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.

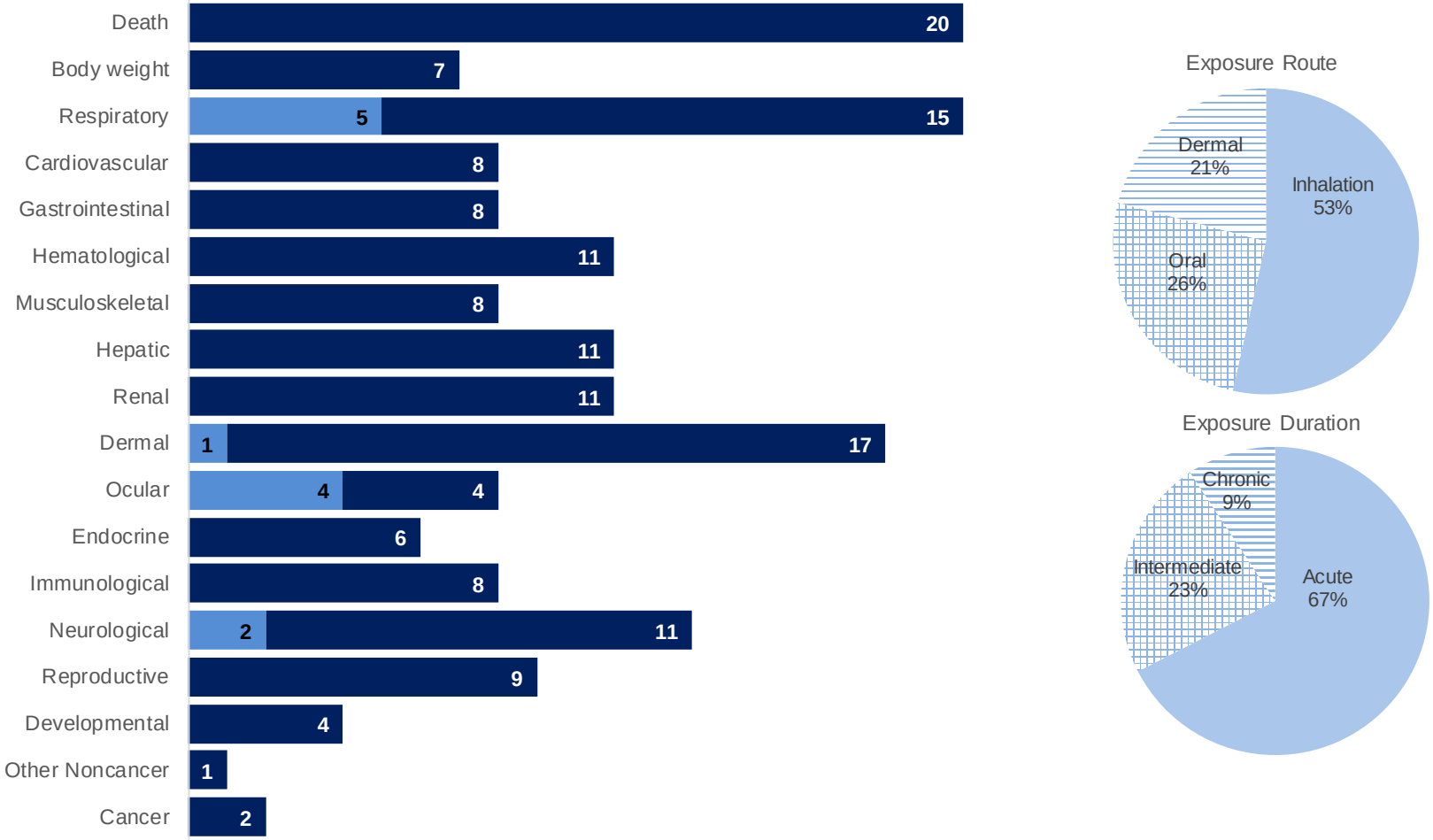
- **Neurological:** Neurological effects, including CNS depression, lethargy, neurobehavioral effects, and staggering have been observed in laboratory animals following acute-duration inhalation exposure and acute- and intermediate-duration oral exposure to isophorone.

- **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)

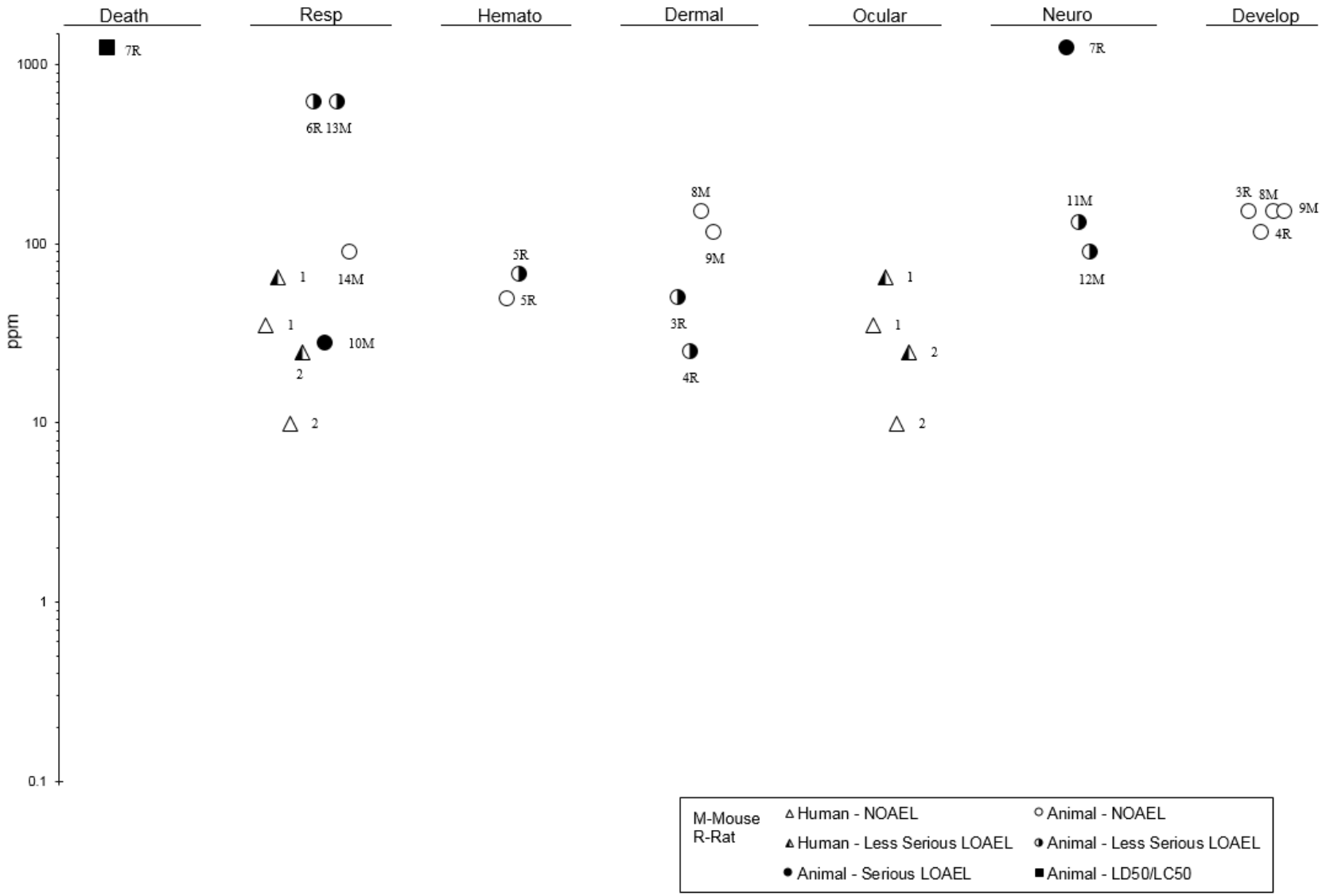


Figure 2-2. Levels of Significant Exposure to Isophorone – Inhalation
Intermediate (15-364)

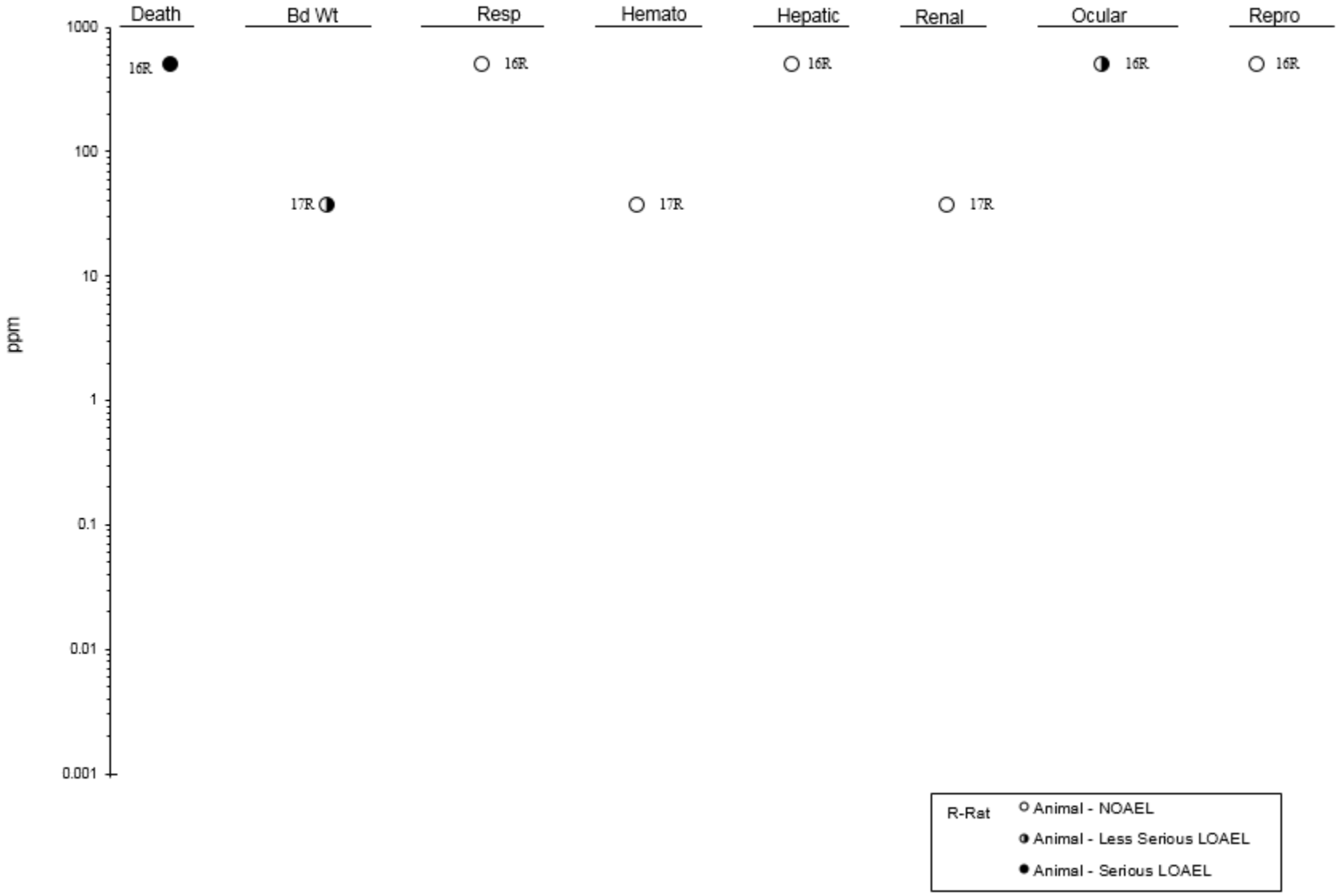


Figure 2-2. Levels of Significant Exposure to Isophorone – Inhalation
Chronic (≥365 days)

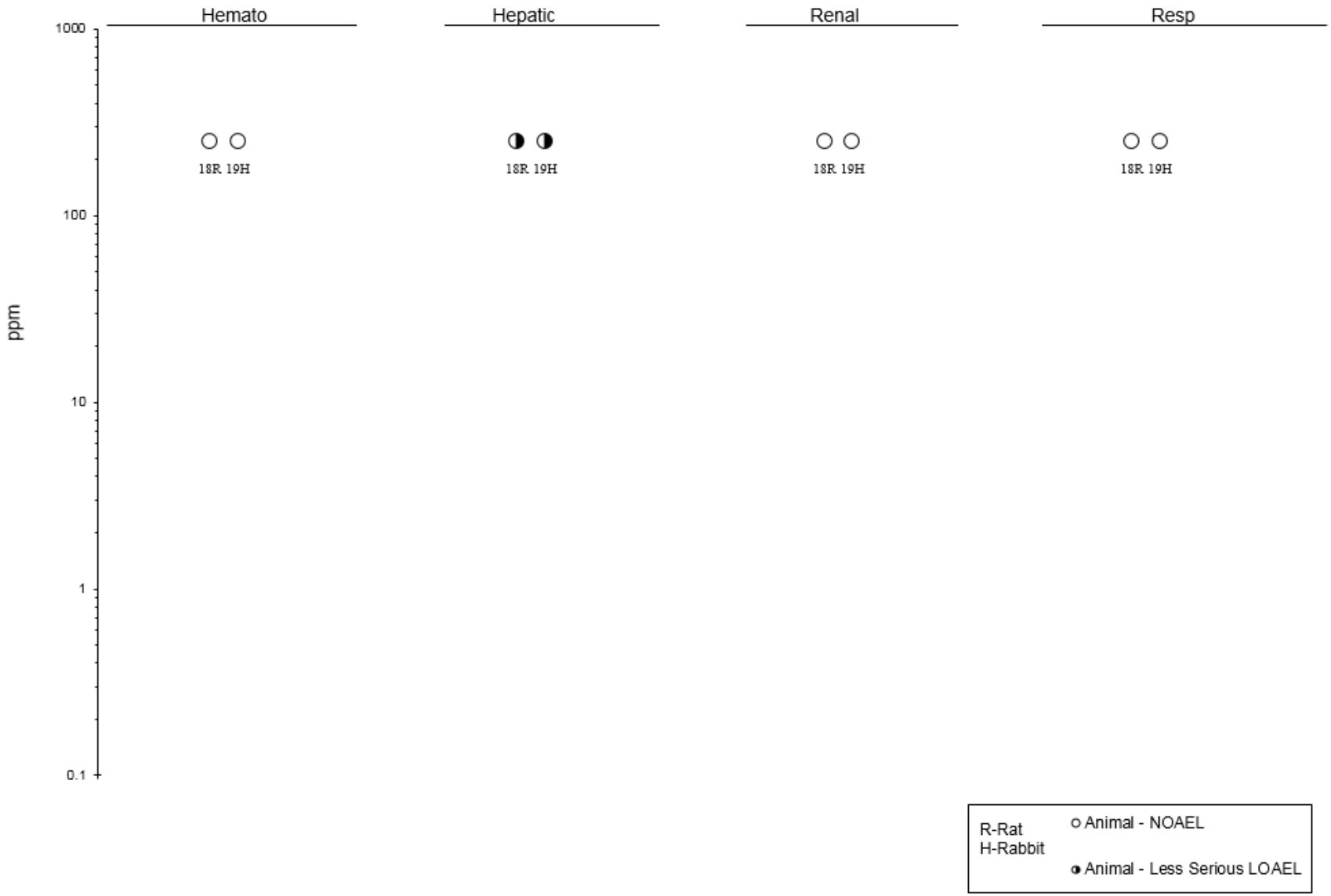


Table 2-2. Levels of Significant Exposure to Isophorone – Oral

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)

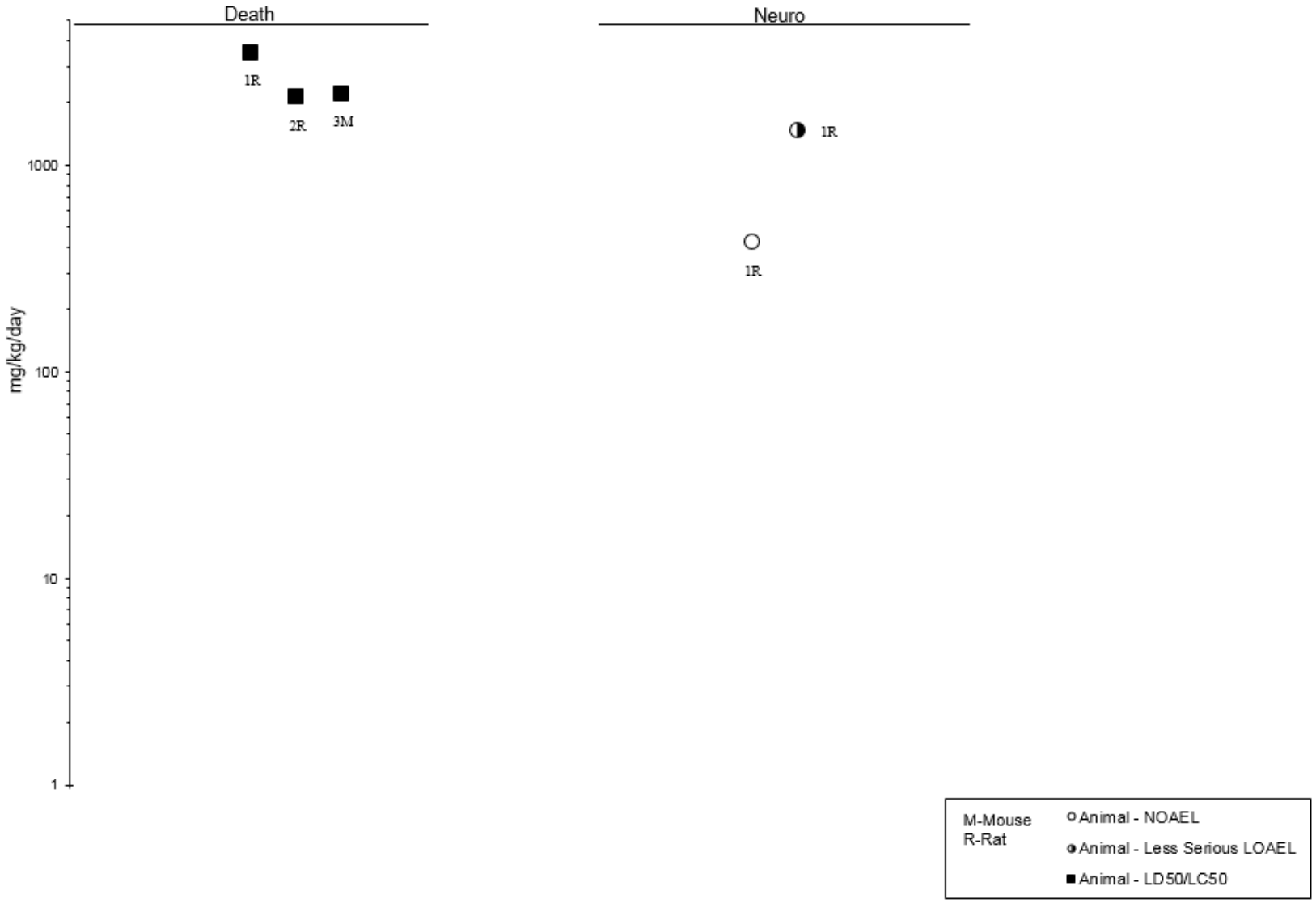


Figure 2-3. Levels of Significant Exposure to Isophorone – Oral
Intermediate (15-364)

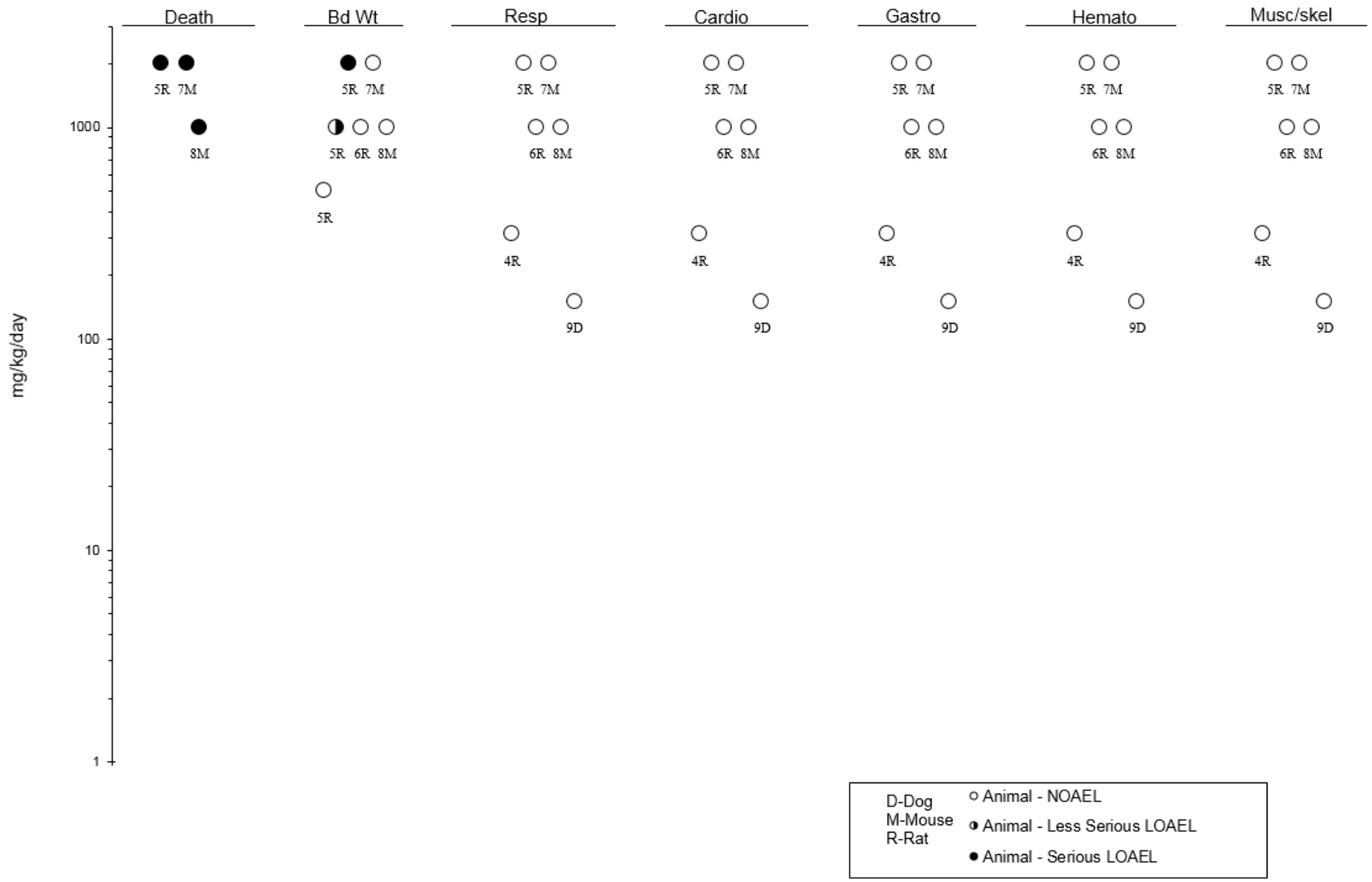


Figure 2-3. Levels of Significant Exposure to Isophorone – Oral
Intermediate (15-364)

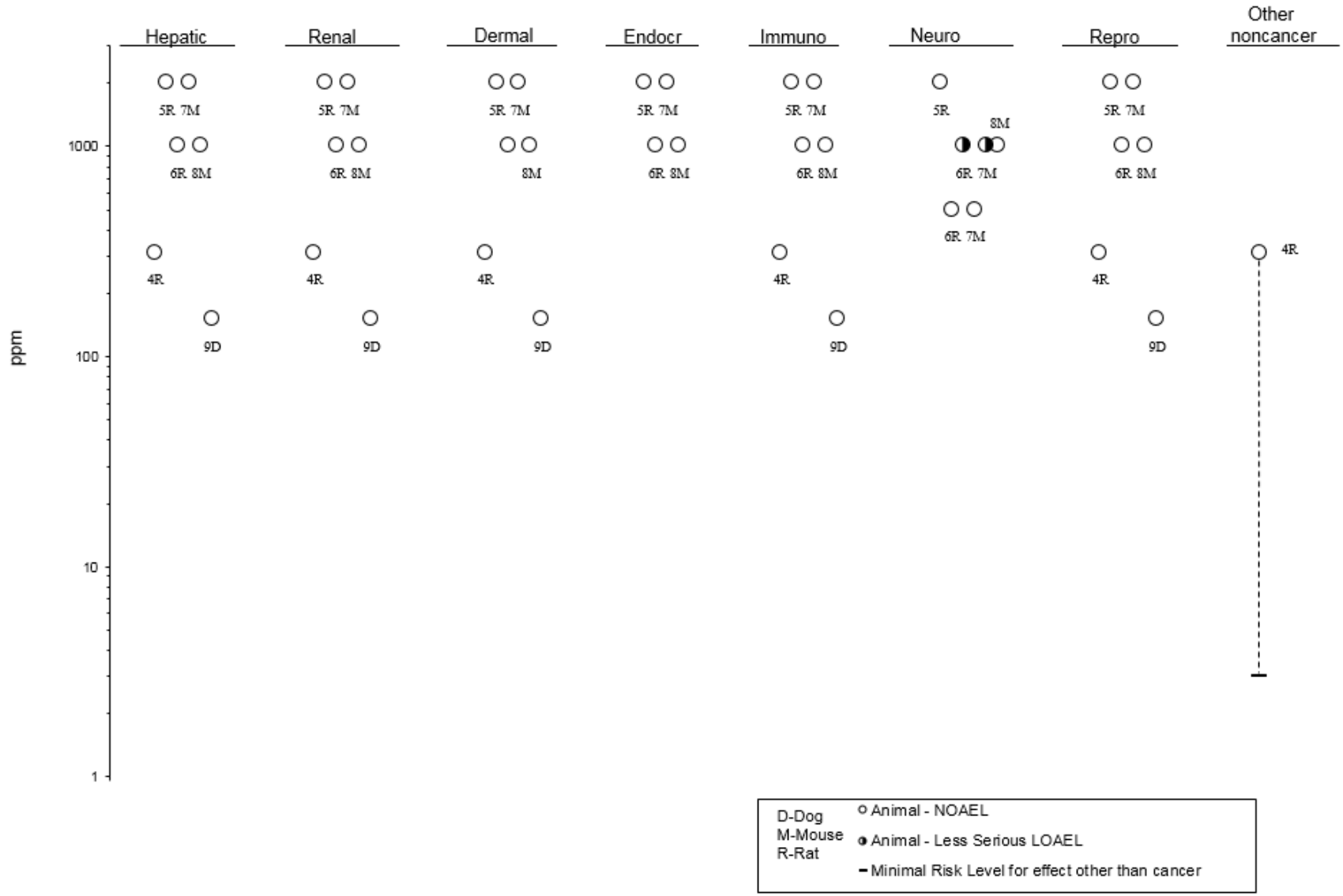


Figure 2-3. Levels of Significant Exposure to Isophorone – Oral

Chronic (≥365 days)

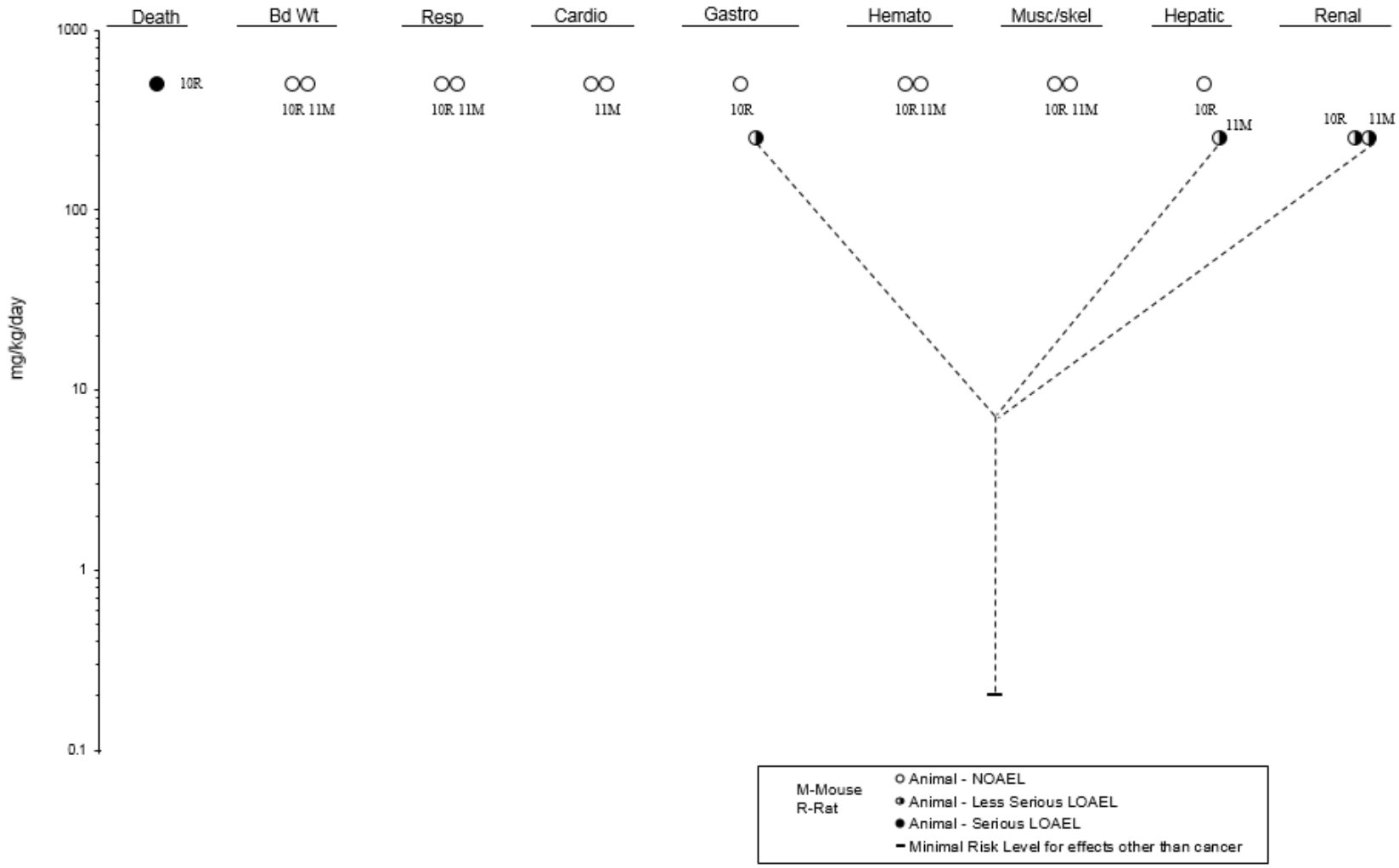


Figure 2-3. Levels of Significant Exposure to Isophorone – Oral

Chronic (≥365 days)

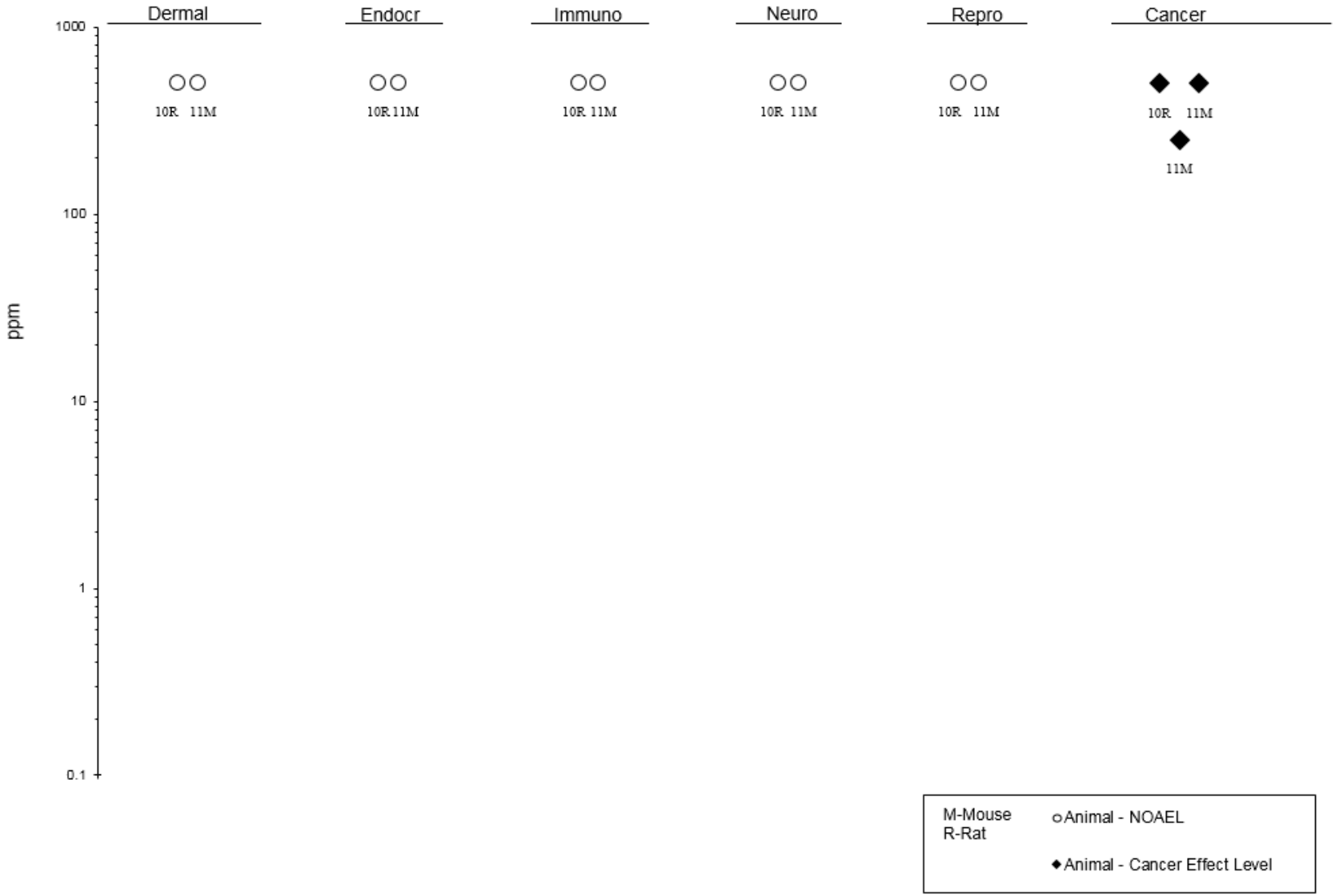


Table 2-3. Levels of Significant Exposure to Isophorone – Dermal

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