Toxicological Profile for Isophorone

July 2018

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) 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 these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a 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 relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. 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 the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute, intermediate, and chronic exposures;

(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, intermediate, 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.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs 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 was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

VERSION HISTORY

Date	Description
July 2018	Update of data in Chapters 2, 3, and 7
December 1989	Final toxicological profile released

CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Melanie Buser, M.P.H.
ATSDR, Division of Toxicology and Human Health Sciences, Atlanta, GA

Julie M. Klotzbach, Ph.D.
SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:

Includes ATSDR; National Center for Environmental Health (NCEH); National Institute of Occupational Health and Safety (NIOSH); U.S. Environmental Protection Agency (EPA); National Toxicology Program (NTP).

Additional reviews for science and/or policy:

ATSDR, Division of Community Health Investigations; ATSDR, Office of Science; NCEH, Division of Laboratory Science; NCEH, Division of Environmental Health Science and Practice.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

ATSDR's *Toxicological Profile for Isophorone* was released in 1989. In order to update the literature in this profile, ATSDR conducted a literature search focused on health effects information as described in Appendix B. Chapters 2 and 3 were revised to reflect the most current health effects data; Chapter 7 was updated to reflect the most current regulations and guidelines for isophorone. In some cases, other sections of the profile were updated as needed or for consistency with the updated health effects data. However, the focus of the update to this profile is on health effects information.

Isophorone (CAS Number 78-59-1) is a clear liquid with a peppermint-like odor. It is a solvent for a large number of natural and synthetic polymers, resins, waxes, fats, and oils. Specifically, it is used as a solvent for concentrated vinyl chloride/acetate-based coating systems for metal cans, other metal paints, nitrocellulose finishes, printing inks for plastics, some herbicide and pesticide formulations, adhesives with food contract, and adhesives for plastics, poly(viny1) chloride, and polystyrene materials (Papa and Sherman 1981). Isophorone is released to the air mainly in urban centers, as a result of evaporation of solvents containing this chemical. The most likely exposure of the general population is to contaminated air.

1.2 SUMMARY OF HEALTH EFFECTS

Little information is available on the effects of isophorone in humans. Acute exposure studies conducted in human subjects show that exposure to isophrone in air is irritating to the eyes and respiratory tract (Hazleton Labs 1965b; Silverman et al. 1946). No information regarding effects of oral exposure of humans to isophorone was identified.

In laboratory animals, several studies have evaluated the acute lethality and irritant effects of inhalation, oral, or dermal exposure to isophorone. By all routes, acute exposure produces irritation and tissue damage at the point of contact (e.g., portal of entry). However, available acute inhalation, oral, and dermal exposure studies did not evaluate comprehensive endpoints. Inhalation studies have evaluated effects of intermediate and chronic exposure to isophorone, although comprehensive toxicological endpoints were not examined and studies evaluated only single exposure concentrations. Therefore, it is not possible to determine the most sensitive effects of intermediate and chronic inhalation exposures. The

oral exposure database includes intermediate- and chronic-duration studies that evalauted comprehensive toxicological endpoints, including cancer.

Effects of inhaled and oral isophorone are depicted in Figures 1-1 and 1-2, respectively. Inhalation studies identify the respiratory tract, eyes, and skin as the most sensitive targets for exposure to isophorone in air. Other observed effects include neurological, hematological, developmental, and hepatic. Oral exposure studies identified several effects including those to the neurological, gastrointestinal, hepatic, and renal systems.

Irritation. Exposure to isophorone produces irritation and damage at the site of contact. Respiratory tract and ocular irritation has been observed in human subjects and laboratory animals exposed to isophorone in air. In animals, dermal and ocular irritation and damage occurred following direct contact exposure. Hyperkeratosis of the forestomach of male mice was observed following chronic gavage exposure to isophorone (NTP 1986).

Neurological Effects. Neurological effects have been observed in laboratory animals following inhalation and oral exposure. Effects observed in acute inhalation studies include central nervous system (CNS) depression, neurobehavioral changes, and coma (DeCeaurriz et al. 1981b, 1984; Hazelton Labs 1965a). The lowest exposure associated with neurological effects is a 4-hour exposure to 89 ppm in mice for neurobehavioral changes (DeCeaurriz et al. 1984). Neurological effects also have been observed in oral exposure studies in animals. Effects include CNS depression in male rats following exposure to a single dose of 1,450 mg/kg (Hazelton Labs 1964), stagger in mice exposed to 1,000 mg/kg/day for 16 days (NTP 1986), and lethargy in rats exposed to 1,000 mg/kg/day for 13 weeks (NTP 1986). However, neurological effects were not observed in rats or mice at oral doses up to 500 mg//kg/day in chornic exposure studies (NTP 1986).

Hepatic Effects. Chronic inhalation and oral exposure studies provided evidence of isophorone-induced hepatic toxicity. Microvacuolization of the liver was observed in mice and rabbits exposed to inhaled isophorone for 18 months at a concentration of 250 ppm (Dutertre-Catella 1976). In the NTP (1986) oral study, necrosis of the liver was observed in mice exposed to 250 mg/kg/day for 103 weeks; however, no hepatic damage was observed in rats at doses up to 500 mg/kg/day (NTP 1986).

Renal Effects. The NTP (1986) chronic study reported renal inflammation in mice exposed to 500 mg/kg/day. In this same study in male rats, renal effects consistent with alpha 2μ-globulin-induced

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Isophorone

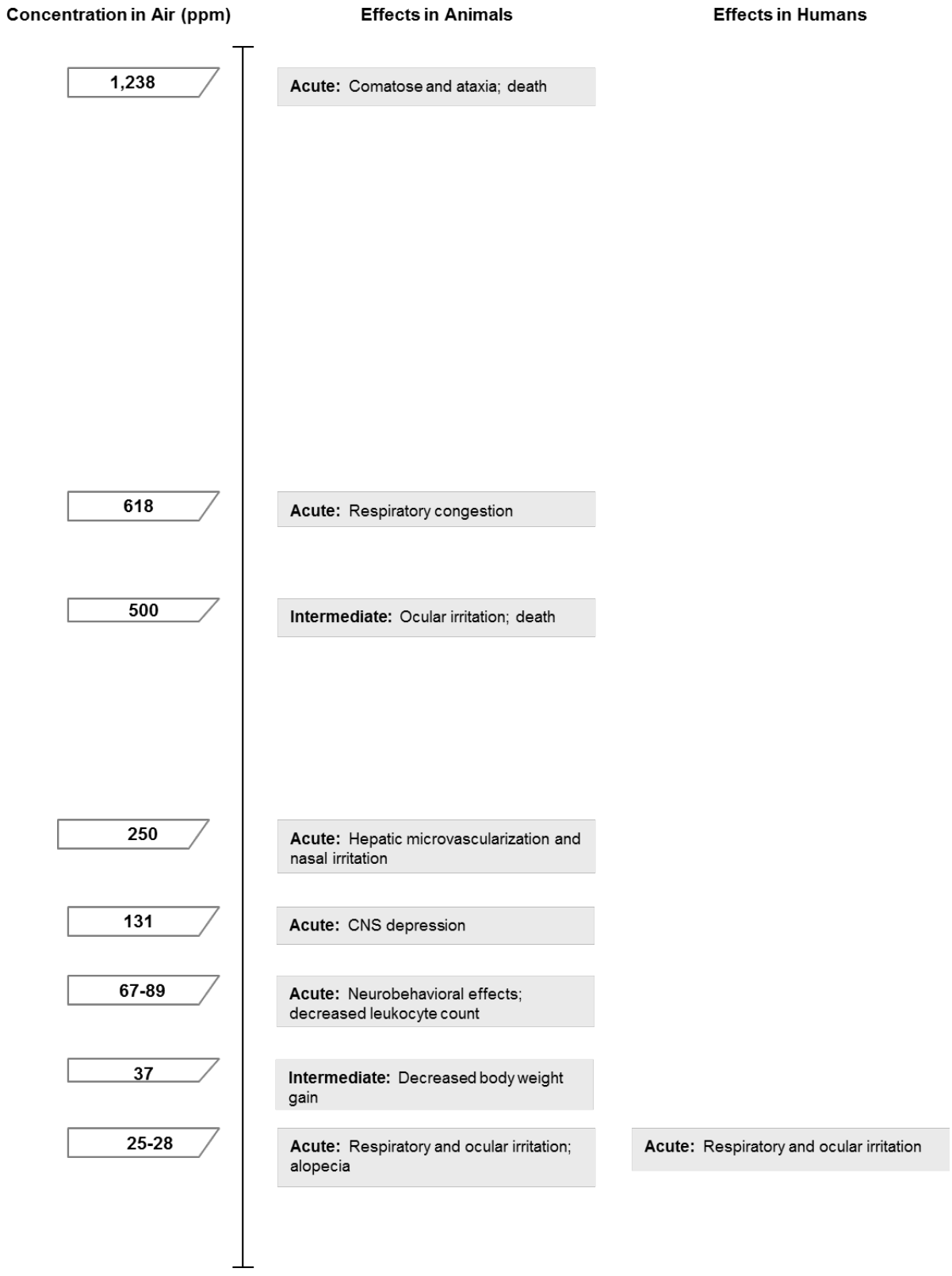
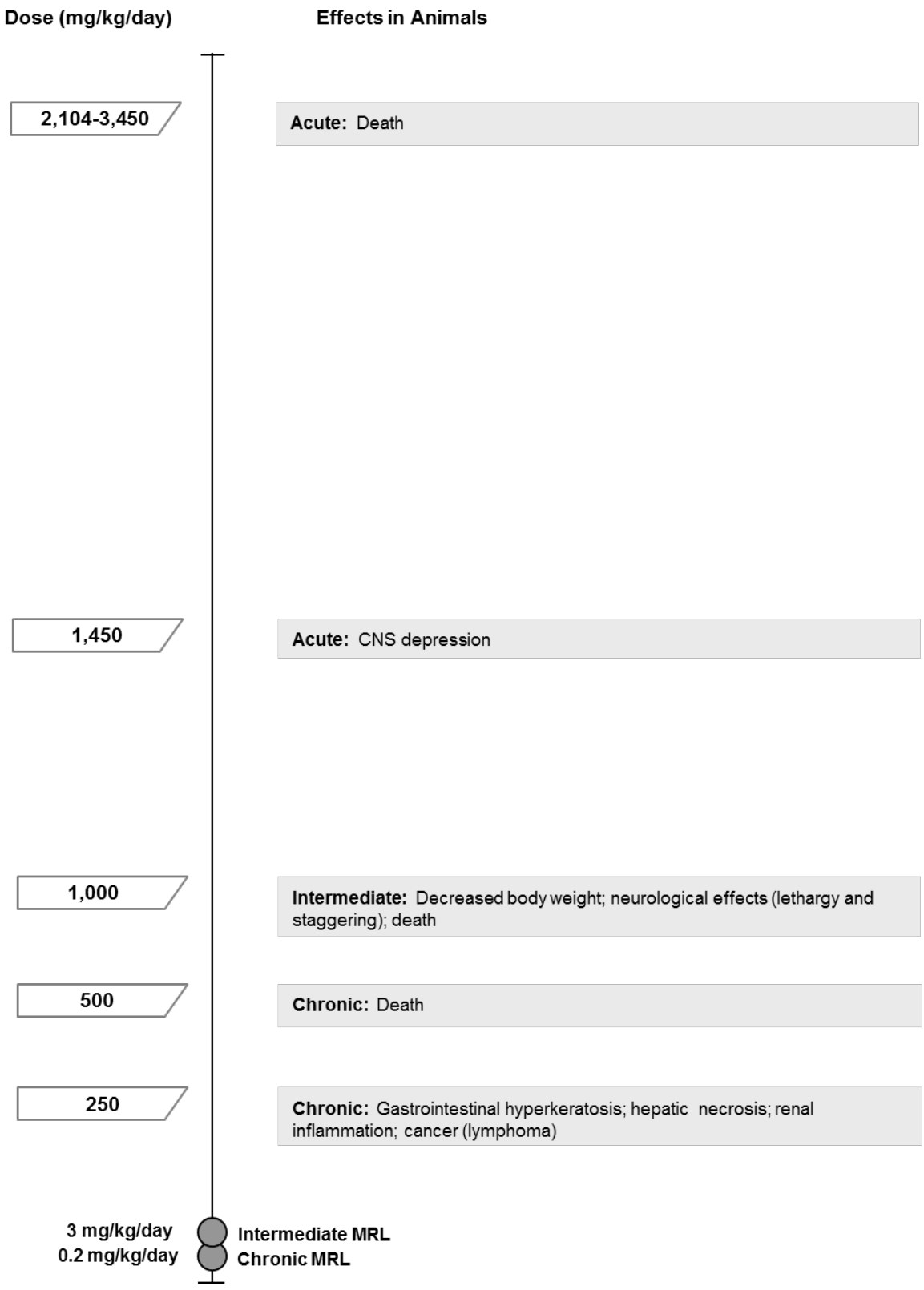


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Isophorone



damage to renal proximal tubules was observed at doses 250 and 500 mg/kg/day. This effect is unique to male rats and is not toxicologically relevant to human health (EPA 1991; Swenberg 1993).

Cancer Effects. Cancer has been observed in rats and mice exposed to oral isophorone for 103 weeks (NTP 1986). The lowest cancer effect level (CEL) of 250 mg/kg/day was observed for lymphoma in mice. At 500 mg/kg/day, liver and skin tumors were observed in mice. In rats, preputial gland tumors were observed in male at a dose of 500 mg/kg/day; although it has been proposed that these tumors may be attributed to alpha 2μ-globulin (WHO 1995). Kidney tumors also were observed in male rats exposed to 250 and 500 mg/kg/day; however, these tumors were due to renal damage induced by accumulation of alpha 2μ-globulin and, therefore, are not relevant to human health (EPA 1991; Swenberg 1993).

The U.S. Department of Health and Human Services (NTP 2016) and the International Agency for Research on Cancer (IARC 2017) have not categorized the carcinogenicity of isophorone. EPA categorized it as a possible human carcinogen (Group C) based on no data in humans and limited evidence of carcinogenicity in animals (IRIS 2003).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was not considered adequate for deriving inhalation MRLs. As presented in Figure 1-3, available information on acute exposure in humans to isophorone in air identifies respiratory and ocular irritation as the most sensitive effects. The acute exposure duration in human subjects was very short (≤15 minutes) and, therefore, not suitable for the basis of the acute-duration inhalation MRL. Acute exposure studies in animals did not examine comprehensive toxicological endpoints. Intermediate- and chronic-duration inhalation studies in animals used only a single exposure level and did not examine comprehensive toxicological endpoints. Therefore, available studies do not provide sufficient information to derive inhalation MRLs.

The oral database was considered adequate for derivation of intermediate- and chronic-duration oral MRLs; these values are summarized in Table 1-1 and discussed in greater detail in Appendix A. The most sensitive effects of oral exposure to isophorone in laboratory animals are shown in Figure 1-4. The available acute oral exposure studies were designed to assess lethality and did not examine comprehensive toxicological endpoints. Thus, data are inadquate to derive an acute-duration oral MRL.

Figure 1-3. Summary of Sensitive Targets of Isophorone – Inhalation

Body weight is the most sensitive target of isophorone inhalation exposure.
Numbers in triangles and circles are the lowest LOAELs (ppm) among health effects in humans and animals, respectively

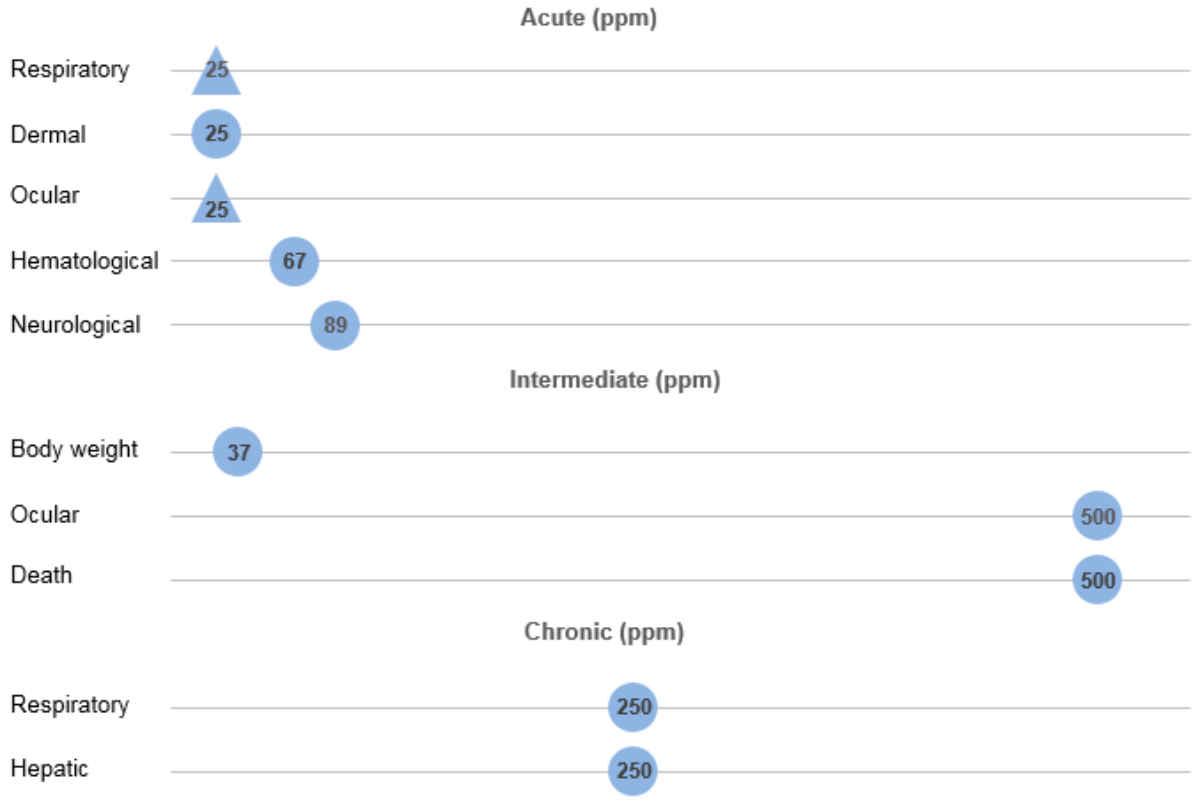


Figure 1-4. Summary of Sensitive Targets of Isophorone – Oral

Gastrointestinal, hepatic and renal are the most sensitive target of isophorone oral exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

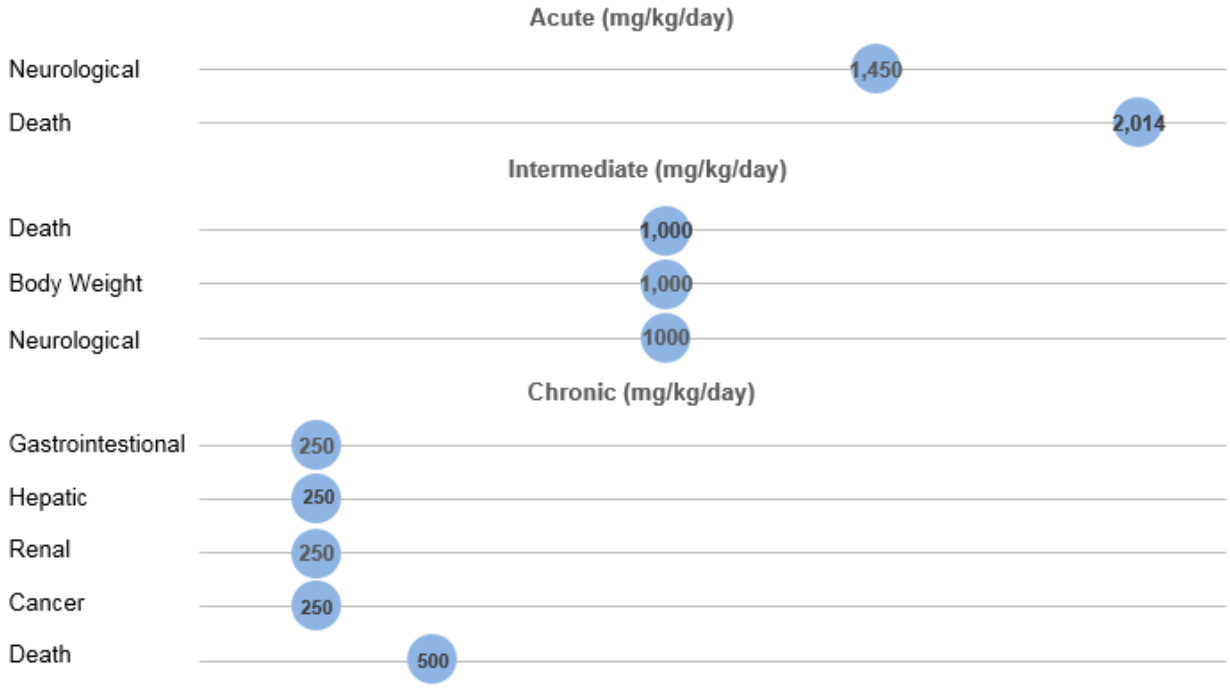


Table 1-1. Minimal Risk Levels (MRLs) for Isophorone[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	3 mg/kg/day	No adverse effects	311.8 (NOAEL)	100	AME Inc. 1972a
Chronic	0.2 mg/kg/day	Renal, hepatic, stomach lesions	179[b] (LOAEL)	1,000	NTP 1986

[a]See Appendix A for additional information.
[b]Adjusted for daily exposure (exposure was to 250 mg/kg/day 5 day/week).

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of isophorone. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to isophorone, but may not be inclusive of the entire body of literature.

Human and animal inhalation studies are presented in Table 2-1 and Figure 2-2, animal oral studies are presented in Table 2-2 and Figure 2-3, and animal dermal data are present in Table 2-3.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be

classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of isophorone are indicated in Table 2-2 and Figure 2-3.

A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

The health effects of isophorone have been evaluated in two human experimental studies and in animal studies. The studies in humans examined effects of brief exposures (≤15 minutes) to isophorone in air and examined respiratory and ocular effects. As illustrated in Figure 2-1, more animal studies on health effects were for inhalation exposure compared to oral exposure. Animal data are available for most health effects, with the most data available on respiratory, hematological, neurological, and dermal effects. It is noted that no studies examined reproductive function or immune function. Of available oral studies in laboratory animals, one study evaluated exposure to dietary isophorone; all other oral studies administered isophorone by gavage or capsule.

Available studies have identified several targets of toxicity for isophorone, as described below. Studies of acute exposure to air identify respiratory and ocular irritation as the most sensitive effect of exposure. For intermediate and chronic inhalation exposures, it is not possible to determine a most sensitive effect, as studies only evaluated one exposure level. For intermediate oral exposure studies, few effects were observed and effects occurred at the highest exposure levels. For chronic oral studies, effects occurred at the lowest dose tested.

- **Respiratory:** Respiratory irritation has been reported by human subjects briefly exposed to isophorone and nasal irritation has been observed in laboratory animals following acute-, intermediate-, and chronic-duration inhalation exposure. Respiratory effects, including irritation, respiratory congestion, and hemorrhagic lungs, have been observed in laboratory animals.

- **Irritation:** Respiratory tract and ocular irritation has been observed in human subjects and laboratory animals exposed to isophorone in air. In animals, dermal and ocular irritation and damage occurred following direct contact exposure. Hyperkeratosis of the forestomach of male mice was observed following chronic gavage exposure to isophorone.

- **Hepatic:** Chronic inhalation and oral exposure studies provided evidence of isophorone-induced hepatic toxicity in laboratory animals. Microvacuolization of the liver was observed following inhalation exposure and hepatocytomegaly and coagulative necrosis were observed following oral exposure to isophorone.

- **Renal:** Renal inflammation was observed in mice following chronic oral exposure.

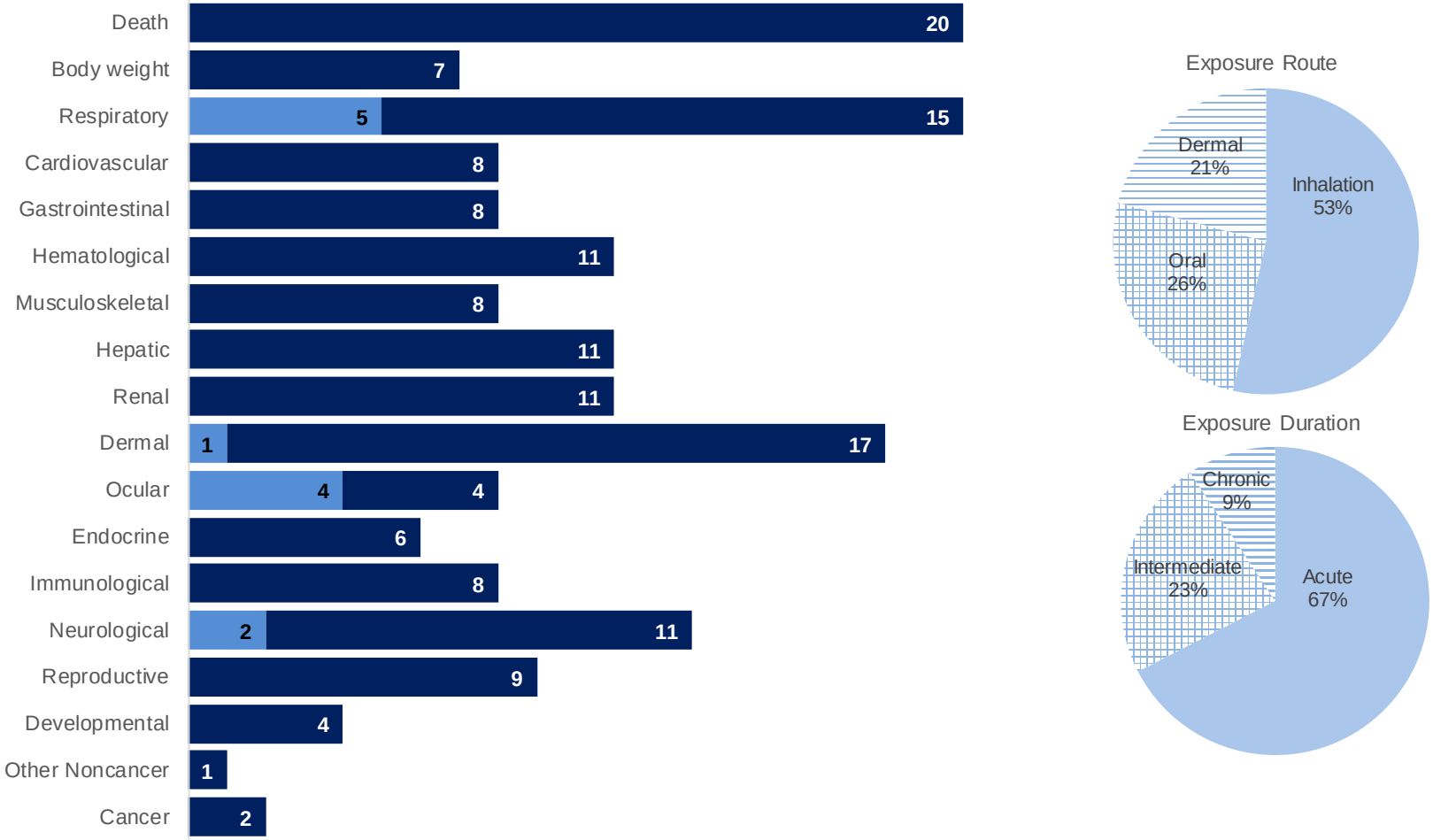
- **Neurological:** Neurological effects, including CNS depression, lethargy, neurobehavioral effects, and staggering have been observed in laboratory animals following acute-duration inhalation exposure and acute- and intermediate-duration oral exposure to isophorone.

- **Cancer.** Following chronic oral exposure of laboratory animals to isophorone, lymphoma and tumors of the liver, skin, and preputial gland have been observed.

Figure 2-1. Overview of the Number of Studies Examining Isophorone Health Effects

Respiratory, hematological, dermal and neurological effects of isophorone were the most widely examined potential toxicity outcomes

More studies examined exposure in **animals** than in **humans** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 34 studies (including those finding no effect) have examined toxicity; most animal studies examined multiple endpoints. No studies examined the effects of oral exposure in humans.

Table 2-1. Levels of Significant Exposure to Isophorone – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
ACUTE EXPOSURE									
1	Human 6 NS	7 minutes	18, 35, 65, 90, 105	Odor, irritation thresholds	Resp	35	65		Throat congestion
					Ocular	35	65		Eye irritation
Hazleton Labs 1965b									
2	Human 12 M,F	15 minutes	10, 25	Odor, irritation thresholds	Resp	10	25		Irritation to the nose and throat
					Ocular	10	25		Irritation to the eyes
Silverman et al. 1946									
3	Rat (NS) 12 F	GDs 6–15 6 hours/day	0, 50, 100, 150	BW, OW, FI, FX, GN, CS	Dermal Develop	150	50		Alopecia
Bio/dynamics 1984a									
4	Rat (NS) 22 F	GDs 6–15 6 hours/day	0, 25, 50, 115	BW, OW, FX, GN, CS	Dermal Develop	115	25		Alopecia
Bio/dynamics 1984b									
5	Rat (Sprague-Dawley) 5 M	4 hours	0, 19, 49, 67, 90		Hemato	49	67		Decreased leukocyte count (43% and 40% at 67 and 90 ppm, respectively)
Brondeau et al. 1990									
6	Rat (NS) 10 F	Once 6 hours	619	GN, CS	Death				No death
					Resp		619		Congestion
Hazelton Labs 1964									
7	Rat (NS) 10 M	Once 4 hours	885,1,238, 1,769, 3,149	GN, CS	Death			1,238	LC_{50}; 1/10 animals died at 885 ppm
					Neuro	855		1,238	Overt signs of neurotoxicity (comatose, ataxic)
Hazelton Labs 1965a									

Table 2-1. Levels of Significant Exposure to Isophorone – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
8	Mouse (NS) 12 F	GDs 6–15 6 hours/day	0, 50, 100, 150	BW, OW, FI, FX, GN, CS	Dermal Develop	150 150			
Bio/dynamics 1984a									
9	Mouse (NS) 22 F	GDs 6–15 6 hours/day	0, 25, 50, 115	BW, OW, FX, GN, CS	Dermal Develop	115 150			
Bio/dynamics 1984b									
10	Mouse (NS) 5 M	5 minutes	NR	Sensory irritation	Resp			27.8	RD_{50}
DeCeaurriz et al. 1981a									
11	Mouse (NS) 10 M	4 hours	0, 131	CNS depression	Neuro		131		Central nervous system depression
DeCeaurriz et al. 1981b									
12	Mouse (NS) 10 M	4 hours	0, 89, 112, 127, 137		Neuro		89		Behavioral test
DeCeaurriz et al. 1984									
13	Mouse (NS) 10 F	Once 6 hours	619	GN, CS	Death Resp		 619		No mortality Congestion
Hazelton Labs 1964									
14	Mouse (Swiss) 10M	4, 9, or 14 days 6 hours/day	0, 29, 89	HP	Resp	89			
Zissu 1995									

Table 2-1. Levels of Significant Exposure to Isophorone – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
15	Guinea pig (NS) 10 F	Once 6 hours	619	GN, CS	Death				No mortality
Hazelton Labs 1964									
INTERMEDIATE EXPOSURE									
16	Rat (NS) 10 M, 10 F	4–6 months 6 hours/day 5 days/week	0, 500	CS, DX, MX	Death			500	1/10 females and 3/10 males died
					Resp	500			
					Hepatic	500			
					Ocular		500		Ocular irritation
					Repro	500			No change in pregnancy rate or litter size
Dutertre-Catella 1976									
17	Rat (NS) 10 M, 10 F	4 weeks 6 hours/day 5 days/week	0, 37	BW, OW, GN, HP, CS	Bd wt		37		Decreased body weight gain
					Hemato	37			
					Renal	37			
Hazelton Labs 1968									
CHRONIC EXPOSURE									
18	Rat (NS) 10 M, 10 F	18 months 6 hours/day 5 days/week	0, 250	BW, GN, CS HP, UR	Death				No mortality
					Resp	250			
					Hemato	250			
					Hepatic		250		Microvacuolization
					Renal	250			
Dutertre-Catella 1976									

Table 2-1. Levels of Significant Exposure to Isophorone – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
19	Rabbit (NS) 2 M, 2 F	18 months 6 hours/day 5 days/week	0, 250	BW, GN, CS HP, UR	Death				No mortality
					Resp	250			
					Hemato	250			
					Hepatic		250		Microvacuolization
					Renal	250			
Dutertre-Catella 1976									

[a]The number corresponds to entries in Figure 2-2.

Bd Wt or BW = body weight; CNS = central nervous system; CS = clinical signs; Develop = developmental; DX = developmental toxicity; F = female(s); FI = food intake; FX = fetal toxicity; GD = gestation day; GN = gross necropsy; Hemato = hematological; HP = histopathology; LOAEL = lowest-observed-adverse-effect level; LC_{50} = lethal concentration, 50% kill; M = male(s); MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NR = not reported; NS = not specified; OW = organ weight; RD_{50} = exposure concentration producing 50% respiratory rate decrease; Resp = respiratory; UR = urinalysis

Figure 2-2. Levels of Significant Exposure to Isophorone – Inhalation
Acute (≤14 days)

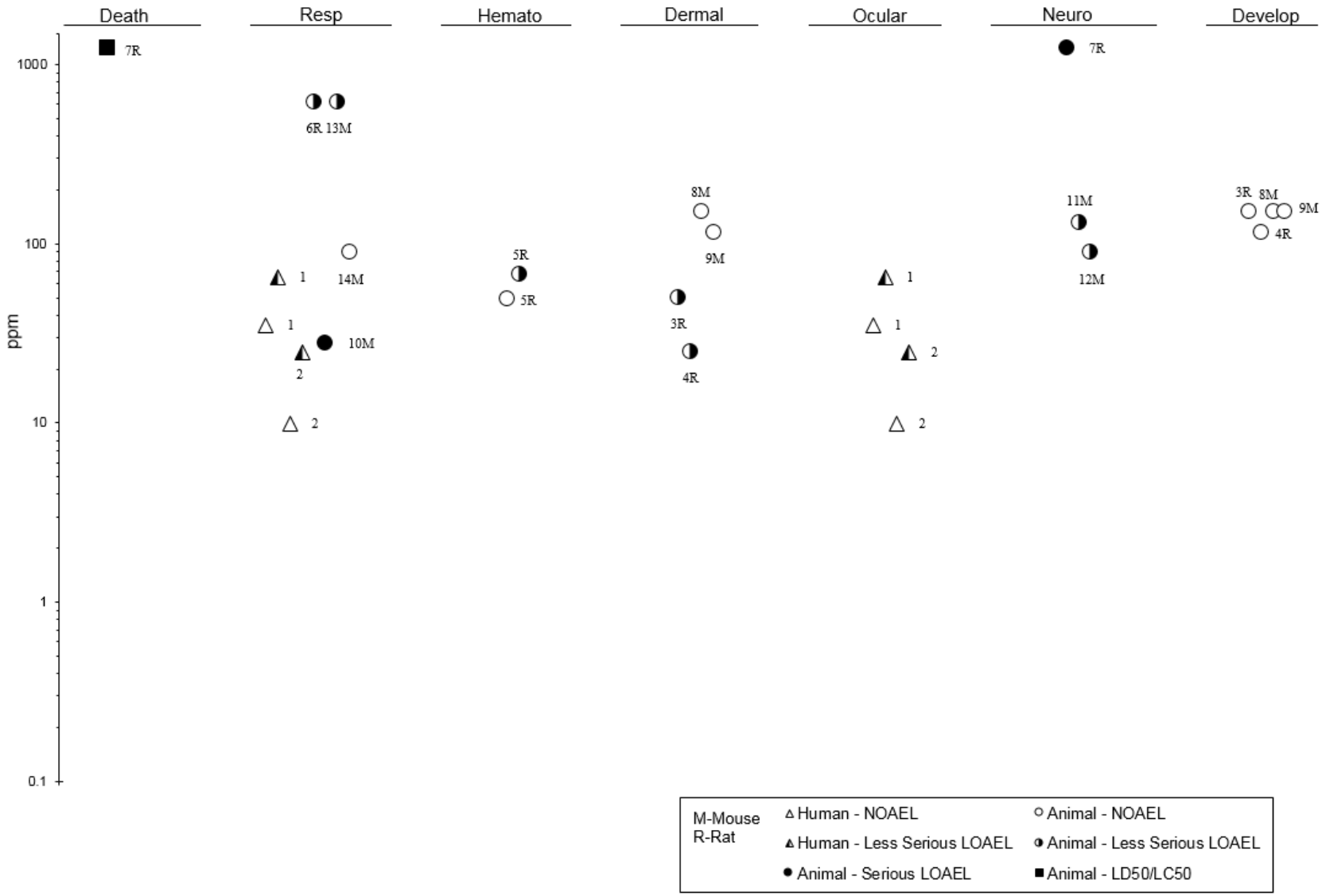


Figure 2-2. Levels of Significant Exposure to Isophorone – Inhalation
Intermediate (15-364)

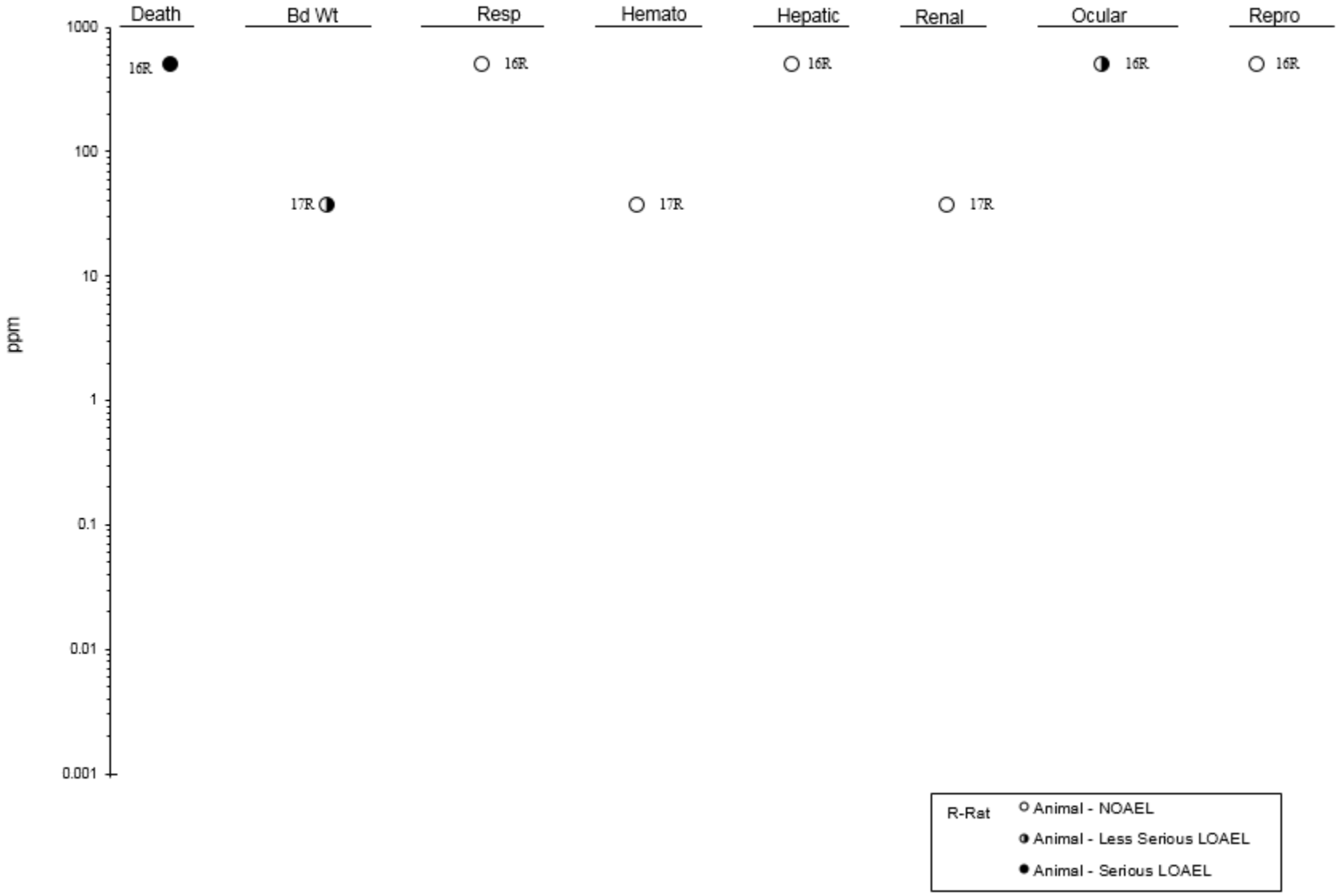


Figure 2-2. Levels of Significant Exposure to Isophorone – Inhalation
Chronic (≥365 days)

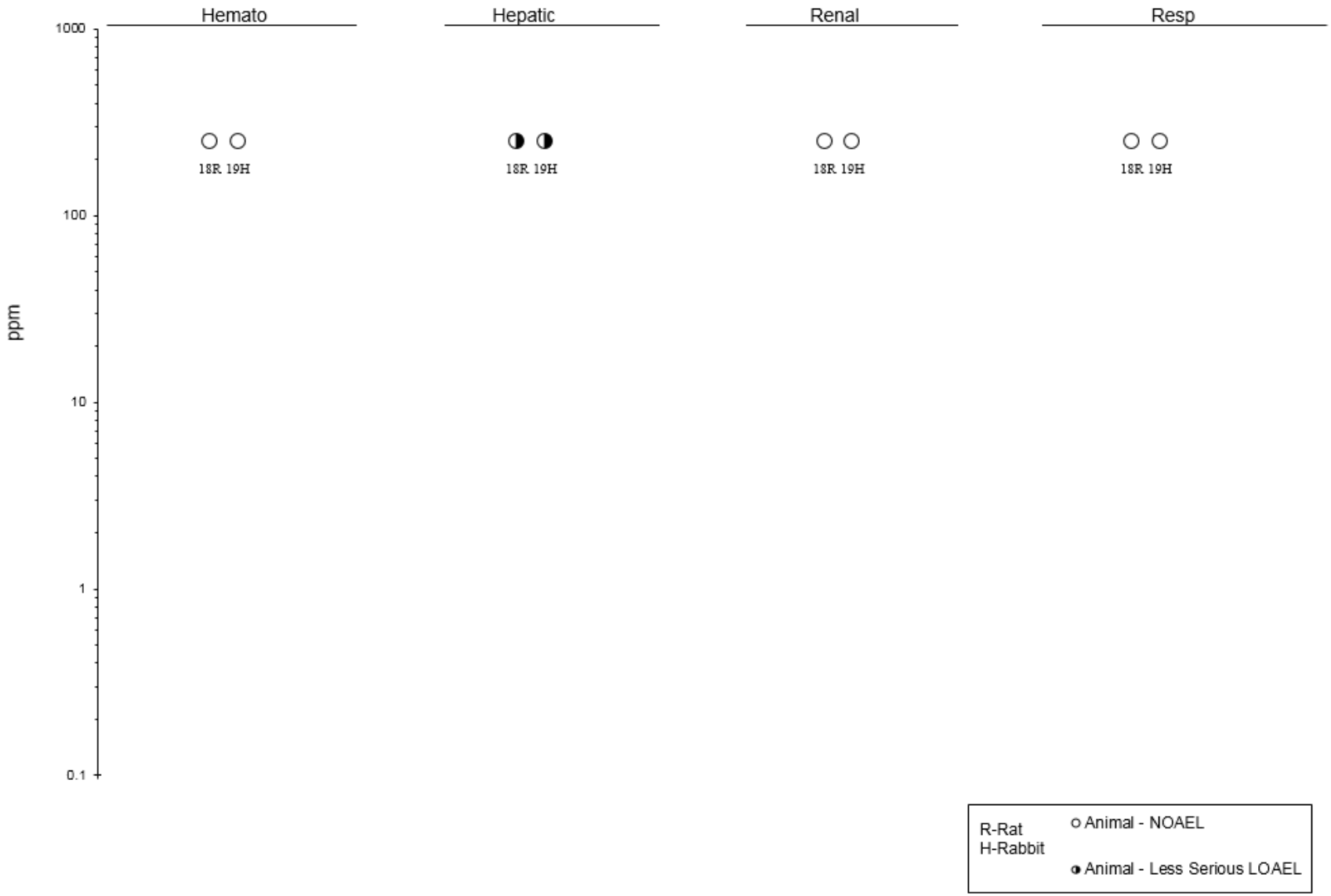


Table 2-2. Levels of Significant Exposure to Isophorone – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
ACUTE EXPOSURE									
1	Rat (NS) 5 M	Once (G)	34.6,120, 417,1,450, 5,000, 10,000	GN, CS, LE	Death			3,450	LD_{50}
					Neuro	417	1,450		CNS depression at 1,450 mg/kg/day;
Hazleton Labs 1964									
2	Rat (NS) F	Once (G)	NR	LE	Death			2,104–2,150	LD_{50}
Smyth et al. 1969, 1970									
3	Mouse (NS) 6 M	Once (G)	1,000, 1,500, 2,000, 2,500, 3,000, 4,000	CS, GN, HP	Death			2,200	LD_{50}
Dutertre-Catella 1976									
INTERMEDIATE EXPOSURE									
4	Rat (NS) 20 F	90 days (F)	0, 78.9, 163.8, 311.8	BW, OW, FI, GN, HP, BC, CS, UR,	Death				No mortality
					Resp	311.8			
					Cardio	311.8			
					Gastro	311.8			
					Hemato	311.8			
					Musc/Skel	311.8			
					Hepatic	311.8			
					Renal	311.8			
					Dermal	311.8			
					Immuno	311.8			

Table 2-2. Levels of Significant Exposure to Isophorone – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Repro	311.8			
					Other noncancer (unspecified)	311.8[b]			
AME Inc. 1972a									
5	Rat (F344/N) 5 M, 5 F	16 days 5 days/week (12 doses in 16 days) (G)	0, 125, 250, 500, 1,000, 2,000	BW, GN, HP, CS	Death			2,000	4/5 females and 1/5 males died
					Bd wt	500M 1,000F	1,000M 2,000F	2,000M	Decreased final mean body weight (males 1,000 mg/kg/day: 13.9%; males 2,000 mm/kg/day: 25.2%; females 2,000 mg/kg/day: 11.4%)
					Resp	2,000			
					Cardio	2,000			
					Gastro	2,000			
					Hemato	2,000			
					Musc/skel	2,000			
					Hepatic	2,000			
					Renal	2,000			
					Dermal	2,000			
					Endocr	2,000			
					Immuno	2,000			
					Neuro	2,000			
					Repro	2,000			
NTP 1986									

Table 2-2. Levels of Significant Exposure to Isophorone – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
6	Rat (F344/N) 10 M, 10 F	13 weeks 5 days/week (G)	0, 62.5, 125, 250, 500, 1,000	BW, GN, HP, CS	Death				1/10 females died
					Bd wt	1,000			
					Resp	1,000			
					Cardio	1,000			
					Gastro	1,000			
					Musc/skel	1,000			
					Hemato	1,000			
					Hepatic	1,000			
					Renal	1,000			
					Dermal	1,000			
					Endocr	1,000			
					Immuno	1,000			
					Neuro	500	1,000		Lethargy
					Repro	1,000			
NTP 1986									
7	Mouse (B6C3F1) 5 M, 5 F	16 days 5 days/week (12 doses in 16 days) (G)	0, 125, 250, 500, 1,000, 2,000	BW, GN, HP, CS	Death			2,000	100% mortality
					Bd wt	2,000			
					Resp	2,000			
					Cardio	2,000			
					Gastro	2,000			
					Musc/skel	2,000			
					Hemato	2,000			
					Hepatic	2,000			
					Renal	2,000			
					Dermal	2,000			
					Endocr	2,000			

Table 2-2. Levels of Significant Exposure to Isophorone – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Immuno	2,000			
					Neuro	500	1,000		Stagger
					Repro	2,000			
NTP 1986									
8	Mouse (B6C3F1) 10 M, 10 F	13 weeks 5 days/week (G)	0, 62.5, 125, 250, 500, 1,000	BW, GN, HP, CS	Death			1,000F	3/10 females died
					Bd wt	1,000			
					Resp	1,000			
					Cardio	1,000			
					Gastro	1,000			
					Musc/skel	1,000			
					Hemato	1,000			
					Hepatic	1,000			
					Renal	1,000			
					Dermal	1,000			
					Endocr	1,000			
					Immuno	1,000			
					Neuro	1,000			
					Repro	1,000			
NTP 1986									
9	Dog (NS) 4 M, 4 F	90 d (C)	0, 35,75, 150	OW, FI, GN, HP, BC, CS, UR	Resp	150			
					Cardio	150			
					Gastro	150			
					Hemato	150			
					Musc/Skel	150			
					Hepatic	150			
					Renal	150			

Table 2-2. Levels of Significant Exposure to Isophorone – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Dermal	150			
					Immuno	150			
					Repro	150			
AMC Inc. 1972b									
CHRONIC EXPOSURE									
10	Rat (F344/N) 50 M, 50 F	103 weeks 5 days/week (G)	0, 250, 500	BW, GN, HP, CS	Death			500M	36/50 males died compared to 17/50 controls
					Bd wt	500			
					Resp	500			
					Cardio	500			
					Gastro	500			
					Hemato	500			
					Musc/skel	500			
					Hepatic	500			
					Renal	500F	250M		Nephropathy due to alpha-2-microglobulin accumulation (not relevant to humans)
					Dermal	500			
					Endocr	500			
					Immuno	500			
					Neuro	500			
					Repro	500			
					Cancer	500F		500M	CEL: preputial gland tumors CEL: renal tumors due to alpha-2-microglobulin accumulation (not relevant to humans)
NTP 1986									

Table 2-2. Levels of Significant Exposure to Isophorone – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
11	Mouse (B6C3F1) 50 M, 50 F	103 weeks 5 days/week (G)	0, 250, 500	BW, GN, HP, CS	Death				No mortality
					Bd wt	500			
					Resp	500			
					Cardio	500			
					Gastro		250[c]		Hyperkeratosis
					Hemato	500			
					Musc/skel	500			
					Hepatic	500F	250M[c]		Necrosis
					Renal	500F	250M[c]		Inflammation
					Dermal	500			
					Endocr	500			
					Immuno	500			
					Neuro	500			
					Repro	500			
					Cancer	500F		250M 500M	CEL: lymphoma CEL: liver, integumentary system tumors

NTP 1986

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive the intermediate MRL of 3 mg/kg/day based on the NOAEL of 311.8 mg/kg/day and an uncertainty factor of 100 (10 for intraspecies variability, 10 for interspecies variability).
[c]Used to derive a chronic MRL of 0.2 mg/kg/day based on a duration-adjusted LOAEL of 179 mg/kg/day and an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation for intraspecies variability, 10 for interspecies variability).

BC = serum (blood) chemistry; Bd wt or BW = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Endocr = endocrine; F = female(s); (F) = feed; FI = food intake; (G) = gavage; Gastro = gastrointestinal; GN = gross necropsy; Hemato = hematological; HP = histopathology; Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; LD50 = lethal dose, 50% kill; LE = lethality; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; UR = urinalysis

Figure 2-3. Levels of Significant Exposure to Isophorone – Oral
Acute (≤14 days)

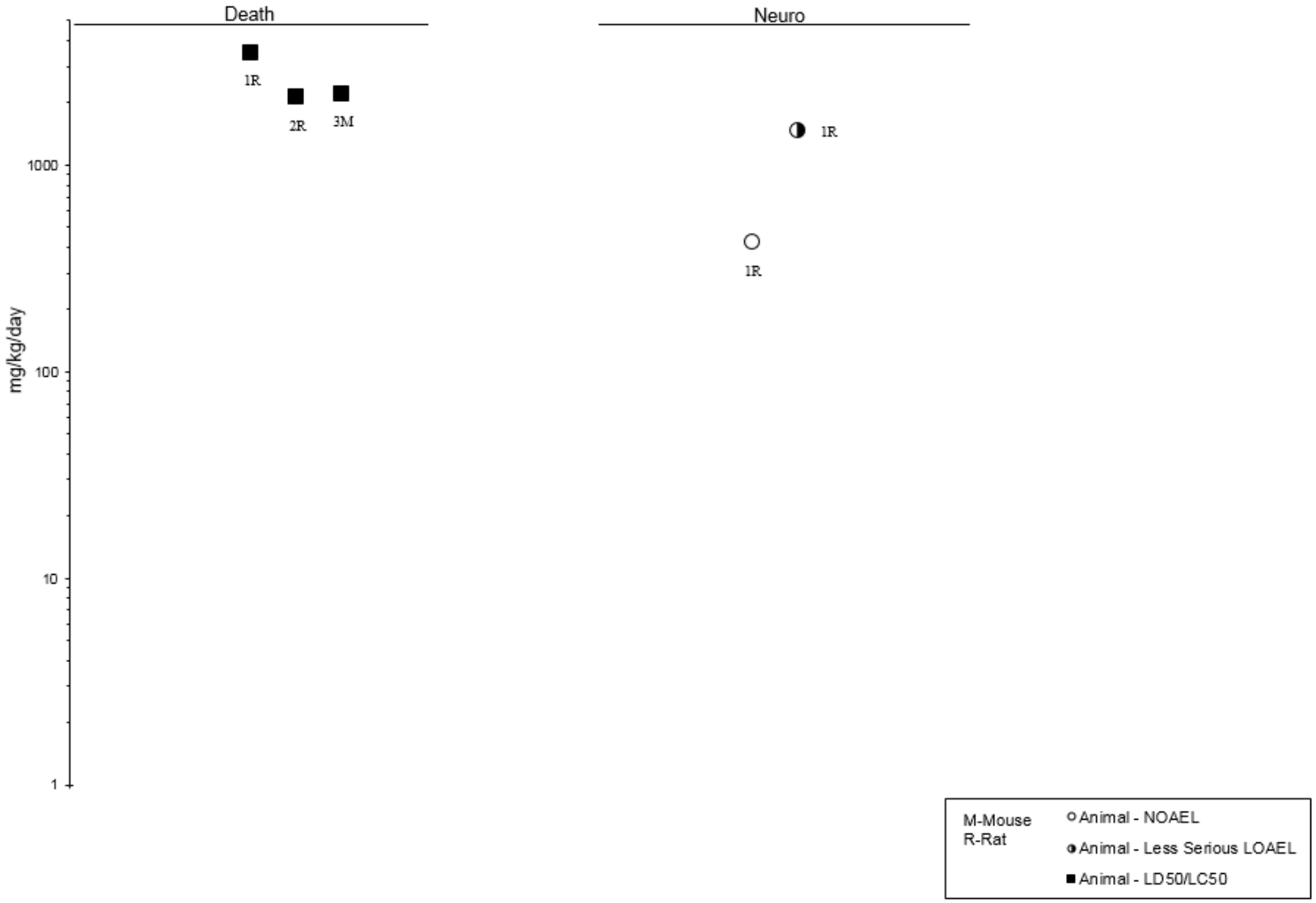


Figure 2-3. Levels of Significant Exposure to Isophorone – Oral
Intermediate (15-364)

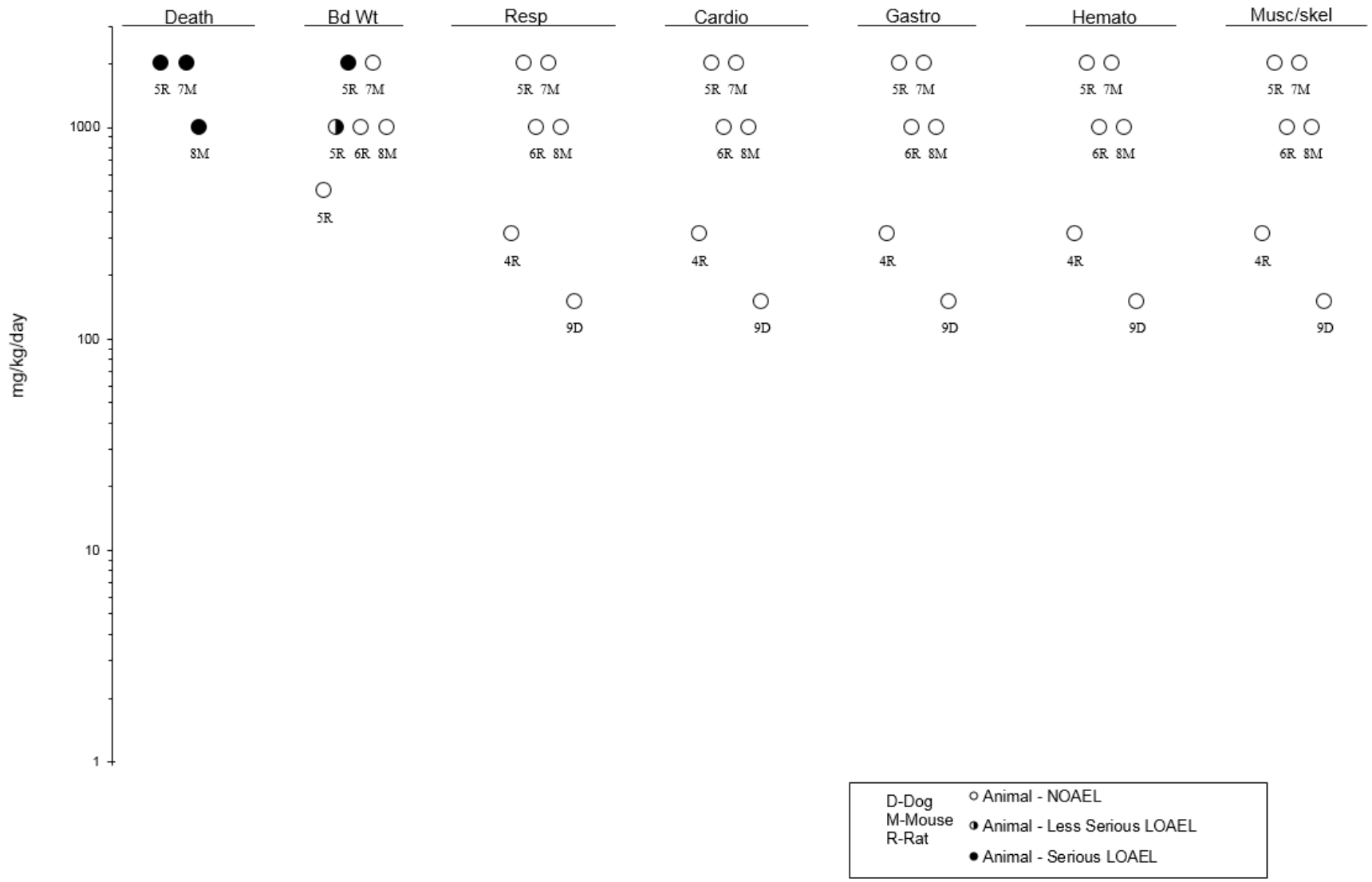


Figure 2-3. Levels of Significant Exposure to Isophorone – Oral
Intermediate (15-364)

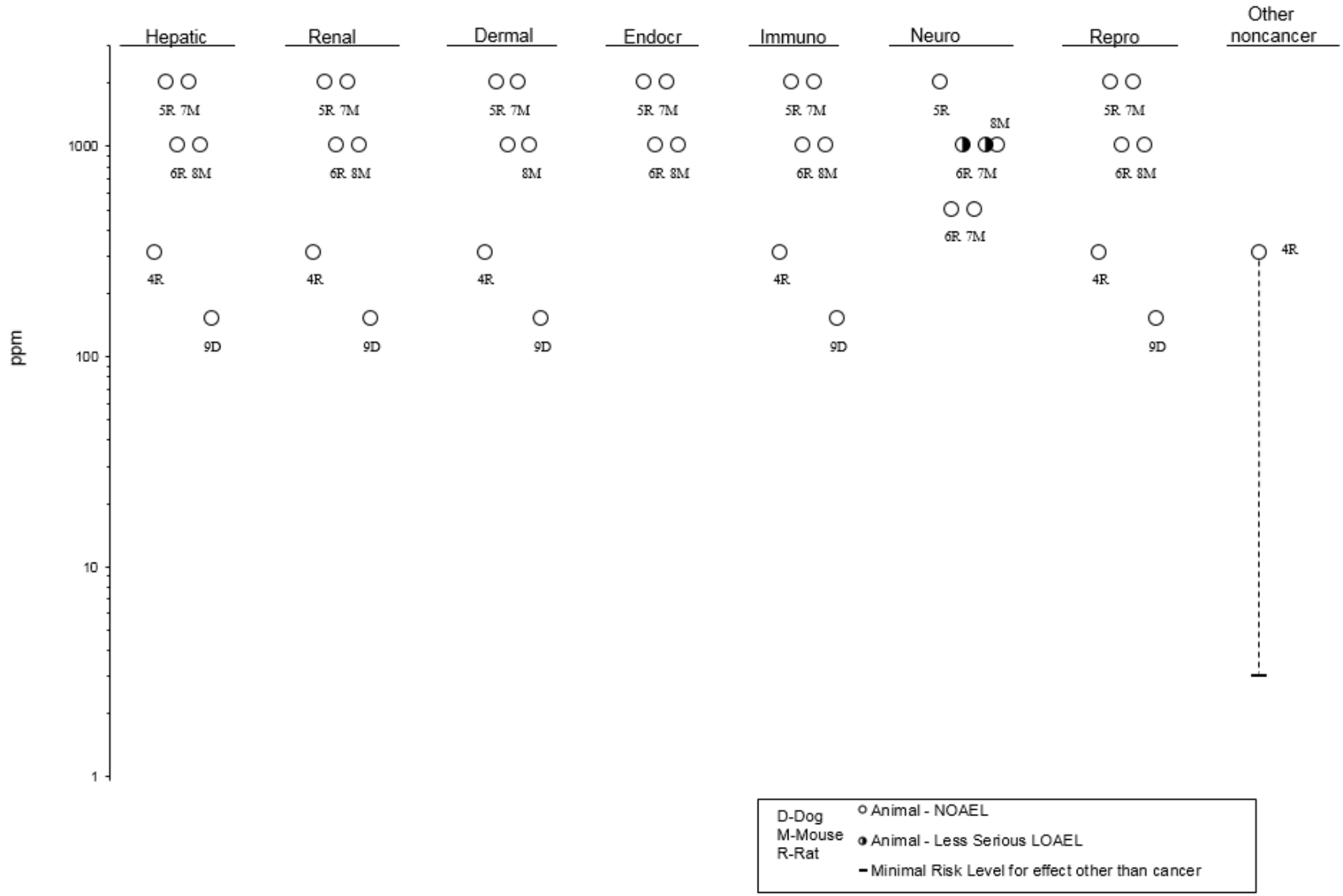


Figure 2-3. Levels of Significant Exposure to Isophorone – Oral

Chronic (≥365 days)

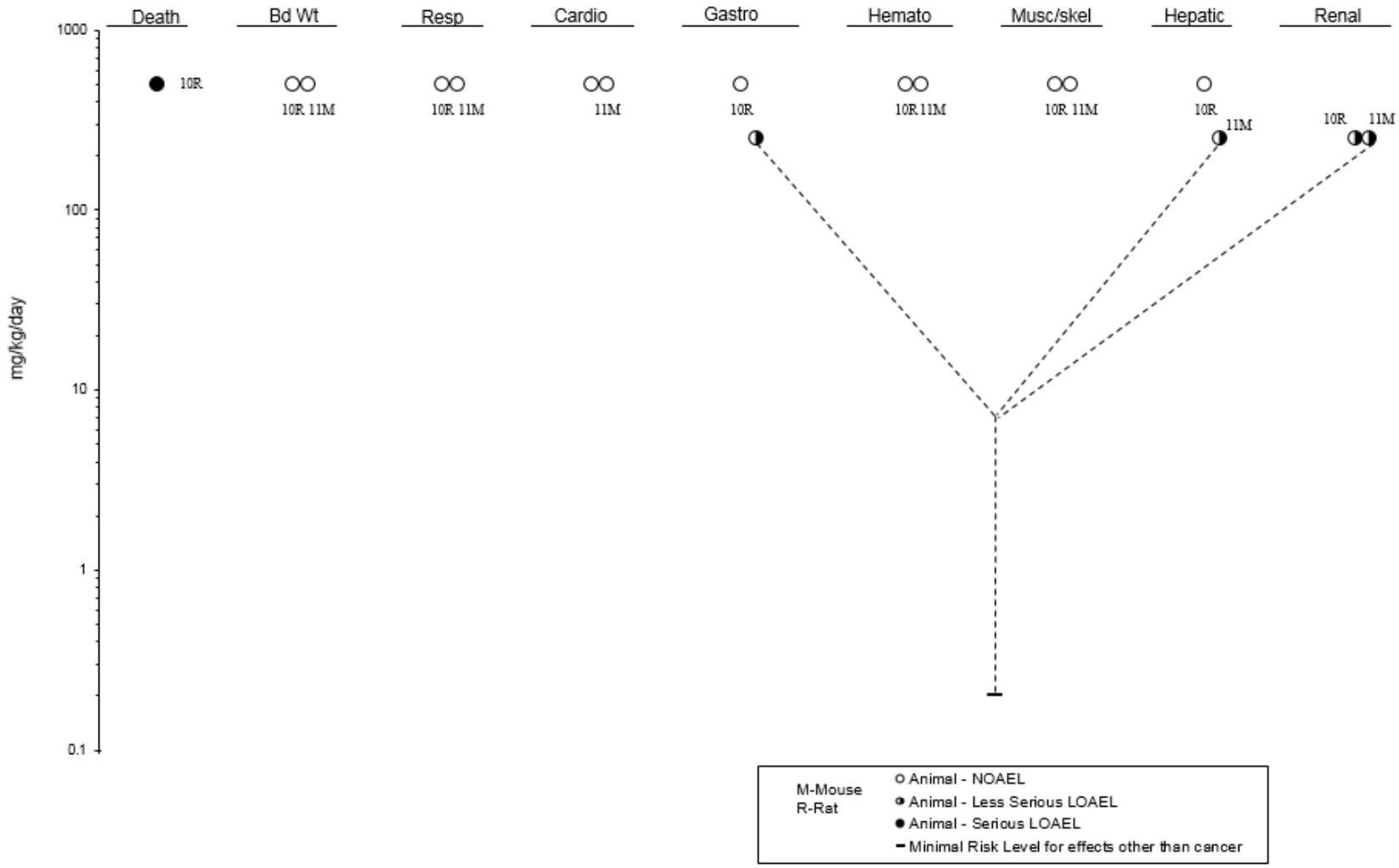


Figure 2-3. Levels of Significant Exposure to Isophorone – Oral

Chronic (≥365 days)

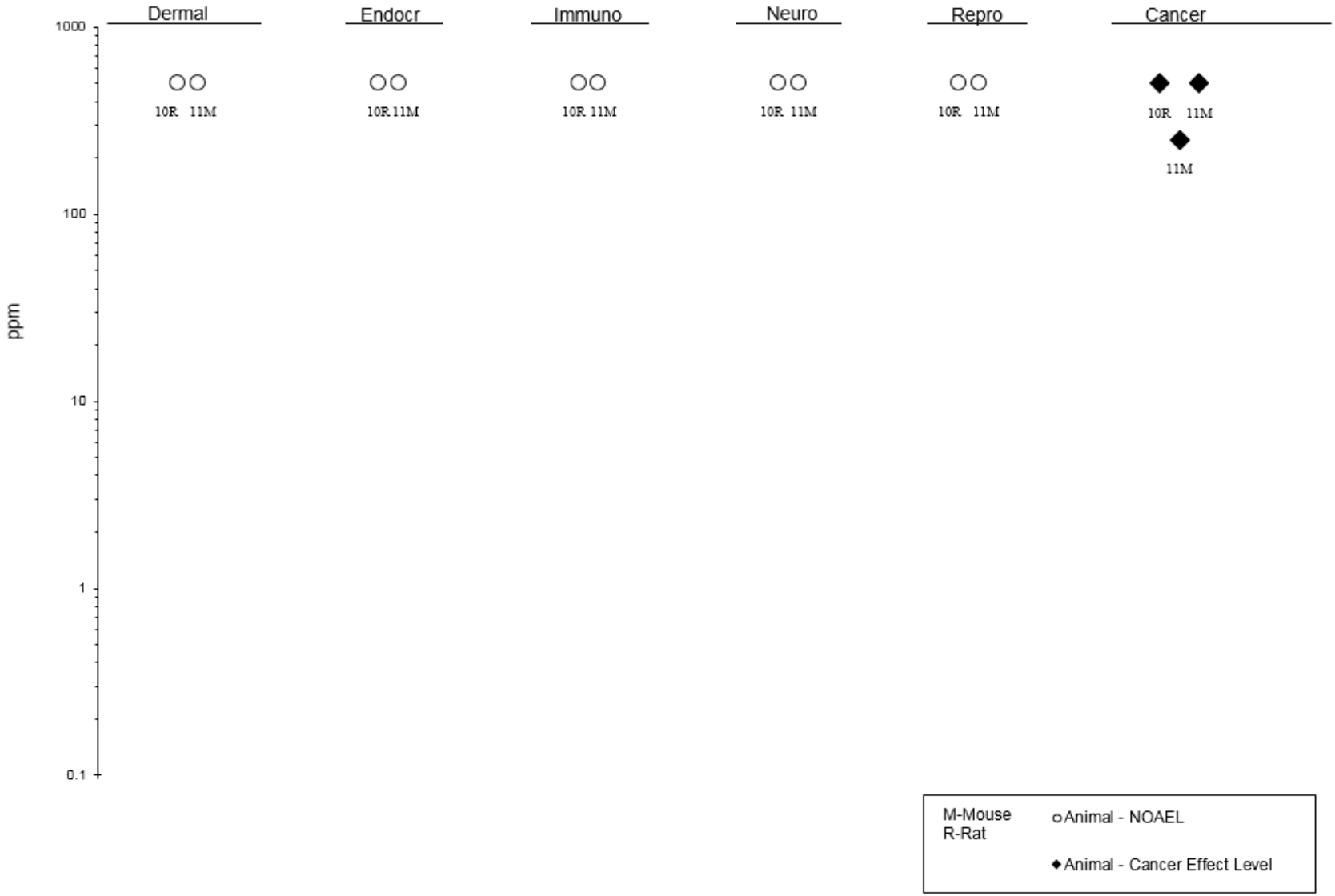


Table 2-3. Levels of Significant Exposure to Isophorone – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
ACUTE EXPOSURE								
Rabbit (NS) 5 NS	Once	0.02–0.1 mL	VI	Ocular			0.02 mL	Necrosis
Carpenter and Smyth 1946								
Rabbit (NS) 3 M, 3 F	Once	1,200 mg/kg	LE	Death			1,200 mg/kg	LD_{50}
Dutertre-Catella 1976								
Rabbit (NS) 6 NS	30 seconds	0.1 mL	CS	Ocular			0.1 ml	Corneal opacity
Hazleton Labs 1964								
Rabbit (NS) 4 NS	Once 24 hours	50, 200, 794, 3,160 mg/kg	CS	Dermal	50 mg/kg	200 mg/kg		Desquamation
				Neuro	794 mg/kg		3,160 mg/kg	Central nervous system depression in 1/4 rabbits
Hazleton Labs 1964								
Rabbit (NS) 6 NS	Once 1 or 4 hours	0.5 mL	VI	Dermal		0.5 mL		Irritation
Potokar et al. 1985								
Rabbit (NS) 6 NS	Once	0.1 mL	HP, VI	Ocular			0.1 mL	Eye injury
Truhaut et al. 1972								
Rabbit (NS) 6 NS	Once	0.5 mL	HP, VI	Dermal		0.5 mL		Irritation
Truhaut et al. 1972								

Table 2-3. Levels of Significant Exposure to Isophorone – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
Guinea pig (NS)	Once 24 hr	NR	VI	Dermal				Dose not specified; irritation
Eastman Kodak 1967								
INTERMEDIATE EXPOSURE								
Rat (NS) 10 M, 10 F	8 weeks 7 days/week	0, 0.1, 0.2 mL	HP, CS	Death			0.1 mL	20% of males died
				Dermal		0.1 mL		Erythema and scar tissue
Dutertre-Catella 1976								

CS = clinical signs; F = female(s); HP = histopathology; LD_{50} = lethal dose, 50 % kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-effect-level; NR = not reported; NS = not specified; VI = visual impairment

2.2 DEATH

In laboratory animals, death has been reported following acute inhalation, oral, and dermal exposure (Dutertre-Catella 1976; Hazelton Labs 1964, 1965a; Smyth et al. 1969, 1970). Hazelton Labs (1965a) reported a 4-hour LC_{50} value in rats of 1,238 ppm. No deaths occurred in rats, mice, or guinea pigs exposed to inhaled 619 ppm for 6 hours (Hazelton Labs 1964). Following gavage administration of single doses of isophorone, the range of LD_{50} values in rats was 2,104–3,450 mg/kg/day (Hazelton Labs 1964; Smyth et al. 1969, 1970). An LD_{50} value of 2,200 mg/kg/day was reported in mice (Dutertre-Catella 1976). Dutertre-Catella (1976) also reported a dermal LD_{50} value in rabbits of 1,200 mg/kg.

Repeated exposure to isophorone for intermediate durations resulted in death following inhalation, oral, and dermal exposure of rats (Dutertre-Catella 1976; NTP 1986) and inhalation exposure of mice (NTP 1986). Increased mortality was also reported in rats exposed chronically by gavage to isophorone (NTP 1986).

2.3 BODY WEIGHT

No information regarding effects of isophorone on body weight in humans was identified.

Results of studies in animals are equivocal regarding effects of isophorone on body weight. In the 4-week Hazleton Labs (1968) inhalation study, exposure of rats to 37 ppm resulted in statistically significant decreased body weight gain. The terminal body weight in rats was approximately 10% less than control rats. The NTP (1986) study in rats and mice evaluated body weight following gavage exposure to isophorone for 16 days, 90 days, and 103 weeks. In female rats exposed to 2,000 mg/kg/day for 16 days, terminal body weight was decreased by 11.4% compared to controls; in male rats exposed to 1,000 and 2,000 mg/kg/day, terminal body weight was reduced by 13.9 and 25.2%, respectively, compared to controls. For the 90-day exposure, no clear dose-related effects on body weight were observed in rats or mice. Over the course of the 103-week study in rats, mean body weights of males exposed to 500 mg/kg/day of isophorone were approximately 5% lower than those of the vehicle controls; however, the magnitude of effect is small and not considered to be toxicologically significant. No effects on body weight were observed in mice exposed for 103 weeks.

2.4 RESPIRATORY

Acute exposure of humans to inhaled isophorone is irritating to the respiratory tract. Human subjects reported nasal and throat irritation following a 15-minute exposure to 25 ppm, but not 10 ppm (Silverman

et al. 1946). Nasal irritation was also observed in subjects exposed to 65 ppm, but not 35 ppm, of isophorone for 7 minutes (Hazleton Labs 1965a). The same results were observed upon retesting 2 weeks later. Smyth and Seaton (1940) reported that exposure of humans for a few minutes to 40–400 ppm resulted in irritation of the nose and throat at all exposures; however, this study has been criticized for impure isophorone and overestimating the exposure concentrations (Rowe and Wolf 1963). Irritation of the respiratory tract has been observed in humans occupationally exposed to inhaled isophorone (Kominsky 1981; Lee and Frederick 1981). In an industrial hygiene survey, Kominsky (1981) reported that the nose irritation complained of by a screen printer could have been caused by 4-minute exposure to 25.7 ppm isophorone, which was measured in the personal breathing zone while the worker was washing a screen. Lee and Frederick (1981) reported respiratory irritation in 27/35 workers in a printing plant. Two of the workers (screen printers) were exposed to 8-hour time-weighted average (TWA) concentrations of isophorone of 0.7 and 14 ppm, but it was not clear whether these two individuals were among those who complained of respiratory irritation. In addition to isophorone, workers were exposed to other solvents (xylene, methylene chloride, and toluene).

Inhalation studies in animals show that isophorone produces adverse effects to the respiratory tract. DeCeaurriz et al. (1981a) reported that exposure to 27.8 ppm for 5 minutes caused a 50% decrease in the reflex respiratory rate of mice (RD_{50}), indicative of respiratory irritation. Slight lung congestion was observed in rats and mice sacrificed immediately after exposure to 619 ppm isophorone for 6 hours, but not in rats or mice sacrificed 14 days after the exposure; no control group was included (Hazleton Labs 1964). Hemorrhagic lungs with vascular dilation of the alveolar capillaries and peribronchial vessels were observed in rats and rabbits that died following a 5-hour exposure to 7,000 ppm (Dutertre-Catella 1976). No histopathological effects were observed in nasal, trachea, or lung tissues of mice exposed intermittently to 89 ppm for 4, 9, or 14 days (Zissu 1995).

Results of intermediate- and chronic-duration inhalation studies in animals are mixed. Severe lung injury consisting of congestion, necrosis, and degeneration was reported in rats and guinea pigs exposed intermittently to 100 ppm, but not to 25 ppm, isophorone for 6 weeks (Smyth et al. 1942). However, the isophorone used in this study contained several highly volatile impurities; thus, it is not possible to determine if these respiratory effects were due to exposure to isophorone, other chemicals, or a mixture of chemicals (Rowe and Wolf 1963). No treatment-related histopathological lesions were observed in the lungs of rats exposed intermittently to 37 ppm for 4 weeks (Hazleton Labs 1968), rats exposed to 500 ppm isophorone for up to 6 months (Dutertre-Catella 1976), or rats and rabbits exposed to 250 ppm for 18 months (Dutertre-Catella 1976).

Intermediate and chronic oral exposure of rats, mice, and dogs to isophorone showed no adverse effects to the respiratory tract (AME Inc. 1972a, 1972b; NTP 1986). For intermediate exposure, the highest doses tested in rats and mice were 2,000 mg/kg/day for 16 days and 1,000 mg/kg/day for 90 days (NTP 1986), and 150 mg/kg/day for dogs (AME Inc. 1972b). The highest dose tested for chronic exposure was 500 mg/kg/day for rats and mice (NTP 1986).

The mechanisms by which isophorone produces respiratory damage has not been established. Recent *in vitro* investigations by Lehmann et al. (2016a, 2016b) indicate that the respiratory irritant effects of isophorone may be due to agonist activity of isophorone of the transient receptor potential (TRP) ion channels, specifically TRPV1 channels. It has also been proposed that isophorone may also produce irritation by reacting with thiol groups in sensory receptors in the respiratory tract (Nielen 1991).

2.5 CARDIOVASCULAR

No information on cardiovascular effects of humans exposed to isophorone was identified.

No abnormal histopathological findings to cardiovascular tissues were observed following intermediate and chronic oral exposure of animals to isophorone (AME Inc. 1972a, 1972b; NTP 1986). For intermediate exposure, the highest doses tested in rats and mice were 2,000 mg/kg/day for 16 days and 1,000 mg/kg/day for 90 days (NTP 1986), and 150 mg/kg/day for dogs (AME Inc. 1972b). The highest dose tested for chronic exposure was 500 mg/kg/day for rats and mice (NTP 1986).

2.6 GASTROINTESTINAL

No information on gastrointestinal effects of humans exposed to isophorone was identified.

No gross or histopathological lesions of the gastrointestinal tract were observed following oral exposure to isophorone to rats and mice to 2,000 mg/kg/day for 16 days, or rats, mice, and dogs for 3 months at doses up to 1,000, 1,000, and 150 mg/kg/day, respectively (AME Inc. 1972b; NTP 1986). Gavage administration of isophorone for 103 weeks produced hyperkeratosis of the forestomach in male and female mice (NTP 1986). Incidences of hyperkeratosis in the control, 250 and 500 mg/kg/day groups were 0/47, 5/49, and 4/49, respectively, for male mice and 1/50, 0/50 and 5/50, respectively, for female mice. No stomach lesions were observed in male or female rats at doses up to 500 mg/kg/day for 103 weeks.

2.7 HEMATOLOGICAL

No studies were located regarding hematological effects in humans following exposure to isophorone.

An acute inhalation exposure study found significant decreases in white blood cell count, although no hematological effects were observed following intermediate- and chronic-duration inhalation and oral studies. In rats exposed to 67 and 90 ppm isophorone for 4 hours, total leukocyte count was decreased by approximately 43 and 40%, respectively, compared to controls (Brondeau et al. 1990). No effects on leukocyte count were observed in rats exposed to 19 or 49 ppm for 4 hours. No additional acute exposure studies examining hematological effects were located. In contrast, results of intermediate- and chronic-duration inhalation and oral studies show no effects of isophorone on hematological parameters (AME Inc. 1972b; Dutertre-Catella 1976; Hazleton Labs 1968; NTP 1986). Available inhalation studies examined one exposure level: 37 ppm for 4 weeks in rats (Hazleton Labs 1968) and 250 ppm for 18 months in rats and rabbits (Dutertre-Catella 1976). For oral studies, the highest doses tested for intermediate-duration exposure were 2,000 mg/kg/day for 16 days in rats and mice (NTP 1986), 1,000 mg/kg/day for 13 weeks in rats and mice (NTP 1986), and 150 mg/kg/day for 90 days in dogs (AME Inc. 1972b); in chronic-duration studies, the highest dose tested was 500 mg/kg/day in rats and mice for 103 weeks (NTP 1986)

2.8 MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects in humans following exposure to isophorone.

Potential musculoskeletal effects of exposure isophorone in laboratory animals have not been well studied. No musculoskeletal effects were observed on gross examination of rats exposed to oral isophorone at a dose of 311.8 mg/kg/day or dogs exposed to 150 mg/kg/day for 90 days (AME Inc. 1972a, 1972b). The NTP (1986) intermediate- and chronic-duration oral studies in rats and mice did not identify any histopathological effects to musculoskeletal tissues.

2.9 HEPATIC

No studies were located regarding hepatic effects in humans following exposure to isophorone.

Little information is available regarding the hepatotoxic effects of acute exposure to isophorone. No differences between pre-exposure and post-exposure levels of serum liver enzymes (aspartate aminotransferase, alanine aminotransferase, creatine phosphokinase, or lactic dehydrogenase) were found in rabbits treated by gavage with isophorone at a dose of 1,000 mg/kg/day, 2 days/week for 2 weeks (Dutertre-Catella 1976). However, no gross or histopathological examinations of the liver were conducted. No other studies were located regarding hepatic effects in animals following acute exposure to isophorone.

Intermediate-duration inhalation and oral studies did not observe hepatic effects in rats, mice, or dogs (AME Inc. 1972a, 1972b; Dutertre-Carella 1976; NTP 1986). The inhalation study in rats evaluated an exposure level of 500 ppm for 4–6 months (Dutertre-Carella 1976). The highest doses tested in oral studies were 2,000 mg/kg/day for 16 days in rats and mice (NTP 1986), 1,000 mg/kg/day for 13 weeks in rats and mice (NTP 1986), and 150 mg/kg/day in dogs for 90 days (AME Inc. 1972b).

Information on hepatic effects of chronic exposure to isophorone is available from inhalation studies in rats and rabbits and oral studies in rats and mice (Dutertre-Carella 1976; NTP 1986). Results of an inhalation study showed microvacuolization of hepatocytes in rats and rabbits exposed to 250 ppm isophorone (only exposure level tested) for 18 months (Dutertre-Catella 1976). Conflicting results were observed in the chronic gavage study in rats and mice (NTP 1986). No hepatotoxicity was observed in rats administered doses of 500 mg/kg/day for 103 weeks. In contrast, hepatocytomegaly was observed in male mice administered 250 and 500 mg/kg/day and coagulative necrosis was observed in male mice administered 500 mg/kg/day. The incidences of hepatocytomegaly in male mice in the control, 250, and 500 mg/kg/day groups were 23/48 (48%), 39/50 (78%), and 37/50 (74%), respectively; for coagulative necrosis, incidences were 3/42 (6%), 2/49 (4%), and 10/48 (20%), respectively. In male mice, increased incidences of hepatocellular adenomas and carcinomas were also observed (see Section 2.19, Cancer). No treatment-related liver lesions were observed in female mice administered up to 500 mg/kg/day.

2.10 RENAL

No studies were located regarding renal effects in humans following exposure to isophorone.

Acute exposure studies in laboratory animals did not examine renal function or conduct gross or histopathological examinations of the kidneys. Smyth et al. (1942) found severe kidney damage, consisting of congestion, necrosis, and degeneration, in rats and guinea pigs exposed intermittently to

100 ppm isophorone for 6 weeks. However, the isophorone used in this study contained several highly volatile impurities; thus, it is not possible to determine if these renal effects were due to exposure to isophorone, other chemicals, or a mixture of chemicals (Rowe and Wolf 1963). Other intermediate-duration inhalation and oral studies did not find adverse renal effects. No treatment-related renal effects were observed in rats exposed to 37 ppm for 4 weeks (Hazleton Labs 1968). No gross or histopathological lesions were observed in kidneys of rats and mice treated with up to 2,000 mg/kg/day for 16 days or with up to 1,000 mg/kg/day for 90 days by gavage (NTP 1986), rats fed diets containing isophorone at daily doses up to 311.8 mg/kg/day (AME Inc. 1972a), or dogs administered isophorone in gelatin capsules at doses up to 150 mg/kg/day for 90 days (AME Inc. 1972b).

No renal effects were observed following inhalation to 250 ppm isophorone for 18 months in rats or rabbits (Dutertre-Catella 1976). However, the kidney appears to be a target organ for chronic oral exposure to isophorone in male mice. In the NTP (1986) 103-week gavage study, male mice, but not female mice, had increased incidences of chronic focal inflammation of the kidney, but no other renal lesions. Incidences of renal inflammation in male mice in the control, 250, and 500 mg/kg/day groups were 7/48 (15%), 18/50 (36%), and 21/50 (42%), respectively. In male rats, but not female rats, tubular cell hyperplasia, epithelial cell hyperplasia of the renal pelvis, and tubular mineralization were observed at 250 and 500 mg/kg/day (NTP 1986). Incidences of tubular mineralization in male rats in the control, 250, and 500 mg/kg/day groups were 1/50 (2%), 31/50 (62%), and 20/50 (40%), respectively. Although the NTP (1986) study did not detect protein droplet formation in the kidneys of rats or mice treated with isophorone (Bucher 1988), protein droplets were found in the kidneys of male rats exposed by inhalation to dihydroisophorone (Hazleton Labs 1968), a metabolite of isophorone. Furthermore, Strasser (1988) found that isophorone and its metabolites, dihydroisophorone and isophorol, induced significant protein droplet formation in the kidneys of male rats treated acutely by gavage. Isophorone also was identified in cytosol of kidney cells in rats treated with isophorone. Following treatment with isophorol, isophorone was found in the alpha 2μ-globulin, indicating that isophorol was metabolized to isophorone. In male NCI-Black-Reiter rats, the only rat strain that does not synthesize alpha 2μ-globulin, gavage administration of 1,000 mg/kg/day of isophorone for 4 consecutive days did not induce renal damage (Dietrich and Swenberg 1991). Thus, it appears that isophorone and its metabolites bind to alpha 2μ-globulin and induce protein droplet nephropathy in male rats. This effect is unique to male rats and is not toxicologically relevant to human health (EPA 1991; Swenberg 1993).

2.11 DERMAL

Very little information on dermal effects of isophorone exists in humans. Lee and Frederick (1981) reported that skin irritation was among the complaints of 27/35 workers in a printing plant where isophorone and other solvents (xylene, methylene chloride, and toluene) were used. The 8-hour TWA for isophorone for two screen printers were 0.7 and 14 ppm. However, it was not clear whether these two individuals were among the workers complaining of skin irritation.

In gestational exposure studies in rats, concentration-related alopecia was observed in dams at all isophorone concentrations tested (25–150 ppm) (Bio/dynamics 1984a, 1984b). This effect was not observed in mice under that same exposure conditions.

Skin irritation was observed in rabbits and guinea pigs following dermal application of isophorone (Eastman Kodak 1967; Hazleton Labs 1964; Potokar et al. 1985; Truhaut et al. 1972). In these studies, undiluted isophorone was applied to the clipped skin of the animals and held under an occlusive covering. Hazleton Labs (1964) reported doses of ≥200 mg/kg resulted in desquamation and erythema, while 50 mg/kg was without effect.

Application of 0.1 or 0.2 mL isophorone to the shaved skin of rats for 8 weeks resulted in erythema and scar tissue formation (Dutertre-Catella 1976). These effects disappeared rapidly after exposure ceased. The Smyth et al. (1942) inhalation study reported skin irritation in rats and guinea pigs exposed to 100 ppm isophorone for 6 weeks; however, as discussed above, exposure estimates for this study are not considered reliable and impure isophorone was used (Rowe and Wolf 1963).

No adverse dermal effects were observed in animals exposed to oral isophorone for intermediate and chronic durations (AME Inc. 1972a, 1972b; NTP 1986). For intermediate-duration oral exposures, the highest doses tested were 1,000 mg/kg/day for rats and mice (NTP 1986) and 150 mg/kg/day for dogs (AME Inc. 1972b). For chronic exposures, the highest dose tested in rats and mice was 500 mg/kg/day (NTP 1986).

2.12 OCULAR

Ocular irritation has been reported in humans exposed to isophorone in air (Hazleton Labs 1965b: Silverman et al. 1946). Eye irritation was observed in subjects exposed to 25 ppm for 15 minutes, but not to 10 ppm, for 15 minutes (Silverman et al. 1946). Hazleton Labs (1965b) reported eye irritation in

subjects exposed to 65 ppm, but not to 16 or 35 ppm, for 7 minutes. The same results were observed when the exposures were repeated 2 weeks later. Smyth and Seaton (1940) reported that exposure of humans for a few minutes to 40–400 ppm resulted in eye irritation at all exposures; however, this study has been criticized for impure isophorone and overestimating the exposure concentrations (Rowe and Wolf 1963). In an industrial hygiene survey, Kominsky (1981) reported that the eye irritation a screen printer reported could have been caused by a 4-minute exposure to 25.7 ppm isophorone, which was measured in the personal breathing zone while the worker was washing a screen.

Isophorone also produces ocular damage in animals. Ocular application of 0.1 mL of isophorone to the eyes of rabbits has been reported to cause irritation, corneal opacity, and "eye damage" (Carpenter and Smyth 1946; Hazleton Labs 1964; Truhaut 1972). Smyth et al. (1942) reported conjunctivitis in rats and guinea pigs exposed to 100 ppm isophorone; however, as discussed above, exposures in this study are not considered reliable (Rowe and Wolf 1963). Eye irritation was observed in rats exposed to 500 ppm isophorone in air for up to 6 months and rats and rabbits exposed to 250 ppm for 18 months (Dutertre-Catella 1976).

No adverse ocular effects were observed in animals exposed to oral isophorone for intermediate and chronic durations (AME Inc. 1972a, 1972b; NTP 1986). For intermediate-duration oral exposures, the highest doses tested were 2,000 mg/kg/day for 16 days and 1,000 mg/kg/day for 90 days in rats and mice (NTP 1986) and 150 mg/kg/day for dogs (AME Inc. 1972b). For chronic exposures, the highest dose tested in rats and mice was 500 mg/kg/day (NTP 1986).

2.13 ENDOCRINE

No information regarding immune effects of humans exposed to isophorone was identified.

Based on gross and histopathological examinations of endocrine organs and tissues, no endocrine effects were observed in rats or mice treated by gavage with isophorone for 13 (up to 1,000 mg/kg/day) or 103 weeks (up to 500 mg/kg/day) (NTP 1986), in rats treated with isophorone in the diet for 13 weeks (up to 311.8 mg/kg/day) (AME Inc. 1972a), or in dogs treated with isophorone in gelatin capsules for 13 weeks (up to 150 mg/kg/day) (AME Inc. 1972b).

2.14 IMMUNOLOGICAL

No information regarding immune effects of humans exposed to isophorone was identified.

No studies examining the effects of isophorone on immune system function were identified. Histological examination of immune system organs and tissues did not reveal any effects in rats or mice treated by gavage with isophorone for 16 days (up to 2,000 mg/kg/day), 13 weeks (up to 1,000 mg/kg/day), or 103 weeks (up to 500 mg/kg/day) (NTP 1986), in rats treated with isophorone in the diet for 13 weeks (up to 311.8 mg/kg/day) (AME Inc. 1972a), or in dogs treated with isophorone in gelatin capsules for 13 weeks (up to 150 mg/kg/day) (AME Inc. 1972b). However, none of these studies conducted were specific tests of immune function.

2.15 NEUROLOGICAL

Occupational exposure to inhaled isophorone adversely affects the nervous system. In an industrial hygiene survey report, Lee and Frederick (1981) attributed complaints of dizziness by workers to exposure to isophorone and other solvents (xylene, toluene, methylene chloride). However, data are difficult to interpret due to exposure to a mixture of solvents. In a communication to the American Conference of Governmental Industrial Hygienists (ACGIH 2001), Ware (1973) reported that employees exposed for 1 month to 5–8 ppm isophorone complained of fatigue and malaise. Complaints stopped when workroom exposure levels of isophorone were lowered to 1–4 ppm.

Neurological effects of isophorone have been reported in animals following inhalation, oral, and dermal exposure. Inhalation studies provide evidence of neurotoxicity following acute exposure of rats to isophorone. DeCeaurriz et al. (1984) found dose-related neurobehavioral effects (decreased immobility in a behavioral despair swimming test) in mice exposed for 4 hours. The lowest concentration resulting in the behavioral effects was 89 ppm (the lowest dose tested in this study), a less serious LOAEL. DeCeaurriz et al. (1981b) also reported that inhalation of isophorone for 4 hours by mice increased the threshold for onset of seizures produced by intravenous administration of pentrazole, indicating that isophorone depressed the central nervous system. The concentration of isophorone that resulted in a 50% increase in the seizure threshold (STI_{50}) was 131 ppm with 95% confidence intervals of 113–145 ppm. At the 4-hour LC_{50} of 1,238 ppm and higher, rats were ataxic and comatose during exposure, after which they displayed CNS depression and inactivity (Hazleton Labs 1965a). These overt signs of neurotoxicity were not observed at 885 ppm. Rats and rabbits that were exposed to isophorone for 5 hours at concentrations up to 7,000 ppm became comatose and died (Dutertre-Catella 1976). However, there is uncertainty regarding exposure values, as the study report noted that a considerable amount of isophorone was present in the exposure atmosphere as an aerosol rather than as a vapor. Narcosis and ataxia occurred

in rats and guinea pigs at high exposure concentrations for 6–24 hours (Smyth and Seaton 1940), but Rowe and Wolf (1963) noted that this study used impure isophorone and overestimated the concentrations.

Neurological effects of isophorone have been observed in animals after acute and intermediate-duration oral exposure. In an acute study, rats treated by gavage with isophorone at 5,000 mg/kg displayed CNS depression, ptosis, absence of righting reflex, and prostration; 4/5 died within 2 days after dosing (Hazleton Labs 1964). At 1,450 mg/kg, CNS depression was observed, but the rats recovered within 2 days. No signs of neurotoxicity occurred at 417 mg/kg. In rats administered isophorone by gavage at doses of 125–2,000 mg/kg/day for 16 days, all rats were lethargic after dosing (NTP 1986). The study report did not indicate if lethargy also occurred in control rats or only rats administered isophorone (NTP 1986); no information on incidence or dose-related severity was reported. Thus, it is not possible to determine if this effect is toxicologically significant. In the 13-week NTP (1986) study, rats given 1,000 mg/kg/day, but not 500 mg/kg/day, were sluggish and lethargic after dosing, also indicating an initial response to the high dose. Based on this information, it is unlikely that the lethargy observed in rats treated for 16 days at doses <500 mg/kg/day was related to isophorone exposure. In the 16-day NTP (1986) study, mice treated by gavage at 1,000 mg/kg/day, but not at 500 mg/kg/day, staggered after dosing, indicating an acute response to the high dose. No effects were noted in the rats or mice exposed to up to 500 mg/kg/day for 103 weeks (NTP 1986).

In the study by Hazleton Labs (1964), l/4 rabbits exposed dermally to 3,160 mg/kg under an occlusive bandage for 24 hours displayed marked CNS depression, labored respiration, sprawling, and depressed reflexes. The other three rabbits at this dosage and at ≤794 mg/kg did not display any signs of toxicity.

The mechanism by which isophorone induces neurotoxicity have not been established. However, neurological effects may involve interference with neuronal impulse transmissions via physical interaction of isophorone with nerve membrane components, as is seen with many organic solvents.

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans following exposure to isophorone.

Reproductive effects of isophorone in animal studies have not been well-studied. No differences in pregnancy rate or litter size were observed in rats exposed to isophorone in air at 500 ppm for 3 months

before mating (Dutertre-Catella 1976). In animals exposed to oral isophorone for intermediate or chronic durations, gross and histological examination of reproductive organs did not reveal any effects (AME Inc. 1972a, 1972b; NTP 1986). For intermediate-duration oral exposures, the highest doses tested in rats and mice were 2,000 mg/kg/day for 16 days and 1,000 mg/kg/day for 90 days (NTP 1986); in dogs, the highest dose tested was 150 mg/kg/day for 90 days (AME Inc. 1972b). For chronic exposures, the highest dose tested in rats and mice was 500 mg/kg/day (NTP 1986).

2.17 DEVELOPMENTAL

No studies were located regarding developmental effects in humans following exposure to isophorone.

Developmental effects of inhalation exposure to isophorone in animals have been evaluated in a few studies (Bio/dynamics 1984a, 1984b; Dutertre-Catella 1976). However, examinations of comprehensive developmental endpoints were not conducted, and/or interpretation of study results is complicated by inadequate exploration of exposure-response relationships. No studies were located regarding developmental effects of oral or dermal exposure of animals to isophorone.

As part of an intermediate duration inhalation study in which rats were exposed to 500 ppm isophorone, Dutertre-Catella (1976) mated exposed males with exposed females, control males with exposed females, exposed males with control females, and control males with control females after 3 months of exposure. Exposure of females continued throughout gestation, and they were allowed to deliver. No external abnormalities were observed in pups, but internal and skeletal malformations were not examined; therefore, this study was inadequate to determine developmental effects of isophorone.

Possible developmental effects were evaluated in a pilot developmental toxicity study, in which pregnant rats and mice were exposed by inhalation to isophorone at concentrations up to 150 ppm on days 6–15 of gestation (Bio/dynamics 1984a). No statistically significant fetal effects were observed at concentrations up to 150 ppm, although in the 150 ppm group, exencephaly was observed in one late resorption of one litter of rats, in one late resorption of one litter of mice, and in two live fetuses in another litter of mice. Dose-related mild maternal toxicity (clinical signs) occurred at all concentrations (≥50 ppm) in rats, but there was no clear indication of maternal toxicity in mice.

A second, more complete developmental toxicity study was also performed in rats and mice (Bio/dynamics 1984b). No fetal effects were observed on a per-litter basis. A reduction in mean crown-

rump length was observed among rat fetuses in the group exposed to 115 ppm; however, this effect was not observed on a per-litter basis. In rats, concentration-related maternal toxicity (alopecia) was seen at all concentrations (≥25 ppm). In addition, rat dams exposed to 115 ppm had lower body weights than controls on some days. No other indications of maternal toxicity were noted. In mice, the only effect noted was that mean body weight of dams exposed to 115 ppm isophorone was decreased during one day of the treatment period, with no effects observed in fetuses. Bio/dynamics (1984b) concluded that isophorone did not produce developmental effects at concentrations up to 115 ppm.

2.19 CANCER

No studies evaluating cancer on humans exposed to isophorone were located.

The chronic gavage study by NTP (1986) provides some evidence of isophorone-induced carcinogenicity in male rats and mice. In male rats, an increased incidence of relatively rare renal tubular cell adenomas and adenocarcinomas at 250 and 500 mg/kg/day and rare preputial gland carcinomas at 500 mg/kg/day were observed. The renal tumors in male rats are most likely due to renal accumulation of alpha 2μ-globulin and induction of protein droplet nephropathy (see discussion in Section 2.10). This effect is unique to male rats and is not toxicologically relevant to human health (EPA 1991; Swenberg 1993). Based on the increased incidence of rare preputial gland carcinomas in 5/50 male rats administered 500 mg/kg/day, NTP (1986) concluded that there is "some evidence of carcinogenicity." However, it has been proposed that preputial gland carcinomas may be attributed to alpha 2μ-globulin (WHO 1995). In the NTP (1986) study, male mice had marginally increased incidences of hepatocellular tumors and mesenchymal tumors of the integumentary system at 500 mg/kg/day and of malignant lymphomas at 250 mg/kg/day. NTP (1986) considered this evidence to be equivocal. Clitoral gland adenomas were observed in 2/50 female rats in the 250 mg/kg/day group, but none were observed in the 500 mg/kg/day group; thus, it appears that these tumors are not related to treatment. There was no evidence of carcinogenicity in female mice.

NTP and IARC have not classified isophorone regarding carcinogenicity. The U.S. Environmental Protection Agency (IRIS 2003) has categorized isophorone as a possible human carcinogen based on no data in humans and limited evidence of carcinogenicity in animals (Group C; see discussion of evidence from animal studies below).

2.20 GENOTOXICITY

No studies investigating genotoxicity of exposed humans or studies investigating effects *in vivo* human cells were located. Results of *in vivo* and *in vitro* genotoxicity studies in animals and bacterial and mammalian cell lines are summarized in Tables 2-4 and 2-5, respectively. *In vivo* exposure did not result in DNA binding or micronucleus formation in rats or mice following oral exposure (Thier and Xu 1990; Thier et al. 1990) or intraperitoneal exposure (Atochem 1978b; CMA 1984b; Gandy et al. 1990; McKee et al. 1987; O'Donoghue et al. 1988). Results of the sex-linked recessive lethal test in *Drosophila melanogaster* also were negative (Foureman et al. 1994). Results of *in vitro* genotoxicity test are mixed for gene mutations, unscheduled DNA synthesis, chromosome aberrations, and sister chromatid exchange. Gene mutation studies in mammalian primary cultures or cell lines reported positive (Honma et al. 1999b; McGregor et al. 1988; NTP 1986) and negative results (CMA 1984a, 1984c; Honma et al. 1999a; McKee et al. 1987; O'Donoghue et al. 1988; NTP 1986). Gene mutation in bacterial cells (*Salmonella typhimurium*) were negative (Mortelmans et al. 1986; NTP 1986). Unscheduled DNA synthesis in rat primary hepatocytes was observed in one study (Selden et al. 1994), although results in this same test system were negative in other studies (CMA 1984c; McKee et al. 1987; O'Donoghue et al. 1988). Chromosome aberrations were reported in one study using Chinese hamster lung cells (Matsuoka et al. 1996), but not in two other studies using Chinese ovary cells (Gulati et al. 1989; NTP 1986). In Chinese hamster ovary cells, sister chromatid exchange was observed in two studies (Gulati et al. 1989; NTP 1986), but results were negative in another study (Tennant et al. 1987). A transformation assay in BALB/c-3T3 mouse cells was positive (Matthews et al. 1993). Overall, results suggest that isophorone may be weakly mutagenic; however, evidence is insufficient to predict the genotoxicity of isophorone in humans.

Table 2-4. Genotoxicity of Isophorone *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mammalian cells			
Rat (intraperitoneal)	DNA binding (caudal sperm heads)	–	Gandy et al. 1990
Rat (oral)	DNA binding	–	Thier et al.1990; Thier and Xu, 1990
Mouse (oral)	DNA binding	–	Thier et al.1990; Thier and Xu 1990
Mouse (intraperitoneal)	Micronucleus test	–	Atochem, 1978b
Mouse (intraperitoneal)	Micronucleus test	–	CMA 1984b
Mouse (intraperitoneal)	Micronucleus test	–	McKee et al. 1987

Table 2-4. Genotoxicity of Isophorone *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mouse (intraperitoneal)	Micronucleus test	–	O'Donoghue et al. 1988
Invertebrate systems			
Drosophila melanogaster	Sex Linked Recessive Lethal (SLRL) test	–	Foureman et al. 1994

– = negative results; DNA = deoxyribonucleic acid

Table 2-5. Genotoxicity of Isophorone *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Prokaryotic organisms				
Salmonella typhimurium	Gene mutation	–	–	Mortelmans et al. 1986
S. typhimurium	Gene mutation	–	–	NTP 1986
Mammalian cells				
Mouse (L5178Y/TK+/- lymphoma cells)	Gene mutation	–	–	CMA 1984a
Mouse (L5178Y/TK+/- lymphoma cells)	Gene mutation	+	+	McGregor et al. 1988
Mouse (L5178Y/TK+/- lymphoma cells)	Gene mutation	+/–	–	Honma et al. 1999a
Mouse (L5178Y/TK+/- lymphoma cells)	Gene mutation	ND	+	Honma et al. 1999b
Mouse (L5178Y/TK+/- lymphoma cells)	Gene mutation	–	–	McKee et al. 1987
Mouse (L5178Y/TK+/- lymphoma cells)	Gene mutation	–	–	O'Donoghue et al. 1988
Mouse (L5178Y/TK+/- lymphoma cells)	Gene mutation	ND	(+)	NTP 1986
Rat (primary hepatocytes)	Unscheduled DNA synthesis	–	ND	CMA 1984c
Rat (primary hepatocytes)	Unscheduled DNA synthesis	–	ND	McKee et al. 1987
Rat (primary hepatocytes)	Unscheduled DNA synthesis	–	–	O'Donoghue et al. 1988
Rat (primary hepatocytes)	Unscheduled DNA synthesis	ND	+	Selden et al. 1994
Chinese hamster ovary (CHO) cells	Chromosome aberrations	–	–	Gulati et al. 1989
CHO cells	Chromosome aberrations	–	–	NTP 1986

Table 2-5. Genotoxicity of Isophorone *In Vitro*

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
Chinese hamster lung (CHL) cells	Chromosome aberrations	+	+	Matsuoka et al. 1996
CHO cells	Sister chromatid exchange	–	+	Gulati et al. 1989
CHO cells	Sister chromatid exchange	–	+	NTP 1986
CHO cells	Sister chromatid exchange	+	–	Tennant et al. 1987
Mouse (BALB/c-3T3 cells)	Transformation assay	ND	+	Matthews et al. 1993

– = negative result; + = positive result; (+) = weakly positive result; +/- = inconclusive results; Ara^r = L-arabinose resistance; CHL = Chinese hamster lung cells; CHO = Chinese hamster ovary cells; DNA = deoxyribonucleic acid; ND = not determined

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

No studies were located regarding the toxicokinetics of isophorone in humans, but there are limited data from animal studies. These data are summarized below.

- Isophorone is absorbed following inhalation, oral, and dermal exposure. However, quantitative estimates of bioavailability have not been determined for any route of exposure.
- Isophorone is widely distributed throughout the body, although percentages of the absorbed dose distributed to each tissue have not been reported.
- Several metabolites of isophorone have been identified in urine. Proposed metabolic schemes for isophorone include several types of reactions, including methyl oxidation, reduction, dismutation, and conjugation.
- Urine appears to be the primary excretory pathway for isophorone and metabolites, although exhaled air and fecal excretion also occur.

3.1.1 Absorption

No studies were located regarding the absorption of isophorone following inhalation, oral, or dermal exposure of humans to isophorone.

Studies in animals show that isophorone is absorbed following inhalation, oral, and dermal exposure. Isophorone was widely distributed to the organs of rats exposed for 4 hours to a concentration of 400 ppm (Dutertre-Catella 1976), indicating that isophorone is absorbed after inhalation exposure. That isophorone is absorbed by the lungs can also be inferred from the systemic toxicity observed in animals following inhalation exposure (see discussion of health effects in Chapter 2). Imbriani et al. (1985) measured a blood/air partition coefficient of 2,349 for isophorone, indicating that isophorone is well absorbed from the lungs.

Preliminary results of a pharmacokinetic study indicate that rats treated orally with ^{14}C-isophorone excreted 93% of the radiolabel in the urine, expired air, and feces in 24 hours (Strasser 1988). The majority was found in the urine indicating that isophorone was well absorbed. The wide distribution of isophorone in the organs of rats and a rabbit 1–5 hours after dosing by gavage with 4,000 mg/kg (Dutertre-Catella 1976) indicates rapid gastrointestinal absorption. In two rabbits given a gavage dose of

1,000 mg/kg isophorone, a blood level of isophorone of 102 μg/L was found within 10 minutes. The level increased to 141 μg/L in 30 minutes and declined to ≤0.05 μg/L in 21 hours. The results indicate rapid absorption and elimination. The detection of unchanged isophorone and its metabolites (see Section 3.1.3, Metabolism) in the urine and the observations of systemic toxicity and carcinogenicity (see Chapter 2) in animals exposed orally to isophorone provide qualitative evidence that isophorone is absorbed after oral exposure.

A report that a high dermal dose resulted in signs of central nervous system depression in 1/4 rabbits indicates that isophorone is absorbed following dermal exposure (Hazleton Labs 1964).

3.1.2 Distribution

No studies were located regarding distribution of isophorone in humans.

Little information on distribution of absorbed isophorone is available. In rats exposed to 400 ppm isophorone for 4 hours and sacrificed immediately after exposure or 1.5 or 3 hours after exposure, levels of isophorone were highest immediately after exposure in all tissues examined (brain, lungs, heart, stomach, liver, spleen, pancreas, kidney, adrenals, testicles, and ovaries) (Dutertre-Catella 1976). Levels ranged from 1.5 to 74 μg/g tissue wet weight. Tissue levels declined rapidly in males but declined very little in females by 3 hours after exposure.

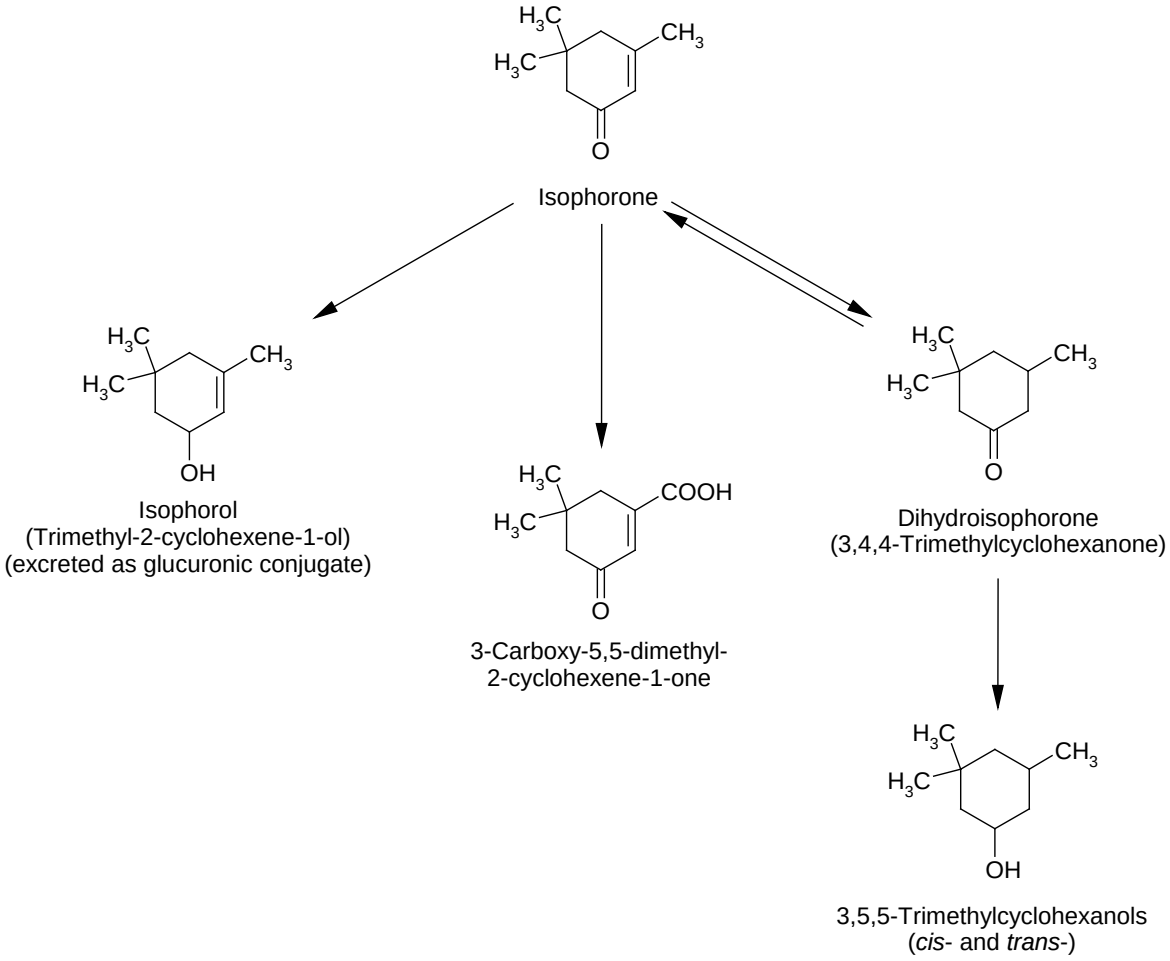
An oral exposure study of ^{14}C-isophorone in corn oil administered to male rats showed that ^{14}C was widely distributed, with highest levels in the liver, kidney, preputial gland, testes, brain, and lungs (Strasser 1988). Isophorone also was widely distributed to the tissues of rats and a rabbit following treatment with isophorone at a gavage dose of 4,000 mg/kg (Dutertre-Catella 1976). The rats died within 1–5 hours and the rabbit died within an hour after dosing, at which times tissues were sampled for analysis. In rats, tissue levels of isophorone in μg/g tissue wet weight were as follows: stomach 6,213; pancreas 2,388; adrenals 1,513; spleen 1,038; liver 613; brain 378; lung 383; heart 387; kidney 465; testes 275, and ovaries 471. In rabbits, tissue levels in μg/g tissue wet weight were as follows: stomach 5,395; adrenals 1,145; ovaries 3,000; spleen 545; liver 515; kidney 295; heart 260, and lungs 50.

3.1.3 Metabolism

No information regarding metabolism of isophorone in humans was identified.

Metabolites of isophorone have been identified in urine of animals administered oral isophorone. In rabbits and rats treated with oral isophorone, the following metabolites were identified in the urine: trimethyl-2-cyclohexene-1-ol (isophorol) and its glucuronic conjugate; 3-carboxy-5,5-dimethyl-2-cyclohexene-l-one; 3,4,4-trimethylcyclohexanone (dihydroisophorone); and cis- and trans-3,5,5-trimethylcyclohexanols (Dutertre-Catella et al. 1978; Truhaut et al. 1970). Rat urine contained more dihydroisophorone and less isophorol than did rabbit urine. Dutertre-Catella et al. (1978) proposed that metabolism of isophorone involves methyl oxidation to 3-carboxy-5,5-dimethyl-2-cyclohexene-l-one, reduction of the ketone group to isophorol, reduction of the ring double bond to dihydroisophorone, and dismutation of dihydroisophorone to cis- and trans-3,5,5-trimethylcyclohexanols. The metabolic pathways are presented in Figure 3-1.

Figure 3-1. Metabolic Scheme for Isophorone



Source: Dutertre-Catella et al. 1976

3.1.4 Excretion

The excretion of isophorone in humans has not been evaluated. Studies in animals suggest that urine is the predominant route of excretion. Dutertre-Catella (1976) found that the excretion of isophorone in air was low (110 μg) and declined further to 30 μg at 2.5–3 hours after exposure of rats to 400 ppm for 4 hours. Rats and rabbits excreted unchanged isophorone and metabolites in the urine and unchanged isophorone in the expired air following oral dosing with isophorone (Dutertre-Catella et al. 1978), but the rate and extent of excretion were not reported. Preliminary results of a pharmacokinetic study indicate that following an oral dose of ^{14}C-isophorone, male rats excreted 93% of the radiolabel in the urine, feces, and expired air in 24 hours, with the majority in the urine (Strasser 1988).

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

No PBPK models for isophorone were identified.

3.1.6 Animal-to-Human Extrapolations

Due to the limited amount of available toxicokinetic data, it is not possible to evaluate differences in metabolism of isophorone between species or humans. Thus, it is not possible to determine which animal model is most relevant to humans. Similar effects are observed in humans and laboratory animals following exposure to isophorone in air (irritation of the respiratory tract, eyes and skin).

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to isophorone are discussed in Section 5.7, Populations with Potentially High Exposures.

No data are available on the toxicity of isophorone in children. It is assumed that the types of effects in children would be similar to those seen in adults, as there is no obvious reason why effects would qualitatively differ from those in adults. However, there is no information to determine if children would be more or less susceptible than adults. Developmental studies in animals suggest that inhalation of isophorone during resulted in reduced body weight of pups, and higher concentrations may possibly cause exencephaly (see study details in Section 2.17). However, no information on developmental effects in humans was identified.

Isophorone produces irritation of the respiratory tract in humans and animals (study details are provided in Section 2.4). Individuals with underlying diseases of the respiratory tract, such as asthma, may be more sensitive to the irritant effects of isophorone.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to isophorone are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for isophorone from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by isophorone are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

The use of isophorone or its metabolites as biomarkers of exposure has not been investigated.

3.3.2 Biomarkers of Effect

There are no specific biomarkers to characterize the effects caused by isophorone.

3.4 INTERACTIONS WITH OTHER CHEMICALS

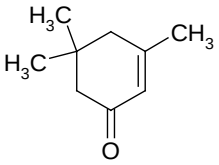
The possible synergistic interactions of isophorone with other solvents are important because mixed exposures occur in occupational settings and may occur in the environment. The joint toxicity of isophorone with 26 other industrial liquid chemicals based on determinations of the oral LD_{50} values in rats of each chemical alone and in a 1:1 (v/v) mixture was determined (Smyth et al. 1969). The LD_{50} values of the mixtures were predicted based on the assumption of additivity of the LD_{50s} of each component, and the ratios of the predicted values to experimentally determined values were calculated. Greater-than-additive toxicity was observed for the mixtures of isophorone with nine chemicals: tetrachloroethylene, propylene glycol, morpholine, ethyl alcohol, ethyl acetate, carbon tetrachloride, acrylonitrile, acetonitrile, and acetone. Less-than-additive toxicity was observed for the mixtures of isophorone with 17 chemicals: Ucon LB-250, Ucon 50-HB-260, toluene, Tergitol XD, propylene oxide, polyethylene glycol 200, Phenyl Cellosolve, nitrobenzene, acetophenone, aniline, Butyl Cellosolve, butyl ether, diethanolamine, dioxane, ethyl acrylate, ethylene glycol I, and formalin. When the frequency distribution of the ratios for all combinations of all chemicals were adjusted to give a normal distribution, however, none of the ratios for mixtures with isophorone deviated significantly from the mean ratios, indicating, essentially, additive toxicity. In a subsequent study, the additivity of equitoxic mixtures, defined as a mixture of chemicals in volumes directly proportional to their oral LD_{50} in rats, was determined (Smyth et al. 1970). Isophorone showed less-than-additive toxicity with Phenyl Cellosolve and Ucon Fluid 50-HB-260 and greater-than-additive toxicity with propylene oxide. The mechanism for such interactions is not known.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Table 4-1 lists common synonyms, trade names and other pertinent identification information for isophorone.

Table 4-1. Chemical Identity of Isophorone

Characteristic	Information	Reference
Chemical name	2-Cyclohexen-1-one,3,5,5-trimethyl-	CAS 1988
Synonym(s) and registered trade name(s)	Isophorone; Isoacetophorone; 1,5,5-Trimethyl-3-oxocyclohexene	CAS 1988; SANSS 1988
Chemical formula	$C_9H_{14}O$	CAS 1988
Chemical structure		SANSS 1988
CAS Registry Number	78-59-1	CAS 1988

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 4-2 lists important physical and chemical properties of isophorone.

Table 4-2. Physical and Chemical Properties of Isophorone

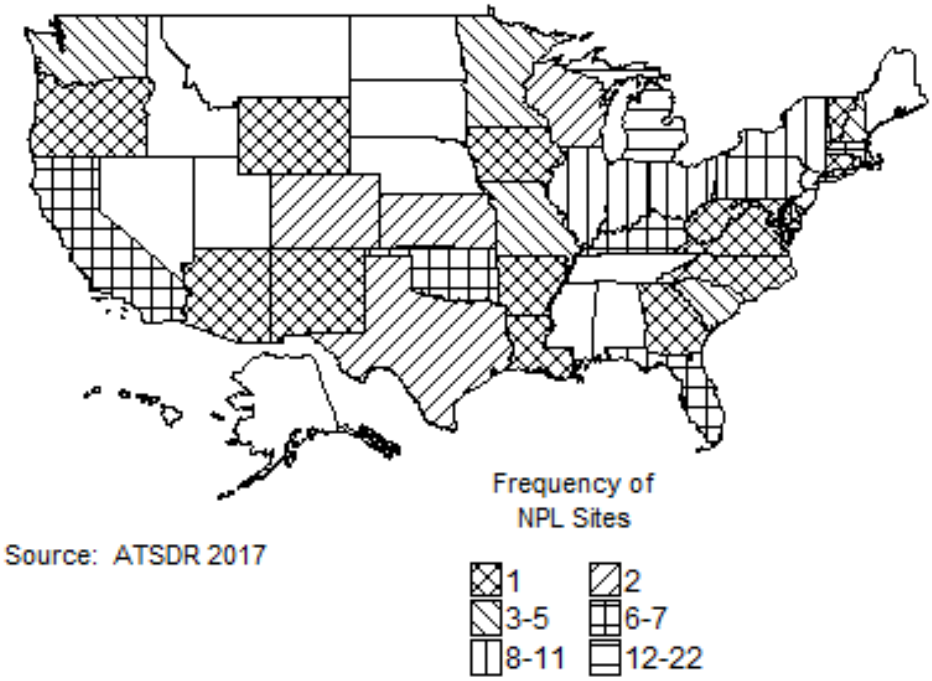
Property	Information	Reference
Molecular weight	138.1	Union Carbide 1968
Color	Water-white	Hawley 1981
Physical state	Liquid	Hawley 1981
Freezing point	-8.1°C	Union Carbide 1968
Boiling point	215.3°C	Union Carbide 1968
Density at 20°C	0.9229 g/m^3	Union Carbide 1968
Odor	Mild	Union Carbide 1968
Odor threshold:		
Water	5.4 ppm (w/v)	Amoore and Hautala 1983
Air	0.20 ppm (v/v)	Amoore and Hautala 1983
Solubility:		
Water at 20°C	12,000 mg/L	Union Carbide 1968
Organic solvents	Soluble in ether, acetone, alcohol	Weast 1985
Partition coefficients:		
Log K_{ow}	1.67 (20°C, experimental)	Veith et al. 1980
Log K_{oc}	No data	
Vapor pressure at 20°C	0.3 mmHg	Extrapolated using data from Union Carbide 1968
Henry's law constant at 20°C	$4.55x10^{-6}$ atm-m^3/mol	Calculated from vapor pressure and water solubility data
Autoignition temperature	864°F (462°C)	Hawley 1981
Flashpoint	184°F (84°C) (open cup)	Dean 1985
Flammability limits	0.8–3.5 vol%	HSDB 1988
Conversion factors (in air, 20°C)	ppm (v/v)x5.75=mg/m^3	
	mg/m^3x0.174=ppm (v/v)	

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Isophorone has been identified in at least 156 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which isophorone has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, all 156 are located within the United States

Figure 5-1. Number of NPL Sites with Isophorone Contamination



- Isophorone is used mainly as a solvent that is evaporated during or after use; therefore, most environmental releases are to the air.
- Isophorone can enter surface waters from industrial effluent discharges or from runoff from soils at hazardous waste or other contaminated sites.
- Isophorone disappears rapidly from air by hydroxyl radical reaction but may persist in surface waters for up to one month.
- The most likely routes of exposure for the general population is by inhalation of isophorone in air and ingestion of isophorone in water

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

No information is available in the TRI database on facilities that manufacture or process isophorone because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005).

According to a 1987 edition of the United States International Trade Commission (USITC) publication on U.S. production and sales of synthetic organic chemicals (USITC 1987), Union Carbide (Institute, West Virginia) was the only domestic manufacturer of isophorone in 1987. A comparison of the list of isophorone manufacturers in USITC (1987) and USITC (1986) shows that Exxon Corporation (Bayway, New Jersey) also manufactured this chemical but discontinued production in 1985. Because of the limited number of domestic manufacturers of isophorone and their desire to maintain confidentiality, up-to-date information regarding the production volume of isophorone in the United States is not available. In 1973, 35 million pounds of isophorone were produced in the United States (Papa and Sherman 1981), and in 1980, approximately 20–30 million pounds were produced (CMA 1981). The decrease may be because of replacement of isophorone with less costly solvents (CMA 1981).

Isophorone can be prepared by: (1) passing acetone vapor over a catalyst bed of magnesium aluminate, zinc oxide-bismuth oxide, or calcium oxide under pressure at 300–400°C or (2) reacting acetone, water (up to 30%), and potassium hydroxide (~1%) in a column under a pressure of about 35 atm and at a temperature of about 200°C (Papa and Sherman 1981). Commercial isophorone usually contains some unconjugated isomer (up to 5%) and small amounts (<l%) of xylitone (Papa and Sherman 1981). Isophorone tends to discolor on prolonged storage; stabilization against color formation can be provided by treatment with p-toluenesulfonic acid, acidified Fuller's earth, diazines, or diisopropylamine (Papa and Sherman 1981).

5.2.2 Import/Export

During 1984, 2,158 million pounds of isophorone were imported into the United States (HSDB 1988).

5.2.3 Use

Isophorone is a solvent for a large number of natural and synthetic polymers, resins, waxes, fats, and oils. Specifically, it is used as a solvent for concentrated vinyl chloride/acetate-based coating systems for metal cans, other metal paints, nitrocellulose finishes, printing inks for plastics, some herbicide and pesticide formulations, adhesives with food contract, and adhesives for plastics, poly(viny1) chloride and polystyrene materials (Papa and Sherman 1981). Isophorone also is an intermediate in the synthesis of 3,5-xylenol, 3,3,5-trimethylcyclohexanol (Papa and Sherman 1981), and plant growth retardants (Haruta et al. 1974). Of the total production, 45–65% is used in vinyl coatings and inks, 15–25% in agricultural formulations, 15–30% in miscellaneous uses and exports, and 10% as a chemical intermediate (CMA 1981).

5.2.4 Disposal

Isophorone may be disposed of by incineration, waste water treatment, or sanitary landfill (OHM-TADS 1988).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

Isophorone is released to the air mainly in urban centers, as a result of evaporation of solvents containing this chemical. Isophorone can enter surface waters from industrial effluent discharges or from runoff

from soils at hazardous waste or other contaminated sites. Isophorone disappears rapidly in air by hydroxyl radical reaction (half-life <5 hours) but may persist in natural waters from several days to about a month.

Volatilization and sorption are not expected to be significant removal mechanisms from water. In soils, isophorone is expected to degrade microbially, but no rate data are available. Isophorone has been monitored in effluents (range <5–1,380 ppb), ambient water (range <0.6–100 ppb), drinking water (from contaminated surface water) (range 0.02–9.5 ppb), and soils at hazardous waste sites (range 0.16–6,500 ppm).

Occupational exposures occur mainly by inhalation and dermal contact and are documented most frequently in the printing trades. Air concentrations in screen printing facilities range from <0.47 to 25.7 ppm. A 1988 estimate by the National Institute for Occupational Safety and Health reported that 37,469 workers (9,211 of whom were female) were exposed to isophorone in both trade name products and chemical named products.

5.3.1 Air

There is no information on releases of isophorone to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Since isophorone is used mainly as a solvent that is evaporated during or after use, the vast majority of environmental releases are to the air. Use patterns indicate that most air releases are in urban centers, with a smaller percentage of release in rural areas. Nonetheless, very little ambient air monitoring data exist to confirm this, probably because of its short atmospheric lifetime (half-life <5 hours).

Apparently, a major source of isophorone in the environment is the printing industry, since these operations usually do not use emission control technologies to reduce emitted isophorone concentrations (Bierbaum and Parnes 1974; Kominsky 1981; Lee and Frederick 1981; Samimi 1982). Other industries (e.g., metal coating) that use similar ventilation methods (NIOSH 1978a) are major sources of atmospheric isophorone. Coal-fired power plants may also emit isophorone to the air, since isophorone has been detected in the fly ash of one such plant (Harrison et al. 1985).

Volatilization from surface waters is not expected to be a significant source of isophorone in the atmosphere, since this is anticipated to be a slow process (based on the Henry's law constant of $4.55x10^{-6}$ atm-m^3/mol).

Waste water treatment plants may, however, emit some isophorone from influent water to the air, particularly if gas stripping methods are used (Hawthorne and Sievers 1984; Hawthorne et al. 1985). Drinking water plants that practice aeration of influent water may also emit small amounts of isophorone to air.

5.3.2 Water

There is no information on releases of isophorone to water from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Little data are available to quantitatively estimate releases of isophorone to water. Available information is summarized below.

During isophorone manufacture, process water may contact the isophorone and carry some of it to waste water streams. During use of isophorone, paint spray booths that use water curtains, wash water, and process water all may contain isophorone. Isophorone has been detected in the United States in industrial effluent discharges (Bursey and Pellizzari 1982; Hawthorne and Sievers 1984; Hawthorne et al. 1985; Jungclaus et al. 1976), hazardous waste landfill leachate and runoff (Ghassemi et al. 1984; Hauser and Bromberg 1982; Stonebraker and Smith 1980), and urban runoff (Cole et al. 1984).

Specific industrial categories that produce wastewaters containing isophorone include timber products, petroleum refining, paint and ink, pulp and paper, automobile and other laundries, pharmaceuticals, foundries, transportation equipment, and publicly-owned treatment works (Bursey and Pellizzari 1982). It is likely that treated waters from these industries that are often discharged to surface waters will contain isophorone (Bursey and Pellizzari 1982).

5.3.3 Soil

There is no information on releases of isophorone to soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

The only direct measurements of isophorone in soil were found for samples taken from hazardous waste sites. Ghassemi et al. (1984) found isophorone in leachates from hazardous waste landfills, and Hauser and Bromberg (1982) detected the presence of isophorone in the "sediment/soil/water" of Love Canal. These studies suggest that isophorone also was present in the soil.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Isophorone has a water solubility of 12,000 ppm, a log octanol/water partition coefficient of 1.67, a Henry's law constant of $4.55x10m^{-6}$ atm m^3-mol, a vapor pressure of 0.3 mm Hg at 20°C, a log sediment sorption coefficient of approximately 1.46, and a log bioconcentration factor (BCF) of 0.85.

Air. Isophorone is released to air and water from its manufacturing and use. Based on its water solubility, some isophorone may wash out of the atmosphere; however, only limited amounts will be washed out because of the short atmospheric half-life of isophorone. Particularly during the day, when hydroxyl radical (HO·) concentrations are highest, very little atmospheric transport will occur due to its fast reaction with HO·.

Water. In water, neither volatilization nor sorption to sediments is expected to be an important transport mechanism. The results of two EXAMS model runs and the value of the Henry's law constant (calculated from the solubility and the vapor pressure) suggest that volatilization will not be important in shallow ponds or in lakes. EXAMS is an environmental model that predicts the behavior of a chemical in surface waters (EPA 1985a). Using the code test data for a pond developed by the Athens Environmental Research Laboratory of EPA, the half-life for volatilization was calculated to be 104 days, while for a lake, the half-life was calculated to be 288 days. Input data included molecular weight, vapor pressure, Henry's law constant, octanol/water partition coefficient, sediment sorption coefficient, and water solubility. Equations correlating solubility or octanol/water partition coefficients with sorption partition coefficients (K_{oc}) were not developed using structures similar to isophorone, however, and the K_{oc} value entered into the EXAMS model thus should be viewed as tentative (EPA 1985a). The volatilization rates predicted by the EXAMS model appear to be consistent with the observation of Hawthorne and Sievers (1984), who reported that isophorone could be analyzed in wastewater by purge and trap methods but was not found in the air above the wastewater in a closed system without a purge.

Sediment and Soil. McFall et al. (1985) reported isophorone concentrations in sediments of Lake Pontchartrain, Louisiana, an estuary located in the Mississippi River delta.

Sediments containing isophorone were detected in the Inner Harbor Navigation Canal (IHNC), the Rigolets, and the Chef Menteur Pass. Concentrations in the overlying waters were not reported. Therefore, the sorption partition coefficient in these sediments could not be derived from these experimental data.

Other Media. The bioconcentration of isophorone in bluegill sunfish has been reported by Barrows et al. (1978, 1980) and Veith et al. (1980) (all reports used the same BCF value). These researchers reported a BCF of 7 (log BCF of 0.85) as determined in a continuous dilution flow-through system using ^{14}C-labeled isophorone. This value suggests that concentrations of isophorone in fish living in isophorone contaminated waters will not be more than an order of magnitude higher than concentrations in the water. Nonetheless, concentrations of isophorone have been found in fish in Lake Michigan tributaries and embayments (Camanzo et al. 1987) at concentrations ranging from below the detection limit (~0.02 mg/kg) to 3.61 mg/kg wet weight. McFall et al. (1985) also analyzed oysters from the IHNC and clams from the Rigolets and the Chef Menteur Pass in Lake Pontchartrain for isophorone. Oysters from the IHNC had detectable levels of isophorone (38 ppb dry weight), but clams did not; the detection limits were not specified and no BCF can be calculated with the data supplied. These data indicate, however, that isophorone can be found in aquatic organisms at mg/kg levels, although no correlation was found between the concentration of isophorone and lipid content in the organism (Camanzo et al. 1987).

5.4.2 Transformation and Degradation

Air. No studies were located regarding the rates or products of reaction of isophorone in the atmosphere. Isophorone does not significantly absorb light above wavelengths of 290 nm (Sadtler Index 1966 [UV #44]); hence, it is not expected to undergo direct photolysis. However, isophorone can react with photochemically produced NOx in the atmosphere (usually formed at higher concentrations in photochemical smogs) producing moderate eye irritation, NO_2, other oxidants (including ozone, various peroxy compounds, and free radicals), and formaldehyde as indicated in smog chamber studies (Altshuller and Bufalini 1971; Farley 1977; Levy 1973). The most significant reaction of isophorone in the atmosphere is probably its reaction with HO·.

Addition of HO· will occur at the double bond of the compound and may be followed by multiple reaction pathways (Atkinson 1985). Atkinson (1987) developed a method to estimate the HO· reaction rate based on structure. Using this method, an overall reaction rate of $81.5x10^{-12}$ cm^3 molecule-second was calculated. This reaction rate yields a half-life of 4.7 hours for an atmospheric 24-hour average HO· concentration of $0.5x10^6$ molecules-cm (Atkinson 1985). In indoor air, HO· concentrations probably are significantly lower (Atkinson 1985); therefore, reaction half-lives of HO· with isophorone in indoor air probably will be much longer than in outdoor air. Thus, isophorone is expected to persist much longer in indoor air than in outdoor air unless the indoor/outdoor air exchange rate is high.

Water. The aerobic biodegradation of isophorone has been studied using sludge and waste water inocula as well as combined biological and physical treatment methods. Isophorone appears to biodegrade under most conditions simulating those in sewage treatment plants. No studies regarding biodegradation or abiotic reactions involving photolysis or oxidation of isophorone in surface and groundwater were located in the literature.

Aerobic biodegradation of isophorone appears to be possible in sewage sludge or settled domestic waste water. The exact conditions, however, appear to be important. For example, Tabak et al. (1981a, 1981b) reported 100% degradation of isophorone in 7 days using settled domestic waste water amended with 5 ppm of yeast extract. Price et al. (1974) reported that the equivalent of 42% theoretical oxygen demand for the compound was consumed in 20 days with a domestic wastewater seed without the yeast extract, and Kawasaki (1980) reported that isophorone was resistant to biodegradation in a test developed by the Japanese Ministry of International Trade and Industry (MITI). The MITI test is essentially a biological oxygen demand (BOD) test conducted over 14 days with a seed obtained from soil and sludge samples taken throughout Japan. The results are reported as a pass if 30% or more of the theoretical BOD is consumed and as a fail if <30% is consumed. During the operation of two model sewage treatment plants, Hannah et al. (1986) and McShane et al. (1987) reported that virtually all of the isophorone added to the influent water was removed during the activated sludge portion of the treatment process. The hydraulic detention times for both systems were on the order of several hours. None of the test concentrations were near the activated sludge EC_{50} of 100 ppm (Yoshioka et al. 1986). Some of the removal may have been due to adsorption to the sludge as Hannah et al. (1986) reported that the sludge from their process contained isophorone at concentrations that exceeded the influent water concentrations.

While the evidence presented in the literature cited above suggests that isophorone can be virtually completely removed under sewage treatment plant conditions, monitoring data indicate that isophorone is still present in treated wastewater and in ambient water.

This, in turn, suggests that the exact conditions under which isophorone is rapidly biodegraded or removed are not well understood. The presence of this compound in treated wastewater is indicative that the proper removal conditions were not employed for these systems, or that the input concentrations into sewage treatment plants were high enough that the capacity of the treatment plants were exceeded.

Sediment and Soil. No studies were located regarding the transformation of isophorone in soils. Based on the information presented above and the lack of any monitoring data that report isophorone in groundwater or soils (except for hazardous waste sites), it appears that isophorone may not be discharged to soils in large amounts, and the small amounts that are deposited may degrade rapidly in soil. Another explanation, however, is that there is a lack of studies determining isophorone content in soil.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to isophorone depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of isophorone in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on isophorone levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-1 shows the lowest limit of detections that are achieved by analytical analysis in environmental media.

Table 5-1. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	2 mg/m^3	NIOSH 1984
Water	2.2 µg/L	EPA 1982, 1987a
Soil/sediment	330 µg/kg	EPA 1987a
Whole blood	No method identified	

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Detections of isophorone in air, water, and soil at NPL sites are summarized in Table 5-2.

Table 5-2. Isophorone Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	40	72.2	9,430	18	17
Soil (ppb)	2,500	4,300	14,600	22	17
Air (ppbv)	No data				

[a]Concentrations found in ATSDR site documents from 1981 to 2015 for 1,832 NPL sites (ATSDR 2017). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

No ambient air monitoring for isophorone was located in the literature.

The estimated atmospheric half-life of isophorone, <5 hours, may account for the lack of monitoring data, since concentrations will decrease rapidly with distance from the source. Another explanation, however, is that no studies have been conducted that analyzed for isophorone in air.

5.5.2 Water

Isophorone has been detected in surface waters, sediments, drinking water, industrial effluents, urban runoff, and in runoff waters from hazardous waste sites. Table 5-3 summarizes the available data.

In general, isophorone is found in urban centers and appears to result from industrial activities. For example, its presence in the Delaware River near Philadelphia is the result of industrial effluents that are discharged into the sewer system (Hites 1979). The sewage is treated in Philadelphia's Northeast Sewage Treatment plant, which discharges its effluent into the Delaware River. Isophorone was detected in the Delaware River in the winter only; in the summer, biodegradation or other processes (e.g., sorption) may have removed it from the water column. Isophorone has been detected in the sediments of Lake Pontchartrain, which is located in the delta plain of the Mississippi River, its presence probably is due to

Table 5-3. Detection of Isophorone in Water

Media type	Location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppb)		% Occurrence	Reference
						Range	Mean		
Surface water	Delaware River	8/77–3/78	NS	Grab/composite	GC/MS	<0.6–3	NS	NS	Hites 1979
	Delaware River	Winter 1976–1977	18	Grab	GC/MS	Trace	NS	NS	Sheldon and Hites 1978
	Delaware River	Summer 1976	18	Grab	GC/MS	ND	ND	NA	Sheldon and Hites 1978
	Olentangy River, OH	NS	NS	Grab	GC/FID	<5	ND	0	Shafer 1982
	Potomac River by Quantico	1986	NS	Grab	GC/MS	<2	ND	0	Hall et al. 1987
Sediments	Lake Pontchartrain	5/80–6/80	10	Grab	GC/MS	0.9[a]–23	2.9	NS	McFall et al. 1985
Drinking water	Cincinnati, OH	NS	NS	NS	NS	0.02	NS	NS	EPA 1975
	New Orleans, LA	8/74–9/74	NS	Continuous adsorption	GC/MS	1.5–9.5	NS	NS	EPA 1974
	Philadelphia, PA	2/75–1/77	12	Grab	GC/MS	NS	NS	17	Keith et al. 1976
Effluents	Shale oil sites	7/81–12/82	NS	Grab	GC/MS	0.34–5.8[b]	NS	100	Suffet et al. 1980
	Tire manufacturing plant	NS	NS	Grab	GC/MS	40	NS	100	Hawthorne and Sievers 1984
	Unspecified effluent	NS	NS	NS	GC/MS	NS	NS	NS	Jungclaus et al. 1976
	Philadelphia sewage treatment plant influent	8/77–3/78	NS	Grab/composite	GC/MS	100	NS	NS	Perry et al. 1976
	Philadelphia sewage treatment plant effluent	8/77–3/78	NS	Grab/composite	GC/MS	10	NS	NS	Hites 1979
	Plastics effluents	NS	NS	Grab	GC/FID	40.5	NS	100	Shafer 1982
	Ship holding tank	NS	NS	Grab	GC/FID	<50	NS	0	Shafer 1982
	Secondary sewage effluent	NS	NS	Grab	GC/FID	120	NS	100	Shafer 1982
	Chemical industry final effluent	NS	NS	Grab	GC/FID	<5	NS	0	Shafer 1982

Table 5-3. Detection of Isophorone in Water

Media type	Location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppb) Range	Concentration (ppb) Mean	% Occurrence	Reference
	Chemical manufacturing plant final effluent	NS	NS	Grab	GC/FID	<20	NS	0	Shafer 1982
	Timber products	NS	2[c]	NS	GC/MS	55–111	83	NS	Bursey and Pellizzari 1982
	Petroleum refining	NS	1[c]	NS	GC/MS	1,380	NS	NS	Bursey and Pellizzari 1982
	Paint and ink	NS	5[c]	NS	GC/MS	24–946	185	NS	Bursey and Pellizzari 1982
	Pulp and paper	NS	1[c]	NS	GC/MS	753	NS	NS	Bursey and Pellizzari 1982
	Auto and other laundries	NS	2[c]	NS	GC/MS	43–44	43	NS	Bursey and Pellizzari 1982
	Pharmaceuticals	NS	1[c]	NS	GC/MS	237	NS	NS	Bursey and Pellizzari 1982
	Foundries	NS	1[c]	NS	GC/MS	136	NS	NS	Bursey and Pellizzari 1982
	Transportation equip.	NS	2[c]	NS	GC/MS	28–318	173	NS	Bursey and Pellizzari 1982
	POTWs[d]	NS	15[c]	NS	GC/MS	4.2–114	11.5	NS	Bursey and Pellizzari 1982
Urban runoff	Washington DC	NS–7/82	86	Grab	NS	10	NS	4	Cole et al. 1984
Hazardous waste sites	Love Canal	8/80–10/80	NS	Grab	GC/MS	NS[f]	NS	NS	Hauser and Browberg 1982
	Valley of the Drums	1979	2[c]	Grab	NS	15–37[g]	26	NS	Stonebraker and Smith 1980
	11 Disposal sites	NS	8	Grab/composite	NS	29[h]	NS	12.5	Ghassemi et al. 1984
	Cooper Road site, NJ	NS	NS	NS	NS	NS[i]	NS	NS	VIEW database 1988
	Sheridan Disposal Services, TX	NS	NS	NS	NS	2,500[e]	NS	NS	VIEW database 1988
	Summit National site, OH	NS	NS	NS	NS	NS[g]	NS	NS	VIEW database 1988
	Unspecified site	NS	1	NS	NS	NS[g]	78	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	91	NS	CLSDB 1987
	Unspecified site	NS	2	NS	NS	NS[g]	315	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	1	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	360	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	538	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	48	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	12	NS	CLSDB 1987

Table 5-3. Detection of Isophorone in Water

Media type	Location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppb) Range	Mean	% Occurrence	Reference
	Unspecified site	NS	1	NS	NS	NS[g]	20	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	48	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	137	NS	CLSDB 1987
	Unspecified site	NS	1	NS	NS	NS[g]	11	NS	CLSDB 1987
	Unspecified site	NS	2	NS	NS	NS[g]	57.6	NS	CLSDB 1987

[a]Average of 8 samples
[b]µg in air per mL wastewater from purge and trap analysis
[c]Number of positive samples
[d]Publicly owned treatment works
[e]Detected in groundwater
[f]Detected in sediment, soil, or water
[g]Detected in water
[h]Detected in leachate
[i]Detected in groundwater

GC/FID = gas chromatography/flame ionization detector; GC/MS = gas chromatography/mass spectroscopy; NA = not applicable; ND = not detected; NS = not specified

the many industries that are situated along the Mississippi River and use the river water as process water (EPA 1974).

The presence of isophorone in drinking water is probably the result of using contaminated surface water as a source of drinking water. Of the three cities for which drinking water data are listed, Philadelphia receives its drinking water from the Delaware River, Cincinnati from the Ohio River, and New Orleans from the Mississippi River. These rivers receive numerous industrial effluents.

As listed in Table 5-3, isophorone has been detected in the effluents of a variety of industries. Levels in industrial effluents range from 4.2 to 1,380 ppb. Five reports of positive identifications were found in the open literature: a shale oil site; a tire manufacturing plant; sewer pump sample receiving wastes from phenolic resins manufacturing or processing, vinyl acetate, and polyvinylchloride process areas; final effluent from a sewage treatment system receiving wastes from plants producing plasticizers, butyl rubber, and olefin; and an unspecified effluent. The remaining samples listed in Table 5-3 are from an EPA database of over 4,000 analyses of organic pollutants in industrial wastewater made during the survey conducted in response to the consent decree between the Natural Resources Defense Council and EPA, June 7, 1976 (Bursey and Pellizzari 1982).

Isophorone also has been detected in urban runoff from Washington, DC (Cole et al. 1984).

5.5.3 Sediment and Soil

Isophorone has been identified in soil only at hazardous waste sites.

5.5.4 Other Media

Isophorone has been detected in oysters (but not in clams) in Lake Pontchartrain, Louisiana; the mean of eight samples of oysters from the Inner Harbor Navigation Canal section of the lake contained 38 ppb dry weight of isophorone. Hall et al. (1987) and De Vault (1985) did not detect isophorone in the fish in the Potomac River and Great Lakes Harbors and tributaries, respectively; in these cases, isophorone was not detected in the water either. Camanzo et al. (1987) reported finding isophorone in nearshore fish from 14 Lake Michigan tributaries and embayments; their results are presented in Table 5-4. Sampling was performed in 1983.

Table 5-4. Detection of Isophorone in Fish near Lake Michigan

Location	Fish	Sampling dates	Number of samples[a]	Mean concentration[b]	% Lipid
St. Joseph River	Common Carp	1983	5	ND[c]	23.1
	Smallmouth Bass	1983	7	0.74	3.7
Kalamazoo River	Common Carp	1983	4	0.12	5.9
	Largemouth Bass	1983	4	0.72	3.1
Grand River	Common Carp	1983	3	ND	4.0
	Channel Catfish	1983	6	ND	13.5
Muskegon River	Common Carp	1983	4	0.94	17.9
	Pumpkinseed	1983	3	0.40	2.4
White Lake	Common Carp	1983	4	0.66	15.4
	Bowfin	1983	5	ND	12.1
Pere Marquette River	Common Carp	1983	6	3.13	11.0
	Bowfin	1983	8	ND	13.5
Manistee River	Common Carp	1983	4	ND	10.5
	Bowfin	1983	4	0.76	11.5
Platte River	Common Carp	1983	3	2.32	14.7
	Northern Pike	1983	6	ND	3.5
Boardman River	Smallmouth Bass	1983	6	3.61	5.4
	Rock Bass	1983	3	1.44	3.5
Grand Traverse Bay	Common Carp	1983	3	0.47	16.2
	Lake Trout	1983	4	2.33	18.8
Manistique River	Smallmouth Bass	1983	5	1.03	4.5
	Northern Pike	1983	3	ND	2.1
Whitefish River	Common Carp	1983	11	0.88	16.4
	Rock Bass	1983	7	0.69	3.0
Escanaba River	Common Carp	1983	5	0.41	12.9
	Northern Pike	1983	6	0.48	2.9

Table 5-4. Detection of Isophorone in Fish near Lake Michigan

Location	Fish	Sampling dates	Number of samples[a]	Mean concentration[b]	% Lipid
Ford River	Northern Pike	1983	6	ND	3.0
	Rock Bass	1983	5	ND	3.1

[a]All samples are composites of the stated number of fish and were analyzed by gas chromatography/mass spectroscopy.
[b]mg/kg wet weight

ND = not detected

Isophorone was detected in fish samples from all but two of the sites; the mean of the samples that had detectable levels of the compound was 1.17 mg/kg wet weight. In addition to isophorone, the authors also reported the lipid content of the composite fish samples. No correlation could be found between isophorone concentration and lipid content.

Johansson and Ryhage (1976) reported that isophorone was present in one of three samples of the pharmaceutical clofibrate [ethyl 2-(4-chlorophenoxy)-2-methylpropionate], which lowers elevated serum lipids. The analysis was performed on samples available from Sweden, but clofibrate is also available in the United States. The concentration of isophorone present in samples of the drug available in the United States was not reported.

5.6 GENERAL POPULATION EXPOSURE

No ambient air monitoring data are available for isophorone; consequently, no potential inhalation exposures from ambient air can be estimated. Inhalation of isophorone from showering with contaminated water cannot be estimated from the available data (no measurements have been made).

Isophorone concentrations in surface waters and drinking waters are expected to vary considerably with season and with fluctuations in industrial discharges. Considering the dates of most of the positive identifications in surface and drinking water (middle to late 1970s), the effect of more stringent discharge limits in some industries since that time, and the probable seasonal, spatial, and temporal variations in concentrations, it is not possible to make an accurate estimate of ingestion intake of isophorone from drinking water without significant uncertainty. From the available data, it appears that long-term ingestion of isophorone from drinking water will be limited to those systems that receive their water from contaminated surface water sources and the seasonally averaged concentration in these waters probably will be <l ppb.

Isophorone, in addition to several other volatile compounds, was extracted from inflatable aquatic toys, providing an exposure pathway for children (Wiedmer et al. 2017).

Anjou and von Sydow (1967) reported that 0.2% of the essential oil of the American cranberry, *Vaccinium macrocarnon*, consisted of isophorone; they did not report the percentage of isophorone or the percentage of essential oil in whole cranberries. Without this information, it is not possible to estimate the concentration of isophorone in whole cranberries and compare the concentration to other sources.

However, frequent consumption of cranberry containing products is unlikely to represent significant intake of isophorone. Ingestion of isophorone from consumption of fish and shellfish cannot be robustly estimated from the available data (see Table 5-4).

Potential dermal exposure levels also are difficult to estimate from the available data. Dermal exposure from bathing in contaminated waters cannot be estimated without significant uncertainty. Other potential dermal exposures cannot be estimated with the available data.

Occupational exposures have been documented most frequently in the screen printing trade and are summarized in Table 5-5. During screen printing operations, both dermal and inhalation exposures can occur.

Breathing zone concentrations during screen printing range from <l to 25.7 ppm, while general area concentrations range from <l to 16 ppm. The exposure level varies significantly with the ventilation present in the work area. While exposure estimate for a specific screen printing operation is possible, no reasonable estimates can be made for other operations that may use isophorone because of lack of data.

The relative contributions of the exposure routes and sources are as follows. For persons exposed to isophorone in the workplace, total doses will probably be substantially higher than those exposed only to ambient air and drinking water, and their inhalation and dermal exposures for the occupationally exposed can be assumed to result exclusively from the workplace exposures. Inhalation and dermal exposure for persons not exposed to isophorone in the workplace will most likely result from showering or bathing, but only in locations that receive their drinking water from contaminated surface water sources. These exposures are expected to be very small. In locations that do not have the potential for isophorone in the drinking water, any ingestion, inhalation, or dermal exposure is unlikely.

Table 5-5. Occupational Monitoring of Isophorone

Company	Process	Sample type	Concentration (ppm) Range	Mean[a]	Number of samples	% Positive	Reference
Pre-Finish Metals	Wire coating	Area	<1–3.37	1.13	24	33	NIOSH 1978a
Pre-Finish Metals	Wire coating	Personal	<1–3.37	1.13	19	42	NIOSH 1978a
Joel and Aronoff	Screen printing	Personal	<0.5–14	7.35	14	14	Lee and Fredrick 1981
Unspecified	Screen printing	Area	3.5–16	10.2	46	100	Samimi 1982
Unspecified	Screen printing	Personal	8.3–23	14.7	78	100	Samimi 1982
Electrocal	Screen printing	Area	0.70–1.22	0.957	6	100	Bierbaum and Parnes 1974
Electrocal	Screen printing	Personal	0.84–1.39	1.10	3	100	Bierbaum and Parnes 1974
Swinston Co.	Screen printing	Personal	<0.47–25.7	12.9	7	29	Kominsky 1981
Garden City Engraving	Screen printing	Area	<0.67–2.5	1.18	7	57	Salisbury 1983
Garden City Engraving	Screen printing	Personal	<0.58–3.4	1.42	8	75	Salisbury 1983

[a]Mean of the positive samples

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Populations with potentially high exposure include those occupationally exposed to isophorone (e.g., screen print workers, some adhesives formulators and users, some coatings manufacturing and use workers).

Individuals living near hazardous waste sites may be exposed to isophorone dermally, but probably not by inhalation. These individuals also may be exposed to isophorone by ingestion if they drink water from contaminated wells located down gradient from the site.

CHAPTER 6. 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 isophorone is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of isophorone.

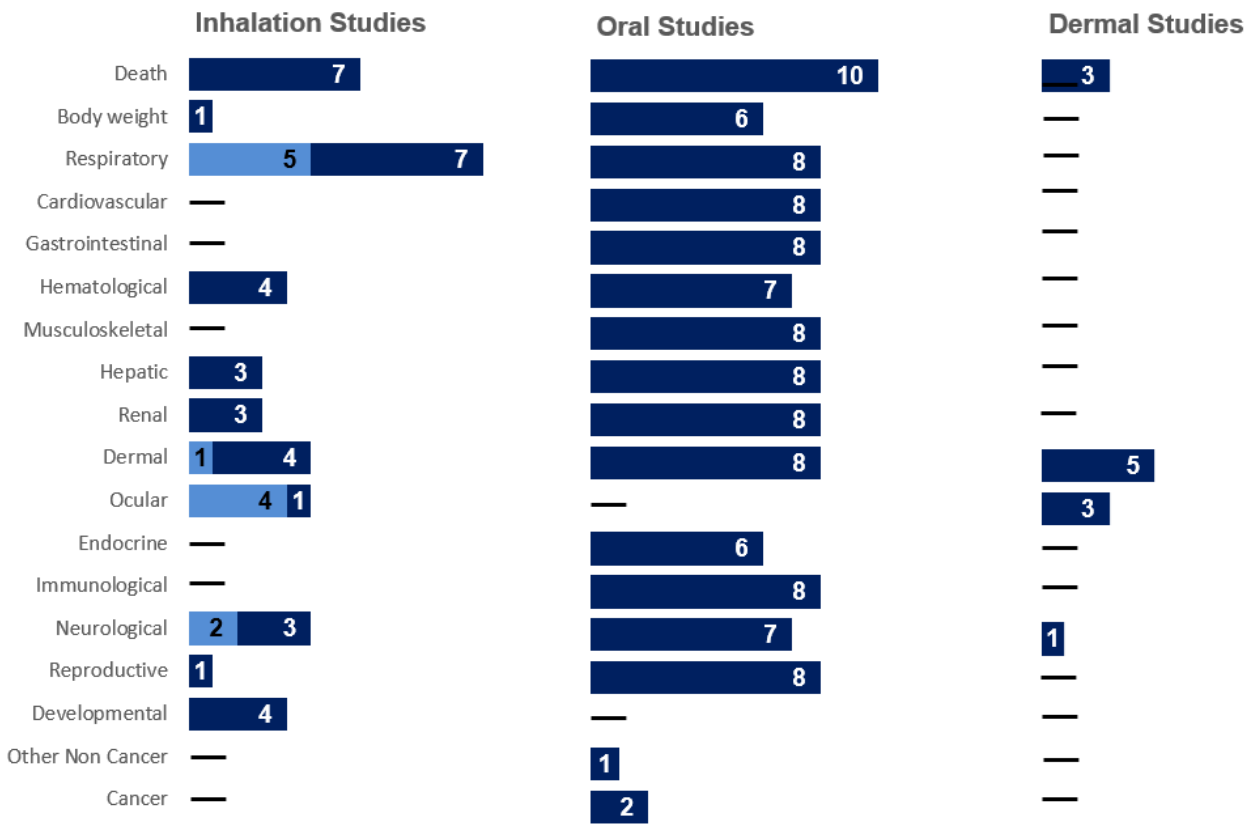
Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to isophorone that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of isophorone. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

As illustrated in Figure 6-1, most studies evaluated toxicity of oral exposure to isophorone. The most commonly examined endpoints were respiratory, dermal, hematological, and neurological effects. Two oral exposure studies evaluated a wide range of potential endpoints of intermediate- and chronic-duration exposure to isophorone in several animal species (AME Inc. 1972a, 1972b; NTP 1986). In addition, eight studies examined the acute lethality of isophorone following inhalation, oral, or dermal exposure.

Figure 6-1. Summary of Existing Health Effects Studies on Isophorone By Route and Endpoint



6.2 Identification of Data Needs

Missing information in Figure 6-1 should not 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* (ATSDR 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.

Acute-Duration MRLs. The acute-duration inhalation database was not considered suitable for derivation of MRLs for isophorone. Acute inhalation studies in human subjects identify NOAEL and LOAEL values for irritation of the nose and eyes; however, study exposures were very short (≤15 minutes). Studies in animals also identified respiratory tract irritation as the most sensitive effect of exposure to isophorone in air; however, none of the available studies evaluated comprehensive toxicological endpoints. Acute oral exposure studies were designed to assess lethality and did not conduct evaluations of a wide range of potential targets of toxicity. Acute-duration inhalation and oral studies are needed to fully define the effects of acute exposure, identify sensitive targets of toxicity, and establish dose-response relationships.

Intermediate-Duration MRLs. The database for intermediate-duration oral exposure to isophorone was considered adequate for derivation of an MRL. The intermediate-duration inhalation database was not sufficient to derive an MRL because available studies evaluated only single exposure levels and did not assess comprehensive endpoints. Intermediate-duration inhalation studies are needed to fully define the effects of acute exposure, identify sensitive targets of toxicity, and establish dose-response relationships.

Chronic-Duration MRLs. The database for chronic-duration oral exposure to isophorone was considered adequate for derivation of an MRL. Similar to the intermediate-duration inhalation database, chronic inhalation studies were not sufficient to derive an MRL because available studies evaluated only single exposure levels and did not assess comprehensive endpoints. Chronic-duration inhalation studies are needed to fully define the effects of acute exposure, identify sensitive targets of toxicity, and establish dose-response relationships.

Health Effects.

Reproductive. Reproductive effects of isophorone in animal studies have not been well-studied. One inhalation study reported no effect on pregnancy rate following intermediate-duration inhalation exposure. Other studies conducting gross and histopathological evaluations of reproductive tissues have not identified effects of exposure to isophorone. However, no rigorous assessments of reproductive function have been conducted. Such data would be important to more fully explore potential reproductive effects of isophorone.

Developmental. Developmental effects of inhaled expose to isophorone in animals have been evaluated in a few studies (Bio/dynamics 1984a, 1972b; Dutertre-Catella 1976); however, studies examining comprehensive developmental endpoints were not available. Additional studies investigating developmental effect are needed to fully evaluate the potential for isophorone to adversely affect the developing organism.

Immunological. Studies conducting histopathological assessments of immune system tissues have not identified adverse effects of exposure to isophorone. However, none of these studies conducted specific tests of immune function. Such tests of immune function are needed to evaluate potential effects of isophorone. Isophorone is a skin irritant in rabbits, guinea pigs, and humans, but tests for sensitization were not identified in publicly available literature. Such tests might provide information on whether an allergic response to isophorone is likely.

Neurological. Isophorone has been shown to produce signs of neurotoxicity (lethargy, depression) in acute- and intermediate-duration exposure studies. However, only one study evaluated the effects of isophorone on neurobehavioral outcomes. Additional information, including dose-response information, is needed to provide a full evaluation of the neurological effects of isophorone.

Epidemiology and Human Dosimetry Studies. A limited number of epidemiological studies examining respiratory, dermal, and neurological endpoints were identified for isophorone. Additional studies could be helpful in evaluating the chronic human health risk from isophorone exposure, including the potential for isophorone to induce cancer.

Biomarkers of Exposure and Effect. No biomarkers of exposure to isophorone were located. Studies evaluating whether levels of isophorone or one of its metabolites in biological fluids are reflective of exposure levels would be useful.

Absorption, Distribution, Metabolism, and Excretion. Studies evaluating the toxicokinetics of isophorone provide information to general descriptions of the absorption, distribution, metabolism, and excretion of isophorone. However, studies to determine quantitative estimates for these parameters have not been determined. Additional studies providing quantitative estimates of toxicokinetic parameters would provide important information for isophorone.

Comparative Toxicokinetics. Available information on toxicokinetics of isophorone is from studies conducted in rats and rabbits. However, as discussed above, comparisons between these species are only qualitative. Therefore, additional studies providing quantitative information on toxicokinetics is needed to provide comparisons between species. In addition, because toxicity studies on isophorone also have been in mice, toxicokinetic studies in mice may provide essential information regarding differences in toxicological responses between species. In addition, studies of the pattern of isophorone degradation products in human urine would be helpful in evaluating whether isophorone is metabolized in humans as it is in rats.

Children's Susceptibility. No studies have evaluated the toxicity of isophorone in children or young animals. Studies in young animals and/or children would be useful to address potential concerns of that children may be more susceptible to the toxicity of isophorone than adults.

Physical and Chemical Properties. Many physical and chemical properties are available for isophorone, but most do not have extensive experimental descriptions accompanying the data; therefore, an evaluation of the accuracy of the data is difficult. Specifically, measured vapor pressure, K_{oc}, and Henry's Law constant at environmentally significant temperatures would help to remove doubt regarding the accuracy of the estimated data. The data on physical properties form the basis of much of the input requirements for environmental models that predict the behavior of a chemical under specific conditions, including hazardous waste landfills. The data on the chemical properties, on the other hand, can be useful in predicting certain environmental fates of this chemical.

Production, Import/Export, Use, Release, and Disposal. Data on current uses and disposal practices would be valuable in determining whether industrial activities pose an important source of human exposure to isophorone.

Environmental Fate. Sensitized photolysis studies in water and oxidation/reduction studies in both air and water are lacking, as are biodegradation studies in surface water and groundwater. These kinds of studies are important, since they represent the fundamental removal mechanisms available to isophorone in the environment. In addition, the kinetic studies for the atmospheric reactions are important for understanding the significance of a removal mechanism and predicting the reactions that may control the fate of a chemical in the environment.

Bioavailability from Environmental Media. No studies were located regarding the bioavailability of isophorone from environmental media. Furthermore, no reports were located indicating that isophorone or its metabolites have been detected in human tissues or fluids. Since the monitoring literature reports that isophorone is present in the environment as well as in environmental organisms, the lack of data does not necessarily indicate a lack of bioavailability. Fish may be the only source of isophorone in the environment that is not subject to large spatial and temporal variations in concentration, as appears to be the case with drinking water. In particular, fish in the Lake Michigan area are known to contain isophorone (Camanzo et al. 1987), and analysis of the body fluids of people who consume the fish may allow a determination of the existence of exposure and an estimation of the degree of exposure.

Food Chain Bioaccumulation. No studies were located regarding the food chain bioaccumulation of isophorone from environmental media. The monitoring literature reports that isophorone is present in the environment as well as in environmental organisms. The monitoring data further suggest that isophorone levels in fish do not correlate well with the lipid content of the fish. Thus, structure-activity relationships developed to estimate levels in biological media based on the partitioning properties of a chemical may not provide accurate information for isophorone. Furthermore, only one bioaccumulation study was available. In this study, which indicated a low potential for bioaccumulation, fish were exposed to isophorone in water rather than in food. From these data, it appears that food chain bioaccumulation may be occurring, and a clearer understanding of the potential for this would aid in determining how levels in the environment affect the food chain and potentially impact on human exposure levels.

Exposure Levels in Environmental Media. Environmental monitoring data are not available for soil and air, and the data available for water, sediments, and biota are not sufficient to determine ambient

concentrations. These data would be helpful in determining the ambient concentrations of isophorone so that exposure estimates of the general population and the bioconcentration factor of this chemical in aquatic organisms can be made.

Exposure Levels in Humans. After the establishment of biomarkers of exposure, a program involving analyses of human tissues would be useful in assessing the magnitude of environmental exposures. Monitoring of human tissues from different locations and seasons and using different category of the population would be helpful so that the effects of such variables as occupational, geographical, and seasonal can be assessed.

Exposures of Children. No studies are available to assess whether children are at a higher exposure risk than adults to isophorone. Studies examining potential exposure sources for children would be useful.

6.3 Ongoing Studies

No ongoing studies were identified for isophorone.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding isophorone in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for isophorone.

Table 7-1. Regulations and Guidelines Applicable to Isophorone

Agency	Description	Information	Reference
	Air		
EPA	RfC	No data	IRIS 2003
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2012
	1-Day health advisory for a 10-kg child	15 mg/L	
	10-Day health advisory for a 10-kg child	15 mg/L	
	DWEL	7 mg/L	
	Lifetime health advisory	0.1 mg/L	
	10^{-4} Cancer risk	4 mg/L	
	National primary drinking water regulations	No data	EPA 2009
	RfD	$2x10^{-1}$ mg/kg/day	IRIS 2003
WHO	Drinking water quality guidelines	No data	WHO 2017
FDA	EAFUS	Yes[a,b]	FDA 2013
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	Group C[d]	IRIS 2003
	Oral slope factor	$9.5x10^{-4}$ per (mg/kg)/day	
IARC	Carcinogenicity classification	No data	IARC 2017
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, construction, and shipyards	25 ppm[e]; 140 mg/m^3[f]	OSHA 2016a, 2016b, 2017
NIOSH	REL (up to 10-hour TWA)	4 ppm (23 mg/m^3)	NIOSH 2016
	IDLH	200 ppm	

Table 7-1. Regulations and Guidelines Applicable to Isophorone

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2016
DOE	PACs-air		DOE 2016a
	PAC-1[g]	12 ppm	
	PAC-2[g]	33 ppm	
	PAC-3[g]	200 ppm	

[a]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[b]Status: fully up-to-date toxicology information has been sought.
[c]A3: confirmed animal carcinogen with unknown relevance to humans.
[d]C: possible human carcinogen.
[e]Parts of vapor or gas per million parts of contaminated air by volume at 25°C and 760 torr.
[f]Approximate milligrams of substance per cubic meter of air.
[g]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2016a).

AEGL = acute exposure guideline levels; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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 noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. 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 NOAEL/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) 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 substance-induced endpoint 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.

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 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, 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 MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Isophorone
CAS Numbers: 78-59-1
Date: December 1989
March 2017—Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL.

Rationale for Not Deriving an MRL: The acute-duration inhalation database was not considered suitable for derivation of an MRL. Although acute inhalation studies in human subjects identify NOAEL and LOAEL values of 10 and 25 ppm, respectively, for irritation of the nose and 35 and 65 ppm, respectively, for irritation of the eyes, study exposures were very short (≤15 minutes) (Hazleton Labs 1965b; Silverman et al. 1946). An acute-duration inhalation MRL based on data from these short exposure durations may not be considered protective for continuous exposure for up to 2 weeks. Studies in animals also identified respiratory tract irritation as the most sensitive effect of isophorone in air. Respiratory effects have been observed over a wide range of exposures, from 27.8 ppm for 5 minutes in mice for an RD_{50} value (indicative of respiratory irritation) to 619 ppm for 6 hours in mice for respiratory tract congestion (DeCeaurriz et al. 1981a; Hazelton Labs 1964). Other effects observed in animals exposed acutely to inhaled isophorone include decreased leukocyte count at 67 ppm (Brondeau et al. 1990) and neurological effects at ≥89 ppm (Bio/dynamics 1984a; DeCeaurriz et al. 1981b, 1984). Developmental effects of inhalation exposure to isophorone in animals have been evaluated in a few studies; however, examinations of comprehensive developmental endpoints were not conducted, and/or interpretation of study results is complicated by inadequate exploration of exposure-response relationships (Bio/dynamics 1984a, 1984b; Dutertre-Catella 1976).

Because comprehensive toxicological endpoints were not examined in acute inhalation studies in animals, available data do not allow for identification of the most sensitive effect of exposure. Therefore, data are not suitable for derivation of an acute-duration inhalation MRL for isophorone.

Agency Contact (Chemical Manager): Melanie Buser

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Isophorone
CAS Numbers: 78-59-1
Date: December 1989
March 2017—Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL.

Rationale for Not Deriving an MRL: The intermediate-duration database for inhalation exposure consists of 2 studies in rats: a 4-week study with exposures to 0 or 37 ppm for 6 hours/day, 5 days/week (Hazleton Labs 1968) and a 4–6-month study with exposures to 0 or 500 ppm for 6 hours/day, 5 days/week (Dutertre-Catella 1976). The Hazleton Labs (1968) study reported decreased terminal body weights in male rats (10% lower than controls), but no hematological or renal effects were observed in male or female rats. The Dutertre-Catella (1976) study observed irritation of the nasal mucosa and hepatic microvacuolization; no hematological or renal effects were observed. Comprehensive toxicological endpoints were not examined in either study and both studies only evaluated a single exposure level of isophorone. Therefore, data are not sufficient for derivation of an intermediate-duration inhalation MRL.

Agency Contact (Chemical Manager): Melanie Buser

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Isophorone
CAS Numbers: 78-59-1
Date: December 1989
March 2017—Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: One study evaluated the effects of chronic inhalation of isophorone (Dutertre-Catella 1976). Rats and rabbits were exposed to 0 or 250 ppm isophorone for 6 hours/day, 5 days/week for 18 months. In both rats and rabbits, irritation of the nasal mucosa and hepatic microvacuolization was observed. No hematological or renal effects were found in either species. However, because comprehensive toxicological endpoints were not examined and only a single exposure level of isophorone was evaluated, data are not sufficient for derivation of a chronic-duration inhalation MRL.

Agency Contact (Chemical Manager): Melanie Buser

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Isophorone
CAS Numbers: 78-59-1
Date: December 1989
March 2017—Updated literature search
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL.

Rationale for Not Deriving an MRL: The acute oral exposure database consists of studies designed to assess lethality in rats and mice following single doses of isophorone (Dutertre-Catella 1976; Hazleton Labs 1964; Smyth et al. 1969, 1970). These studies report LD_{50} values in rats ranging from 2,104 to 3,450 mg/kg in rats (Hazleton Labs 1964; Smyth et al. 1969, 1970) and an LD_{50} value of 2,200 mg/kg in mice (Dutertre-Catella 1976). At a sublethal dose in rats (1,450 mg/kg), neurotoxicity (depression) was observed (Hazleton Labs 1964). No other effects occurring at sublethal or lethal doses were reported in acute oral studies, and studies did not assess comprehensive toxicological endpoints. Therefore, data are not adequate to derive an acute-duration oral MRL.

Agency Contact (Chemical Manager): Melanie Buser

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Isophorone
CAS Numbers:	78-59-1
Date:	December 1989 March 2017—Updated literature search
Profile Status:	Final
Route:	Oral
Duration:	Intermediate
***MRL*:**	3 mg/kg/day
Critical Effect:	NOAEL
Reference:	AME Inc. 1972a
Point of Departure:	NOAEL of 311.8 mg/kg/day
Uncertainty Factor:	100
LSE Graph Key:	4R
Species:	Rat

MRL Summary: An intermediate-duration oral MRL of 3 mg/kg/day was derived for isophorone. The MRL is based on a NOAEL of 311.8 mg/kg/day reported in a dietary study in rats (AME Inc. 1972a). The NOAEL was divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: The AME Inc. (1972a) study examined comprehensive toxicological endpoints, including histopathological assessments of tissues. No adverse effects of isophorone were observed.

Other intermediate-duration oral studies examining comprehensive toxicological endpoints did not identify any adverse effects of isophorone (AME Inc. 1972b; NTP 1986). AME Inc. (1972b) reported a NOAEL of 150 mg/kg/day for exposure of dogs administered isophorone by capsule for 90 days, 5 days/week. NTP (1986) also evaluated exposure of rats and mice by gavage for 16 days or 13 weeks. The following values were identified as NOAELs for adverse effects or doses at which no lethality occurred: 1,000 mg/kg/day for decreased body weight in rats exposed for 16 days; 500 mg/kg/day for staggering observed in mice exposed for 16 days; 500 mg/kg/day for lethargy and for no lethality in rats exposed for 13 weeks; and 500 mg/kg/day for stagger in mice exposed for 13 weeks.

Selection of the Principal Study: The AME Inc. (1972b) and NTP (1986) 13-week studies identified similar NOAEL values: 311.8 mg/kg/day for no adverse effects in rats exposed to isophorone in the diet (AME Inc. 1972b) and 500 mg/kg/day for lethargy and death in rats and stagger in mice exposed by gavage (NTP 1986). The AME Inc. (1972b) study was selected as the principal study because dietary exposure is considered more relevant to humans than gavage exposure.

Summary of the Principal Study:

AME Inc. 1972a. 90-Day subchronic toxicity of isophorone in the rat (final report). Submitted by Affiliated Medical Enterprises, Inc. to the U.S. Environmental Protection Agency under TSCA 8D. OTS0205975.

Groups of 20 female rats were exposed to dietary isophorone for 90 days. Based on food consumption and body weight, daily doses were 0, 78.9, 163.8, 311.8 mg/kg/day. The following parameters were assessed: body weight, food intake, clinical signs, organ weight, serum (blood) chemistry, urinalysis,

gross necropsy, and histopathology. Relative to controls, no adverse effects of isophorone were observed in any dose group. Thus, a NOAEL of 311.8 mg/kg/day was identified for this study.

Selection of the Point of Departure for the MRL: The NOAEL of 311.8 mg/kg/day was selected as the basis of the MRL.

Uncertainty Factor: The NOAEL was divided by a total uncertainty factor of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

Other Additional Studies or Pertinent Information that Lend Support to this MRL: As noted previously, intermediate-duration oral studies have also identified several NOAEL values for isophorone.

Agency Contact (Chemical Manager): Melanie Buser

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Isophorone
CAS Numbers:	78-59-1
Date:	December 1989 March 2017—Updated literature search
Profile Status:	Final
Route:	Oral
Duration:	Chronic
***MRL*:**	0.2 mg/kg/day
Critical Effect:	Hepatic, renal and gastrointestinal lesions
Reference:	NTP 1986
Point of Departure:	LOAEL of 179 mg/kg/day
Uncertainty Factor:	1,000
LSE Graph Key:	11M
Species:	Mouse

MRL Summary: A chronic-duration oral MRL of 0.2 mg/kg/day was derived for isophorone. The MRL is based on a LOAEL of 179 mg/kg/day (adjusted for intermittent exposure from 250 mg/kg/day) for lesions of the liver, kidney, and gastrointestinal tract reported in a gavage study in mice (NTP 1986). The LOAEL was divided by a total uncertainty factor of 100 (10 for use of a LOAEL,10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: The NTP (1986) study examined comprehensive toxicological endpoints, including histopathological assessments of tissues. At the lowest dose tested (250 mg/kg/day administered by gavage 5 days/week for 103 weeks), non-neoplastic lesions were observed in male mice in the gastrointestinal tract (hyperkeratosis of the forestomach), liver (hepatocytomegaly), and kidney (chronic focal inflammation). It is not possible to determine which of these findings were the most sensitive, as lower doses were not evaluated

The NTP (1986) study also evaluated effects of chronic-duration oral exposure to isophorone in rats at the same doses as in mice. At a dose of 250 mg/kg/day, alpha-2µ-globulin-induced nephropathy was observed in male rats. At the 500 mg/kg/day dose, renal tumors subsequent to alpha-2µ-globulin-induced nephropathy were observed. As discussed in the profile, this effect is unique to male rats and is not toxicologically relevant to human health (EPA 1991; Swenberg 1993). No other effects were observed in rats. Thus, the most sensitive effects of chronic-oral exposure to isophorone were selected as the critical effect for derivation of the MRL.

Selection of the Principal Study: One study evaluated the effects of chronic-duration oral exposure to isophorone in rats and mice (NTP 1986). The study was well-conduced with appropriate controls and examined comprehensive toxicological endpoints.

Summary of the Principal Study:

NTP. 1986. Technical report series no. 291. Toxicology and carcinogenesis studies of isophorone (CAS No. 78-59-1) in F344/N rats and B6C3Fl mice (gavage studies). National Toxicology Program. Research Triangle Park, NC: U.S. Department of Health and Human Services. Public Health Service, National Institutes of Health, NIH publication no. 86-2547.

Groups of 50 male and female mice were exposed to 0 (vehicle control), 250, or 500 mg/kg/day isophorone administered by gavage 5 days/week for 103 weeks. The following parameters were assessed:

body weight, clinical signs, and gross and microscopic evaluation of comprehensive tissues. In the 250 and 500 mg/kg/day groups, non-neoplastic lesions were observed in male mice in the gastrointestinal tract (hyperkeratosis of the forestomach), liver (hepatocytomegaly), and kidney (chronic focal inflammation). Incidence data for these lesions are shown in Table A-1. In the 500 mg/kg/day group, lymphoma and tumors of the liver and skin were observed. In female mice, hyperkeratosis of the forestomach was observed in 10% of mice, compared to 2% in controls. However, the incidences of hepatocytomegaly and chronic focal inflammation of the kidney in female mice in both isophorone treatment groups were similar to controls.

Table A-1. Non-neoplastic Lesions in Mice exposed to Isophorone for 103 Weeks

	Dose (mg/kg/day)[a]		
Lesion type	Vehicle control	250	500
Gastrointestinal (hyperkeratosis of forestomach)	0/47	5/49 (10%)	4/49 (8%)
Liver (hepatocytomegaly)	23/48 (48%)	39/50 (78%)	37/50 (74%)
Kidney (chronic focal inflammation)	7/48 (15%)	18/50 (36%)	21/50 (42%)

[a]Administered by gavage 5 days/week.

Source: NTP 1986

Selection of the Point of Departure for the MRL: The LOAEL of 179 mg/kg/day (adjusted for intermittent exposure from 250 mg/kg/day) for non-neoplastic lesions of the gastrointestinal tract, liver, and kidney was selected as the basis of the MRL. Note that benchmark dose analysis to determine the point of departure was not considered valid because the incidence of all lesions reached an apparent maximum at the lowest dose tested.

Adjustment for Intermittent Exposure: The LOAEL was adjusted for intermittent exposure (5 days/week).

Uncertainty Factor: The LOAEL was divided by a total uncertainty factor of 1,000:

- 10 for use of a LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The NTP (1986) study is the only study that evaluated chronic-duration oral exposure to isophorone (see discussion above).

Agency Contact (Chemical Manager): Melanie Buser

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR ISOPHORONE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to isophorone.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions for isophorone. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of isophorone have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of isophorone are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

Table B-1. Inclusion Criteria for the Literature Search and Screen

Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals

B.1.1 Literature Search

The current literature search was intended to update the health effects sections of the existing toxicological profile for isophorone (ATSDR 1989), thus, the literature search was restricted to studies published between January 1987 to March 2017.

The following main databases were searched in March 2017:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for isophorone. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to isophorone were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
03/2017	(("isophorone"[supplementary concept] OR 78-59-1[rn] OR 2BR99VR6WA[rn] OR "isophorone"[nm]) AND (1987/01/01 : 3000[dp] OR 1987/01/01 : 3000[mhda])) OR (("1,1,3-Trimethyl-3-cyclohexene-5-one"[tw] OR "3,5,5-trimethyl-2-Cyclohexen-1-one"[tw] OR "3,5,5-Trimethyl-2-cyclohexen-1-on"[tw] OR "3,5,5-Trimethyl-2-cyclohexenone"[tw] OR "3,5,5-Trimetil-2-cicloesen-1-one"[tw] OR "Isoacetophorone"[tw] OR "Isoforon"[tw] OR "Isoforone"[tw] OR "Isooctopherone"[tw] OR "Isophorone"[tw] OR "Izoforon"[tw] OR "3,5,5-Trimethylcyclohex-2-enone"[tw]) AND (1987/01/01 : 3000[dp] OR 1987/01/01 : 3000[crdat] OR 1987/01/01 : 3000[edat]))
Toxline	
03/2017	("1 1 3-trimethyl-3-cyclohexene-5-one" OR "3 5 5-trimethyl-2-cyclohexen-1-one" OR "3 5 5-trimethyl-2-cyclohexen-1-on" OR "3 5 5-trimethyl-2-cyclohexenone" OR "3 5 5-trimetil-2-cicloesen-1-one" OR "isoacetophorone" OR "isoforon" OR "isoforone" OR "isooctopherone" OR "isophorone" OR "izoforon" OR "3 5 5-trimethylcyclohex-2-enone" OR 78-59-1 [rn]) AND 1987:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
03/2017	(FILE 'HOME' ENTERED AT 12:57:19 ON 31 MAR 2017) FILE 'TOXCENTER' ENTERED AT 12:57:56 ON 31 MAR 2017 CHARGED TO COST=EH011.13.01.01 L1 1115 SEA 78-59-1 L2 1041 SEA L1 NOT TSCATS/FS L3 883 SEA L2 NOT PATENT/DT L4 704 SEA L3 AND PY>=1987 ACTIVATE TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)

Table B-2. Database Query Strings

Database search date	Query string
	L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (NONHUMAN MAMMALS)/ORGN
	L35 QUE L33 OR L34
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L37 QUE L35 OR L36

	L38 424 SEA L4 AND L37
	L39 6 SEA L38 AND MEDLINE/FS
	L40 27 SEA L38 AND BIOSIS/FS
	L41 357 SEA L38 AND CAPLUS/FS
	L42 34 SEA L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)

Table B-2. Database Query Strings

Database search date	Query string
	L43 394 DUP REM L39 L40 L42 L41 (30 DUPLICATES REMOVED) L*** DEL 6 S L38 AND MEDLINE/FS L*** DEL 6 S L38 AND MEDLINE/FS L44 6 SEA L43 L*** DEL 27 S L38 AND BIOSIS/FS L*** DEL 27 S L38 AND BIOSIS/FS L45 26 SEA L43 L*** DEL 357 S L38 AND CAPLUS/FS L*** DEL 357 S L38 AND CAPLUS/FS L46 331 SEA L43 L*** DEL 34 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 34 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L47 31 SEA L43 L48 388 SEA (L44 OR L45 OR L46 OR L47) NOT MEDLINE/FS D SCAN L48

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
03/2017	Compound searched: 78-59-1
NTP	
03/2017	78-59-1 Isophorone
NPIRS	
mo/year	PC Codes searched: xxxxxx; xxxxxx
NIH RePORTER	
10/2017	"1,1,3-Trimethyl-3-cyclohexene-5-one" OR "3,5,5-trimethyl-2-Cyclohexen-1-one" OR "3,5,5-Trimethyl-2-cyclohexen-1-on" OR "3,5,5-Trimethyl-2-cyclohexenone" OR "3,5,5-Trimetil-2-cicloesen-1-one" OR "Isoacetophorone" OR "Isoforon" OR "Isoforone" OR "Isooctopherone" OR "Isophorone" OR "Izoforon" OR "3,5,5-Trimethylcyclohex-2-enone" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2017 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 748
- Number of records identified from other strategies: 28
- Total number of records to undergo literature screening: 776

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on isophorone:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

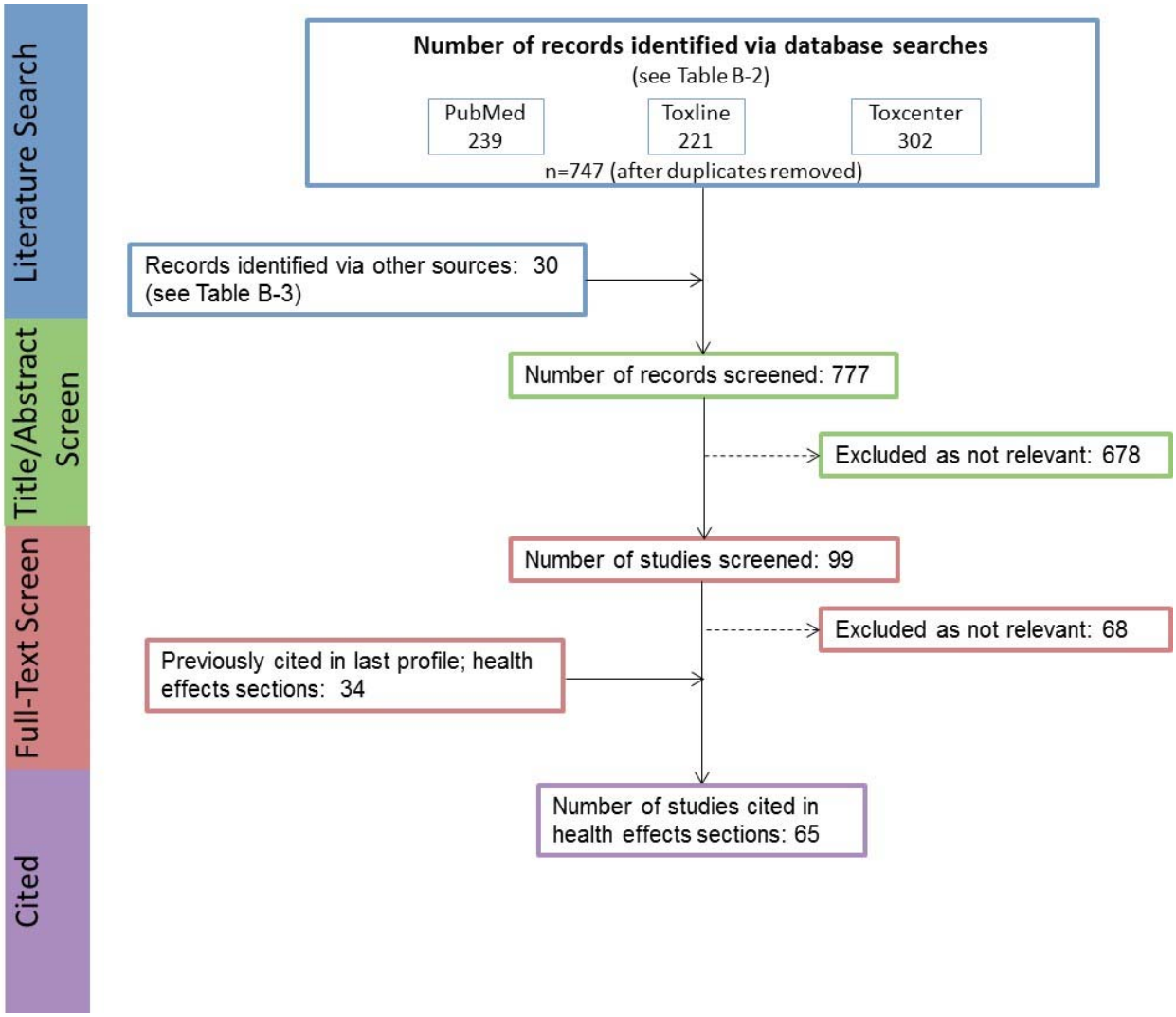
- Number of titles and abstracts screened: 777
- Number of studies considered relevant and moved to the next step: 99

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 99
- Number of studies cited in the health effects sections of the existing toxicological profile: 34
- Total number of studies cited in health effects sections of the profile: 65

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. March 2017 Literature Search Results and Screen for Isophorone



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints 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?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives 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.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance 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. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, 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 that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint 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 endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (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 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 levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures 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 and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used 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 NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page C-5)

(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. Typically, when sufficient data exist, 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 figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are 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) Figure key. 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 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, 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.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse 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 endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. 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. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

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 chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints 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) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

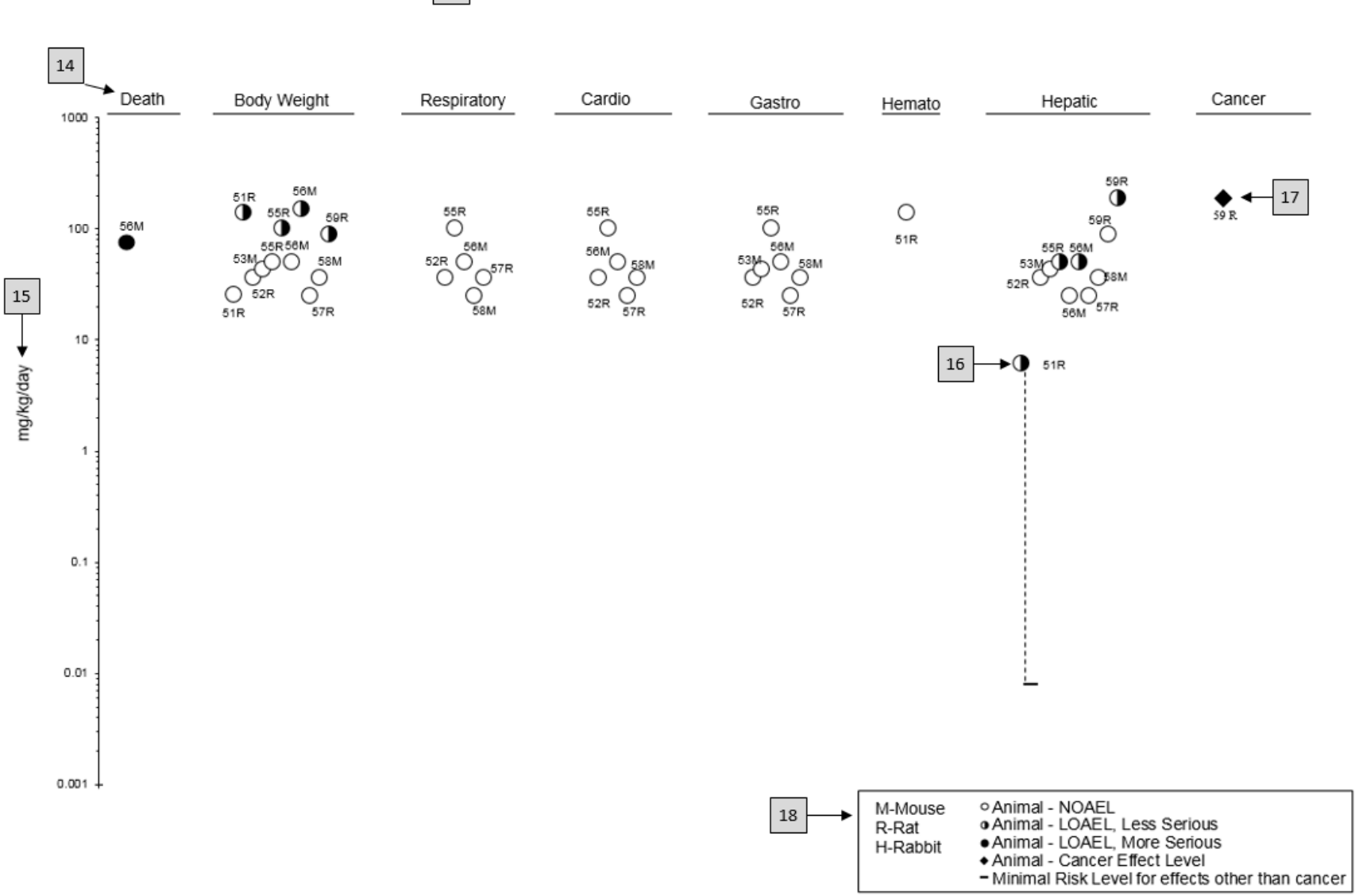
[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX C

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX D. 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 may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:
Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

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 (see https://www.atsdr.cdc.gov/MHMI/index.asp). 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 (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

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 • Web Page: https://www.cdc.gov/nceh/.

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, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/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 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

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@AOEC.ORG • Web Page: http://www.aoec.org/.

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, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to 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, 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 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) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

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—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a 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 that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

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, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

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

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk 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 response or amount of the response.

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 effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—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.

Excretion—The process by which metabolic waste products are removed from the body.

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.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and 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.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases 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.

***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 that 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 that 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.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

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—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the 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, which are changes 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 hazardous substance.

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. Although effects may be produced at this dose, 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 (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that 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 that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work 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 (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict 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—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, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. 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—A type of physiologically based dose-response model that 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, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air 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 a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration 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 RfC is 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 oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

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

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. 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 causal 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 hazardous substance.

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

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

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

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 it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), 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 from data 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 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act

FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey

NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
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

USNRC	U.S. Nuclear Regulatory Commission
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
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result