal administration of beryllium compounds, with the sensitizing potential increasing with increasing solubility (Marx and Burrell 1973).

Chronic-Duration Exposure and Cancer. Health effects in humans and animals after chronic exposure to beryllium and its compounds are reported in the available literature. The lung is the main target organ in human (Andrews et al. 1969; Cullen et al. 1987; Eisenbud and Lisson 1983; Hardy and Tabershaw 1946; Kreiss et al. 1993a, 1996, 1997; Rossman et al. 1988; Stange et al. 1996b) and animals (Reeves et al. 1967; Vorwald and Reeves 1959; Wagner et al. 1969) after inhalation exposure to beryllium and its compounds. Occupational exposure to soluble and insoluble beryllium compounds caused delayed granulomatous disease of the lung, known as chronic beryllium disease or berylliosis (Cotes et al. 1983; Cullen et al. 1987; Eisenbud and Lisson 1983; Eisenbud et al. 1949; Kreiss et al. 1993a, 1996, 1997; Stange et al. 1996b). Acute lung inflammation was also observed after occupational exposure to soluble beryllium compounds (Eisenbud et al. 1948a). These serious respiratory effects in humans were found even at the lowest occupational exposure concentrations, which were lower than concentrations used in chronic inhalation experiments in animals. Therefore, NOAELs for respiratory effects due to occupational exposure or chronic inhalation exposure in animals have not been determined. An environmental exposure study did identify a NOAEL for chronic beryllium disease (Eisenbud et al. 1949); however, technology available at the time of the study did not allow for the detection of beryllium sensitization or subclinical chronic beryllium disease and it is not known if the identified NOAEL would be protective for these effects. Hence, derivation of a chronic inhalation MRL is precluded. Data were not located regarding effects in humans after chronic oral exposure to beryllium. The results of a chronic dog study suggests that the gastrointestinal tract is a target of beryllium sulfate toxicity (Morgareidge et al. 1976). This study is the basis for a chronic-duration oral MRL for beryllium. The MRL was derived using a benchmark dose approach and the dose-response data for small intestinal lesions in dogs (Morgareidge et al. 1976). Data regarding the effects of chronic dermal exposure to beryllium were limited to findings of dermatitis in occupationally exposed individuals (Curtis 1951; Van Ordstrand et al. 1946; Williams et al. 1987).

Studies regarding inhalation and dermal exposure to low concentrations of beryllium for chronic durations would be useful for determining the respective NOAELs for respiratory and dermal effects. Studies in dogs exposed to beryllium oxide by inhalation (Finch et al. 1990) and in guinea pigs (Barna et al. 1981, 1984) and in mice (Huang et al. 1992) exposed to beryllium oxide intratracheally have been performed to identify an appropriate model to elucidate the pathogenesis of chronic beryllium disease in humans. However, an animal model that exactly mimics chronic beryllium disease in humans has not been found. Further inhalation studies conducted in several species of animals designed to identify the most appropriate animal model that mimics chronic beryllium disease in humans would be useful to for determining mechanisms for induction and treatment of chronic beryllium disease. This work is in progress (see Section 3.12.3). This information would be useful to the general population and to populations residing at or near hazardous waste sites.

Data regarding occupational exposure to beryllium and its compounds appear to indicate an increased incidence of lung cancer (Infante et al. 1980; Mancuso 1970, 1979, 1980; Sanderson et al. 2001a; Steenland and Ward 1992; Wagoner et al. 1980; Ward et al. 1992). However, the quality of some of these studies has been severely criticized (EPA 1987). Animal studies indicate increases in lung cancer due to inhalation exposure to beryllium or its soluble and insoluble compounds (Nickell-Brady et al. 1994; Reeves et al. 1967; Vorwald 1968; Vorwald and Reeves 1959; Wagner et al. 1969), but these studies are also flawed. Nevertheless, these data and studies conducted by intratracheal, intravenous, and intramedullary routes taken as a whole support the carcinogenic potential of beryllium, and inhaled beryllium is considered a human carcinogen (IARC 2001; NTP1999, 2002); EPA considers beryllium to be a probable human carcinogen (IRIS 2002). A well-conducted chronic inhalation study in rats and mice using several exposure levels would add confidence to the database and eliminate uncertainties due to the flaws in the existing studies. Beryllium has not been found to cause cancer in animals after oral exposure (Morgareidge et al. 1975, 1976; Schroeder and Mitchener 1975a, 1975b); although, as previously noted, these studies may not have been adequate to assess carcinogenic potential. Beryllium and its compounds are poorly absorbed from the gastrointestinal tract. Therefore, conducting oral studies at doses high enough to affect plausible target organs would be difficult.

Genotoxicity. Genotoxicity data regarding exposure to beryllium or its compounds are contradictory. Forward and reverse mutation bacterial assays yielded both positive (Kanematsu et al. 1980; Ulitzur and Barak 1988) and negative (Arlauskas et al. 1985; Ashby et al. 1990; Rosenkranz and Poirier 1979; Simmon et al. 1979) results for the same compounds. The results are also contradictory for chromosomal aberrations induced by beryllium in mammalian cell cultures (Ashby et al. 1990; Brooks et al. 1989; Hsie et al. 1979; Larramendy et al. 1981; Miyaki et al. 1979; Williams et al. 1989). Studies to examine the mechanism of mutagenic activity of beryllium would be useful. Studies regarding the genotoxic potential of beryllium in occupationally exposed workers also would be useful, especially if exposure levels were related to genotoxic effects. In addition, studies regarding the *in vivo* genotoxic potential of beryllium in animals, particularly by the inhalation route, would be helpful.

Reproductive Toxicity. No studies were located regarding reproductive toxicity in humans after inhalation, oral, or dermal exposure to beryllium or its compounds. A chronic duration study that allowed continuous mating did not find any adverse reproductive effects in dogs exposed to beryllium sulfate in the diet (Morgareidge et al. 1976). A study involving histological examination of rats exposed to beryllium sulfate in drinking water for 2 years reported no alterations of the reproductive organs (Morgareidge et al. 1975); beryllium compounds are not well absorbed by the gastrointestinal tract. Another study involving intratracheal injection of beryllium oxide in rats reported no effects on reproductive function (Clary et al. 1975). Additional inhalation studies should examine reproductive organs in order to determine whether the potential for reproductive effects due to beryllium exposure exists.

Developmental Toxicity.No studies were located regarding developmental toxicity in humans after inhalation, oral, or dermal exposure to beryllium or its compounds. No developmental effects were observed in the offspring of dogs chronically exposed to beryllium sulfate in the diet (Morgareidge et al. 1976); although the usefulness of this study in establishing the potential developmental toxicity of ingested beryllium is limited by the nonconventional study design. No inhalation or dermal exposure studies examining developmental toxicity in animals were identified. Rats injected intravenously with beryllium nitrate during gestation delivered pups that died soon after birth (Mathur et al. 1987). Increased fetal mortality and fetal weight and increased abnormalities were observed after pregnant rats were injected intratracheally with beryllium oxide or beryllium chloride (Selivanova and Savinova 1986). Other studies in which beryllium salts were injected into pregnant mice indicated that beryllium can penetrate the placenta and reach the fetus and cause behavioral abnormalities in the offspring (Bencko et al. 1979; Tsujii and Hoshishima 1979). Additional animal studies would be useful to determine if developmental effects may occur after inhalation or oral exposure to beryllium.

Immunotoxicity. While beryllium has not been shown to be toxic to the immune system, beryllium and the soluble and insoluble compounds can be sensitizing and induce a cell-mediated immune response to beryllium (Cullen et al. 1987; Johnson 1983; Rossman et al. 1988; Saltini et al. 1989). This heightened immune response to beryllium is the cause of chronic beryllium disease and certain skin lesions (Williams et al. 1987). Granuloma formation and dermatitis are the principal immunological effects caused by exposure to beryllium. Although beryllium is not well absorbed by the gastrointestinal tract, studies evaluating the immunological effects of beryllium exposure to the associated lymphoid tissue would be useful to determine the local immunological reaction. Intermediate-duration studies designed to characterize the effects on the immune system would be helpful. The elucidation of the molecular mechanisms of the immune response to beryllium and the identification of the specific T-cell families that are reactive to beryllium would aid in the identification and treatment of patients with chronic beryllium disease. In addition, identification of potential differences in allelic phenotypes between people with chronic beryllium and people exposed to beryllium but without chronic beryllium disease might help identify potentially susceptible populations based on genetic differences.

Neurotoxicity. No studies were located regarding neurotoxicity in humans after inhalation, oral, or dermal exposure to beryllium or its compounds. Histological examination of rats and dogs chronically exposed to beryllium sulfate in drinking water did not reveal any abnormalities in nerve tissues (Morgareidge et al. 1975, 1976). Beryllium is not well absorbed by the gastrointestinal tract or after dermal exposure; therefore, neurological effects are not expected to occur as a result of oral or dermal exposure. Inhalation studies involving low-level exposure to beryllium would be useful for determining its neurotoxicity.

Epidemiological and Human Dosimetry Studies. The general population is exposed to beryllium through contaminated air, water, and food. The highest exposure levels are incurred by workers in beryllium ore processing, manufacturing, or fabricating plants (Eisenbud and Lisson 1983). Few studies correlate beryllium exposure with effects on the respiratory system. Epidemiology data have been criticized for using inappropriate cohorts and including nonexposed workers. Studies that correlate occupational exposure to beryllium with cancer and other health effects would be useful and would offset the limitations of the now available studies.

Biomarkers of Exposure and Effect.There are several tests for detecting beryllium in biological fluids and tissues (Frame and Ford 1974; Foreman et al. 1970; Hurlburt 1978; IARC 1980; Martinsen and Thomassen 1986; Paschal and Bailey 1986; Shan et al. 1989). Increased levels of beryllium in urine and blood indicate exposure (Stiefel et al. 1980; Zorn et al. 1986). Beryllium has also been measured in granulomas in the lung tissue of individuals with chronic beryllium disease (Kanarek et al. 1973) and in the skin of beryllium sensitive individuals (Williams et al. 1987). Laser ion mass analysis for beryllium is the most sensitive test for identifying beryllium on histological sections from lung or skin granulomas of patients with chronic beryllium disease (Williams and Kelland 1986). A lymphocyte proliferation test has also been used to identify workers with chronic beryllium disease; positive test results rarely occur in workers who are not exposed to beryllium or its compounds (James and Williams 1985; Stokes and Rossman 1991).

Chronic exposure to beryllium can result in decreased lung function (Andrews et al. 1969; Johnson 1983). This decrease can be measured by spirometry such as forced expiratory volume in 1 second or forced vital capacity (Andrews et al. 1969; Kriebel et al. 1988a,b). Measurements of lung function cannot distinguish between chronic beryllium disease and sarcoidosis, and lung opacities are not definitively captured by x-rays (Kanarek et al. 1973). Lymphocyte proliferation assays on cells obtained from individuals by bronchoalveolar lavage are sensitive in confirming chronic beryllium disease in symptomatic individuals (James and Williams 1985; Rossman et al. 1988). The lymphocyte proliferation test also distinguishes between chronic beryllium disease and sarcoidosis. A less invasive method of determining sensitivity to beryllium would be useful, especially for monitoring health effects in individuals living at or near hazardous waste sites.

Absorption, Distribution, Metabolism, and Excretion. Beryllium and its compounds are absorbed primarily through the lungs in humans and animals (Finch et al. 1990; Reeves and Vorwald 1969; Stiefel et al. 1980; Zorn et al. 1986), but the available information is not sufficient to determine the rate and extent of pulmonary absorption. Soluble compounds are absorbed more readily than insoluble compounds (Finch et al. 1990). Information from animal studies indicates that beryllium is poorly absorbed from the gastrointestinal tract, with the majority of the dose excreted in the feces (Furchner et al. 1973; Le Fevre and Joel 1986; Morgareidge et al. 1975; Reeves 1965). Dermal absorption is also poor (Petzow and Zorn 1974). Studies regarding the rate and extent of beryllium absorption via the lungs would be useful.

The only study on the distribution of beryllium and its compounds in humans was conducted on tissue taken from autopsies (Meehan and Smythe 1967); distribution studies in animals exposed to beryllium via inhalation were more available (Finch et al. 1990; Rhoads and Sanders 1985; Sanders et al. 1975; Stiefel et al. 1980; Stokinger et al. 1950; Wagner et al. 1969; Zorn et al. 1977). The target organs identified in these studies were the lung, lymph nodes, kidney, liver, and bone. Distribution of beryllium is more widespread for the soluble compounds, reflecting the degree of absorption (Finch et al. 1990). Rats and guinea pigs achieved steady state concentrations in the lungs 36 weeks after initial exposure to beryllium sulfate (Reeves and Vorwald 1969). Steady state concentrations in the blood were reached after 8–12 hours (Stiefel et al. 1980). After oral exposure to beryllium metal, beryllium sulfate, or beryllium oxide, beryllium was distributed primarily to the liver and then to the kidneys, lymph nodes, blood, and bone (Le Fevre and Joel 1986; Morgareidge et al. 1975; Reeves 1965; Watanabe et al. 1985). Studies investigating distribution patterns of dermally absorbed beryllium would be useful to determine if sensitization to beryllium can occur after dermal exposure.

Beryllium is not biotransformed in the body. Studies involving the conversion of soluble beryllium compounds to insoluble compounds would be useful to determine the residence time of the compounds in

the gastrointestinal tract. Studies investigating the binding of beryllium to proteins or nucleic acids would be useful in determining the antigenic forms of beryllium, as well as a possible mechanism for genotoxicity.

Information regarding the clearance of beryllium from serum in humans (Stiefel et al. 1980; Zorn et al. 1986) and animals (Finch et al. 1990; Rhoads and Sanders 1985; Sanders et al. 1975; Stiefel et al. 1980; Zorn et al. 1977) after inhalation exposure to beryllium compounds is reported in the available literature. Beryllium compounds are poorly absorbed by the gastrointestinal tract, and primarily eliminated in the feces (Furchner et al. 1973; Morgareidge et al. 1975; Reeves 1965). Studies regarding excretion after dermal exposure to beryllium and its compounds were not located in the available literature.

Comparative Toxicokinetics. Studies in cats, rats, monkeys, and dogs indicate quantitative and qualitative differences in the distribution of inhaled beryllium to the lung, bone, spleen, and lymph nodes (Finch et al. 1990; Rhoads and Sanders 1985; Sanders et al. 1975; Stiefel et al. 1980; Stokinger et al. 1950; Wagner et al. 1969; Zorn et al. 1977). No studies were located comparing the differences in inhalation exposures among species with respect to absorption or excretion. Since beryllium is not well absorbed by the gastrointestinal tract or after dermal exposure, comparative studies for these routes of exposure would not be particularly valuable. Additional comparative toxicokinetics studies regarding distribution, absorption, and excretion of inhaled beryllium would be helpful to determine the use of the appropriate animal model to study acute and chronic beryllium disease.

Methods for Reducing Toxic Effects. Beryllium is poorly absorbed after oral and dermal exposure, obviating the need to develop methods to reduce absorption following these routes. While beryllium is absorbed by the lungs, the major effects of inhalation exposure to beryllium are acute chemical pneumonitis, which is associated with soluble beryllium compounds and chronic berylliosis, which is associated with retention of unabsorbed less soluble beryllium compounds in the lungs (Finch et al. 1990). Testing of bronchoalveolar lavage to enhance beryllium clearance from the lungs might prevent or reduce the severity of berylliosis. The chelating agent, aurine tricarboxylic acid, by combining with beryllium ions, increases the urinary excretion of beryllium in animals (Venugopal and Luckey 1978). However, metal chelating agents available for use in human clinical medicine have not been shown to be effective in reducing the toxicity of beryllium (Hall and Rumack 1992). Effects of soluble beryllium compounds (liver necrosis due to sequestration of insoluble beryllium phosphate formed from the interaction with phosphate, acute pneumonitis, immunological effects) are probably due to beryllium ions (Price and Skilleter 1985, 1986). Further studies on the influence of chelating agents on beryllium-induced effects would aid in establishing effective strategies for preventing or reducing the severity of these effects. Absorbed beryllium appears to preferentially accumulate in bone, and beryllium may substitute for calcium in bone, resulting in rickets or osteoporosis (Guyatt et al. 1933; Jacobson 1933). Studies could be performed to determine whether a high calcium diet would be effective in preventing the replacement of calcium by beryllium in bone.

Children's Susceptibility. No information on the toxicity of beryllium in children has been located. Studies that examine sensitive end points such as the lung, immune, and gastrointestinal effects in young animals would be useful for assessing whether children will be unusually susceptible to beryllium toxicity. The available animal data are inconclusive to determine whether the developing organism is sensitive to beryllium toxicity. As discussed in Chapter 2 and in Section 3.2.2.6, the only available oral study did not find developmental effects in the offspring of dogs chronically exposed to beryllium sulfate in the diet (Morgareidge et al. 1976). However, injection studies have found developmental effects (fetal/neonatal mortality, internal abnormalities, and behavioral effects) (Bencko et al. 1979; Mathur et al. 1987; Selivanova and Savinova 1986; Tsujii and Hoshishima 1979). Data needs relating to development are discussed in detail in the Developmental Toxicity subsection above. There are some data to suggest that

beryllium can cross the placenta and be transferred to an infant via breast milk (Krachler et al. 1999a).

The available toxicokinetic data did not evaluate the potential differences between adults and children. Toxicokinetic studies examining how aging can influence the absorption, distribution, and excretion of beryllium would be useful in assessing children's susceptibility to beryllium toxicity. There are no data to determine whether there are age-specific biomarkers of exposure or effects or any interactions with other chemicals that would be specific for children. Research in adults on methods for reducing beryllium toxic effects or body burdens would also be applicable to children.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Ongoing studies pertaining to beryllium have been identified and are shown in Table 3-6.

Table 3-6. Ongoing Studies on Beryllium

Investigator	Affiliation	Research description	Sponsor
Albertini, RJ	University of Vermont	Biomarkers for beryllium sensitization	EM
Marian, B	University of California, Los Alamos National Laboratory	Screening of beryllium worker cohorts using the immun.- flow lymphocyte proliferation test	NCR
Newman, L	University of Colorado	Immunopathogenesis of beryllium disease	NCR
Rossman, M	University of Pennsylvania	Examination of exposure-response relationship for various measures of beryllium exposure	NCR
Kotzin, BL	University of Colorado	Examination of T–cell clones in individuals with CBD and beryllium sensitized individuals	NHLBI
King, TE	National Jewish Medical and Research Center	Prevention of pulmonary fibrosis in individuals with granulomatous inflammation	NHLBI
Newman, L	National Jewish Medical and Research Center	Role of T–cells and mast cells in the development of pulmonary fibrosis	NHLBI
Mason, RJ	National Jewish Medical and Research Center	Immunologic regulation of pulmonary fibrosis	NHLBI
Warren, JS	University of Michigan	Study of oxidant-induced β-chemokines in granuloma formation	NHLBI
Fontenot, AP	University of Colorado	Pathogenic cells in beryllium-induced lung disease	NHLBI
LA Maier	National Jewish Medical and Research Center	Local angiotensin system in lung fibrogenesis	NHLBI
Bell, J	Fayetteville State University	Mutagenic effects of beryllium on the fidelity of DNA synthesis	NIGMS
Newman, L	National Jewish Medical and Research Center	Cytokine regulation in CBD	NIEHS
Finch, GL	Lovelace Biomedical and Environmental Research Institute	Mechanisms of granulomatous disease from inhaled beryllium	USDOE

CBD = chronic beryllium disease; NCR = National Center for Research Resources; NHLBI = National Heart, Lung, and Blood Institute; NIEHS = National Institute of Environmental Health and Science; NIGMS = National Institute of General Medical Sciences; USDOE = U.S. Department of Energy

6.8 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of beryllium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of beryllium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The relevant physical and chemical properties of beryllium are known (see Section 4.2). Additional information regarding the chemical forms of beryllium in coal fly ash and aerosols produced by specific industrial processes, and the mode by which beryllium compounds are incorporated into biological systems would be useful. Additional information about the chelation of beryllium (especially about chelating agents that may be used in the development of beryllium-specific chelation therapy) would also be useful.

Production, Import/Export, Use, Release, and Disposal. Data regarding the production, import/export, and use of beryllium and beryllium compounds are available (see Sections 5.1 through 5.3). According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The TRI is updated yearly and provides a list of industrial production facilities and emissions.

As reported in Tables 6-2 and 6-3, the most significant amount of beryllium and beryllium compounds from production and use facilities is disposed of on land. Little is known about the methods used for land disposal of beryllium, except that small amounts of beryllium waste are discharged into public sewers (TRI99 2002). Additional data examining the method used for land disposal of beryllium waste and the routes by which beryllium might find its way from land disposal sites into groundwater would be useful.

Environmental Fate. For solids, there is a need to determine uptake factors into edible portions of plants and not just adherence to the root structure. Dry or wet deposition from the atmosphere to soil and water can occur. Little experimental data on the particle size and residence time of beryllium and beryllium compounds present in the ambient atmosphere are available. Additional data examining the possible chemical transformation reactions of beryllium and its half-life in air would be useful. Data regarding the dominant types of sorption mechanisms for beryllium (e.g., ion exchange vs. chemical sorption) for different mineral and environmental conditions are limited. Additional information elucidating the fate of beryllium with respect to its chemical speciation in soil is necessary.

Bioavailability from Environmental Media. Although the absorption of specific beryllium compounds from skin contact, inhalation, and ingestion have been studied in animals (see Section 3.3.1), the bioavailability of beryllium or its compounds from contaminated air, water, soil, or plant material may differ significantly from the studied values. Additional information on the dependence of absorption of beryllium on such parameters as chemical form, extent of sorption in the host medium, and other possible variables would be useful.

Food Chain Bioaccumulation. Beryllium does not bioconcentrate to high levels in aquatic animals (EPA 1980), although the bioconcentration in bottom-dwelling animals may be higher than non bottom-dwelling animals (Byrne and DeLeon 1986). There is no evidence of biomagnification of beryllium within terrestrial or aquatic food chains (Fishbein 1981). Further studies establishing the biomagnification potential for beryllium would be useful. Data regarding the intake of beryllium from food are lacking (Vaessen and Szteke 2000; Wolnik et al. 1984). The accuracy of the available database of beryllium in foods is questionable (Vaessen and Szteke 2000). More reliable concentration information is needed on levels of beryllium in food stuff to reduce or eliminate the uncertainties in estimating the dietary intake of beryllium (Vaessen and Szteke 2000). Such information would be important in assessing the contribution of food to the total intake of beryllium from different pathways.

Exposure Levels in Environmental Media. Some data on the levels of beryllium in air and drinking water are available. Limited data regarding the ambient concentration of beryllium near beryllium-containing hazardous waste sites in the United States are available. These monitoring data are important for assessing the potential health risk for individuals living near the waste sites (Eckel and Langley 1988). Nationwide monitoring data determining the levels of beryllium in U.S. drinking water at a detection limit <10 ng/L would be useful. Reliable and more recent monitoring data for the levels of beryllium in air, drinking water, soil (particularly at NPL sites), and food would be useful in estimating exposure from each source. Remedial investigations and feasibility studies conducted at the NPL sites contaminated with beryllium will add to the available database on exposure levels in environmental media. Investigations at these sites will also increase the current knowledge regarding the transport and transformation of beryllium at hazardous waste sites.

Exposure Levels in Humans. Beryllium levels in the urine and lung of both the control and occupationally exposed populations are available (Kanarek et al. 1973; Stiefel et al. 1980). No data on the beryllium levels in body tissues or fluids of populations living near hazardous waste sites or coal-fired power plants are available. Such information would be useful in assessing exposure levels for this population. Further studies regarding the possibility of increased exposure to beryllium via dental implants may be useful.

Exposures of Children. Children will be exposed to beryllium in the same manner as adults in the general population (i.e., ingestion of food and water, and inhalation of air).

Child health data needs relating to susceptibility are discussed in Section 3.12.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries. The Beryllium Case Registry (BCR) was established at Massachusetts General Hospital, Boston, Massachusetts in 1952 and taken over by NIOSH in the late 1970s. Since its transfer to NIOSH, no additional cases were added. Presently, the BCR is not an active registry. This element is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The element will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this element.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2001) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-8.

Table 6-8. Ongoing Studies on Human Exposure to Beryllium

Investigator	Affiliation	Subject	Sponsor
Peters, EL	Chicago State University	Fluctuating asymmetry in isopods as indicator of hazardous metals in urban area	National Institute of General Medical Sciences
Grew, ES	University of Maine	Beryllium in antarctic ultrahigh-temperature granulite-facies rocks and its role in partial melting of the lower continental crust	NSF

Source: FEDRIP 2001

NSF = National Science Foundation

DRAFT

SUPPLEMENTAL DOCUMENT TITLE PAGE FOR [Substance X]

Prepared by:
[Contractor Name]
Under Contract No. [XXXXXX]

Prepared for:
Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

[Month, year]

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U.S. Public Health Service

[Month, year]

FOREWORD

This document presents summary tables for studies reviewed for the Toxicological Profile for [Substance X]. Tables are divided into two sections:

Section 1. Summary Tables for Toxicity Studies
Section 2. Summary Tables for Toxicokinetic Studies

SECTION 1

SUMMARY TABLES FOR TOXICITY STUDIES

SECTION 2

SUMMARY TABLES FOR TOXICOKINETIC STUDIES

LEGEND FOR SUMMARY TABLES FOR TOXICITY STUDIES FOR [SUBSTANCE X]

Header

NOAEL	No observed adverse effect level
LOAEL	Lowest observed adverse effect level
mg	Milligram
kg_3	Kilogram
m^3	Cubic meter
cm^2	Centimeter squared

Duration/Frequency of Exposure

1x	One time
hr	Hour
mo	Month
wk	Week
g	Gestation
d	Day
gen	Generation
min	Minutes
yr	Year
pg	Post-generation

Route

(C)	Capsule
(F)	Feed
(GO)	Gavage – oil
(W)	Drinking water
(GW)	Gavage – water
(SC)	Subcutaneous
(IV)	Intravenous
(IP)	Intraperitoneal

No/Sex/Group

F	Female
M	Male
NS	Not specified

Species

gn pig	Guinea pig

Parameters Monitored

BW	Body weight
BC	Serum (blood) chemistry
OW	Organ weight
CS	Clinical signs
FI	Food intake
BI	Biochemical changes
WI	Water intake
OF	Organ function
GN	Gross necropsy
UR	Urinalysis
HP	Histopathology

Effect

Cardio	Cardiovascular
Hemato	Hematological
Derm/oc	Dermal/Ocular
Musc/skel	Musculoskeletal
Gastro	Gastrointestinal
Resp	Respiratory

Results

>	Increased
<	Decreased
aden	Adenoma
adrlectmy	Adrenalectomy
bil sec	Biliary secretion
biochem	Biochemical
CEL	Cancer effect level
degen	Degeneration
Deg LivCel	Degraded liver cells
deg tub ep	Degraded tubular epithelium
development	Development
dispos	Disposition
enz act	Enzyme activity
fetl anom	Fetal anomalies
GSH	Glutathione transferase
hemoglob	Hemoglobin
histo	Histopathology

Legend for Summary Tables for Toxicity Studies for [Substance X] (cont)

Results (continued)

Implnt los	Implantation loss
Inflt	Infiltration
Inflamatn	Inflammation
Lesn	Lesions
Midzon nec	Midzonal necrosis
Mort	Mortality
Nx	Next
Path chg	Pathological change
Resorp	Resorption
SD	Sorbitol dehydrogenate
Sens	Sensitivity
Ser AKT	Serum AKT
Ser creat	Serum creatinine
Skel anom	Skeletal anomalies
Skel alt	Skeletal alterations
Tub neph	Tubular nephrosis
TWA	Time-weighted average
Vacuolatn	Vacuolation
Wt	Weight

LEGEND FOR SUMMARY TABLES FOR TOXICOKINETIC STUDIES FOR [SUBSTANCE X]

Header

Mg	Milligram
m^3	Cubic meter
Fg	Kilogram
cm^2	Centimeter squared

Duration/Frequency of Exposure

1x	One time
D	Day
Hr	Hour
Gen	Generation
Mo	Month
Min	Minutes
Wk	Week
Yr	Year

Route

(C)	Capsule
(F)	Feed
(GO)	Gavage – oil
(W)	Water
(GW)	Gavage – water
(SC)	Subcutaneous
(IV)	Intravenous
(IP)	intraperitoneal

No/Sex/Group

F	Female
M	Male
Ns	Not specified

Species

Gn pig	Guinea pig

Parameters monitored

AB	Absorption
FM	Fecal metabolites
DI	Distribution
RM	Respiratory metabolites
EX	Excretion
TM	Tissue metabolites
UM	Urinary metabolites
EA	Enzyme activity

SUMMARY TABLE FOR TOXICITY STUDIES FOR EXPOSURE TO CARBON DISULFIDE - INHALATION

Chemical	Species/ No. & Sex/	Duration/ Fre-quency	Dose	Parameters Moni-tored	System	Less Serious (ppm)	Serious (ppm)	Reference
ACUTE EXPOSURE								
Systemic								
600	Strain	18 hrs	(ppm) 0, 803	CS BI OR	Resp	803 M (decreased respiratory rate) 803 M (decreased cardiac rate) 803 M (decreased body temperature)		Tarkowski and Sobczak 1971
	Rat							
			NOAEL					

CALCULATIONS: 2.5 mg/L x 1000 L/m3 x (24.45/76.14) ppm/mg/m3 = 803 ppm. COMMENTS: White male Wistar rats weighing 200 – 250 g were exposed via inhalation to 8 ppm carbon disulfide for 18 hours. Also reported were data from an intermediate exposure to the same dose which lasted 10 months. Acute dosing produced severe narcosis, reduced cardiac and respiratory rate, straightening of hindlimbs, and lower body temperature. Intermediate dosing produced loss of motor equilibrium, muscular weakness, and hindlimb paresis. Although rats in these two groups developed different symptoms of poisoning, brain mitochondria of both groups of animals exhibited the same types of disturbances in oxidative phosphorylation. This study is limited by its use of a small number of animals of one sex in a group, and only one dose tested. No dose-effect relationship can be estimated from this study.

35	Human	NS	NS	CS BI OR	Resp	NS (transient changes in pulmonary function)		Spyker et al.
	27NS							

COMMENTS: Twenty-seven individuals were exposed to carbon disulfide following a railroad tank car accident. Airborne carbon disulfide levels were 20 ppm during the transfer of carbon disulfide from the leaking tanker to an intact railroad tank car. However, no measurements were made during the accident. Subtle and transient changes occurred in pulmonary function, such as breath or chest pains. Slow vital capacity ($p<0.02$) and decreased partial pressure of arterial oxygen ($p<0.02$) were noted in 11 and 9 individuals, respectively, but these parameters returned to normal within 9 days of exposure. Study limitations included lack of well-characterized exposure concentrations, possible exposure to other chemicals, and small sample size. Effects reported may have had other causative factors.

29	8-30M Porton-	2 d 4hr/d	0, 1285	HP		1285 M (myocardial lesions in		Chandra et al 1972
	Rat			Cardio		pretreated rats)		
			LOAEL					

COMMENTS: Male albino rats were fasted prior to treatment with carbon disulfide. Group A was administered 2 i.p.injections of sodium phenobarbitol, then fasted overnight prior to exposure to 1285 ppm carbon disulfide for 4 hours for 2 consecutive days. Rats were sacrificed at 0,2,4,6,8,14,18,48 hours and 3,5,7 and 15 days after the second exposure. Noradrenaline tartrate was injected intraperitoneally immediately before each exposure to carbon disulfide. Five control groups exposed to carbon disulfide alone, phenobarbitone and noradrenaline together, or noradrenaline and carbon disulfide together were run concurrently. The myocardium was examined histologically. Rats exposed to phenobarbitone, noradrenaline and carbon disulfide exhibited grade 3 histological lesions, which was characterized by necrosis of papillary muscles and the endocardial half of the left ventricle, marked interstitial edema and cellular infiltration with a fibroblastic proliferation. Rats treated with phenobarbitone and noradrenaline alone had grade 1 lesions of the myocardium which consisted of light interstitial edema, leukocytic infiltration, and small areas of degenerated muscle fibers. No histochemical changes were observed in any other exposure group. This experiment demonstrated that the hepatic toxicity of carbon disulfide can be influenced by drug treatment and relatively mild nutritional anomalies. Noradrenaline given in a dose of 1.5 mg/kg did not cause histological damage in the myocardium of fasted rats, caused slight damage if given after phenobarbitone treatment, and more extensive damage if the phenobarbitone treatment was followed by exposure to 1285 ppm carbon disulfide. The mechanism of action of carbon disulfide in increasing the myocardial toxicity of noradrenaline and the role of phenobarbiton is unknown. The results of this study lend support to the hypothesis that disorders of catecholamine metabolism induced by carbon disulfide may be connected with changes in the incidence of ischemic

SUMMARY TABLE FOR TOXICOKINETIC STUDIES FOR EXPOSURE TO CARBON DISULFIDE - INHALATION

Exposure Duration/ Frequency	Route	Species no/sex group	Dose (ppm)	Parameters monitored		Reference	Comments
ACUTE EXPOSURE					Results		
522 1 d		Rat	0, 1500	EA	Measurements of acid proteinase activity, RNA uptake and amino acid uptake in rat brain following inhalation exposure to carbon disulfide revealed differences in these parameters between Sprague-Dawley rats pretreated with phenobarbitone and those receiving no pretreatment. RNA uptake was greatest in both the cerebral and cerebellar fractions 1 hr after exposure in non pretreated rats. In pretreated rats, RNAS content peaked at 4 hours post exposure. Amino acid uptake (measured by uptake of radiolabelled leucine) in the cerebellum was greatest 4 hours after exposure in pretreated rats. Changes in acid proteinase activity in the cerebellar fraction were also greatest 1 hour after exposure in non-pretreated rats and 4 hours after exposure in pretreated rats. Acid proteinase activity in the cerebrum was higher throughout the measurement period (1 to 46 hours) in exposed non-pretreated rats and highest at 4 hours post exposure in rats pretreated with phenobarbitone. Assays of the brain specific enzymes creatinine kinase and non-specific cholinesterase showed only subtle changes between different treatment groups.	Savolainen and Jarvisalo 1977	COMMENTS: [Other parameters also monitored include amino acid uptake and RNA content]. The results of this in vivo study indicate that acute exposure has some effect on brain protein metabolism. Phenobarbitone pretreatment appears to modify the effect of carbon disulfide on brain protein metabolism. Measurement of serum levels of brain specific enzymes does not seem to be a good measure of the effects of acute carbon disulfide exposure on brain protein metabolism. Data was not analyzed for statistical significance of differences between groups. This is an important study limitation because some differences seem to be within the standard deviations given. No mechanisms were given for the result presented in this paper.
501 1 d 4-12 hr/d		Rat 4-24M	0, 32-642	EA	Male Sprague-Dawley rates exposed to carbon disulfide by inhalation had decreased norepinephrine in brain adrenals and heart, along with decreased epinephrine in adrenals. Dopamine was increased in adrenals and brain. Brain norepinephrine decrease was concentration Dependent. Brain epinephrine concentrations immediately at end of exposure period were 61% of controls and increased to 90% of controls by 16 hours post exposure. [In vitro study showed that carbon disulfide preincubated with an amine or amino acid inhibited dopamine-beta-hydroxylase (DBH) activity in the pure enzyme preparations. Carbon disulfide also inhibited DBH activity in Medullary granula preparations. Dithiocarbamates were observed in a gas chromatogram of the intra-granular contents.	McKenna and Distefano 1977b	CALCULATIONS: (2 mg/L) x (24.45/76.14g/mole) x (1000 mg/g) = 642 ppm. COMMENTS: [other parameter monitored is catecholamine Concentration] Carbon disulfide appears to Inhibit dopamine-beta-hydroxy-lase activity causing decreases in brain levels of epinephrine and norepinephrine and increase in brain dopamine Formation of dithiocarbamates by interaction of carbon disulfide with amino acids and/or intragranular catecholamines seems to be a likely mechanism of action for this inhibition In vitro data appears to support this mechanism.

WORKSHEET FOR TOXICITY STUDIES

Worksheet # _____ Rec No(s) _____ to _____
Data Set: 1/ _____
Added to Draft # _____ Initials: (reviewer) _____

Profile Number: _____ Chemical: _____ Chemical Species: _____

Reference: _____

Route: ☐ (O) oral ☐ (I) inhalation ☐ (D) dermal ☐ (N) other
If other: (subroute) ☐ (IP) i.p. ☐ (IM) i.m. ☐ (IV) ☐ (SB) s.b. ☐ (IT) i.t.

If oral: Subroute: ☐ (GW) gavage – water ☐ (GO) gavage – oil ☐ (G) gavage – not specified ☐ (F) feed (diet) ☐ (W) Drinking water ☐ (C) capsule

Duration and Frequency of Exposure

Duration:
☐ (AC) acute
☐ (IN) intermediate
☐ (CH) chronic

Number/Sex/Group:

Species:
☐ (R) rat ☐ (B) rabbit ☐ (M) mouse ☐ (S) hamster ☐ (K) monkey ☐ (P) pig ☐ (A) sheep ☐ (J) pigeon ☐ (Q) cow
☐ (HU) human ☐ (GP) guinea pig ☐ (DG) dog ☐ (CT) cat ☐ (OT) other ☐ (FR) ferret ☐ (MN) mink ☐ (E) gerbil

Doses or Concentration:

☐ (MK) mg/kg/day
☐ (MM) mg/m^3
☐ (PP) ppm
☐ (MC) $mg/cm^2/day$

List doses: _____

Strain: _____
Strain No. _____

Parameters Monitored

☐ BW – Body Weight
☐ OW - Organ Weight
☐ FI - Food Intake
☐ WI - Water Intake
☐ GN - Gross Necropsy
☐ HP - Histopathology
☐ BC - Blood Chemistry
☐ CS - Clinical Signs
☐ BI - Biochemical Changes
☐ OR – Organ Function
☐ UR - Urinalysis
☐ FX - Fetotoxicity
☐ MX - Maternal Toxicity
☐ DX - Developmental Toxicity
☐ TG - Teratogenicity
☐ BH - Behavior
☐ LT - Lethality
☐ HE - Hematology

Attach a separate sheet with the comments corresponding to this worksheet. Include any dose conversions on this attached sheet (preceding the comments section).

WORKSHEET FOR TOXICITY STUDIES

RESULTS

Effect Category	NOAEL	SEX	LOAEL Less Serious Value	Less Serious Sex	Less Serious (Effect)	LOAEL Serious Value	Serious Sex	Serious (Effect)	LSE	Rec No.
LE Death										
IE Immuno										
NE Neuro										
DE Develop										
RE Repro										
CE Cancer										
SE Systemic										
SR Resp										
SC Cardio										
SG Gastro										
SH Hemato										
SM Musc/sk										
SL Hepatic										
SK Renal										
SN Endocr										
SD Dermal										
SV Occular										
SW Body wt										
SO Other										

WORKSHEET FOR TOXICOKINETIC STUDIES

Worksheet # _____ Rec No(s) _____ to _____
Data Set: 1/ _____
Added to Draft # _____ Initials: (reviewer) _____

Profile Number: _____ Chemical: _____ Chemical Species: _____
Reference: _____

Route: ☐ (O) oral ☐ (I) inhalation ☐ (D) dermal ☐ (N) other
If other: (subroute) ☐ (IP) i.p. ☐ (IM) i.m. ☐ (IV) ☐ (SB) s.b. ☐ (IT) i.t.

If oral: Subroute: ☐ (GW) gavage – water ☐ (GO) gavage – oil ☐ (G) gavage – not specified
☐ (F) feed (diet) ☐ (W) Drinking water ☐ (C) capsule

Duration and Frequency of Exposure

Duration:
☐ (AC) acute
☐ (IN) intermediate
☐ (CH) chronic

Number/Sex/Group:

Species:
☐ (R) rat ☐ (B) rabbit ☐ (M) mouse ☐ (S) hamster ☐ (K) monkey ☐ (P) pig ☐ (A) sheep ☐ (J) pigeon ☐ (Q) cow
☐ (HU) human ☐ (GP) guinea pig ☐ (DG) dog ☐ (CT) cat ☐ (OT) other ☐ (FR) ferret ☐ (MN) mink ☐ (E) gerbil

Doses or Concentration:
☐ (MK) mg/kg/day
☐ (MM) mg/m^3
☐ (PP) ppm
☐ (MC) $mg/cm^2/day$

List doses: _____

Strain: _____
Strain No. _____

Parameters Monitored (List all those that apply by effect on the next page)

☐ AB Absorption
☐ DI Distribution
☐ EX Excretion
☐ UM Urinary Metabolites
☐ FM Fecal Metabolites
☐ RM Respiratory Metabolites
☐ TM Tissue Metabolites
☐ EA Enzyme Activity

Other parameters, describe:

Either on the back of this worksheet, or on an attached sheet, describe the results and comments correspondence to this worksheet. Include any dose conversions preceding the comments section.

WORKSHEET FOR TOXICOKINETIC STUDIES

RESULTS:

COMMENTS: Discuss (1) your conclusions (and conclusions of the study author, if they differ), (2) study limitations, and (3) mechanisms of action