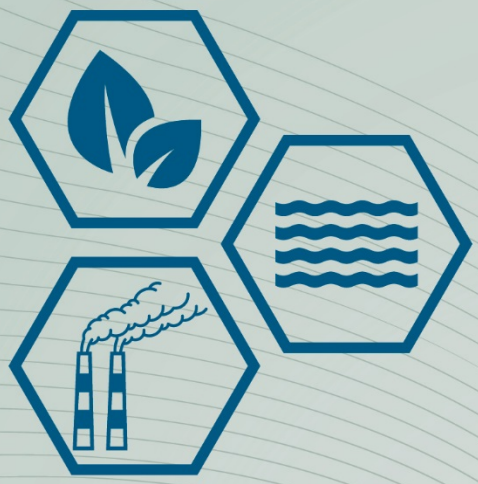

Toxicological Profile for 2-Hexanone

February 2020

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

CS274127-A

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

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.

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*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
February 2020	Final toxicological profile released
April 2018	Draft for public comment toxicological profile released
September 1992	Final toxicological profile released

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These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

2-Hexanone (Chemical Abstracts Service [CAS] Registry Number: 591-78-6; common synonym: methyl-n-butyl ketone) is a waste product of wood pulping, coal gasification, and *in situ* oil shale operations (Pellizzari et al. 1979). 2-Hexanone dissolves very easily in water and can evaporate rapidly into the air as a vapor. Once it is introduced into the environment, 2-hexanone may be degraded by atmospheric photooxidation and direct photolysis or degraded by biodegradation mediated by microorganisms found in most sediment, soils, and water (Atkinson 1989; Babeu and Vaishnav 1987; Calvert and Pitts 1966). 2-Hexanone is likely to migrate through the soil and into groundwater since it is expected to have very high mobility in soils. Volatilization of 2-hexanone from water surfaces has been observed. A large fraction of vapor-phase 2-hexanone will dissolve in water droplets in the atmosphere, and precipitation may be an important physical removal mechanism (Thomas 1990). Bioconcentration of this compound in aquatic organisms is not expected to occur (Lande et al. 1976).

Significant exposure of the general population to 2-hexanone is not likely at present, as it is no longer manufactured, processed, or used for commercial purposes in the United States. 2-Hexanone was formerly used as a solvent in lacquers and varnish removers, and in various chemical substances. Due to the harmful health effects of this chemical, the lone U.S. producer of 2-hexanone discontinued its production in 1979 and sold its remaining reserves by 1981 (EPA 1987). However, while 2-hexanone is no longer manufactured or used in the United States, it may be indirectly generated as a waste product during processing at coal gasification plants, *in situ* oil shale operations, and wood pulping mills (Pellizzari et al. 1979; TCEQ 2011); therefore, human exposure to 2-hexanone may occur. 2-Hexanone has been detected in drinking water and soil near hazardous waste sites, so the general population living near an industry or hazardous waste site that releases the liquid into waste water or the gas form into the surrounding air has an increased risk of exposure (CLPSD 1989; Lucas 1984). In the past decade, there has been an increase in oil and natural gas production from shale in the United States (EIA 2016), and 2-hexanone has been detected at low levels (Grinberg 2014; Hawthorne and Sievers 1984; Pellizzari et al. 1979) in air samples near these operations and aqueous samples related to these processes. Exposure to small amounts of 2-hexanone may also occur by ingestion of foods in which it occurs. It is possible that exposure to small amounts of 2-hexanone may occur through imported products containing 2-hexanone. Individuals may still be exposed from consumer products manufactured prior to 1982, such as lacquers, primers, sealers, and thinners that contain 2-hexanone.

When 2-hexanone was still being manufactured, occupational exposure may have occurred through inhalation and dermal contact. It is unlikely that many persons are currently occupationally exposed to 2-hexanone, other than as a degradation product resulting from wood pulping, *in situ* oil shale processing, or coal gasification operations (EPA 1987; RTECS 2009).

No biomarkers specific to 2-hexanone are currently identified to indicate if exposure to 2-hexanone has occurred.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of 2-hexanone primarily comes from inhalation and oral studies in laboratory animals, with some limited information on effects in humans. Results of these studies provide strong evidence that the nervous system is the most sensitive target of 2-hexanone (Figures 1-1 and 1-2). Other targets include toxicity to male reproductive organs, decreased body weight, possible developmental effects, and effects to the musculoskeletal systems. As stated in Section 1.1, significant exposure of the general population to 2-hexanone is not likely because it is no longer manufactured, processed, or used for commercial purposes in the United States.

It should be noted that most animal studies tested only one concentration/dose of 2-hexanone; therefore, little information on dose-response relationships was provided in these studies. Furthermore, very few studies stated the purity of the 2-hexanone tested, with purity of commercial grade 2-hexanone ranging from 70-96% (Topping et al. 2001); contaminants may include methyl isobutyl ketone (MiBK). This is of concern because MiBK has been shown to potentiate the neurotoxicity of 2-hexanone through induction of hepatic microsomal cytochrome P-450 enzymes, resulting in increased production of the 2-hexanone active metabolite, 2,5-hexanedione (ATSDR 1999).

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to 2-Hexanone

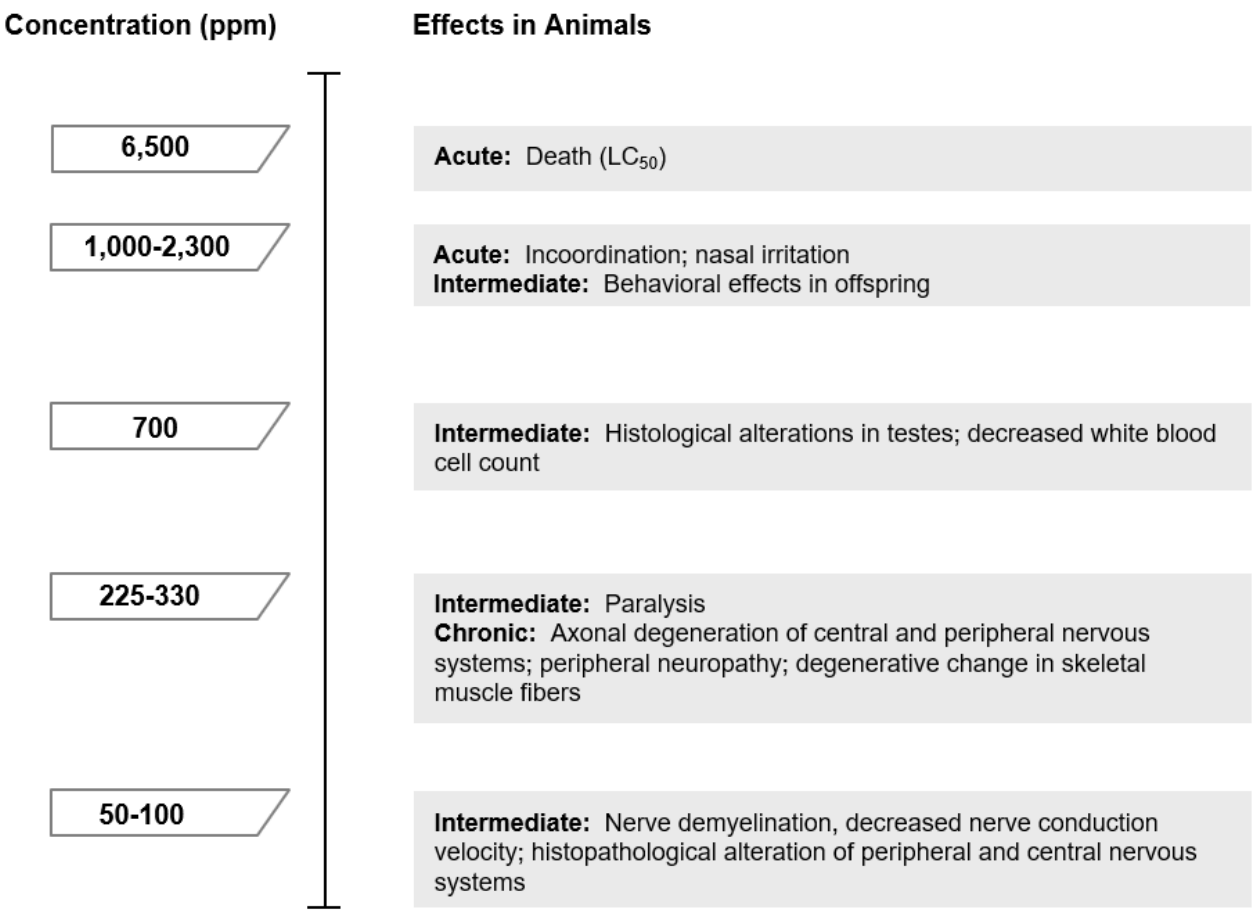
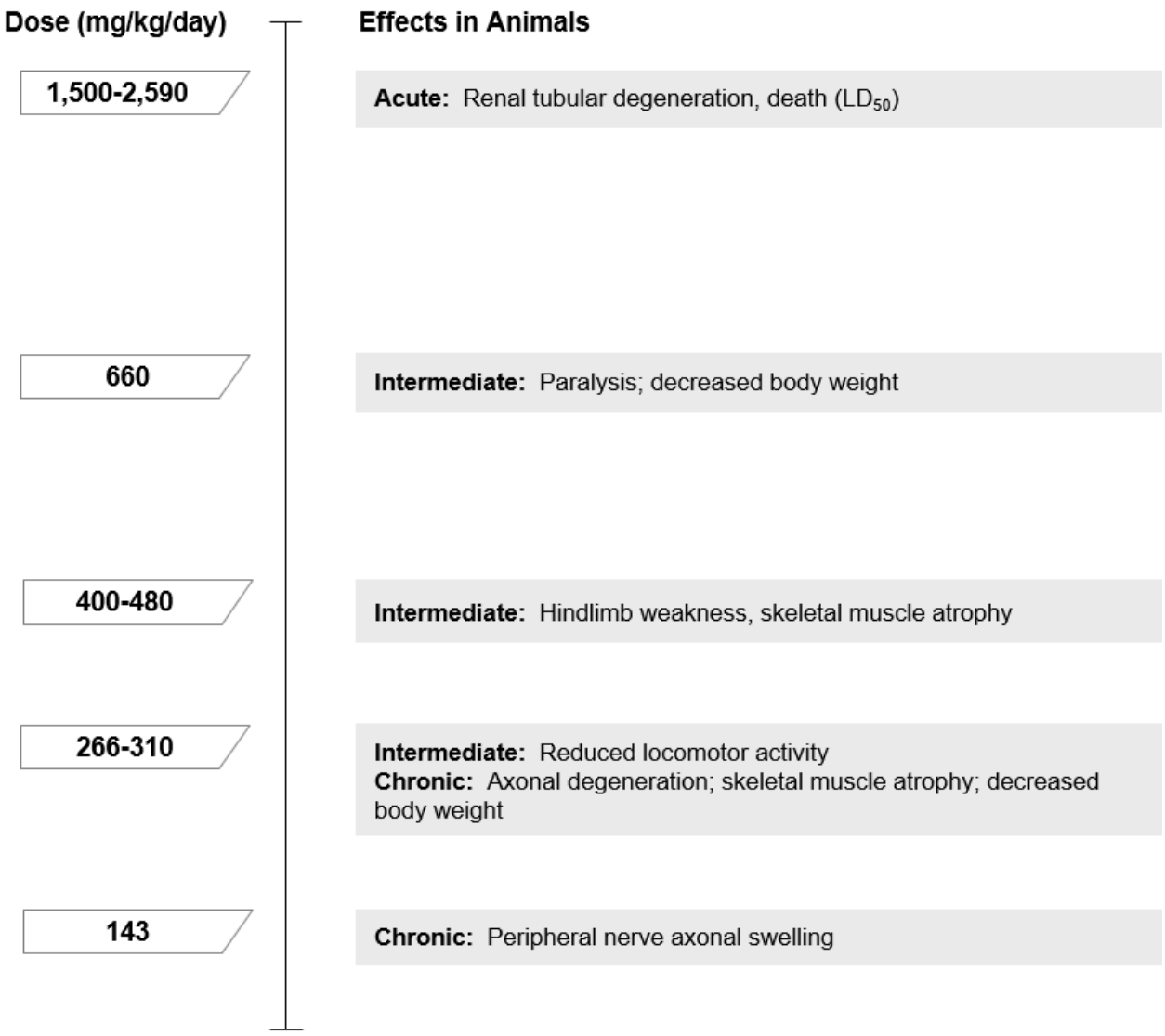


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 2-Hexanone



Neurological Effects. In humans, information on 2-hexanone neurotoxicity is from studies on a population of workers exposed to 2-hexanone in a fabric finishing plant (Allen et al. 1975; Billmaier et al. 1974). Neurological effects attributed to 2-hexanone include peripheral neuropathy characterized by axon and myelin disruption, axonal swellings involving motor and sensory nerves, alterations in nerve conduction velocity, ataxia, sensory deficits, and skeletal muscle weakness accompanied by electromyographic abnormalities. However, lack of reliable exposure data and co-exposure to other chemicals limit the usefulness of these findings other than for hazard identification. In laboratory animals, inhalation and oral exposure to 2-hexanone results in effects to the peripheral nervous system similar to those reported in humans (Abdo et al. 1982; Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Mendell et al. 1974; O'Donoghue and Krasavage 1979; O'Donoghue et al. 1978; Saida et al. 1976; Union Carbide 1977). Involvement of the central nervous system has also been reported in animals (Egan et al. 1980; O'Donoghue and Krasavage 1979). The 2-hexanone metabolite, 2,5-hexanedione, is the toxicologically active chemical responsible for the neurotoxic effects of 2-hexanone (Abdel-Rahman et al. 1978; DiVincenzo et al. 1976; Eben et al. 1979; Krasavage et al. 1980).

Musculoskeletal Effects. Musculoskeletal effects of 2-hexanone appear to be secondary to neurological damage. Muscle weakness has been observed in workers exposed to 2-hexanone, with findings accompanied by electromyographic abnormalities (Allen et al. 1975; Billmaier et al. 1974). 2-Hexanone induced skeletal muscle pathology of neurogenic origin was found in rats following repeated inhalation (Krasavage and O'Donoghue 1977) or oral (O'Donoghue et al. 1978; Union Carbide 1977) exposures. Alterations generally consisted of atrophy and degenerative changes.

Body Weight Effects. In workers exposed to 2-hexanone in a fabric finishing plant, body weight was reduced in some workers with moderate to severe neurological impairment (Allen et al. 1975; Billmaier et al. 1974). However, there was no information regarding the subjects' appetite and/or actual food consumption. These workers regained weight when exposure to 2-hexanone was discontinued. In animal studies, exposure to 2-hexanone also resulted in decreased weight gain in inhalation studies in rats and monkeys (Johnson et al. 1977; Katz et al. 1980; Peters et al. 1981) and in oral studies in rats (Krasavage et al. 1980; O'Donoghue et al. 1978; Union Carbide 1977). However, without data on food consumption in most of these studies, the usefulness of this information is limited.

Reproductive Effects. The evaluation of potential reproductive toxicity of 2-hexanone yielded mixed results. Intermediate-duration inhalation exposure of male rats to 2-hexanone resulted in reduced testes

weight and atrophy of the testicular germinal epithelium of male rats (Katz et al. 1980). However, chronic inhalation exposure of male rats and female cats did not induce microscopic alterations in the reproductive organs of either species (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979). In oral studies, 2-hexanone induced testicular toxicity in male rats when given by gavage (Krasavage et al. 1980), but not when given in the drinking water (O'Donoghue et al. 1978) in comparable doses. Fertility was not assessed in any of these studies.

Developmental Effects. Available data are inadequate to determine if 2-hexanone produces developmental effects, as only one developmental study was identified. In this study, inhalation exposure of rats to 2-hexanone during gestation resulted in reduced maternal weight during gestation, reduced birth weight, and reduced pups per litter, and induced behavioral alterations in the offspring tested at various times between weaning and the geriatric stage (Peters et al. 1981). The investigators concluded that the results suggest that exposure to 2-hexanone may be associated with hyperactivity in the young and subsequent decreased activity in older animals; however, definite conclusions could not be made.

Cancer Effects. Available chronic-duration studies in animals evaluating comprehensive toxicological endpoints did not report any findings of cancer following inhalation or oral exposure (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979; O'Donoghue et al. 1978).

Neither the Department of Health and Human Services (HHS) nor the International Agency for Research on Cancer (IARC) have classified 2-hexanone regarding its carcinogenicity (IARC 2019; NTP 2016). The U.S. Environmental Protection Agency (EPA) stated that "there is inadequate information to assess the carcinogenic potential" of 2-hexanone (EPA 2009a).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database for 2-hexanone was not considered adequate for deriving inhalation MRLs. As presented in Figure 1-3, available inhalation data for 2-hexanone in laboratory animals indicate that the nervous system is the most sensitive toxicity target for all exposure durations.

For oral MRLs, adequate data were available for derivation of a chronic-duration MRL, but not for acute- or intermediate-duration MRLs. Similar to inhalation exposure, available oral exposure data identify the

neurological system as the most sensitive target (Figure 1-4). The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of 2-Hexanone – Inhalation

The neurological system is the most sensitive target of 2-hexanone inhalation exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

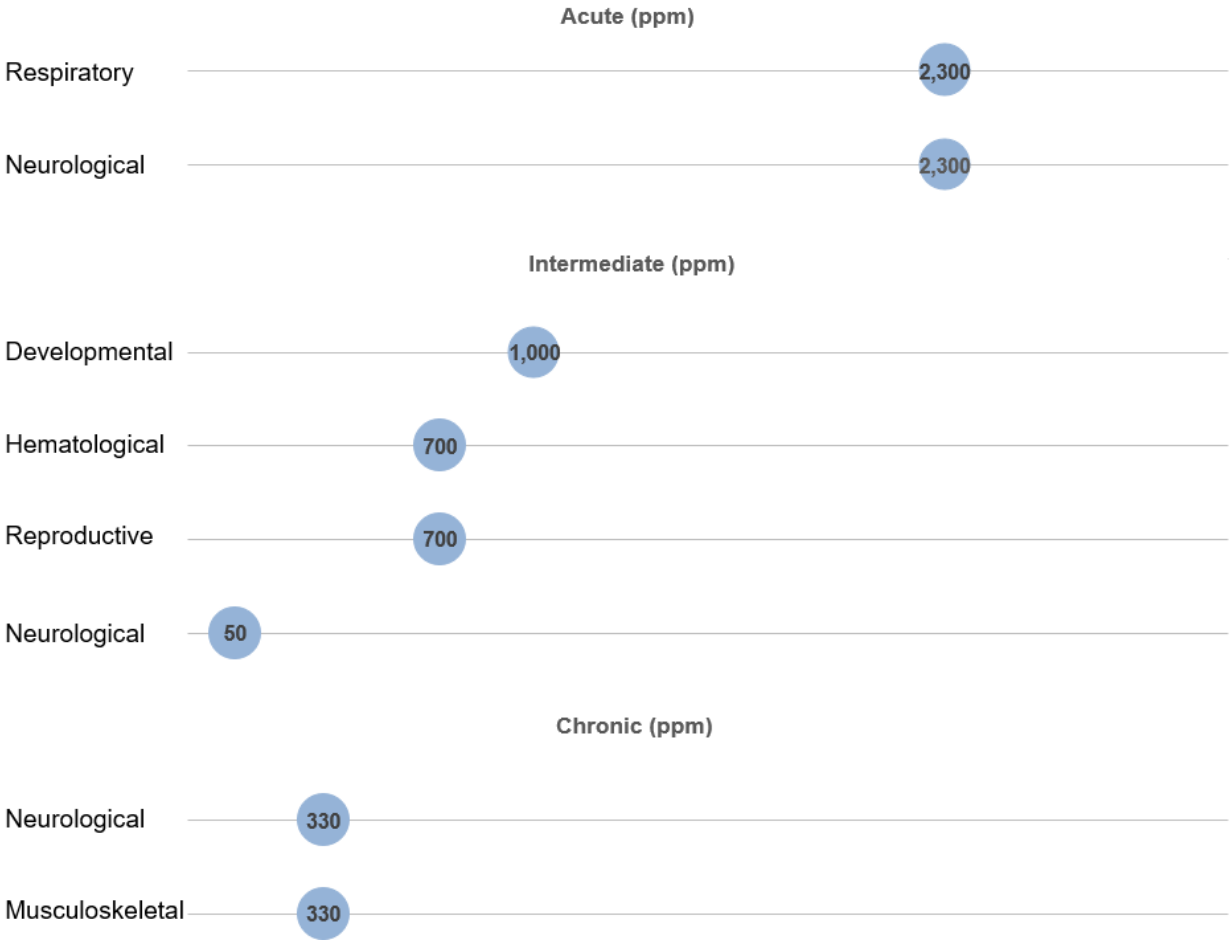


Figure 1-4. Summary of Sensitive Targets of 2-Hexanone – Oral

The neurological system is the most sensitive target of 2-hexanone oral exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

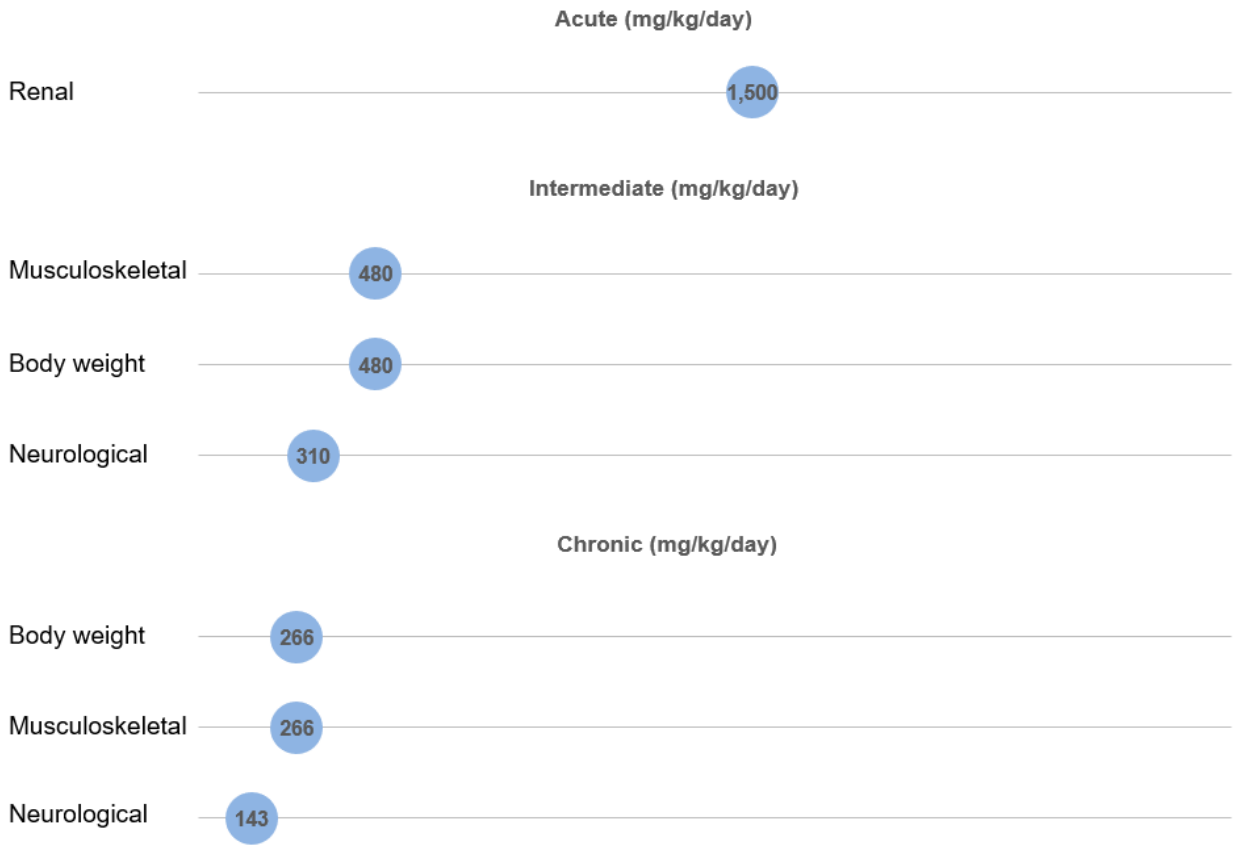


Table 1-1. Minimal Risk Levels (MRLs) for 2-Hexanone[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor and modifying 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	Insufficient data for MRL derivation				
Chronic	0.05	Axonal swelling in spinal cord and peripheral nerves	143 (LOAEL)	UF 1,000 MF 3	O'Donoghue et al. 1978

[a]See Appendix A for additional information.

LOAEL = lowest-observed-adverse-effect level; MF = modifying factor; UF = uncertainty factor

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 2-hexanone. 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.

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 2-hexanone, but may not be inclusive of the entire body of literature.

Animal inhalation studies are presented in Table 2-1 and Figure 2-2, and animal oral studies are presented in Table 2-2 and Figure 2-3; only one dermal study was identified for 2-hexanone.

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.

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 toxicity of 2-hexanone has been evaluated in laboratory animals; limited information on the effects of 2-hexanone in humans comes from studies in workers (Figure 2-1). In humans, almost all available data were obtained from a screening study of 1,157 workers exposed to 2-hexanone in a fabric finishing plant. The primary focus of this study was on neurological effects. Unfortunately, reliable exposure data are not available for this study; furthermore, exposure to other chemicals also occurred. Note that significant exposure of the general population to 2-hexanone is not likely because it is no longer manufactured, processed, or used for commercial purposes in the United States.

Animal data are available for each health effect category and exposure duration category. In animals, most data are from inhalation studies. Endpoints were evaluated for all systems. The most examined endpoints were neurological effects (approximately 25%) and body weight (approximately 12%). Chronic-duration oral and inhalation studies in animals did not report any evidence of cancer. Note that animal studies were conducted with commercial 2-hexanone, with purity ranging from 70-96% (Topping et al. 2001); contaminants may include methyl isobutyl ketone (MiBK). This is of concern because MiBK potentiates the neurotoxicity of 2-hexanone through induction of hepatic microsomal cytochrome P-450 enzymes, resulting in increased production of the 2-hexanone active metabolite, 2,5-hexanedione (ATSDR 1999).

Available data in humans and animals suggest that the nervous system, musculoskeletal system, and effects on body weight are the most sensitive endpoints of 2-hexanone toxicity:

- **Nervous System Endpoints:** Toxicity to the nervous system is the most sensitive target of 2-hexanone. In humans, neurological effects attributed to 2-hexanone include peripheral neuropathy characterized by axon and myelin disruption, axonal swellings involving motor and sensory nerves, alterations in nerve conduction velocity, ataxia, and sensory deficits. In laboratory animals, inhalation and oral exposure to 2-hexanone results in effects to the peripheral nervous system similar to those reported in humans. Toxicity to the central nervous system has also been observed in animal studies.

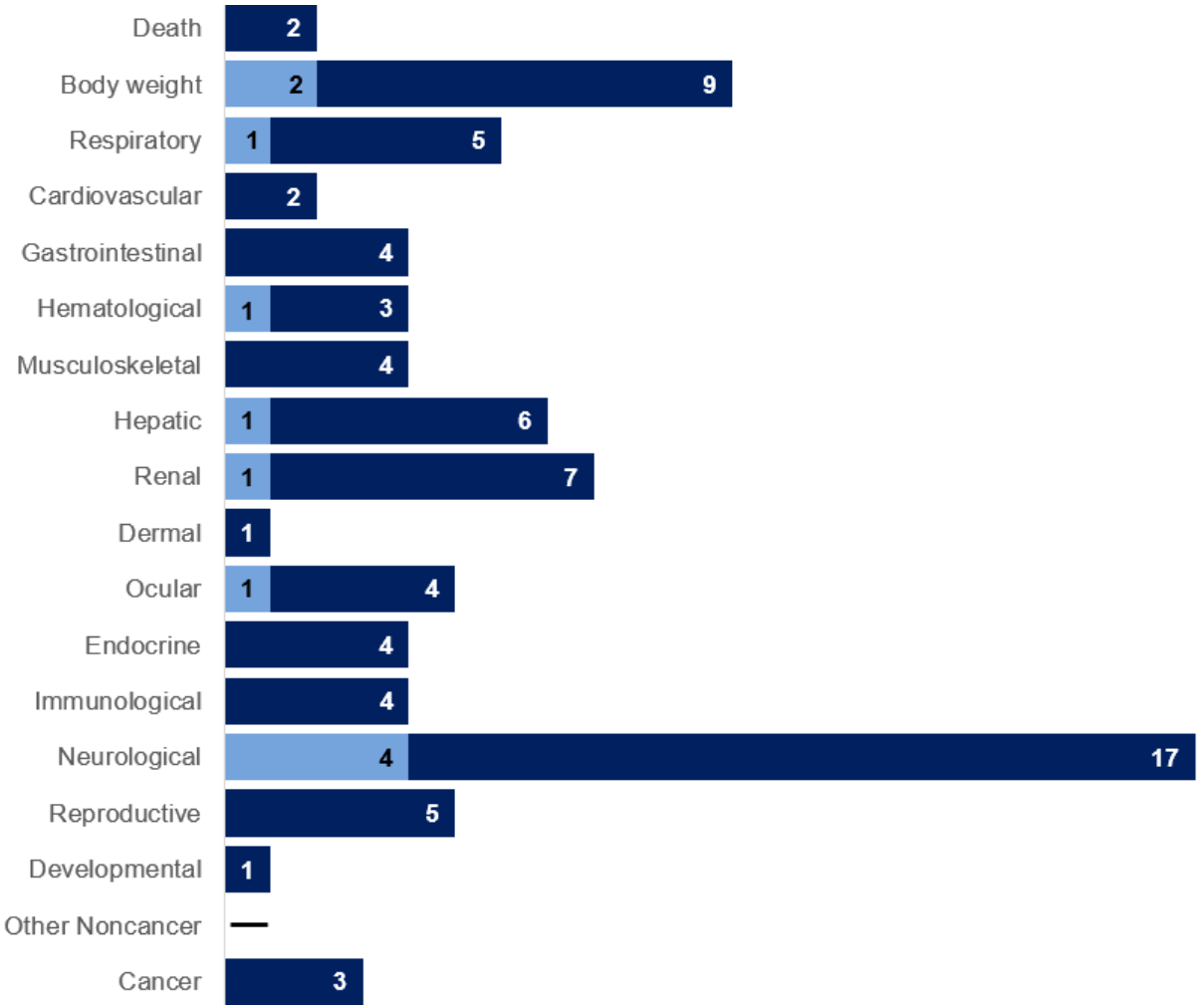
- **Musculoskeletal System Endpoints.** Muscle weakness has been observed in workers exposed to 2-hexanone, with findings accompanied by electromyographic abnormalities. In animals, 2-hexanone induced skeletal muscle pathology, including skeletal muscle atrophy, following repeated inhalation or oral exposure. Alterations generally consisted of atrophy and degenerative changes. These effects are considered secondary to neurological damage.

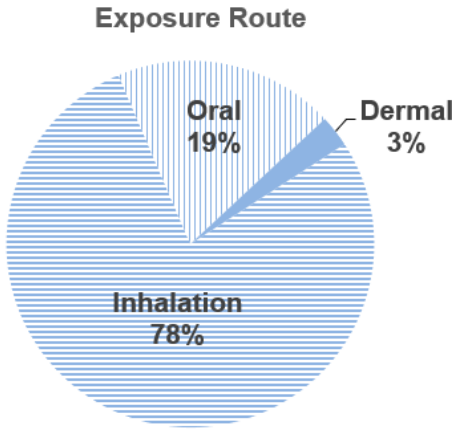
- **Body Weight Endpoint.** In both humans and animals, decreased body weight (humans) and decreased body weight gain (animals) have been observed following 2-hexanone exposure. However, due to lacking information on food intake, the cause of decreased body weight has not been determined.

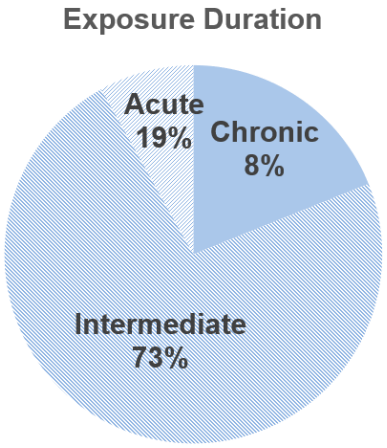
- **Other Endpoints.** Other effects observed in animal studies included male reproductive effects (atrophy of the testicular germinal epithelium), developmental effects (reduced pup weight and hyperactivity), hematological effects (decreased white blood cell count), and renal effects (tubular degeneration). However, these do not appear to be sensitive targets of 2-hexanone toxicity.

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

Most studies examined the potential neurological and body weight effects of 2-hexanone
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)







*Includes studies discussed in Chapter 2. A total of 37 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
ACUTE EXPOSURE									
1	Guinea pig (NS) NS	1 minute	0, 1,000, 2,300	CS	Resp	1,000	2,300		Nasal irritation
Schrenk et al. 1936									
2	Guinea pig (NS) NS	810 minutes	0, 1,000, 2,300, 6,500, 20,000	LE, CS, GN, HP	Death			6,500	Death in 450 minutes
					Neuro	1,000	2,300		Incoordination after 90 minutes of exposure
Schrenk et al. 1936									
INTERMEDIATE EXPOSURE									
3	Monkey 8 M	25–41 weeks 5 day/week 6 hours/day	0, 100, 1,000	BW, CS, NX	Bd wt	100 M			
					Neuro		100 M	1,000 M	Reduced nerve conduction velocity at 100 ppm; 36% reduction in motor nerve conduction velocity
Johnson et al. 1977									
4	Rat (Wistar) 40 NS	6 months 5 days/week 8 hours/day	0, 50	CS, HP	Hepatic	50			
					Renal	50			
					Neuro			50	Sciatic nerve demyelination in 32/40 rats
Duckett et al. 1979									
5	Rat (Sprague-Dawley) 6 M	6 months 7 days/week 22 hours/day	0, 100	BW, CS, HP	Bd wt	100 M			
					Neuro			100 M	Peripheral and central histopathology
Egan et al. 1980									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
6	Rat 10 M	25–29 weeks 5 days/week 6 hours/day	0, 100, 1,000	BW, CS, NX	Bd wt	100 M	1,000 M		Decreased terminal body weight
					Neuro			100 M	45% reduced nerve conduction velocity
Johnson et al. 1977									
7	Rat 5 M	11 weeks 72 hours/week 18 hours/day	0, 700	BC, BW, CS, HP	Bd wt		700 M		Decreased terminal weight
					Hemato			700 M	40% decrease in WBCs
					Neuro			700 M	Severe neuropathy
					Repro			700 M	Decreased testes weight, histopathology
Katz et al. 1980									
8	Rat 4 NS	12 weeks 24 hours/day 7 days/week	0, 400	CS, HP	Neuro			400	Neuropathy
Mendell et al. 1974									
9	Rat 25 F	GDs 0–21 6 hours/day	0, 500, 1,000, 2,000	CS, BW, NX, MX, TG	Develop			1,000 F	Behavioral effects in offspring
Peters et al. 1981									
10	Rat 12 NS	6–9.5 weeks 24 hours/day	0, 225, 400	CS, HP	Neuro			225	Paralysis, histopathology
Saida et al. 1976									
11	Rat 6 NS	4 months 5 days/week 6 hours/day	0, 1,300	BW, CS, HP	Neuro			1,300	Nerve degeneration
Spencer et al. 1975									
12	Cat 4 NS	>8 weeks 24 hours/day 7 days/week	0, 400	CS, HP	Neuro			400 F	Neuropathy, histopathology
Mendell et al. 1974									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
CHRONIC EXPOSURE									
13	Rat (Sprague-Dawley) 18 M	72 weeks 5 days/week 6 hours/day	0, 100, 330	CS, BW, WI, GN, HP	Bd wt	330 M			
					Resp	330 M			
					Gastro	330 M			
					Hemato	330 M			
					Musc/skel	100 M		330 M	Degenerative changes in skeletal muscle fibers
					Renal	330 M			
					Ocular	330 M			
					Endocr	330 M			
					Immuno	330 M			
					Neuro	100 M		330 M	Peripheral neuropathy
					Repro	330 M			
Krasavage and O'Donoghue 1977									
14	Cat (domestic) 4 F	2 years 7 days/week 6 hours/day	0, 100, 330	CS, BW, HE, GN, HP	Bd wt	330 F			
					Resp	330 F			
					Cardio	330 F			
					Gastro	330 F			
					Hemato	330 F			
					Musc/skel	330 F			
					Hepatic	330 F			
					Renal	330 F			
					Ocular	330 F			
					Endocr	330 F			
					Immuno	330 F			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Neuro	100 F		330 F	Axonal degeneration of central and peripheral nervous systems
					Repro	330 F			
O'Donoghue and Krasavage 1979									

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

Bd wt or BW = body weight; Cardio = cardiovascular; CS = clinical signs; Endocr = endocrine; F = female(s); FX = fetal toxicity; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; Hemato = hematological; HP = histopathology; Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = muscular/skeletal; MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; Repro = reproductive; Resp = respiratory; TG = teratogenicity; WBC = white blood cell; WI = water intake

Figure 2-2. Levels of Significant Exposure to 2-Hexanone – Inhalation

Acute (≤14 days)

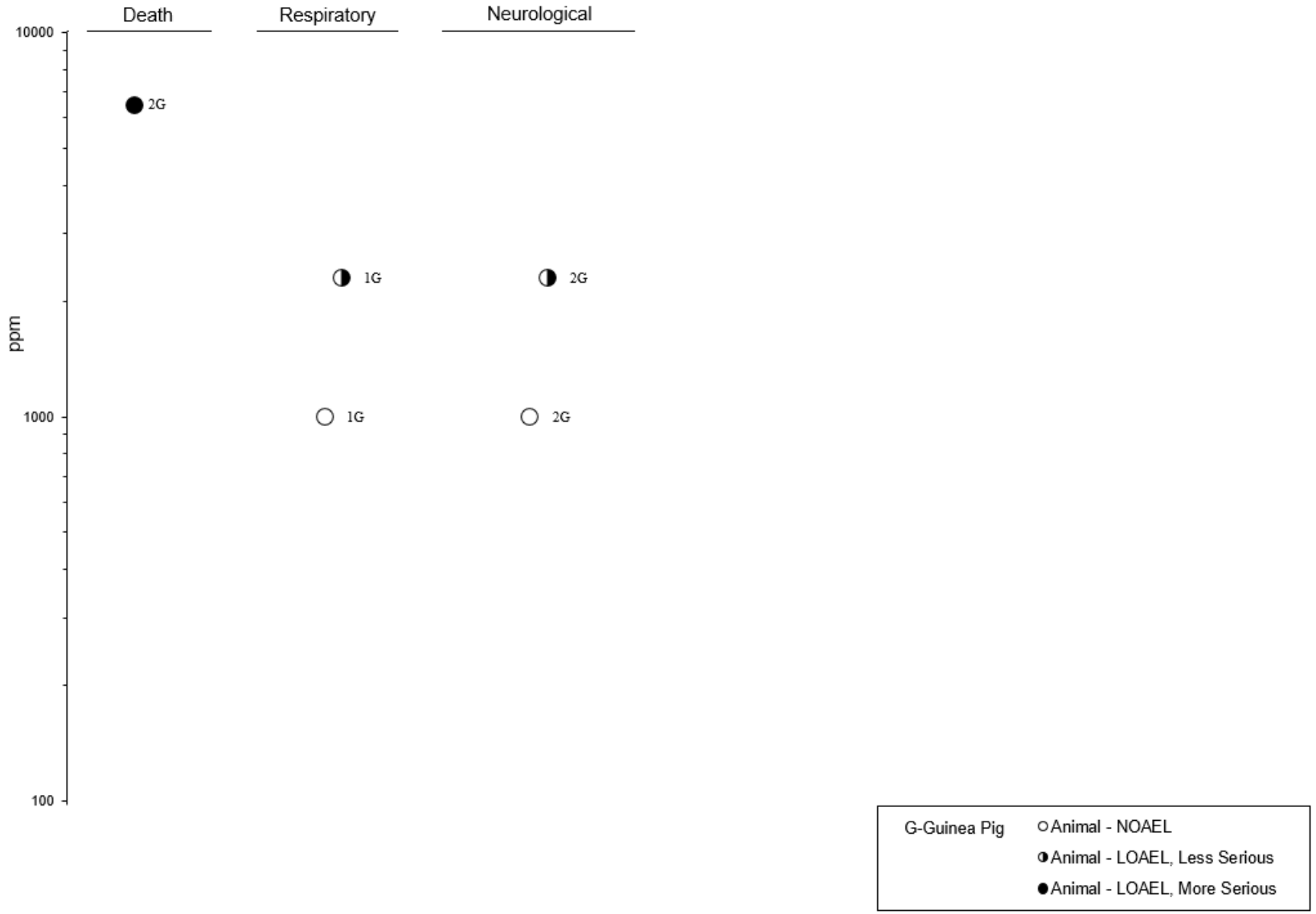


Figure 2-2. Levels of Significant Exposure to 2-Hexanone – Inhalation

Intermediate (15-364 days)

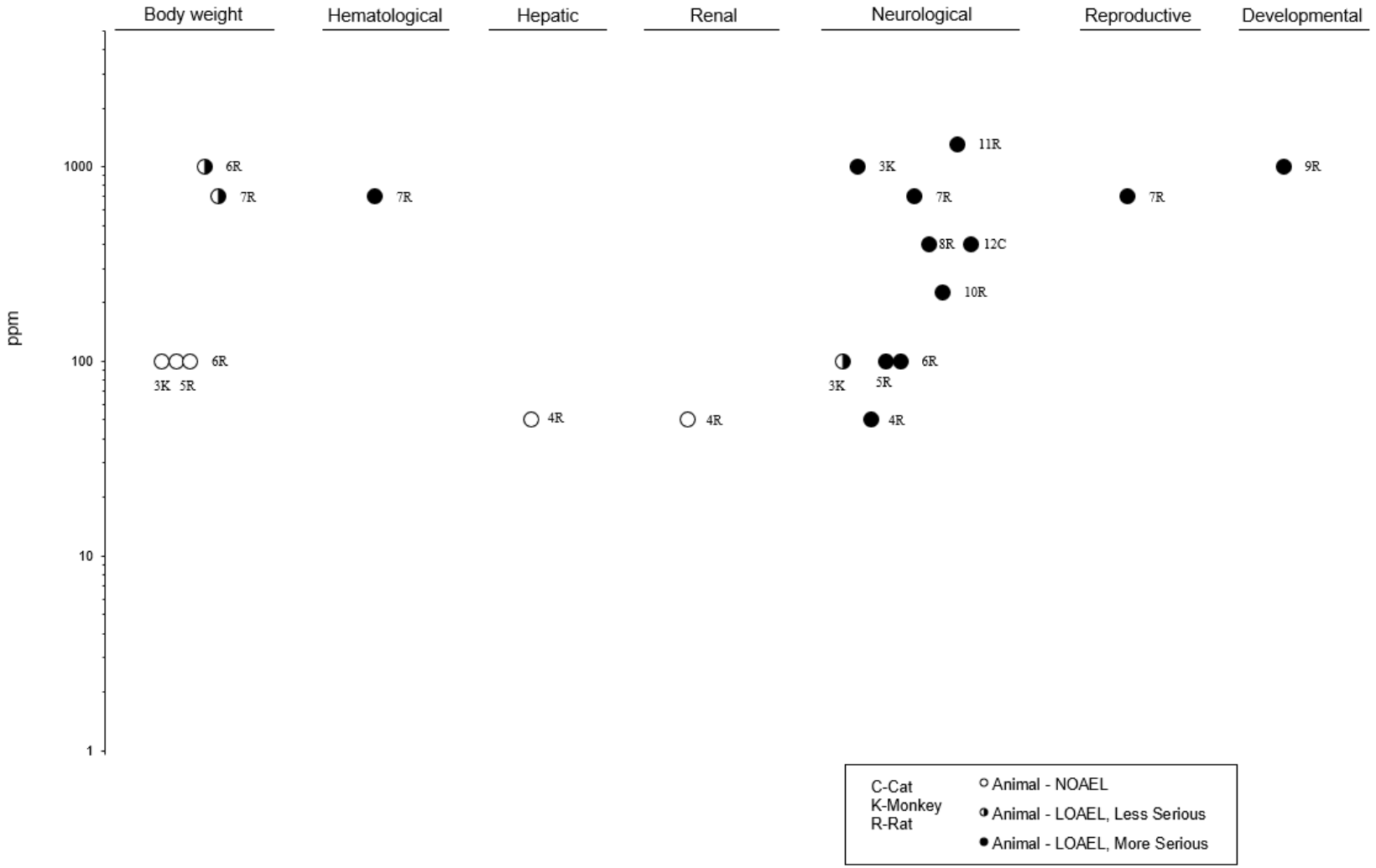


Figure 2-2. Levels of Significant Exposure to 2-Hexanone – Inhalation

Chronic (≥365 days)

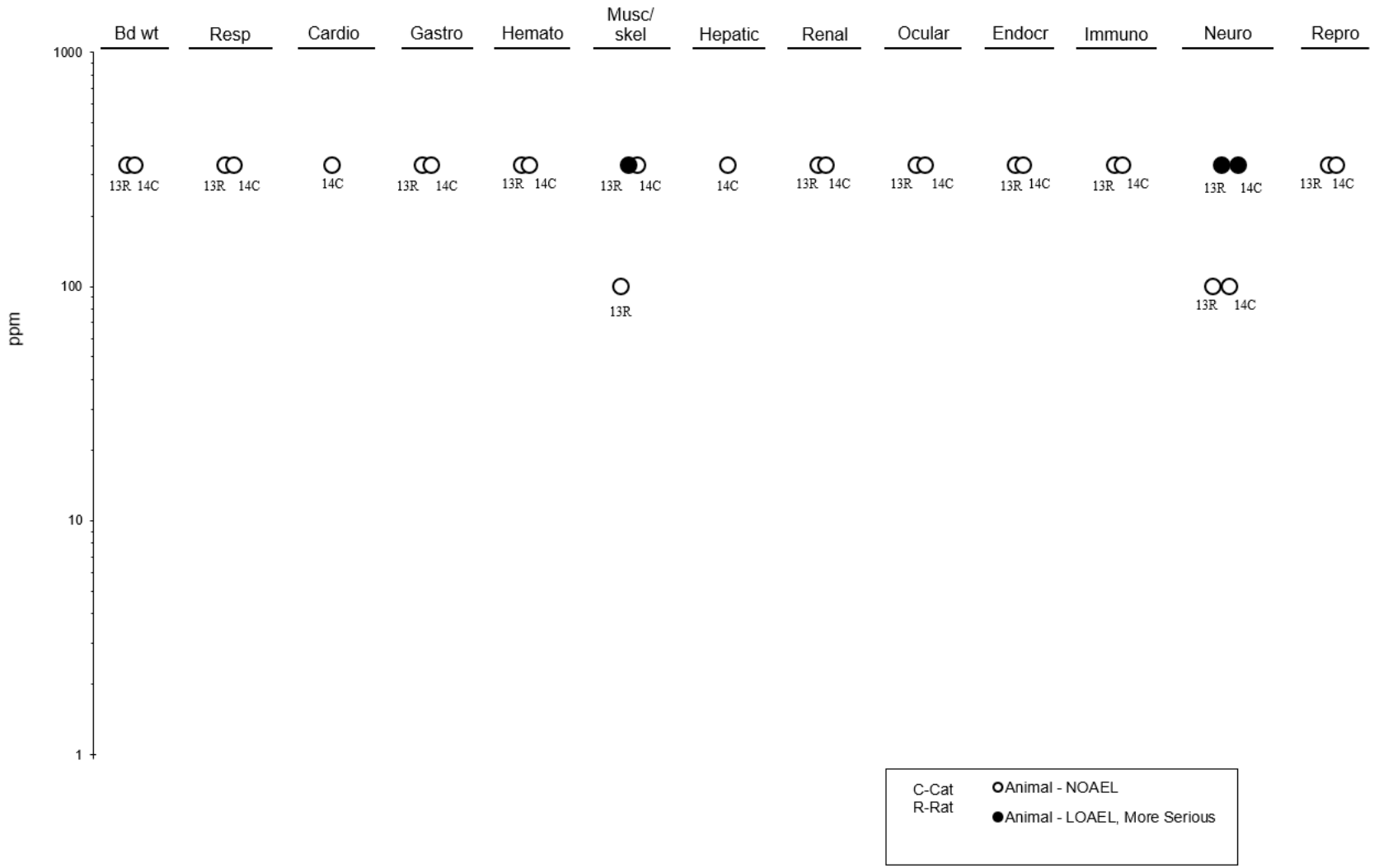


Table 2-2. Levels of Significant Exposure to 2-Hexanone – Oral

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)	Effects
ACUTE EXPOSURE									
1	Rat (Fischer-344) 6 M	Once (GO)	0, 1,500	BI, HP	Hepatic	1,500			
					Renal		1,500		Tubular degeneration
Brown and Hewitt 1984									
2	Rat (Wistar) 5 NS	Once (G)	0, 2, 110, 113, 160	LE	Death			2,590	LD_{50}
Smyth et al. 1954									
INTERMEDIATE EXPOSURE									
3	Rat (Wistar) 60 M	40 weeks 1 time/day (GW)	0, 400	OF, BW, CS	Hepatic	400			
					Renal	400			
					Neuro		400		Hindlimb weakness
Eben et al. 1979									
4	Rat 5 M	90 days 5 days/week 1 time/day (G)	0, 660	CS, HP	Bd wt			660	39% reduced terminal body weight
					Neuro			660	Paralysis, histopathology
Krasavage et al. 1980									
5	Rat (Wistar) 5 F	120 days *ad libitum* (W)	0, 480, 1,010	LE, CS, BW, FI, WI, OW, GN, HP	Bd wt			480	46% reduction in terminal body weight
					Resp	1010			
					Cardio	1010			
					Gastro	1,010			
					Musc/skel			480	Skeletal muscle atrophy
					Hepatic	1,010			
					Renal	1,010			
					Ocular	1,010			
					Endocr	1,010			
					Immuno	1,010			

Table 2-2. Levels of Significant Exposure to 2-Hexanone – 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)	Effects
					Neuro			480	Peripheral neuropathy
					Repro	1,010			
Union Carbide 1977									
6	Guinea pig (English short hair) 5 NS	24 weeks (W)	0, 124, 310	BW, WI, CS	Neuro			310	40% reduction in locomotor activity
Abdel-Rahman et al. 1978									
CHRONIC EXPOSURE									
7	Rat (Sprague-Dawley) 10 M	13 months *ad libitum* (W)	0, 143, 266, 560	CS, BW, OW, FI, HP	Bd wt	143	266	560	14% reduced final weight at 266 mg/kg/day; 36% reduced final weight at 560 mg/kg/day
					Resp	560			
					Cardio	560			
					Gastro	560			
					Musc/skel	143	266		Skeletal muscle myofiber atrophy
					Hepatic	560			
					Renal	560			
					Ocular	560			
					Endocr	560			
					Immuno	560			

Table 2-2. Levels of Significant Exposure to 2-Hexanone – 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)	Effects
					Neuro		143[b]	266	Peripheral nerve axonal swelling at 143 mg/kg/day; axonal and myelin degeneration at 266 mg/kg/day
					Repro	560			
O'Donoghue et al. 1978									

[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 a chronic-duration oral MRL of 0.05 mg/kg/day based on LOAEL of 143 mg/kg/day, an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability), and a modifying factor of 3.

Bd wt or BW = body weight; Cardio = cardiovascular; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; (G) = gavage; (GO) = gavage in oil; (GW) = gavage in water; Gastro = gastrointestinal; GN = gross necropsy; HP = histopathology; Immuno = immunological; LC_{50} = lethal concentration, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; Repro = reproductive; Resp = respiratory; (W) = water; WI = water intake

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

Acute (≤14 days)

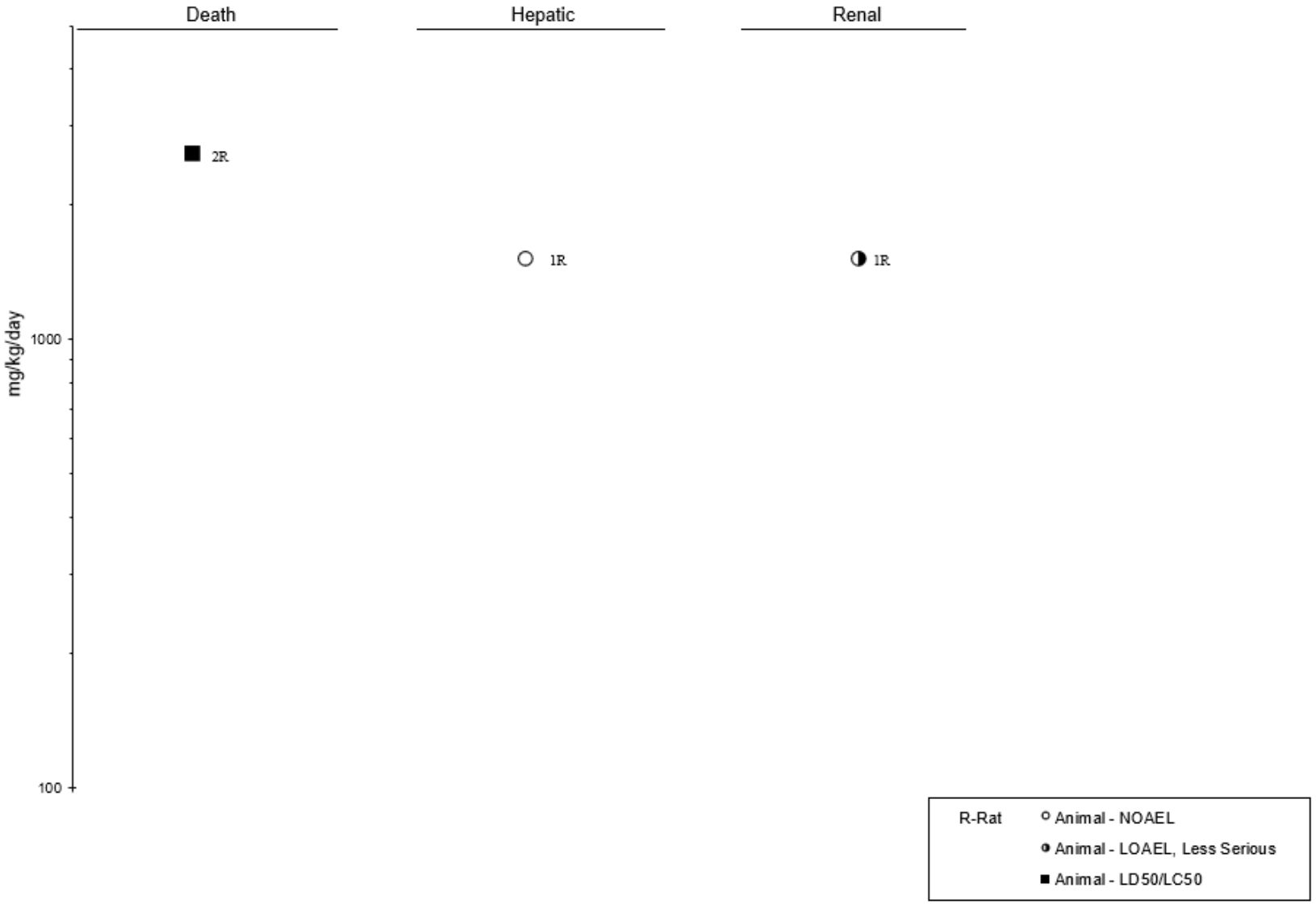


Figure 2-3. Levels of Significant Exposure to 2-Hexanone – Oral

Intermediate (15-364 days)

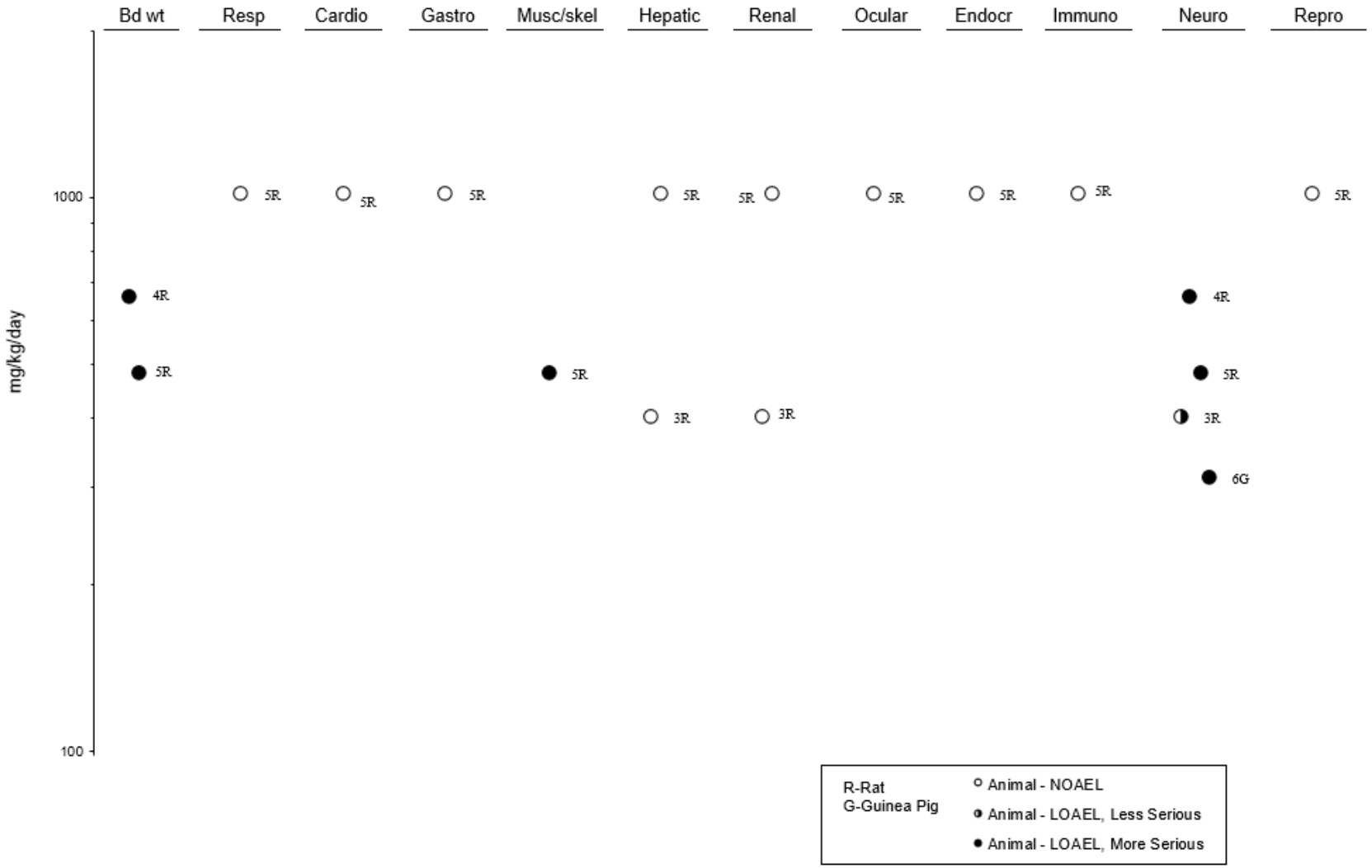
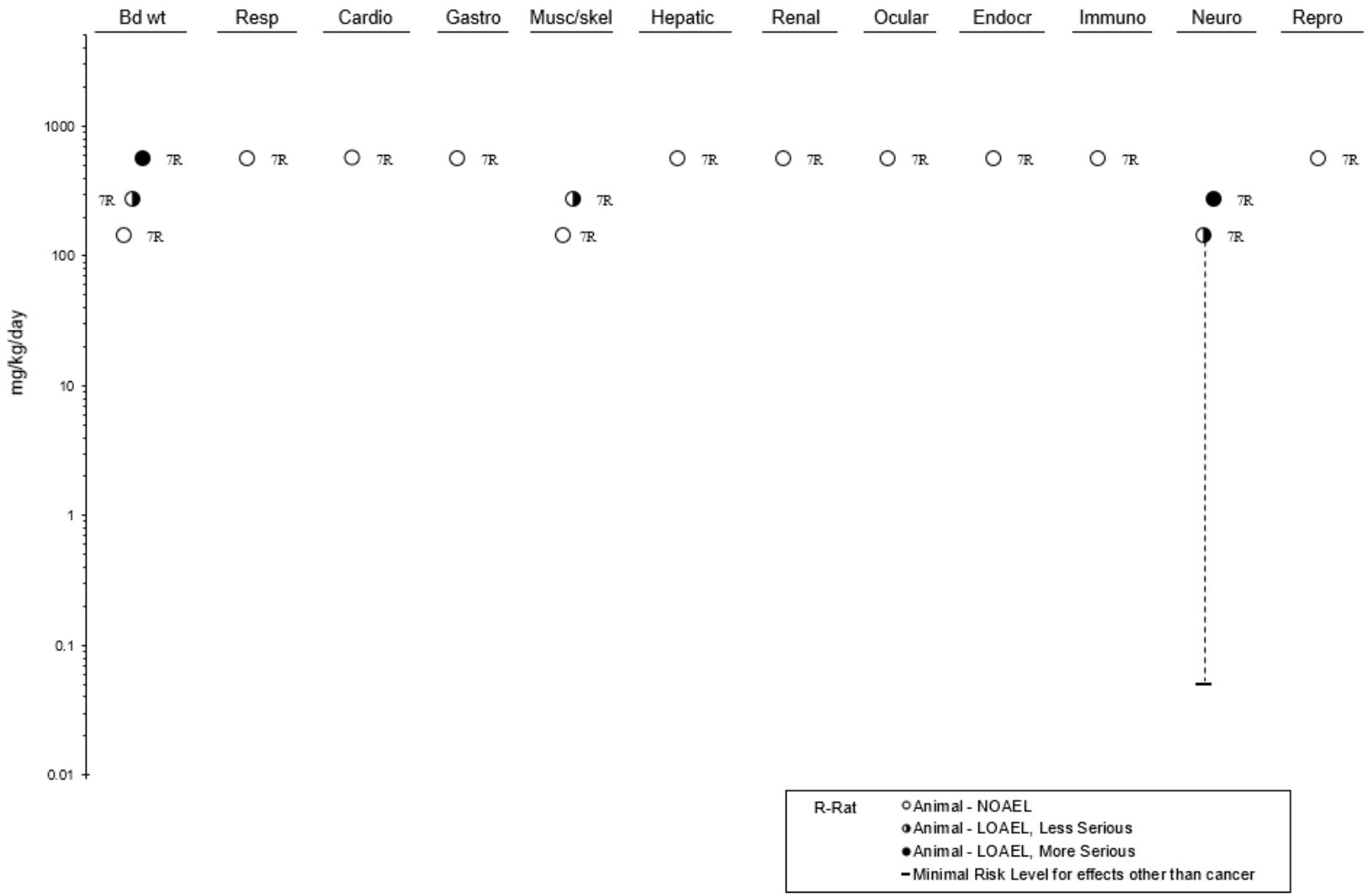


Figure 2-3. Levels of Significant Exposure to 2-Hexanone – Oral

Chronic (≥365 days)



2.2 DEATH

No studies were located regarding death in humans following inhalation exposure to 2-hexanone. Death occurred in guinea pigs following exposure to 6,500 ppm of commercial-grade 2-hexanone for 540 minutes or to 20,000 ppm for 70 minutes (Schrenk et al. 1936). Death was preceded by incoordination, narcosis, and gasping-type respiration.

An LD_{50} of 2,590 mg/kg was calculated for a gavage administration of 2-hexanone (purity not stated) to Wistar rats. No information about the cause of death or sex of the animals was reported (Smyth et al. 1954).

2.3 BODY WEIGHT

Little information is available regarding the effects of 2-hexanone on body weight in humans. A 1973 outbreak of distal polyneuropathy involving 86 of 1,157 employees was reported in a plant that had been using 2-hexanone for about 10 months in the production of plastic-coated and color-printed fabrics (Allen et al. 1975; Billmaier et al. 1974) (neurological effects associated with this exposure are discussed in Section 2.15). Clinical evaluations indicated that of 10 workers whose body weight was recorded, weight loss ranging from 3 to 60 pounds was observed in the eight workers found to have moderate to severe neurological impairment (Allen et al. 1975). It is not clear whether the affected individuals had decreased appetites and/or food consumption levels in conjunction with their weight loss. Of the milder cases, no significant weight change could be correlated with the presence of the disorder. Atmospheric sampling conducted after this incident indicated that 2-hexanone levels averaged 9.2 ppm in front of the printing machines and 36 ppm behind the machines. After the use of 2-hexanone was discontinued, weight gain was uniformly noted in those who had lost weight.

Results of studies in laboratory animals show weight loss or decreased body weight gain following intermediate-duration inhalation exposure and intermediate- and chronic-duration oral exposure. However, the toxicological significance of these observations is uncertain, particularly for inhalation exposures, because information regarding food consumption was not reported. No acute-duration studies evaluating the effects of 2-hexanone were identified.

Intermediate-duration inhalation studies have reported decreases in body weight in animals exposed to 2-hexanone. A NOAEL of 100 ppm was reported in rats in two studies (Egan et al. 1980; Johnson et al.

1977). In the former study, which tested pure 2-hexanone in rats exposed for 22 hours/day, 7 days/week, for 6 months, 100 ppm was the only concentration tested, whereas Johnson et al. (1977), who tested a commercial-grade 2-hexanone of unknown purity in rats exposed for 6 hours/day, 5 days/week for 15 weeks, reported a LOAEL of 1,000 ppm in rats. These rats displayed progressive weight loss, which became statistically significant at 20 weeks. In rats exposed to 700 ppm (only level tested) pure 2-hexanone for 16 or 20 hours/day for 72 hours/week for 11 weeks, terminal body weights were decreased by approximately 44%, compared to controls (Katz et al. 1980). Johnson et al. (1977) also tested monkeys and reported that exposure to 1,000 ppm 2-hexanone induced a progressive nonsignificant loss of body weight beginning 4 months after exposure started; 100 ppm did not induce significant effects.

A developmental study in rats showed decreased weight gain following 2-hexanone inhalation exposure. Weight gain decrements of 10 and 14% relative to controls were reported in groups of 25 pregnant rats exposed to 1,000 or 2,000 ppm 2-hexanone, respectively, 6 hours/day during 21 days of gestation (Peters et al. 1981). No body weight effects were seen in dams exposed to 500 ppm. However, no statistical analysis was performed on these results. Rats in the 2,000 ppm exposure group were observed to eat less than controls, but no quantitative data were presented.

Reductions in weight gain were reported in rats in intermediate- and chronic-duration oral exposure studies. A group of five rats given doses of 660 mg /kg/day pure 2-hexanone by gavage 5 days/week over 90 days weighed about 61% of control rats by 10 weeks of exposure (Krasavage et al. 1980). Treated rats consumed approximately 18% less food (g/rat/day) than control rats, which would suggest that factors other than the reduced food consumption played a role in the reduced weight gain. Similar results were reported in a 120-day drinking water study in rats (Union Carbide 1977). In the chronic study, rats dosed with 266 or 560 mg/kg/day pure 2-hexanone weighed 14 and 36% less than control rats, respectively, after 13 months of treatment (O'Donoghue et al. 1978), and doses of 143 mg/kg/day did not significantly affect weight gain; no data on food consumption were provided in this study. No effects on body weight were observed following chronic-duration oral exposure of rats and cats. Exposure of rats and cats to ≤330 ppm 2-hexanone (purity unknown) for 72 weeks or 2 years, respectively, did not result in significant alterations in body weight (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979).

2.4 RESPIRATORY

Acute inhalation exposure to high concentrations of 2-hexanone produces irritation in humans and animals; however, longer-duration exposure to lower concentrations does not appear to cause respiratory irritation. These effects are likely to occur by direct contact of the chemical with mucosal surfaces rather than a systemic mode of action.

In humans, nasal irritation was observed in an early study in which men were exposed to ≥2,300 ppm 2-hexanone (commercial-grade) vapors for 25–60 seconds. Study subjects considered the contaminated air extremely disagreeable due to a strong odor (Schrenk et al. 1936).

Limited additional data are available in animals regarding respiratory effects of 2-hexanone. Nasal irritation was observed in guinea pigs exposed to 2,300 ppm 2-hexanone after 1 minute of exposure; no such signs were reported in guinea pigs exposed to 1,000 ppm 2-hexanone (Schrenk et al. 1936). In mice, inhalation exposure to high concentrations of 2-hexanone showed a mixed pattern of sensory and pulmonary irritation. In cannulated mice, the concentration of 2-hexanone that reduced the respiratory rate by 50% (RD_{50}) during the first 10 minutes of exposure was 6,183 ppm (Hansen and Nielsen 1994). Intermittent whole-body exposure of rats or cats to ≤330 ppm 2-hexanone vapors (purity unknown) 6 hours/day, 5 days/week for 72 weeks or 2 years, respectively, did not induce treatment-related gross or microscopic alterations in the trachea or lungs (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979).

One study evaluating respiratory effects of oral exposure to 2-hexanone was identified. Exposure to ≤1,010 mg/kg/day 2-hexanone (assumed to be pure) for 120 days (Union Carbide 1977) or ≤560 mg/kg/day pure 2-hexanone for 13 months via the drinking water did not induce gross or microscopic lesions in the lungs or trachea of rats (O'Donoghue et al. 1978).

2.5 CARDIOVASCULAR

Little data are available regarding cardiovascular effects of 2-hexanone. No significant gross or microscopic alterations were reported in the heart of rats or cats exposed following intermittent whole-body inhalation exposure to ≤330 ppm 2-hexanone vapors (purity unknown) for 72 weeks or 2 years, respectively (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979). Oral exposure of rats to ≤1,010 mg/kg/day 2-hexanone for 120 days (Union Carbide 1977) or ≤560 mg/kg/day pure

2-hexanone for 13 months via the drinking water did not induce gross or microscopic lesions in the heart (O'Donoghue et al. 1978).

2.6 GASTROINTESTINAL

Gastrointestinal effects of 2-hexanone have not been well-investigated. Intermittent, whole-body inhalation exposure of rats or cats to ≤330 ppm 2-hexanone vapors (purity unknown) for 72 weeks or 2 years, respectively, did not induce treatment-related gross or microscopic alterations in the gastrointestinal tract (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979). In rats exposed to ≤1,010 mg/kg/day 2-hexanone for 120 days or ≤560 mg/kg/day pure 2-hexanone for 13 months through the drinking water, no treatment-related gross or microscopic lesions in the gastrointestinal tract were observed (O'Donoghue et al. 1978; Union Carbide 1977).

2.7 HEMATOLOGICAL

Limited information is available regarding hematological effects in humans following inhalation exposure to 2-hexanone. In a study of workers exposed to 2-hexanone in a plant producing plastic-coated and color-printed fabrics in Ohio who developed polyneuropathy, hematological tests results were reported to be within normal limits, but quantitative data were not shown and specific tests were not reported (Allen et al. 1975).

The available data are insufficient to determine if exposure of laboratory animals produces hematological effects. A significant reduction in total leukocyte counts to about 60% of control values was observed in rats intermittently exposed to 700 ppm (16 or 20 hours/day for 72 hours/week) pure 2-hexanone after 8 weeks of an 11-week study (Katz et al. 1980). Hemoglobin concentration, hematocrit, and differential white cell counts were similar to control values. Although the decrease in total white blood cell counts suggested an effect on bone marrow, the investigators found no microscopic evidence of such damage. Therefore, the clinical significance of their findings is uncertain.

Chronic-duration intermittent whole-body exposure of rats or cats to ≤330 ppm 2-hexanone vapors (purity unknown) did not induce alterations in the bone marrow of the animals (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979); no hematological tests were conducted in these studies that could have helped interpret the findings of the intermediate-duration study of Katz et al. (1980).

No information was located regarding hematological effects in animals following oral exposure to 2-hexanone.

2.8 MUSCULOSKELETAL

Results of animal studies indicate that effects on skeletal muscles are secondary to neurological effects.

Intermittent whole-body exposure of rats to 330 ppm 2-hexanone vapors (unknown purity) for 72 weeks induced degenerative changes in hindlimb skeletal muscles that resulted in muscle weakness (Krasavage and O'Donoghue 1977). This effect, however, was attributed to damage to the nerves innervating the muscles (see Section 3.2.1.4). No such effect was reported in rats exposed to 100 ppm 2-hexanone. Cats similarly exposed to ≤330 ppm 2-hexanone for 2 years did not develop skeletal muscle alterations (O'Donoghue and Krasavage 1979).

Skeletal muscle pathology of neurogenic origin was reported in rats following exposure to ≥480 mg/kg/day 2-hexanone for 120 days (Union Carbide 1977). Similar findings were reported in rats dosed with ≥266 mg pure 2-hexanone/kg/day for 13 months via the drinking water (O'Donoghue et al. 1978). Gross pathology was limited to atrophy of skeletal muscles of the hind limbs and lumbar muscles. Light microscopy showed significant treatment-related alterations of neurogenic skeletal muscle atrophy in proximal and distal hind limb musculature of high-dose rats. Alterations in rats treated with 266 mg/kg/day 2-hexanone were similar but less severe; no significant alterations were reported at 143 mg/kg/day 2-hexanone.

2.9 HEPATIC

The limited data available suggest that the liver is not a primary target for 2-hexanone. However, few studies have evaluated the potential for 2-hexanone to induce hepatotoxicity.

In the Allen et al. (1975) study of workers exposed to 2-hexanone, clinical tests (liver enzymes, total bilirubin, serum albumin, total protein, serum cholesterol) performed on most workers suspected of a neuropathy were, for the most part, within normal values. Few details were reported.

In rats, no effect on hexobarbital-induced sleep times was observed following continuous inhalation exposure to 225 ppm 2-hexanone (purity not stated) for 7 days (Couri et al. 1977). Results indicate that

2-hexanone exposure under these conditions does not affect the hepatic microsomal enzyme activities associated with this response. No histopathological effects were seen in the liver in rats exposed to 50 ppm 2-hexanone (purity not stated) for 6 months (Duckett et al. 1979) or in rats (Krasavage and O'Donoghue 1977) and cats (O'Donoghue and Krasavage 1979) exposed chronically to ≤330 ppm 2-hexanone (purity not reported).

A single gavage dose of 1,500 mg/kg pure 2-hexanone did not produce histological changes in livers of rats (Brown and Hewitt 1984). In a 40-week study of rats administered gavage doses of 400 mg/kg/day pure 2-hexanone, periodic assessments of serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) showed values within normal limits (Eben et al. 1979). 2-Hexanone (purity unknown) did not affect liver morphology in rats administered doses of ≤1,010 mg/kg/day for 120 days (Union Carbide 1977). The lack of histopathology was also confirmed in a 13-month drinking water study in rats that received doses of ≤560 mg/kg/day pure 2-hexanone (O'Donoghue et al. 1978).

2.10 RENAL

The only relevant information regarding renal effects in humans is that blood urea nitrogen (BUN) appeared to be low (no quantitative data were provided) in some workers studied by Allen et al. (1975) who had signs of neuropathy. However, the difference between subjects affected with neuropathy and not affected was not significant and there was no correlation between BUN values and severity of the neuropathy.

Based on studies in laboratory animals, the kidney does not appear to be a primary target for 2-hexanone. No histopathological effects were seen in the kidneys of rats exposed to 50 ppm 2-hexanone (purity not stated) for 6 months (Duckett et al. 1979) or in rats (Krasavage and O'Donoghue 1977) or cats (O'Donoghue and Krasavage 1979) exposed chronically to ≤330 ppm 2-hexanone (purity not reported).

A single gavage dose of 1,500 mg/kg 2-hexanone produced tubular degeneration in rats (Brown and Hewitt 1984), but no quantitative data were provided. 2-Hexanone (unknown purity) did not induce gross or microscopic changes in the kidneys of rats when given doses of ≤1,010 mg/kg/day for 120 days (Union Carbide 1977). In rats administered 400 mg/kg/day pure 2-hexanone by gavage for 40 weeks, periodic assessments of plasma urea and creatinine, as indices of kidney function, showed no effects of exposure (Eben et al. 1979). Exposure of rats for 13 months to ≤560 mg/kg/day pure 2-hexanone in the drinking water did not induce gross or microscopic alterations in the kidneys (O'Donoghue et al. 1978).

2.11 DERMAL

No studies were located regarding dermal effects in animals following inhalation or in humans or animals following oral exposure to 2-hexanone. Application of undiluted 2-hexanone to the skin of rabbits for 24 hours resulted in Grade 1 (least severe) irritation (Smyth et al. 1954).

2.12 OCULAR

An early study by Schrenk et al. (1936) reported that men exposed to ≥2,300 ppm 2-hexanone (commercial-grade) vapors for 25–60 seconds complained of irritation of the eyes (Schrenk et al. 1936).

Guinea pigs exposed to 2,300 ppm 2-hexanone vapor showed signs of eye irritation after 1 minute of exposure and lacrimation after 10 minutes of exposure; no such signs were reported in guinea pigs exposed to 1,000 ppm 2-hexanone. These effects are likely due to direct contact of 2-hexanone vapors with the eye surface. A long-term exposure study reported that no treatment-related ocular effects were reported in rats or cats exposed whole-body to ≤330 ppm 2-hexanone vapors (purity not reported) (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979).

No treatment-related alterations in the eyes were observed in rats exposed via drinking water to ≤1,010 mg /kg/day 2-hexanone for 120 days (Union Carbide 1977) or ≤560 mg/kg/day pure 2-hexanone for 13 months (O'Donoghue et al. 1978).

Ocular instillation of 2-hexanone in rabbits resulted in Grade 3 (moderate) corneal necrosis (Smyth et al. 1954).

2.13 ENDOCRINE

No information on potential endocrine effects of 2-hexanone in humans was identified.

In animals, no treatment-related histological alterations occurred in the adrenals, thyroid, or parathyroid glands of rats or cats exposed whole-body to ≤330 ppm 2-hexanone vapors (purity not reported) for 72 weeks or 2 years, respectively (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979). Drinking water exposure of rats to ≤1,010 mg/kg/day 2-hexanone for 120 days (Union Carbide 1977) or

to ≤560 mg/kg/day pure 2-hexanone for 13 months did not induce gross or microscopic alterations in adrenals, thyroid, or parathyroid glands, or the pancreas (O'Donoghue et al. 1978).

2.14 IMMUNOLOGICAL

No studies were located regarding immunological effects of 2-hexanone in humans.

The available studies in laboratory animals do not provide sufficient information to assess possible adverse immunological effects due to exposure to 2-hexanone. Intermittent whole-body exposure of rats or cats to ≤330 ppm 2-hexanone vapors (unknown purity) for 72 weeks or 2 years, respectively, did not induce gross or microscopic alterations in the spleen, thymus, or lymph nodes (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979). No tests of immunocompetence were conducted in these studies. Oral exposure of rats to ≤1,010 mg/kg/day 2-hexanone for 120 days (Union Carbide 1977) or to ≤560 mg pure 2-hexanone/kg/day in the drinking water for 13 months (O'Donoghue et al. 1978) did not induce gross or microscopic alterations in the spleen or thymus.

2.15 NEUROLOGICAL

Studies in humans and animals show that the neurological system is the primary target for 2-hexanone. Neurological effects observed in animals are consistent with those reported in workers exposed to 2-hexanone.

In humans, the most important effect associated with inhalation exposure to 2-hexanone is neurological dysfunction, most commonly observed as peripheral neuropathy. Reported effects in human studies include a peripheral neuropathy characterized by axon and myelin disruption and axonal swellings involving motor and sensory nerves and resulting in alterations in nerve conduction velocity, ataxia, sensory deficits, and skeletal muscle weakness accompanied by electromyographic abnormalities. Widespread attention was brought to this phenomenon after a 1973 outbreak of distal neuropathy in an Ohio fabric finishing plant that had introduced the use of 2-hexanone into its processing operations approximately 10 months before the first cases of neuropathy were reported. The time worked in the print department by persons with peripheral neuropathy ranged from 5 weeks to 27 years. The screening of 1,157 employees resulted in the detection of 86 verified cases of neuropathy (Allen et al. 1975; Billmaier et al. 1974). Eleven of these cases were moderate to severe with both motor and sensory involvement; 38 were mild with sensory signs prevailing; and 37 were considered minimal, without clinical

manifestations but with characteristic electrodiagnostic abnormalities. General characteristics of the neuropathy included muscle weakness, sensory loss (inability to discriminate pain, touch, temperature, or vibration) in the hands and feet, and diminution or loss of reflexes. Electromyographic testing generally indicated that nerve conduction velocities were slower, especially in the ulnar, peroneal, tibial, and sural nerves, and the distal latencies (times to response) were prolonged in parallel to the reduction of the nerve conduction velocity. Other abnormalities included waves and fibrillations, especially in the more severe cases, and a decrease in the number and an increase in the size of motor unit potentials. No histological evidence of nerve damage was obtained in any of these patients. Atmospheric sampling conducted after this incident indicated that 2-hexanone levels in the processing plant averaged 9.2 ppm in front of the printing machines, 36 ppm behind them, and 6.1 ppm in the wind-up area. The operators spent 60–80% of their time in front of the printing machines (mean 9.2 ppm). After the use of 2-hexanone was discontinued, marked improvement was seen in the affected employees during the next few months, including all of the moderate-to-severe cases and most of the mild and minimal cases. It should be noted that significant exposure to methyl ethyl ketone also occurred. While methyl ethyl ketone does not induce neuropathy by itself, it has been shown to potentiate the effects induced by 2-hexanone (Saida et al. 1976). Also worth mentioning is that dermal and oral exposures were likely to have occurred due to practices such as eating in/on work areas or washing the hands in solvent.

Mallov (1976) reported three cases of severe peripheral neuropathy among 26 spray painters at one work site. In two cases, exposure to 2-hexanone was the most likely cause of the condition; in the third case, exposure to 2-hexanone was the probable cause. Davenport et al. (1976) also reported a case of peripheral neuropathy in a subject exposed to 2-hexanone at work; in this case, there was also exposure to other compounds, including MiBK. In both case studies, workers were exposed for several months, but <1 year.

In all animal species studied (monkeys, cats, and rats), the clinical observations generally indicated a progression from weakness and ataxia to complete paralysis of the limbs. These clinical observations were accompanied or preceded by morphological changes in the peripheral nerves, including an increase in the number of neurofilaments in the nerve fibers, axonal swelling, and inpouchings and thinning of the myelin sheath. Studies in animals also show involvement of the central nervous system. Studies that have examined the metabolic disposition of 2-hexanone have shown that the chemical entity responsible for the neurotoxic effects of 2-hexanone is 2,5-hexanedione, a metabolite of 2-hexanone in rats, guinea pigs, and humans (Abdel-Rahman et al. 1978; DiVincenzo et al. 1976, 1978; Eben et al. 1979). Comparative studies of the relative neurotoxicities of 2-hexanone, 2,5-hexanedione, and other compounds

have concluded that 2,5-hexanedione is a more potent neurotoxicant than 2-hexanone (Abou-Donia et al. 1982; Krasavage et al. 1980). Comparative studies also have shown the relative species sensitivity to 2-hexanone as cat > dog > primate > rat (Abdo et al. 1982; Mendell et al. 1974).

Limited data regarding acute inhalation exposure were located. Schrenk et al. (1936) reported that exposure of guinea pigs to 2,300 ppm commercial-grade 2-hexanone for 90 minutes produced incoordination; no adverse clinical signs were seen in guinea pigs exposed to 1,000 ppm 2-hexanone for up to 810 minutes. In another study, severe neurotoxicity was reported in rats as a result of 7 days of continuous inhalation exposure to 225 ppm 2-hexanone of unknown purity (Couri et al. 1977). No further details were provided in this study.

Intermediate-duration inhalation studies provide data on neurotoxicity of 2-hexanone in rats, cats, and monkeys. Evaluation of the data, however, is complicated because several studies tested only one exposure level, which caused neurotoxicity, so NOAELs were not defined. In addition, the true LOAEL was probably lower than the exposure level tested. Furthermore, in most studies, the purity of the compound tested was not stated and it could have varied between 70 and 98% 2-hexanone. Intermediate-duration inhalation studies in rats reported neuropathies that affected axons and the myelin sheath; axonal swelling was commonly seen (Duckett et al. 1979; Egan et al. 1980; Mendell et al. 1974; Saida et al. 1976; Spencer et al. 1975). These effects can lead to nerve degeneration. The lowest LOAEL was histopathological effects in rats at 50 ppm 2-hexanone (unknown purity) (Duckett et al. 1979). Histopathological changes were usually accompanied by signs such as weakened hindlimbs (Katz et al. 1980) and forelimbs (Spencer et al. 1975), hindlimb dragging (Mendell et al. 1974), and even paralysis (Saida et al. 1976). In general, the higher the exposure concentration, the earlier the effects appeared. Electrophysiological tests conducted in one study showed significantly decreased motor nerve conduction velocity in the sciatic-tibial nerve after intermittent exposure to ≥100 ppm commercial-grade (unknown purity) 2-hexanone for 29 weeks (Johnson et al. 1977). The latter study also reported impaired operant behavioral performance in rats exposed to 1,000 ppm 2-hexanone. Alterations in the central nervous system were also reported in rats after 4 months of exposure to 100 ppm pure 2-hexanone 22 hours/day (Egan et al. 1980); lesions included giant axonal swellings in the medulla oblongata and cerebellum. Similar findings were reported in cats and monkeys exposed repeatedly to 2-hexanone for intermediate durations. In monkeys, 100 ppm commercial-grade 2-hexanone (unknown purity) was a LOAEL for reduced conduction velocity in the sciatic-tibial nerve (Johnson et al. 1977). In cats, continuous exposure to 400–600 ppm 2-hexanone (unknown purity) induced hind limb dragging followed by forelimb weakness and eventual paralysis (Mendell et al. 1974). Morphological evaluations showed axonal

swelling and demyelination of nerve fibers. In both cats and monkeys, recovery occurred months after exposure to 2-hexanone ceased.

Chronic-duration inhalation studies in rats and cats showed equivocal clinical and morphological signs of neuropathy in rats exposed intermittently (6 hours/day, 5 days/week) to 330 ppm 2-hexanone vapors for 72 weeks (Krasavage and O'Donoghue 1977) and clear morphological signs of neuropathy in cats similarly exposed to 330 ppm 2-hexanone for 2 years (O'Donoghue and Krasavage 1979). No signs of neuropathy were reported in rats or cats exposed to 100 ppm 2-hexanone. In neither study was the purity of 2-hexanone stated. Poor reporting of the results made it difficult to establish a NOAEL and LOAEL in the rat study; however, rats exposed to 330 ppm showed degenerative changes in skeletal muscle that were most likely due to neuropathy in the innervating nerve fibers. No clinical neurological signs were reported in the cats, but all cats in the 330 ppm exposure group showed lesions in the peripheral and central nervous system at and below the levels of the cerebellum and pons. In the periphery, sciatic nerve axons showed organelle accumulations with rare focal discrete "giant" axonal swelling that also involved the myelin. The sensory portion of the peripheral nervous system was least affected. Neuropathological effects in the central nervous system were generally minor; swollen terminals were found in the posterior cerebellar peduncles, folial white matter, nucleus gracilis, fasciculus gracilis, spino-cerebellar tracts, medullary reticular formation, and all levels of the spinal cord. Detailed examination of tibial nerve fibers showed a higher percentage of demyelinated, re-myelinated, swollen, and degenerative fibers in the high-exposure group than in controls and low-exposure groups.

No studies were located regarding neurological effects in humans after oral exposure to 2-hexanone, but based on results from oral studies in animals and on what is known regarding the toxicokinetics of 2-hexanone in humans and in animals, adverse neurological effects will likely occur in humans following high oral exposure to this chemical.

Oral exposures of laboratory animals provide evidence of neurotoxicity of 2-hexanone. Intermediate- and chronic duration studies showed that 2-hexanone causes the same type of neurological effects observed after inhalation exposure, which is not unexpected since both routes of exposure give rise to the toxic entity, 2,5-hexanedione. No information on acute-duration oral studies in animals was identified.

Intermediate-duration oral studies provided LOAELs for clinical signs and morphological alterations in the peripheral nervous system, but NOAELs were not identified. In rats, doses of 400 mg/kg/day 2-hexanone induced transient weakness of the hindlimbs on weeks 17–28 of a 40-weeks study (Eben et al.

1979), and doses of ≥480 mg/kg/day 2-hexanone induced clinical signs such as muscle weakness and hindlimb dragging (Krasavage et al. 1980; Union Carbide 1977). In these two studies (Krasavage et al. 1980; Union Carbide 1977), microscopic examination of peripheral nerves showed evidence of neuropathy involving both axons and the myelin sheath. No histological examinations were conducted by Eben et al. (1979). Both Eben et al. (1979) and Krasavage et al. (1980) used high-purity 2-hexanone. A 40% decrease in locomotor activity was reported in groups of five guinea pigs given 2-hexanone of unknown purity in drinking water at dosage levels of approximately 310 mg/kg/day 2-hexanone during a 24-week study (Abdel-Rahman et al. 1978). Reduced pupillary responses to light (measured by changes in pupillary diameter) were also reported in this study. However, no information was provided regarding effects that may have occurred at a lower exposure level of approximately 124 mg/kg/day 2-hexanone.

In the single oral chronic-duration (13-month) study available for review, the lowest dose of 2-hexanone (high purity) tested, 143 mg/kg/day, caused axonal swellings in peripheral nerves of rats (O'Donoghue et al. 1978). Clinical neurological signs were seen in rats dosed with ≥266 mg/kg/day 2-hexanone and first appeared on day 42 in the rats dosed with 560 mg/kg/day and on day 77 in rats dosed with 266 mg/kg/day. Signs included decreased extension of hindlimbs, hindlimb weakness, waddling gait, dragging of hind paws, and loss of tone in hindlimb musculature with grossly observable atrophy of hindlimb musculature and axial muscles of the lumbar area. Histological examinations showed that rats from all treated groups had "giant" axonal neuropathy, with a LOAEL value of 143 mg/kg/day. Axonal swelling and giant axonopathy were common in peripheral nerves and spinal cord, less common in dorsal root ganglia, and rare in the brain. Myelin alterations were also seen in peripheral nerves. Neurogenic skeletal muscle atrophy occurred in proximal and distal hindlimb musculature. Alterations in the 266 mg/kg/day group were similar but less severe than in the 560 mg/kg/day group. Less severe changes were seen in peripheral nerves in the 143 mg/kg/day group of rats; fewer giant axons were evident, but myelin changes were more common. Spinal lesions and neurogenic muscle atrophy were minimal.

Mechanisms of Neurotoxicity. The neurotoxicity of 2-hexanone is caused by its active metabolite, 2,5-hexanedione. The mechanism of toxicity of γ-diketones (such as 2,5-hexanedione) has been extensively studied, not only with respect to 2-hexanone, but with a wider focus on γ-diketones in general, as this chemical is also a metabolite of other substances that induce neuropathy such as *n*-hexane. Because of the extensive nature of the literature that covers 2-hexanone, *n*-hexane, as well as 2,5-hexanedione itself, the summary below has been extracted from reviews and the reader is referred to references cited therein for more detailed information (LoPachin and DeCaprio 2004, 2005; LoPachin and Gavin 2015; LoPachin et al. 2000). The two main features of 2-hexanone toxicity are the appearance of

giant neurofilamentous axonal swellings and axonal atrophy. As discussed in these reviews, studies have reached different conclusions regarding whether the principal neuropathological manifestation of 2,5-hexanedione toxicity is distal swelling of myelinated fiber (central-peripheral distal axonopathy) or axonal atrophy. However, it appears that axonal atrophy is the most significant component of 2,5-hexanedione-induced neuropathy.

Ruling out axonal swelling as the main feature of 2,5-hexanedione intoxication was based on some of the following observations. Studies showed that the *in vivo* neurotoxic potencies of various chemicals whose metabolism lead to the production of 2,5-hexanedione were correlated with the corresponding serum concentration of 2,5-hexanedione. Yet, the frequency of axonal swellings in the nerves examined did not correlate with the concentration of 2,5-hexanedione in serum. In fact, the relative frequency of swollen axons was inversely related to the serum concentration of 2,5-hexanedione and to the manifestation of neurotoxicity. This was shown to occur in both the peripheral and central nervous systems. Studies also showed that axonal swellings appeared during the later stages of 2,5-hexanedione intoxication, indicating lack of temporal association with the expression of neurological deficits. Overall, these results suggested that 2,5-hexanedione induction of neurological dysfunction was not dependent on axonal swelling and that this phenomenon could represent a secondary response to neurotoxic injury or stress.

2,5-Hexanedione-induced axonal atrophy is characterized by reduction in axon cross-sectional area without a significant change in perimeter length and degree of myelination. Morphological evaluations have shown that axon atrophy is associated with faster anterograde slow axonal transport in both peripheral nerves and in white central matter tracts of rats exposed to 2,5-hexanedione, which would lead to proximal axon atrophy and secondary distal accumulation of neurofilaments and swelling. However, subsequent studies that conducted spatio-temporal analyses showed that atrophy was widespread in the central and peripheral nervous systems and that it developed as an early consequence of 2,5-hexanedione intoxication. Observations that reductions in axon perimeter can develop in the absence of axonal swelling supported the view that axonal atrophy is the principal lesion that develops as an early consequence of 2,5-hexanedione intoxication regardless the dose or route of exposure. Further support for axonal atrophy being the main neuropathological feature of 2,5-hexanedione intoxication is the fact that reduced axon diameter is associated with reduced nerve conduction velocity.

The mechanism by which 2,5-hexanedione induces axonal atrophy has not been completely elucidated; however, studies have shown that adduction with cytoskeletal proteins plays a key role. 2,5-Hexanedione, a diketone electrophile, reacts covalently with nucleophilic lysine ε-amino groups to

form 2,5-dimethylpyrrole adducts on neurofilaments and other proteins. This is thought to interfere with turnover and maintenance of the axonal cytoskeleton, and some have suggested that, following formation, pyrrole adducts undergo oxidative reactions that yield cross-linked neurofilament proteins. However, since virtually all proteins, neuronal and non-neuronal, contain one or more lysine ε-amino groups, *in vivo* exposure to 2,5-hexanedione would result in multiple physiological systems being affected; however, this does not seem to be the case. In addition, *in vitro* and *in vivo* studies showed that only a very small fraction of the total available lysyl ε-amino groups on neurofilament proteins were converted to pyrrole adducts, so a specific mechanism needed to be involved. Further *in vitro* experiments showed that the adducted lysine residues were primarily located within the KSP (lysine-serine-proline) repeat on the C-terminal regions of neurofilament-M and neurofilament-H subunit proteins.

Exactly how neurofilament protein adduction can lead to axonal atrophy is not totally understood. Results from some studies suggested that 2,5-hexanedione might reduce phosphorylation of neurofilaments, an important determinant of cytoskeletal protein turnover and axon diameter. Reduced phosphorylation would prevent neurofilaments from associating with the cytoskeletal polymer or cause premature dissociation of integrated neurofilaments. In turn, depletion of neurofilaments by anterograde transport of hypophosphorylated neurofilaments would lead to loss of axon diameter. More recent data have shown that 2,5-hexanedione can affect components of the axon cytoskeleton other than neurofilament subunit proteins. Studies in rats treated orally with 2,5-hexanedione showed that 2,5-hexanedione impaired binding of microtubule associated proteins (e.g., MAP1A, tau) to recognition sites on microtubules. Presumably, this disruption was caused by 2,5-hexanedione adduct formation with ε-amino groups on lysine residues that mediate such protein-protein interactions. Based on the critical role in cytoskeletal physiology, MAPs could represent a relevant target of γ-diketone axonopathy. Studies also suggested that higher molecular weight neurofilament derivatives were not a consequence of 2,5-hexanedione cross-linking of these proteins, because they also appeared in nervous tissues of untreated animals. Rather, these derivatized neurofilaments likely represented baseline levels of proteins that were cross-linked by normal activities of axon transglutaminases that increase cytoskeletal stability. The elevated content of higher molecular weight neurofilament complexes in 2,5-hexanedione-treated rats was thought to represent excess fragmentation of the stationary cytoskeleton possibly as a result of 2,5-hexanedione-impaired polymer maintenance (LoPachin and DeCaprio 2004, 2005; LoPachin and Gavin 2015; LoPachin et al. 2000).

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans after exposure to 2-hexanone.

A few studies evaluated the effects of 2-hexanone on the reproductive system of animals. Although some studies showed testicular damage, these effects have not been rigorously evaluated. Based on exposure levels producing adverse effects, environmental levels of 2-hexanone (mostly water levels reported in the past, ppb range) are unlikely to represent a reproductive risk for humans.

Intermediate-duration inhalation exposure to a high concentration of 2-hexanone caused testicular damage in rats. Marked and significant reductions in absolute and relative testes weight and atrophy of testicular germinal epithelium were observed in male rats exposed to 700 ppm 2-hexanone (96.1% pure) for 11 weeks (Katz et al. 1980); no other exposure level was tested in this study. Chronic-duration exposure of male rats or female cats to ≤330 ppm 2-hexanone (unknown purity) did not induce compound-related gross or microscopic alterations in the reproductive organs of either species (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979).

Oral studies in laboratory animals also show that oral exposure to 2-hexanone may induce adverse reproductive effects; however, limited information is available. Male rats that were given 2-hexanone (96.1% pure) at 660 mg/kg/day by gavage in a 90-day study were reported to develop atrophy of the germinal epithelium of the testes (Krasavage et al. 1980). However, no quantitative data were presented, so this effect is not listed in oral LSE table (Table 2-2). The only additional relevant information regarding reproductive effects of 2-hexanone in animals is that treatment of female rats with ≤1,040 mg/kg/day 2-hexanone for 120 days (Union Carbide 1977) or male rats with ≤560 mg/kg/day 2-hexanone (96.1% pure) via drinking water for 13 months did not induce gross or microscopic alterations in the reproductive organs (O'Donoghue et al. 1978).

2.17 DEVELOPMENTAL

No studies were located regarding developmental effects in humans after exposure to 2-hexanone.

Only one study evaluating developmental effects of 2-hexanone in laboratory animals was identified. Intermittent inhalation exposure of groups of 25 pregnant rats to 2,000 ppm 2-hexanone (unknown purity) 6 hours/day during the entire gestation period resulted in a significant reduction in the number of pups per

litter and in neonatal weight (40%); no such effects were reported in rats exposed to 1,000 ppm (Peters et al. 1981). In this study, behavioral alterations consisting of reduced activity in the open field, increased activity in the running wheel, and deficits in avoidance conditioning were reported in the offspring of exposed dams at all ages (newborn, weanling, puberty, and adult) except geriatric in which results were similar to those of controls. Behavioral tests in most cases indicated that maternal exposure to 2-hexanone was associated with hyperactivity in the young and decreased activity in the geriatric stage, which the authors speculated to be due to premature aging resulting from the earlier hyperactivity. It is not clear whether these effects are the result of transplacental exposure to 2-hexanone or of postnatal exposure to 2-hexanone and/or its metabolites via the milk of the exposed dams.

No firm conclusions can be made regarding developmental effects of 2-hexanone based on a single animal study; further information would be necessary.

2.18 CANCER

Three chronic-duration studies conducted histopathological assessments of comprehensive tissues: two inhalation studies in rats (Krasavage and O'Donoghue 1977) and cats (O'Donoghue and Krasabage 1979) and one oral study in rats (O'Donoghue et al. 1978). No evidence of cancer was reported in any of these studies.

Neither the HHS nor IARC have classified 2-hexanone regarding its carcinogenicity (IARC 2019; NTP 2016). The EPA stated that "there is inadequate information to assess the carcinogenic potential" of 2-hexanone (EPA 2009a).

2.19 GENOTOXICITY

No studies were located regarding the potential genotoxic effects in humans or animals following any route of exposure to 2-hexanone. One study was located that provided data on genotoxicity of 2-hexanone in an *in vitro* system. The study reported that 2-hexanone was mutagenic in *Salmonella typhimurium* 1535 [pSK 1002] as assessed by the SOS/*umu* Test (Nakajima et al. 2006).

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

3.1 TOXICOKINETICS

- Absorption
  - Respiratory tract: 2-Hexanone is well absorbed from the respiratory tract. A small study in humans estimated that approximately 75–92% of the inhaled dose was absorbed. Absorption of inhaled 2-hexanone has also been demonstrated in rats.
  - Gastrointestinal tract: 2-Hexanone is well absorbed from the gastrointestinal tract. A small study in humans estimated that approximately 66% of the oral dose was absorbed. A study in rats showed that almost 100% of an oral dose of 2-hexanone was absorbed.
  - Dermal: 2-Hexanone is absorbed following dermal exposure; however, quantitative estimates of the absorption fraction are not available.
- Distribution. In humans, 2-hexanone was detected in serum, but no additional information regarding distribution was available. Studies in laboratory animals show that 2-hexanone is distributed to the brain and liver.
- Metabolism. 2-Hexanone undergoes metabolism through reduction and oxidation reactions. The metabolite, 2,5-hexanedione, is toxicologically active.
- Excretion. Expired breath and urine appear to be the main routes of excretion for 2-hexanone and its metabolites in both animals and humans.

3.1.1 Absorption

The available data indicate that 2-hexanone is well absorbed after administration via the inhalation route. 2-Hexanone was detected in expired breath of humans who inhaled 2-hexanone at 10 or 50 ppm for 7.5 hours or 100 ppm for 4 hours (DiVincenzo et al. 1978). Concentrations of 2-hexanone in expired air were lower than that of the external exposure concentrations. Analysis of serum showed that 2-hexanone was present in serum in subjects exposed to 100 ppm, but not to 10 or 50 ppm. The study authors stated that results indicate that 75–92% of the inhaled 2-hexanone vapor was absorbed by the lungs and respiratory tract; however, the basis of this quantitative assessment was not reported. Similarly, beagles that inhaled 2-hexanone at 50 or 100 ppm for 6 hours absorbed 65–68% of the inhaled vapor (DiVincenzo et al. 1978). Whole-body exposure of rats to 75, 150, or 300 ppm 2-hexanone for 4 hours resulted in exposure-related amounts of the parent compound and the metabolites, 2-hexanol and 2,5-hexanedione, in

plasma immediately after the last exposure (Duguay and Plaa 1995). At 75 and 150 ppm, the concentration of 2,5-hexanedione in plasma was approximately 5 times that of 2-hexanone; at 300 ppm, it was about 2.5 times. It should be mentioned that in rats from the mid- and high-exposure groups, the concentration of 2,5-hexanedione in plasma was significantly higher following inhalation exposure than following oral exposure (see below).

2-Hexanone also appears to be well absorbed after oral administration. Humans who ingested a single capsule containing ^{14}C-2-hexanone at 0.1 mg/kg excreted about 40% of the ^{14}C in breath and 26% in urine during the next 8 days (DiVincenzo et al. 1978). This indicates that the absorbed amount averaged at least 66% of the administered dose. Administration of 1-^{14}C-2-hexanone at 20 or 200 mg/kg by gavage to rats resulted in excretion of about 1.2% of the administered radioactivity in the feces, about 44% in the breath, 38% in urine, and 16% remaining in the carcass (DiVincenzo et al. 1977). The results were similar at either dosage level. These findings suggest that about 98% of the administered dose was absorbed and that absorption was not saturable at the range of doses administered. Similar results were reported in rats administered three gavage doses of 50, 100, or 200 mg/kg 2-hexanone (Duguay and Plaa 1995). Plasma samples analyzed 1 hour after administration of the last dose showed dose-related amounts of 2-hexanone.

2-Hexanone is also absorbed after dermal application. The excretion of ^{14}C in the breath and urine of two volunteers was measured after a 60-minute occlusive application of ^{14}C-2-hexanone to shaved forearms (DiVincenzo et al. 1978). Calculated skin absorption rates were 4.8 and 8.0 µg/minute/cm^2; however, the fraction of 2-hexanone that was absorbed was not calculated. ^{14}C-Hexanone was also applied to the clipped thorax of beagle dogs, and absorption was observed to be slow at first but increased dramatically after 20 minutes. At 60 minutes, 77 mg of 2-hexanone had penetrated the skin (DiVincenzo et al. 1978). The fraction of applied 2-hexanone that was absorbed was not calculated.

3.1.2 Distribution

Little information on the distribution of 2-hexanone in humans following inhalation exposure is available. In humans exposed to 2-hexanone via inhalation to 10 or 50 ppm for 7.5 hours or to 100 ppm for 4 hours, 2-hexanone was detected in serum in subjects exposed to 100 ppm (DiVincenzo et al. 1978). No information regarding distribution to other tissues was reported.

Studies in laboratory animals provide some information regarding distribution of 2-hexanone; however, this has not been extensively studied. 2-Hexanone and its metabolites, 2-hexanol and 2,5-hexanedione, were detected in the lungs of rats 1 hour after the last of three daily 4-hour inhalation exposures to 75, 150, or 300 ppm 2-hexanone (Duguay and Plaa 1995). Some degree of accumulation seemed to have occurred since the lungs of the mid- and high-exposure groups had 4 and 20 times more 2-hexanone, respectively, than the low-exposure group. The three compounds were also measured in the liver, but in contrast with the lung findings, the concentrations of 2-hexanone in the liver were exposure concentration-related. The lungs and liver were the only tissues examined in the Duguay and Plaa (1995) study. An additional metabolite, 5-hydroxy-2-hexanone, was detected in blood from cats following intermittent chronic exposure to 2-hexanone (O'Donoghue and Krasavage 1979). This metabolite was short-lived since it could not be detected on Mondays following 2 days exposure-free.

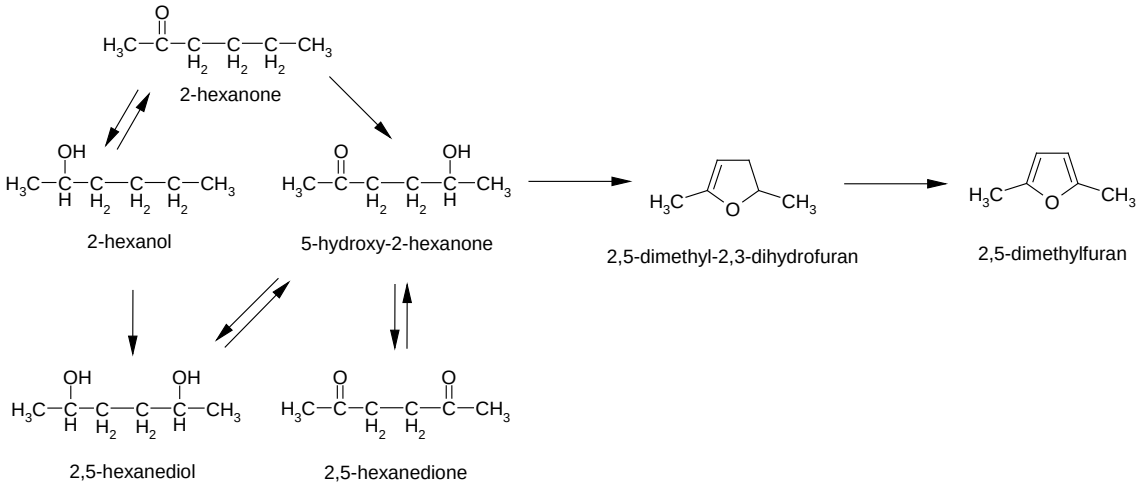
In rats administered a single oral dose of ^{14}C-2-hexanone at 200 mg/kg by gavage, tissue distribution was reported to be widespread with highest counts in the liver and blood. No quantitative data were given on tissue distribution (DiVincenzo et al. 1977). An analysis of subcellular distribution of the ^{14}C label in liver, brain, and kidney tissue indicated highest counts were associated with the crude lipid fraction and protein, with some recovery in DNA, and little or none in RNA. Gavage administration of 50, 100, or 200 mg/kg 2-hexanone to rats for 3 days resulted in measurable amounts of the parent compound and its metabolites, 2-hexanol and 2,5-hexanedione, in the liver 1 hour after the last dose (Duguay and Plaa 1995). However, in contrast to the liver findings, no 2,5-hexanedione was detected in the lungs, which led the investigators to suggest that lung metabolism of 2-hexanone might contribute to plasma metabolite levels.

2-Hexanone was shown to distribute to the brain of mice within 15–90 minutes following intraperitoneal administration of a single dose of approximately 500 mg/kg of the compound (Granvil et al. 1994). Both of its metabolites, 2-hexanol and 2,5-hexanedione, were also found in the brain. Brain concentrations of 2-hexanone seemed to be lower than those measured in blood. 2-Hexanol was detected in the brain considerably earlier than 2,5-hexanedione. The study also showed that the concentrations of 2-hexanol in the brain at the various time intervals measured were approximately twice those found in blood, which according to the investigators, might explain the lower concentrations of 2-hexanone found in brain compared to those found in blood.

3.1.3 Metabolism

The proposed phase I metabolic pathway (oxidation, reduction, and hydrolysis reactions) for 2-hexanone, based on 2-hexanone metabolites identified in blood during intraperitoneal studies in guinea pigs (DiVincenzo et al. 1976) and oral studies in rats (DiVincenzo et al. 1977), is presented in Figure 3-1. DiVincenzo et al. (1978) hypothesized that the metabolic pathway for 2-hexanone is similar in humans and experimental animals based on increases in 2,5-hexanedione in serum following inhalation exposure and radiolabeled carbon dioxide in expired air following oral exposure. The metabolism of aliphatic ketones has generally been found to proceed via reduction to the corresponding secondary alcohol, which accounts for the formation of 2-hexanol. An alternate pathway is oxidation of the 5-methylene group to the corresponding alcohol, 5-hydroxy-2-hexanone, which may be followed by further oxidation to the diketone 2,5-hexanedione. Another possibility in the metabolism of 2-hexanone is the cyclization of 5-hydroxy2-hexanone to the corresponding dihydrofuran and oxidation to 2,5-dimethylfuran (DiVincenzo et al. 1977). However, the formation of these furan moieties may be the result of thermal dehydration and cyclization during gas chromatography (DiVincenzo et al. 1977). In addition, the gamma-valerolactone found in the urine (not shown in figure) is hypothesized to result from α-oxidation of 5-hydroxy-2-hexanone to 2-keto-5-hydroxyhexanoic acid, decarboxylation and oxidation to 4-hydroxypentanoic acid, and lactonization to gamma-valerolactone (DiVincenzo et al. 1977). The specific cytochrome P-450 isozymes involved in the phase I metabolism of 2-hexanone have not been identified. The appearance of glucuronide and sulfate conjugates of 2-hexanone metabolites (Phase II metabolism) in the urine indicate that there is further metabolism; however, no additional information was identified.

Figure 3-1. Proposed Phase I Metabolic Pathway for 2-Hexanone



Source: DiVincenzo et al. 1976, 1977

3.1.4 Excretion

In humans exposed to 2-hexanone via inhalation to 10 or 50 ppm for 7.5 hours or to 100 ppm for 4 hours, unchanged 2-hexanone (but not 2,5-hexanedione) was found in expired air during exposure, and neither 2-hexanone nor any of its metabolites was found in urine during or after exposure (DiVincenzo et al. 1978). 2-Hexanone was not detected in the expired air 3 hours after exposure to 50 or 100 ppm. The study authors stated that results suggest slow clearance and possible accumulation of 2-hexanone in humans exposed by this route.

In beagle dogs exposed to 2-hexanone via inhalation at 50 or 100 ppm for 6 hours, 32 and 35%, respectively, of the inhaled vapor was excreted in the expired breath (DiVincenzo et al. 1978). By 3–5 hours after exposure, 2-hexanone was no longer detected in expired air. Excretion via other routes was not addressed.

In two humans who received a single oral dose of 1-^{14}C-2-hexanone, breath excretion of $^{14}CO_2$ reached a peak within 4 hours, then decreased slowly over the next 3–5 days. Average overall recovery of the ^{14}C-label in 8 days was 40% in breath and 26% in urine. Feces were not analyzed (DiVincenzo et al. 1978).

In rats administered a single oral dose of 1-^{14}C-2-hexanone, DiVincenzo et al. (1977) observed similar results. Radioactivity in breath accounted for about 45% of the administered dose (5% was in unchanged 2-hexanone; 40% was in $^{14}CO_2$); 35% was found in the urine; 1.5% was recovered in the feces; and about 15% remained in the carcass after 6 days. In male rats that received daily gavage doses of 2-hexanone at 400 mg/kg/day for 40 weeks, very low concentrations of free 2-hexanone were detected in the urine from the 3rd week. A maximum concentration of approximately 20 µg was reached in the 17th week (Eben et al. 1979). Similarly, free 2,5-hexanediol was found in the urine after 3 weeks and peaked in the 17th week. Free and conjugated 2,5-hexanedione was present in the urine from the 1st week of the study. The conjugated form peaked in the 7th week, whereas excretion levels of the free form were fairly consistent throughout the study. A strong correlation was observed in this study between the onset of neuropathy and the urinary concentration of 2,5-hexanedione when 2-hexanone, 2,5-hexanedione, or 2,5-hexanediol was administered orally to rats at 400 mg/kg/day.

^{14}C from 1-^{14}C-2-hexanone applied to the forearms of two volunteers was found in the breath and urine (DiVincenzo et al. 1978). In one subject, excretion was similar by both routes; in the other subject, the levels were much higher (about 3:1) in the breath. Levels of radioactivity in feces were not measured.

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.

PBPK models have not been developed for 2-hexanone.

3.1.6 Animal-to-Human Extrapolations

2-Hexanone, via its metabolite, 2,5-hexanedione, affects mainly the nervous system (Abdel-Rahman et al. 1978; DiVincenzo et al. 1976, 1978; Eben et al. 1979). Most animal species tested have shown similar clinical signs and morphological alterations in the peripheral nervous system, as have humans exposed to 2-hexanone itself or to *n*-hexane, a chemical that is also biotransformed into 2,5-hexanedione. Comparative studies have shown the relative species sensitivity to 2-hexanone as chicken > cat > dog > primate > rat (Abdo et al. 1982; Mendell et al. 1974). While many studies have been conducted in hens/chickens and are useful for hazard identification, they are not useful for risk assessment. As mentioned earlier, because their digestive and respiratory systems are different from mammals, it is not known whether the dose-response in this species is applicable to humans.

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 2-hexanone are discussed in Section 5.7, Populations with Potentially High Exposures.

There are no studies of humans that could help determine whether children are more susceptible than adults to the effects of exposure to 2-hexanone. Likewise, there are no studies in animals that examined the comparative sensitivity of young and older animals to 2-hexanone.

To the extent that the metabolism of 2-hexanone involves cytochrome P-450 enzymes, some of which are known to be developmentally regulated, infants may be at higher or lower risk of 2-hexanone toxicity depending on whether oxidative (activation) or reductive (detoxification) reactions prevail in the initial steps of 2-hexanone metabolism.

No specific population has been identified that is unusually susceptible to toxic effects resulting from exposure to 2-hexanone.

Children are expected to be exposed to 2-hexanone by the same routes that affect adults. Ingestion of foods contaminated with small amounts of 2-hexanone is the most likely route of exposure for children. No data were located regarding 2-hexanone in breast milk; therefore, an adequate determination of the importance of this route of child exposure has not been made.

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 2-hexanone 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 2-hexanone 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 2-hexanone 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

2-Hexanone and its various metabolic products (2-hexanol, 2,5-hexanedione, 5-hydroxy-2-hexanone, 2,5-dimethylfuran) can be measured in expired air, biological tissue, fluid, and excreta (Fedtke and Bolt 1986; Nomeir and Abou-Donia 1985; O'Donoghue and Krasavage 1979; White et al. 1979). The currently available information, however, does not indicate whether the levels of these substances can be used to calculate or estimate corresponding levels of exposure to 2-hexanone. Because exposure to other

substances, for example *n*-hexane, also produce 2,5-hexanedione as a metabolite, identification of 2,5-hexanedione in the urine does not necessarily indicate that exposure to 2-hexanone occurred.

It is worth noting that 2,5-hexanedione has been identified in the urine of subjects in Italy who had not been occupationally exposed to 2-hexanone or *n*-hexane (Bavazzano et al. 1998). The investigators proposed that 2,5-hexanedione had both an endogenous and an exogenous origin. The former is related to pollution due to exposure to solvents and the latter is based on the hypothesis that 2,5-hexanedione might be an intermediate catabolite of some biochemical physiological processes. However, the study did not provide any support for an endogenous origin.

3.3.2 Biomarkers of Effect

There are no biomarkers specific for exposure to 2-hexanone. The main effect of exposure to 2-hexanone is neuropathy. Signs of neuropathy can be monitored by non-invasive procedures such as measurement of nerve conduction velocities, amplitude of evoked muscle action potentials, and amplitude of evoked sensory action potentials. However, these signs are not exclusive to exposure to 2-hexanone. They can occur due to exposure to other chemicals or can be caused by conditions not even associated with chemical exposures.

3.4 INTERACTIONS WITH OTHER CHEMICALS

There are limited data on the effect of other chemicals on the toxicity of 2-hexanone. A study in which rats were exposed via inhalation to a combination of 2-hexanone and methyl ethyl ketone resulted in the potentiation of severe neurotoxic effects including paralysis and histopathological changes. These effects were either not observed or they occurred at much lower frequencies when either of the two compounds was administered separately (Saida et al. 1976). Similarly, dermal or inhalation exposure in hens to 2-hexanone in combination with dermal application of the pesticide, *O*-ethyl-*O*-4-nitrophenyl phenylphosphonothioate (EPN), has resulted in earlier onset and far more severe clinical and histological manifestations of neurotoxic effects than with either chemical exposure alone (Abou-Donia et al. 1985a, 1985b). The authors speculated that this potentiation effect may have been due to induction of hepatic microsomal cytochrome P-450 by EPN, leading to increased metabolism of 2-hexanone to its neurotoxic metabolite, 2,5-hexanedione. An alternate explanation is that local trauma to the nervous tissue produced by 2-hexanone and EPN might increase vascular permeability and thus increase the entry of these compounds and their metabolites from circulation.

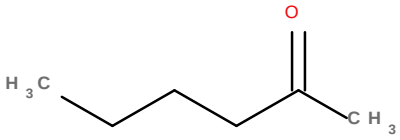
Given that 2-hexanone and *n*-hexane have similar active metabolites, interaction studies with *n*-hexane provide information on potential for interactions for 2-hexanone. As discussed in the toxicological profile for *n*-hexane (ATSDR 1999), co-exposure of *n*-hexane with methyl ethyl ketone or acetone increased the neurotoxicity of *n*-hexane. In contrast, co-exposure of *n*-hexane with xylene or toluene prevented or reversed the decreased nerve conduction velocity that was associated with exposure to *n*-hexane only. This protective effect may have been due to metabolic competition resulting in a decrease in the metabolism of *n*-hexane to 2,5-hexanedione (ATSDR 1999). Although no studies were identified, it is likely that co-exposure to 2-hexanone and *n*-hexane would result in additive or greater-than-additive toxicity. Additionally, co-exposure to other compounds that have similar mechanisms of neurotoxicity or result in alterations that favor the production of 2,5-hexanedione (e.g., methyl isobutyl ketone) may influence the toxicity of 2-hexanone.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Table 4-1 lists common synonyms, trade names, and other pertinent identification information for 2-hexanone. Note that the purity of commercial-grade 2-hexanone ranges from 70 to 96%; contaminants may include methyl isobutyl ketone (MiBK) (Topping et al. 2001).

Table 4-1. Chemical Identity of 2-Hexanone[a]

Characteristic	Information
Chemical name	2-Hexanone
Synonym(s) and registered trade name(s)	Methyl *n*-butyl ketone; MBK; 2-oxohexane; *n*-butyl methyl ketone, propylacetone; MnBK
Chemical formula	$C_6H_{12}O$
Chemical structure	
CAS Registry Number	591-78-6

[a]All information obtained from HSDB (2009), unless otherwise noted.

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

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

Table 4-2. Physical and Chemical Properties of 2-Hexanone

Property	Information
Molecular weight	100.16
Color	Colorless
Physical state	Liquid
Melting point	-55.5°C
Boiling point	127.2°C
Density at 20°C	0.83
Odor	Similar to acetone, but more pungent
Odor threshold:	
Water	0.25 mg/L
Air	0.076 ppm (0.31 mg/m^3)
Solubility:	
Water at 20°C	1.72x10^4 mg/L
Organic solvents	Soluble in acetone; miscible in ethanol and ether
Partition coefficients:	
Log K_{ow}	1.38
Log K_{oc}	No data
Vapor pressure at 25°C	11.6 mm Hg
Henry's law constant	9.32x10^{-5} atm-m^3/mol at 25°C (estimated)
Autoignition temperature	795°F (423°C)
Flashpoint	95°F (35°C) (open cup); 77°F (25°C) (closed cup)
Flammability limits	1.2–8%
Conversion factors at 25°C, 760 mm Hg	1 ppm=4.10 mg/m^3 1 mg/L=244 ppm
Explosive limits	1.22–8%

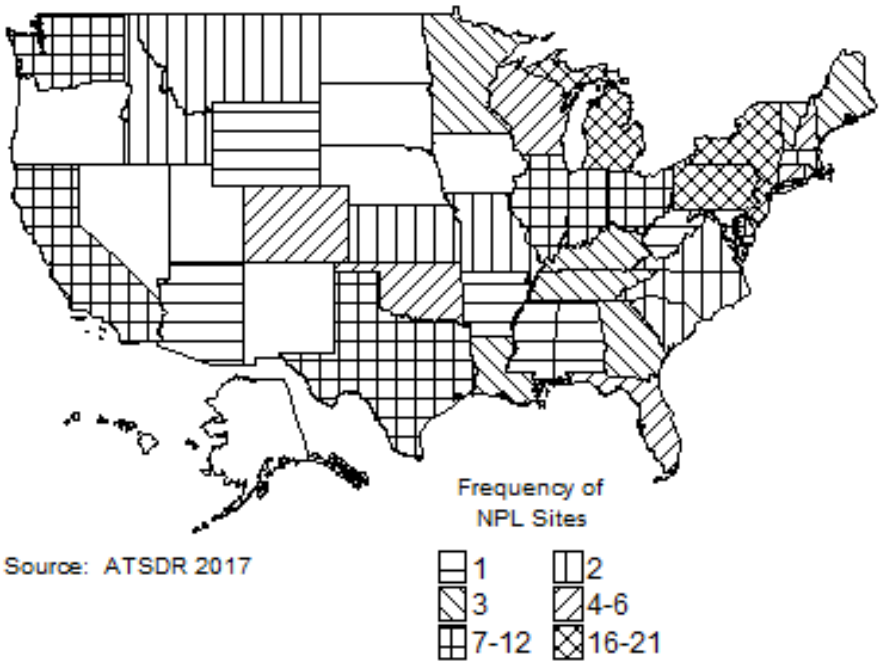
Source: HSDB 2009

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

2-Hexanone has been identified in at least 224 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 2-hexanone has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 221 are located within the United States, 1 is located in the Guam, and 2 are located in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with 2-Hexanone Contamination



- Human exposure to 2-hexanone may occur by inhalation, ingestion, or dermal exposure. Exposure to small amounts of 2-hexanone may occur by ingestion of foods in which it has been detected.
- Because 2-hexanone is not currently manufactured, imported, processed, or used for commercial purposes in the United States (EPA 1987), releases to the environment are not likely to be high.
- 2-Hexanone can be released to the air from activities involving the oil and gas industry if waste water is stored in open containment pits. It may be released to water by activities associated with the oil and natural gas industries and at hazardous waste sites.

- 2-Hexanone exists in the atmosphere as a vapor and is very soluble in water.
- The major fate mechanism of atmospheric 2-hexanone is photooxidation.
- 2-Hexanone may be biodegraded in soil.
- 2-Hexanone is expected to have high mobility in soil, and may therefore leach into groundwater.

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 2-hexanone 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).

In 1977, the combined U.S. production and import of 2-hexanone was between 453 and 4,500 metric tons (EPA 1981, 1987); no breakdown of these figures was provided. The only U.S. producer of 2-hexanone, the Tennessee Eastman Company division of Eastman Kodak, discontinued its production of 2-hexanone in 1979 and sold its remaining reserves by 1981 (EPA 1981, 1987; Lande et al. 1976). 2-Hexanone was commercially produced by the catalyzed reaction of acetic acid and ethylene under pressure (EPA 1987). 2-Hexanone may still be commercially produced in countries outside of the United States.

5.2.2 Import/Export

Currently, 2-hexanone is not produced or approved for commercial use in the United States, and consequently, there is no information on exports or imports (EPA 1987; HHS 2017).

5.2.3 Use

2-Hexanone is not currently manufactured, processed, or used for commercial purposes in the United States (EPA 1987; HHS 2017). 2-Hexanone had been used as a solvent for many materials, primarily in the lacquer industry as a solvent for lacquers and varnish removers. It had also been used as a solvent for ink thinners, resins, oils, fats, and waxes, and as a medium evaporating solvent for alkyd, vinyl, and nitrocellulose acrylate coatings. 2-Hexanone had also been used as an intermediate in the synthesis of organic chemicals (ACGIH 1986; EPA 2009a). 2-Hexanone has been studied as a possible oxygenate in

blended diesel fuels; however, it absorbs water and is susceptible to gum formation (McCormick et al. 2015).

5.2.4 Disposal

No data were located regarding the disposal of 2-hexanone or on regulations and guidelines regarding its disposal. The favored method for disposal of ketones is incineration (Lande et al. 1976).

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).

Because 2-hexanone is not currently manufactured, imported, processed, or used for commercial purposes in the United States (EPA 1987), releases to the environment are not likely to be high. Although it is reported to be released from currently operating wood pulping, coal-gasification, and *in situ* oil-shale processing[1] plants via liquid waste water containing 2-hexanone or as a volatilized gas from waste water into the surrounding air, levels resulting from these operations have been reported as being low (ATSDR 2008; Pellizzari et al. 1979). In the past decade, there has been an increase in oil and natural gas production due to the development of horizontal drilling and hydraulic fracturing (EIA 2016). There is some evidence that 2-hexanone may be released from these operations; however, the data are limited.

[1] *In situ* shale oil processing involves drilling into oil shale strata and heating rocks to release crude shale oil, shale gas, and water (referred to as termed retorting).

5.3.1 Air

There is no information on releases of 2-hexanone to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Limited studies were located regarding the amount of 2-hexanone released to the atmosphere. 2-Hexanone was detected at a maximum average concentration of 1,700 µg/m^3 in the air emissions of eight municipal solid waste composting disposal facilities in the United States (Eitzer 1995). Kumar et al. (2011) also reported 2-hexanone to be a volatile organic compound emission from green waste composting. Municipal solid waste composting facilities collect waste, including yard waste, food scraps, farm waste, cardboard, newspaper, and sewage treatment plant solids, from non-industrial sources such as residential homes, restaurants, retail centers, and office buildings. Therefore, the 2-hexanone detected in air emissions is likely produced from the microbial digestion of large bioorganic compounds.

2-Hexanone can be released to the air from activities involving the oil and gas industry if waste water is stored in open containment pits. For example, a report from an environmental nonprofit group reported that 2-hexanone was detected in air samples above oil and gas waste water open containment ponds located in Kern County, California at a concentration of 12 µg/m^3 (Grinberg 2014). Hawthorne and Sievers (1984) measured 2-hexanone at levels of 0.22–3.6 ng/mL in air samples above shale oil waste water retort water and gas condensate. Since 2-hexanone is no longer produced in the United States (EPA 1987) or used commercially (EPA 1987; Lande et al. 1976; O'Donoghue 1985), atmospheric emissions from industrial sources are likely to be small.

5.3.2 Water

There is no information on releases of 2-hexanone to water from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

2-Hexanone may be released to water by activities associated with the oil and natural gas industries and at hazardous waste sites. 2-Hexanone was detected in process water from a coal gasification site (7 µg/L) located in Wyoming and condensate water (202 µg/L) from the low-BTU gasification of coal from a facility in West Virginia (Pellizzari et al. 1979). It was also detected in retort water (55 µg/L) from an *in situ* oil shale processing location in Wyoming (Pellizzari et al. 1979). It was analyzed for, but not

detected in, flowback water (the water that is returned to the surface following the hydraulic fracturing) from 19 natural gas hydraulic fracturing locations in West Virginia and Pennsylvania as well as flowback water from 5 locations in Texas (Hayes 2009; RPSEA 2012). The compound has also been tentatively identified in 1 of 63 industrial effluents (Perry et al. 1979), the effluent from a chemical plant (Shackelford and Keith 1976), and in one municipal landfill leachate at 0.148 ppm (mg/L) in a study of leachates from 58 municipal and industrial landfills (Brown and Donnelly 1988).

2-Hexanone has also been detected in both groundwater and surface water at hazardous waste sites (CLPSD 1989) (see Section 5.5.2), indicating that this is a source of 2-hexanone release to the environment.

5.3.3 Soil

There is no information on releases of 2-hexanone to soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Soils or sediments may become contaminated with 2-hexanone by landfilling with 2-hexanone-containing solid wastes or by the discharge of contaminated water. 2-Hexanone has been detected in soil samples from hazardous waste sites (CLPSD 1989) (see Section 5.5.3).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. 2-Hexanone exists in the atmosphere as a vapor. Liquid 2-hexanone is volatile; its vapor pressure has been measured as 1.53×10^{-2} atm (11.6 mmHg) at 25°C (Ambrose et al. 1975). Because 2-hexanone is very soluble in water, a large fraction of 2-hexanone released to the atmosphere may dissolve in water vapor (such as clouds and rain drops). A Henry's law constant estimates the tendency of a chemical to partition between its vapor phase and water. An estimated value for Henry's law constant of 2-hexanone is 9.32×10^{-5} atm-m^3/mol at 25°C (HSDB 2009). The magnitude of this value suggests that a large fraction of vapor-phase 2-hexanone will dissolve in water, and that precipitation may be an important physical removal mechanism. An analogous air-water partition coefficient measured for 2-hexanone at 37°C was approximately 2.3×10^{-4} atm-m^3/mole (Sato and Nakajima 1979), which indicates that precipitation will also be an important removal mechanism at this higher temperature.

Water. 2-Hexanone is very soluble in water, approximately 17.2 g/L (Yalkowsky and Yan 2003). The Henry's law constant indicates that a fraction of 2-hexanone will volatilize from water. Estimated half-lives in model river and lake water are about 7 hours and 7 days, respectively (Thomas 1990). Based on its estimated organic carbon partition coefficient (K_{oc}) value of 77, 2-hexanone is expected to have high mobility in soil (Thomas 1990), and may therefore leach into groundwater. This may be a particular concern if contaminated waste water or flowback water is stored in unlined containment ponds or disposed of via underground injection.

2-Hexanone is not likely bioconcentrated by organisms in water. An octanol/water partition coefficient (log K_{ow}) estimates the partitioning of a chemical between octanol and water. Octanol is believed to best imitate the fatty structures in plants and animal tissues. Generally, a log K_{ow} range of 2–7 describes most chemicals of interest with the potential to partition to fatty tissues. The log K_{ow} of 2-hexanone is 1.38 (Hansch et al. 1995). Therefore, this low value suggests that 2-hexanone is not likely to partition to fatty tissues. Further, a bioconcentration factor (BCF) relates the concentration of a chemical in plants or animals to the concentration of that chemical in the medium in which they live. Generally, a BCF value <30 is considered to have low bioconcentration potential. A BCF of 4 was calculated for 2-hexanone (EPA 2012a), suggesting that bioconcentration in aquatic organisms is not expected to be an important fate mechanism for 2-hexanone released into the environment. Biomagnification of 2-hexanone is also not expected to occur to any great extent (Lande et al. 1976). However, no experimental data on the biomagnification potential of 2-hexanone were located to corroborate these assumptions.

5.4.2 Transformation and Degradation

Air. The major fate mechanism of atmospheric 2-hexanone is photooxidation. This ketone is also degraded by direct photolysis (Calvert and Pitts 1966), but the reaction is estimated to be slow relative to reaction with hydroxyl radicals (Laity et al. 1973). The rate constant for the photochemically induced transformation of 2-hexanone by hydroxyl radicals in the atmosphere has been measured at 9.01×10^{-12} cm^3/ molecule-set (Atkinson 1989). Using an average concentration of atmospheric hydroxyl radicals of 5×10^5 molecules/cm^3 (Atkinson 1989), the calculated atmospheric half-life of 2-hexanone is about 2.4 days. However, the half-life may be shorter in polluted atmospheres with higher OH radical concentrations (MacLeod et al. 1984). Consequently, it appears that vapor-phase 2-hexanone is labile in the atmosphere.

Water. 2-Hexanone is a ketone, and ketones are generally not degraded by hydrolysis (Lande et al. 1976). Based on its reactions in air, it seems likely that 2-hexanone will undergo photolysis in surface water; however, no information was located. Based on studies with microorganisms, it is probable that 2-hexanone will be biodegraded in both surface water and groundwater.

Sediment and Soil. 2-Hexanone may be biodegraded in soil. 2-Hexanone has been shown to be degraded by hydrocarbon-utilizing mycobacteria (Lukins and Foster 1963; Perry 1968). Similarly, certain yeasts have been isolated that can use 2-hexanone as a carbon source (Lowery et al. 1968). In a study using acclimated microbial cultures, 2-hexanone was significantly biodegraded (Babeu and Vaishnav 1987). An experimental 5-day biological oxygen demand (BOD) determination was about 61% of the theoretical BOD value. Although these studies have demonstrated that 2-hexanone may be biodegraded under ideal conditions, no information was located on its biological half-life in soils.

Other Media. No studies were located for the environmental fate of 2-hexanone in other media.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to 2-hexanone depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of 2-hexanone 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 2-hexanone 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. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-2.

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

Media	Detection limit	Reference
Air	0.454 µg (0.227 mg/m^3)	NIOSH 1984; OSHA 1995
Drinking water	No data	
Surface water and groundwater	<10 µg/kg	Badings et al. 1985
Whole blood	No data	Anderson and Harland 1980; White et al. 1979

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

Table 5-2. Summary of Environmental Levels of 2-Hexanone

Media	Low	High	For more information
Outdoor air (ppbv)	0.11 µg/m^3	15 µg/m^3	Section 5.5.1
Ground water (ppb)	87 µg/L	150 µg/L	Section 5.5.2
Food (ppb)	1 µg/kg	18 µg/kg	Section 5.5.4
Soil	40 µg/kg	440 µg/kg	Section 5.5.3

Detections of 2-hexanone in air, water, and soil at NPL sites are summarized in Table 5-3.

Table 5-3. 2-Hexanone 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)	74	71.4	21.6	29	25
Soil (ppb)	58.5	244	40.5	20	16
Air (ppbv)	5.37	5.67	27.8	10	8

[a]Concentrations found in ATSDR site documents from 1981 to 2017 for 1,854 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

Limited studies were located that measured or estimated the concentration of 2-hexanone in ambient air. 2-Hexanone was detected, but not quantified, in air samples collected from Whitaker's Forest in the Sierra Nevada Mountains, California in 1990 (Helmig and Arey 1992).

2-Hexanone and several other volatile organic compounds (VOCs) were monitored for in Garfield County, Colorado where several natural gas hydraulic fracturing wells had been operating at the time of the study (ATSDR 2008). Natural gas needs to be separated from fluids and other gases that may release VOCs into the surrounding air. In addition, fracking water may contain small amounts of chemicals containing VOCs used during the hydraulic fracturing process, and these may volatilize to ambient air if the water is stored in uncovered wells at the location. 2-Hexanone was detected in 14.8% of grab samples collected at all of the monitoring sites in Garfield County at levels ranging from 0.7 to 15.0 µg/m^3, with an average concentration of 1.7 µg/m^3 (ATSDR 2008). It was concluded that noncancer adverse health effects were not likely to occur from exposure to the levels of 2-hexanone measured at these sites, based on comparison with the ATSDR chronic health guidelines. In addition to grab samples, 14 fixed sites were monitored for a 24-hour period once per month or once per quarter; this included 8 locations near oil and gas drilling facilities, 4 urban locations, and 2 rural background locations. 2-Hexanone was detected in at least 4% of the samples from three of the oil and natural gas drilling locations and two of the urban locations. It was detected in <4% of the samples in both the rural background sites.

2-Hexanone was detected in ambient air during a monitoring study in the Commonwealth of Pennsylvania to determine the effect that natural gas exploration had on air quality (PA DEP 2011). Levels of 2-hexanone in air related to Marcellus Shale natural gas activities were determined to be at levels similar to, or slightly greater than, levels observed in areas not impacted by hydraulic fracturing operations. Annual average concentrations of 2-hexanone at these locations ranged from 0.11 to 2.1 µg/m^3. 2-Hexanone was detected in air samples above oil and gas waste water open containment ponds located in Kern County, California at a concentration of 12 µg/m^3 (Grinberg 2014).

In the past, workplace air concentrations in facilities where 2-hexanone was manufactured or used as a solvent ranged from 1 to 156 ppm (4.1–640 mg/m^3) (ACGIH 1986), and air concentrations up to 1,636 mg/m^3 were measured in the operations areas of some facilities (Bierbaum and Marceleno 1973; Marceleno et al. 1974). However, because 2-hexanone is no longer produced or used commercially in the United States, and because the federal government has set certain regulations and guidelines to help protect people from the possible health effects of 2-hexanone in the workplace, it is unlikely that current workplace air concentrations are as high as they were in the past. The Occupational Safety and Health Administration (OSHA) has set a Permissible Exposure Limit (PEL) of 100 ppm (100 parts of 2-hexanone in 1 million parts of air) as a time-weighted average (TWA) to this chemical in workplace air during an 8-hour work period, over a 40-hour workweek (OSHA 2018a). The National Institute for Occupational Health and Safety (NIOSH) has set a Recommended Exposure Limit (REL) of 1 ppm

(TWA) 2-hexanone in workplace air as an average exposure during a 10-hour work period (NIOSH 2018) for up to a 40-hour workweek. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a 5 ppm (TWA) Threshold Limit Value (TLV) for 2-hexanone in workplace air as an average during an 8-hour workday (ACGIH 2001, 2003, 2015). ACGIH also has a 15-minute short-term exposure limit (STEL) of 10 ppm.

5.5.2 Water

2-Hexanone was 1 of 70 VOCs monitored for in influent water and flow-back water at 19 hydraulic fracturing locations located in Pennsylvania and West Virginia (Hayes 2009). 2-Hexanone was not detected in the samples collected. It was also not detected in flowback water from five hydraulic fracturing operations in North Texas (RPSEA 2012).

Data estimating 2-hexanone concentrations in water are sparse. 2-Hexanone was identified in one of three groundwater samples at a concentration of 87 µg/L (ppb) near a hazardous waste site in Florida (Myers 1983). 2-Hexanone was detected, but not quantified, in groundwater near a forest waste site in Otisville, Michigan in 1987 (EPA 1988). Groundwater samples collected from the Biscayne Aquifer Superfund sites in Florida contained 2-hexanone at maximum concentrations of 150 µg/L (from the entire study area) and 110 µg/L (from well fields) (Canter and Sabatini 1994). 2-Hexanone was detected in 0.3, 11.1, 3.6, and 1.4% of hazardous waste site groundwater samples collected from 1981 to 1986 in EPA Regions 1, 2, 9, and 10, respectively (Plumb 1992).

2-Hexanone was detected at an unauthorized hazardous waste disposal site in Lang Township, New Jersey in two well water samples collected in 1985 at an average concentration of 7,135 µg/L (maximum concentration of 14,000 µg/L) and in onsite lagoon surface water samples at an average concentration of 20 µg/L (maximum concentration of 30 µg/L) (EPA 1986). This compound was also identified in a study of drinking water concentrates and advanced waste treatment concentrates (Lucas 1984). Richardson et al. (1999) reported that 2-hexanone was identified in drinking water that had been treated by ozone disinfection.

5.5.3 Sediment and Soil

2-Hexanone was detected in soil samples at 3% of hazardous waste sites (both NPL and non-NPL) at a geometric mean concentration of 40 µg/kg (ppb) in positive samples (CLPSD 1989). 2-Hexanone was

detected at an unauthorized hazardous waste disposal site in Lang Township, New Jersey in surface and subsurface soil samples collected in 1985 at concentrations of 440 and 46 µg/kg, respectively (EPA 1986). In residential topsoil samples taken from a 0.5-acre area at the Dona Park Residential site located immediately south of a former smelting and refining plant in Corpus Christi, Texas, 2-hexanone was detected at 274 mg/kg (TCEQ 2011). No other data were located regarding estimation of 2-hexanone in soils or sediments.

5.5.4 Other Media

2-Alkanones and 2-alkanols are formed naturally in some foods as a byproduct of the degradation of free fatty acids (Dumont and Adda 1978; Girolami and Knight 1955). 2-Hexanone has been identified among the natural volatile components of several foods, including blue and Beaufort cheeses, nectarines, roasted filberts (hazelnuts), beef, and chicken muscle (Day and Anderson 1965; Dumont and Adda 1978; Grey and Shrimpton 1967; Kinlin et al. 1972; Ramarathnam et al. 1991; Takeoka et al. 1988); levels were not stated in these reports. It has been detected in canned cream, canned kernel, frozen kernel, and fresh kernel cooked corn products at concentrations of 1, 2, <5, and <1 ppb, respectively (Buttery et al. 1994). 2-Hexanone was also detected in milk and cream at concentrations ranging from 0.007 to 0.018 ppm (7–18 ppb) and in bread (Lande et al. 1976). Because few quantitative data are available, it is not known if food is an important source of human exposure to 2-hexanone.

No studies were located regarding the occurrence of 2-hexanone in any other media.

5.6 GENERAL POPULATION EXPOSURE

Human exposure to 2-hexanone may occur by inhalation, ingestion, or dermal exposure. Exposure to small amounts of 2-hexanone may occur by ingestion of foods in which it has been detected. However, since this compound is no longer manufactured or used commercially in the United States after its discontinuation in 1979 (EPA 1987), widespread or high-level exposure of the general population to 2-hexanone is not likely. 2-Hexanone has been detected in air samples at locations in which hydraulic fracturing has occurred, suggesting that nearby populations could be susceptible to inhalation exposure. No data were located indicating that 2-hexanone has been detected in groundwater at these locations.

According to surveys conducted by NIOSH, the number of employees potentially exposed to 2-hexanone dropped from 41,600 in the early 1970s to 1,100 in the early 1980s (RTECS 2009). Neither the National

Occupational Hazard Survey (NOHS) nor the National Occupational Exposure Survey (NOES) databases contain information on the frequency, concentration, or duration of exposures of workers to any chemicals listed. These surveys provide only estimates of the number of workers potentially exposed to chemicals in the workplace. This dramatic reduction in the extent of occupational exposure parallels the halt of production and the reduction in commercial use of this chemical (EPA 1987). It is unlikely that many persons are currently occupationally exposed to 2-hexanone, other than as a degradation product resulting from wood pulping, *in situ* oil shale processing, or coal gasification operations. NIOSH does not list 2-hexanone among the chemicals considered in an occupational exposure evaluation of coal gasification plants (NIOSH 1978).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Populations with potentially high exposure to 2-hexanone include people living near or working in areas affected by oil and natural gas activities, or living near the hazardous waste sites where 2-hexanone is likely present. The most likely exposure routes are ingestion or dermal contact with water contaminated from these sources or inhalation of 2-hexanone that has volatilized from contaminated water or soil. Individuals may still be exposed by ingestion, inhalation, skin absorption from use of consumer products manufactured prior to 1982 such as lacquers, primers, sealers, and thinners that contain 2-hexanone, or through currently imported products containing 2-hexanone, including foods.

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 2-hexanone 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 2-hexanone.

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

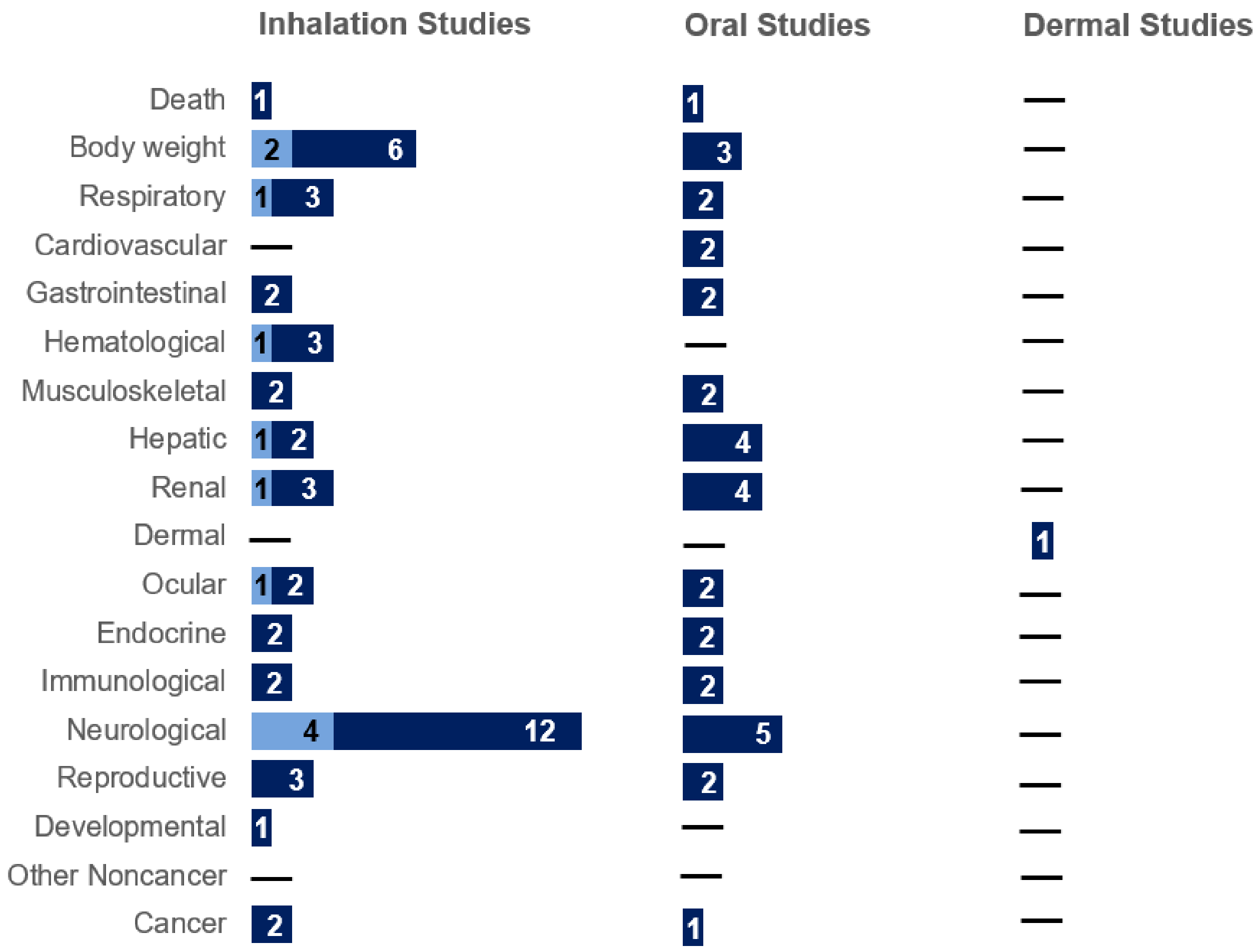
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to 2-hexanone that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of 2-hexanone. The number of human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

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.

Figure 6-1. Summary of Existing Health Effects Studies on 2-Hexanone By Route and Endpoint*

Potential neurological and body weight effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the numbers of studies include those finding no effect. Studies may have evaluated multiple endpoints.

Acute-Duration MRLs. The only acute-duration data available on humans is that exposure to concentrations ≥2,300 ppm 2-hexanone in the air caused irritation of the eyes and nasal passages in men (Schrenk et al. 1936). Acute inhalation exposure to ≥2,300 ppm caused nose and eye irritation in guinea pigs (Schrenk et al. 1936). Acute lethality data are available for guinea pigs via inhalation exposure (Schrenk et al. 1936) and for rats via the oral route (Smyth et al. 1954). Neither an acute-duration inhalation nor oral MRL could be derived due to lack of adequate studies. Acute-duration studies would be useful for determining minimal doses and exposure durations that can induce neurological effects of short-term exposure.

Intermediate-Duration MRLs. The currently available data on humans exposed to 2-hexanone for intermediate durations is based on a study of workers exposed to 2-hexanone for ≥5 weeks (Allen et al. 1975; Billmaier et al. 1974). Peripheral neuropathy and weight loss were the major observations. Several limitations including exposure to other chemicals and possibly significant oral and dermal exposure precluded using this study for derivation of an intermediate-duration inhalation MRL. Repeated-dose studies in rats, cats, monkeys, and guinea pigs indicate that the nervous system is the primary target of 2-hexanone exposure via inhalation (Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Mendell et al. 1974; Saida et al. 1976; Spencer et al. 1975) or orally (Abdel-Rahman et al. 1978; Eben et al. 1979; Krasavage et al. 1980; Union Carbide 1977). Most intermediate-duration studies tested only one exposure concentration or dose level and many did not provide information regarding the purity of the test material. Because the lowest exposure levels tested were serious LOAELs for neurological effects, no intermediate-duration MRLs were derived. Intermediate-duration inhalation and oral studies that examine multiple endpoints, including neurotoxicity, would be valuable for establishing dose-response relationships and deriving MRLs.

Chronic-Duration MRLs. Some of the workers exposed to 2-hexanone who developed peripheral neuropathy studied by Allen et al. (1975) had been exposed to the chemical for chronic durations. No additional chronic-duration studies in humans were located. As mentioned above, however, confounders in the Allen et al. (1975) study precluded its use for MRL derivation. There are two chronic-duration inhalation studies in animals (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979). Both studies examined multiple endpoints and the lowest exposure concentration tested, 100 ppm, was a NOAEL for neurological effects. Because the exposure level of 100 ppm was a serious LOAEL for neurological effects in intermediate-duration studies, a chronic-duration inhalation MRL for 2-hexanone could not be derived based on the studies by Krasavage and O'Donoghue (1977) and O'Donoghue and Krasavage (1979). There is one chronic-duration oral study available in rats exposed to pure 2-hexanone

that examined multiple endpoints (O'Donoghue et al. 1978); this study was used to derive a chronic-duration oral MRL for 2-hexanone. Additional chronic-duration studies providing data to derive a chronic-duration inhalation MRL would be valuable.

Health Effects.

Neurotoxicity. The nervous system has been clearly established as the major target for 2-hexanone in humans exposed via inhalation (Allen et al. 1975; Billmaier et al. 1974) and in animals exposed via any route of exposure (Abdel-Rahman et al. 1978; Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Krasavage et al. 1980; Krasavage and O'Donoghue 1977; O'Donoghue et al. 1978; O'Donoghue and Krasavage 1979; Saida et al. 1976; Spencer et al. 1975; Union Carbide 1977). However, most of the available information is derived from studies using 2-hexanone of low or unknown purity or using it at a single dosage level, so its usefulness is limited. Animal data that would clearly establish dose-response relationships for neurological effects, including histopathological damage as well as clinical manifestations, as a result of exposure to pure 2-hexanone via all routes of exposure and using a range of exposure durations would be useful. This information would be valuable in assessing the potential risks of neurotoxicity in persons exposed to 2-hexanone in the vicinity of hazardous waste sites. In addition, continued research aimed at determining the mode of action of 2,5-hexanedione, the active neurotoxic metabolite at the molecular level, would be valuable.

Reproductive Toxicity. There is no information on the effects of 2-hexanone on reproductive parameters in exposed humans via any route of exposure. Limited studies in animals have not produced conclusive results. Reduced testes weight and induced atrophy of the testicular germinal epithelium of male rats were reported in an intermediate-duration inhalation study (Katz et al. 1980); however, chronic exposure of male rats and female cats to ≤330 ppm 2-hexanone of unreported purity did not induce gross or microscopic alterations in the reproductive organs of either species (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979). In oral studies, 2-hexanone induced testicular toxicity in male rats when given by gavage (Krasavage et al. 1980), but not when given in the drinking water to male rats (O'Donoghue et al. 1978) in comparable doses. Exposure to 2,5-hexanedione can result in testicular damage (increased spermatid heads) in rats (Bryant et al. 2008). None of the available 2-hexanone studies assessed fertility. A 2-generation reproductive toxicity study could provide useful data.

Developmental Toxicity. There is no information on the effects of exposure to 2-hexanone via any route on human development. There are no animal studies using the oral or dermal routes. The currently available data for animals is based on a single inhalation study in pregnant rats in which relatively high 2-hexanone exposure resulted in decreased litter size and pup weight and in behavioral effects in the offspring tested later in life (Peters et al. 1981). Additional studies would be useful to confirm or refute the findings of Peters et al. (1981).

Immunotoxicity. There are currently no data on the effects of 2-hexanone on the human immune system via any route of exposure. 2-Hexanone did not induce morphological alterations in lymphoreticular organs or tissues of rats or cats in long-term inhalation or oral studies (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979; O'Donoghue et al. 1978; Union Carbide 1977). However, none of these studies examined parameters of immunocompetence. A screening (Tier I) study using a battery of tests (immunopathology, humoral- and cell-mediated immunity, nonspecific immunity) (Luster et al. 1988) would provide valuable results.

Epidemiological and Human Dosimetry Studies. The only epidemiological information that is currently available is the study of workers in a plant producing plastic-coated and color-printed fabrics (Allen et al. 1975; Billmaier et al. 1974). Some workers developed peripheral neuropathy whose origin was traced to exposure to 2-hexanone, although exposure to other chemicals also occurred. Because 2-hexanone is no longer manufactured or used commercially in the United States, it is unlikely that many persons are currently occupationally exposed to 2-hexanone, other than as a degradation product resulting from wood pulping, *in situ* oil shale processing, or coal gasification operations. Identification and evaluation of populations having long-term exposure to 2-hexanone due to, for example, contamination of drinking water, for neurological, reproductive, developmental, and cancer effects would be useful.

Biomarkers of Exposure and Effect.

Exposure. Measurement of 2-hexanone and its metabolites in blood or urine may not provide an adequate indication of exposure to this substance, since these metabolites may also result from exposure to *n*-hexane (Fedtke and Bolt 1986; Nomeir and Abou-Donia 1985; White et al. 1979). Further work in the characterization of the neurofilament protein adduct produced by the active metabolite, 2,5-hexanedione, would be useful.

Effect. The major target organ of 2-hexanone in humans is the nervous system (Allen et al. 1975), and morphological effects may occur before clinical manifestations of toxicity (Egan et al. 1980). Development of noninvasive imaging procedures that can identify morphological alterations in peripheral nerves and in central tracts would be useful.

Absorption, Distribution, Metabolism, and Excretion. Although some information is available on each of these topics from studies conducted in several species, more information in each of these areas would be useful. In addition, because most of these studies were conducted by the same group of researchers, further studies in other laboratories in each of these areas would be useful in confirming the available data.

Available data indicate that 2-hexanone is readily absorbed by humans and various animal species after inhalation, oral, or dermal administration (DiVincenzo et al. 1977, 1978). Estimates are available regarding the rates of absorption via the inhalation and oral routes in humans (DiVincenzo et al. 1978), but information is lacking regarding rates of dermal absorption. Also lacking is information regarding possible mechanism(s) by which 2-hexanone is absorbed through the lungs, gastrointestinal tract, and skin.

Limited information on distribution of 2-hexanone is available. An inhalation study in rats reported distribution of 2-hexanone and metabolites to the lungs and liver but did not examine any other organ or tissue (Duguay and Plaa 1995). It also appeared that some accumulation occurred in the lungs at exposure concentrations ≥150 ppm. Further studies, particularly longer-term studies that examine potential distribution to additional tissues, especially the nervous system would be valuable. An environmentally relevant route of exposure (i.e., oral, dermal) is preferred over parenteral dosing.

The proposed metabolic pathway for 2-hexanone is based on blood metabolites identified during intraperitoneal studies in guinea pigs (DiVincenzo et al. 1976) and oral studies in rats (DiVincenzo et al. 1977). The metabolite, 2,5-hexanedione, has also been found in human serum after inhalation exposure (DiVincenzo et al. 1978). Because studies in rats exposed to 2-hexanone have indicated a strong relationship between the concentration of 2,5-hexanedione in the urine and the onset of neuropathic signs (Eben et al. 1979), it would be useful to also have this information for humans. In addition, information on specific enzymes involved in phase I metabolic reactions and details on phase II conjugation reactions would provide important information to advance the understanding of 2-hexanone metabolism in humans.

Limited excretion data are available in humans receiving 2-hexanone via inhalation, oral, and dermal exposure, in dogs via inhalation exposure, and in rats via oral exposure (DiVincenzo et al. 1977, 1978). However, human data on excretion of 2-hexanone via feces are not available, and the available information in dogs concerns excretion via exhaled breath only. In these and any other studies, information on all routes of excretion would help to evaluate the potential for 2-hexanone clearance in the exposed species. Excretion data in rats receiving 2-hexanone via inhalation and dermal application and in other species receiving 2-hexanone via all three routes would be useful for comparison with the human data and to assess the comparative risks of exposure by each route. In addition, information on excretion rates in each species via each route would be helpful in understanding how long 2-hexanone and its metabolites may persist in the body.

Comparative Toxicokinetics. The toxicokinetic studies available in both humans and animals (dogs, rats, and guinea pigs) suggest that there may not be any major differences in the kinetics of this compound across certain species. Metabolites of 2-hexanone in the expired breath (carbon dioxide) of humans and rats exposed via the oral route and the presence of 2,5-hexanedione in the serum of humans exposed via inhalation, as well as in the blood and urine of orally exposed rats and the intraperitoneally exposed guinea pigs, suggest that there is a similar metabolic pathway in humans and experimental animals (DiVincenzo et al. 1976, 1977, 1978). Confirmation of this assumption would be useful. Similar toxic effects, neuropathy and weight loss, have been noted in several species (humans, monkeys, rats, cats, hens, and guinea pigs) (Abdel-Rahman et al. 1978; Allen et al. 1975; Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Krasavage et al. 1980; O'Donoghue et al. 1978; Saida et al. 1976; Spencer et al. 1975). Therefore, it would also be useful to investigate patterns of distribution, to identify target organs, and to measure rates of excretion in several species and to identify blood metabolites in humans in order to investigate interspecies similarities and differences. Studies in this area would be valuable for predicting toxic effects in humans and for studying the mechanisms of action of this chemical.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There are no studies of children exposed to 2-hexanone or animal studies that compare the susceptibility of animals of various ages to 2-hexanone. Any research in this area could provide valuable information.

Physical and Chemical Properties. The physical and chemical property data available for 2-hexanone are sufficient to allow a limited estimation of the potential environmental fate of this chemical. The estimated Henry's law constant (EPA 2012a) and K_{oc} (Thomas 1990) need to be verified experimentally to help confirm the estimates of partitioning in environmental media.

Production, Import/Export, Use, Release, and Disposal. No information is available in the TRI database on facilities that manufacture or process 2-hexanone 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).

2-Hexanone is no longer produced, imported, or used commercially in the United States (EPA 1987). Any future manufacture or use is required to be reported to EPA (EPA 1987). No data on disposal of 2-hexanone were located. Information on disposal practices for wastes containing 2-hexanone is necessary for estimations of human exposure from this source. No regulations govern the disposal of 2-hexanone.

Environmental Fate. The probable transport and partitioning of 2-hexanone in environmental media have been predicted based on estimated partition coefficients. Experimental confirmation of these values would help to increase the accuracy of transport and partitioning assessments. The loss mechanisms of 2-hexanone transformations in the atmosphere are fairly-well understood (Atkinson et al. 1985; Calvert and Pitts 1966; Laity et al. 1973; MacLeod et al. 1984), but the reaction pathways and environmental fates of the transformation products are not known. Very little is known about the fate of 2-hexanone in water or soil (Babeu and Vaishnav 1987; Lande et al. 1976; Lowery et al. 1968; Lukins and Foster 1963; Perry 1968). Data on photodegradation and biodegradation of 2-hexanone in surface water and biodegradation of 2-hexanone in groundwater and soil may be helpful in assessing the persistence of 2-hexanone in these media.

Bioavailability from Environmental Media. Information on absorption by humans and other animal species indicates that it is well absorbed via the oral and dermal routes (DiVincenzo et al. 1977, 1978). 2-Hexanone has also been demonstrated to be well absorbed by humans and animals following inhalation exposure (DiVincenzo et al. 1978). Information on its bioavailability from contaminated soils would be useful in assessing the risk from exposure to this medium by populations in the vicinity of hazardous waste sites likely contaminated with 2-hexanone.

Food Chain Bioaccumulation. There are no data on the bioaccumulation of 2-hexanone in food chains. This lack of data may not be a major limitation in the database because it is unlikely that 2-hexanone is bioconcentrated by plants, aquatic organisms, or animals at lower trophic levels based on its high water solubility (Lande et al. 1976). However, data confirming that bioconcentration does not occur would help to more accurately assess the probability of bioaccumulation of 2-hexanone.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of 2-hexanone in contaminated media at hazardous waste sites are needed so that the information obtained on levels of 2-hexanone in the environment can be used in combination with the known body burden of 2-hexanone to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Very few data are available regarding the presence of 2-hexanone in any environmental media (CLPSD 1989; Lucas 1984; Myers 1983). Although high levels of this compound are not expected to occur in ambient air, water, or soil, concentrations of 2-hexanone in these media near effluent sources or hazardous waste sites would be helpful in assessing the potential extent and magnitude of human exposures.

Exposure Levels in Humans. No specific biomarkers for 2-hexaonone exposure have been identified. It would be useful to collect information on levels of exposure to 2-hexanone in the environment and associated blood, urine, or tissue levels of 2-hexanone and/or its metabolites in the exposed populations. Additional information relating those levels to the subsequent development of health effects would also be extremely useful.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. No information has been located on exposure levels of children to 2-hexanone in the vicinity of hazardous waste sites. It would be useful to collect information on levels of exposure to 2-hexanone in the environment and associated blood, urine, or tissue levels of 2-hexanone and/or its metabolites in the exposed populations. Additional information relating those levels to the subsequent development of health effects would also be extremely useful.

6.3 ONGOING STUDIES

Relevant ongoing research regarding 2-hexanone identified in the National Institutes of Health (NIH) RePORTER (2019) database is presented in Table 6-1.

Table 6-1. Ongoing Studies on 2-Hexanone

Investigator	Affiliation	Research description	Sponsor
Boekelheide, K	Brown University	Study to develop sperm molecular biomarkers to improve detection and monitoring of toxicant-induced testicular injury	NIEHS

NIEHS = National Institute of Environmental Health Sciences

Source: RePORTER (2019)

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding 2-hexanone 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 2-hexanone.

Table 7-1. Regulations and Guidelines Applicable to 2-Hexanone

Agency	Description	Information	Reference
	Air		
EPA	RfC	$3x10^{-2}$ mg/m^3 [a]	IRIS 2009
WHO	Air quality guidelines	Not listed	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories	Not listed	EPA 2018a
	National primary drinking water regulations	Not listed	EPA 2009b
	RfD	$5x10^{-3}$ mg/kg-day[b]	IRIS 2009
WHO	Drinking water quality guidelines	Not listed	WHO 2017
FDA	Substances Added to Food	Not listed[c]	FDA 2019
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	Inadequate information to assess carcinogenic potential	IRIS 2009
IARC	Carcinogenicity classification	Not listed	IARC 2019
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	100 ppm (410 mg/m^3)	OSHA 2018a, 2018b, 2018c
NIOSH	REL (up to 10-hour TWA)	1 ppm (4 mg/m^3)	NIOSH 2018
	IDLH	1,600 ppm	NIOSH 1994

Table 7-1. Regulations and Guidelines Applicable to 2-Hexanone

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2018b
DOE	PACs-air		DOE 2018a
	PAC-1[d]	10 ppm	
	PAC-2[d]	830 ppm	
	PAC-3[d]	5,000 ppm	

[a]The RfC is based on a $BMCL_{05(HEC)}$ of 90 mg/m^3 for reduced motor conduction velocity of the sciatic-tibial nerve in monkeys in a subchronic inhalation study.
[b]The RfD is based on a $BMDL_{10}$ of 5 mg/kg-day for axonal swelling of the peripheral nerve in rats in a chronic drinking water study.
[c]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited in food, delisted color additives, and some substances "no longer FEMA GRAS."
[d]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

AEGL = acute exposure guideline levels; BMCL = 95% lower confidence limit on the benchmark concentration; BMDL = 95% lower confidence limit on the benchmark dose; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association; GRAS = generally recognized as safe; HEC = human equivalent concentration; 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; JECFA = Joint Expert Committee on Food Additives; 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 S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Hexanone
CAS Numbers: 591-78-6
Date: February 2020
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: An acute-duration inhalation MRL for 2-hexanone was not derived due to lack of appropriate studies in humans or in animals. The only information located regarding effects in humans is that men (unknown number) exposed to ≥2,300 ppm vapors of a commercial-grade 2-hexanone for brief periods of time (25–60 seconds) found the atmospheres extremely disagreeable due to a strong odor and had irritation of the eyes and nasal passages (Schrenk et al. 1936). The same group of investigators reported that an unspecified number of guinea pigs exposed to 2,300 ppm 2-hexanone showed signs of eye and nose irritation after 1 minute of exposure and lacrimation after 10 minutes of exposure; no such signs were reported in guinea pigs exposed to 1,000 ppm 2-hexanone. Exposure of guinea pigs to 6,500 ppm for 540 minutes caused lethality.

Agency Contacts (Chemical Managers): Nickolette Roney

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Hexanone
CAS Numbers: 591-78-6
Date: February 2020
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: An intermediate-duration inhalation MRL for 2-hexanone was not derived because the lowest dose tested in an animal study induced serious neurological effects; ATSDR does not derive MRLs based on serious LOAELs. The lowest LOAEL reported was 50 ppm for sciatic nerve demyelination (a serious effect) in rats exposed for 8 hours/day, 5 days/week for 6 months (Duckett et al. 1979). Other intermediate-duration inhalation studies reported neurological effects (decreased nerve conduction velocity, neuropathy, and histopathological changes to central and peripheral nerves) occurring at higher exposure levels (≥100–1,000 ppm) (Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Mendell et al. 1974; Saida et al. 1976; Spencer et al. 1975). Other adverse effects included decreased body weight and decreased white blood cell count (Johnson et al. 1977; Katz et al. 1980); however, these effects were observed at exposure levels of 700–1,000 ppm.

Agency Contacts (Chemical Managers): Nickolette Roney

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Hexanone
CAS Numbers: 591-78-6
Date: February 2020
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: A chronic-duration inhalation MRL for 2-hexanone was not derived due to lack of adequate data. Peripheral neuropathy, rated as moderate to severe, was observed in workers exposed to 2-hexanone (Allen et al. 1975; Billmaier et al. 1974). Workers were also exposed to methyl ethyl ketone, which has been shown to potentiate the effects induced by 2,5-hexanedione, the toxic metabolite of 2-hexanone (Saida et al. 1976; Yu et al. 2002). Therefore, these data are not suitable for derivation of the chronic-duration inhalation MRL. Two chronic-duration inhalation studies have been conducted in animals, one in rats exposed intermittently to 2-hexanone for 72 weeks (Krasavage and O'Donoghue 1977) and one in cats similarly exposed for 2 years (O'Donoghue and Krasavage 1979). In both studies, the lowest LOAEL reported was 330 ppm for serious neurological effects (peripheral neuropathy and axonal degeneration of central and peripheral nerves), with a NOAEL of 100 ppm. However, because a serious LOAEL of 50 ppm for sciatic nerve demyelination was observed in an intermediate-duration study in rats (Duckett et al. 1979), a chronic-duration inhalation MRL was not derived.

Agency Contacts (Chemical Managers): Nickolette Roney

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Hexanone
CAS Numbers: 591-78-6
Date: February 2020
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: An acute-duration oral MRL was not derived for 2-hexanone because of insufficient database. There are no human data, and the database in animals consists of a report of an oral LD_{50} in rats (Smyth et al. 1954) and a study of the potentiation action of 2-hexanone on liver and kidney toxicity caused by chloroform (Brown and Hewitt 1984). In that study, a single high dose of 1,500 mg/kg alone (only dose tested) did not induce morphological alterations in the liver, but produced epithelial degeneration in proximal tubules of the kidneys. However, the Brown and Hewitt (1984) study did not assess neurological effects, the most sensitive effect of 2-hexanone for both inhalation and oral exposure. Therefore, an acute-duration oral MRL was not derived.

Agency Contacts (Chemical Managers): Nickolette Roney

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Hexanone
CAS Numbers: 591-78-6
Date: February 2020
Profile Status: Final
Route: Oral
Duration: Intermediate

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

Rationale for Not Deriving an MRL: An intermediate-duration oral MRL for 2-hexanone was not derived because the lowest dose tested in an animal study induced serious neurological effects; a serious LOAEL is not considered a suitable basis for an MRL. The lowest LOAEL reported was 310 mg/kg/day for an approximately 40% reduction in locomotor activity in guinea pigs exposed to 2-hexanone in drinking water for 24 weeks; this effect was classified as a serious LOAEL. Pupillary responses to light stimuli were also significantly reduced at this dose level. Other intermediate-duration oral studies reported adverse neurological effects at higher daily doses. These effects include peripheral neuropathy in rats administered ≥480 mg/kg/day (Union Carbide 1977); hindlimb weakness in rats administered 400 mg/kg/day (Eben et al. (1979), and paralysis in rats exposed to 660 mg/kg/day (Krasavage et al. 1980).

Agency Contacts (Chemical Managers): Nickolette Roney

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Hexanone
CAS Number: 591-78-6
Date: February 2020
Profile Status: Final
Route: Oral
Duration: Chronic
MRL: 0.05 mg/kg/day
Critical Effect: Axonal swelling in peripheral nerve and spinal cord
Reference: O'Donoghue et al. 1978
Point of Departure: LOAEL of 143 mg/kg/day
Uncertainty Factor: 1,000
Modifying factor: 3
LSE Graph Key: 7
Species: Rat

MRL Summary: A chronic-duration oral MRL of 0.05 mg/kg/day was derived for 2-hexanone based on axonal swelling in peripheral nerve in rats administered via drinking water for 13 months (O'Donoghue et al. 1978). The MRL is based on a LOAEL of 143 mg/kg/day and a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, 10 for human variability) and a modifying factor of 3 for a high response at the lowest dose tested.

Selection of the Critical Effect: One chronic-duration oral study evaluated the toxicity of 2-hexanone (O'Donoghue et al. 1978). The lowest LOAEL reported was 143 mg/kg/day for neurotoxicity. The study also reported reduced body weight at 266 mg/kg/day and skeletal muscle myofiber atrophy at 560 mg/kg/day. Neurotoxicity also has been observed in intermediate-duration oral studies and in animals and humans exposed to 2-hexanone via inhalation; see discussion below (*Other Additional Studies or Pertinent Information that Lend Support to this MRL*).

Selection of the Principal Study: One chronic-duration oral exposure study was identified (O'Donoghue et al. 1978). This is a well-conducted study that conducted neurological examinations and microscopic examinations of numerous tissues.

Summary of the Principal Study:

O'Donoghue JL, Krasavage WJ, Terhaar CJ. 1978. A comparative chronic toxicity study of methyl n-propyl ketone, methyl n-butyl ketone, and hexane by ingestion. Eastman Kodak Co. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. EPA Document No. 88920008233. OTS0555051.

Groups of male Sprague-Dawley rats (10/group) were exposed to drinking water containing 0, 0.25, 0.5, or 1.0% 2-hexanone (96.1% purity) for 13 months. Based on water consumption and body weight data, the investigators calculated daily doses of 2-hexanone of 0, 143, 266, or 560 mg/kg/day. There were two control groups, each with 10 rats. Rats were observed daily for clinical signs; body weight measurements and neurological examinations were performed weekly. At termination of exposure, the hindlimb sciatic-plantar nerve, multiple levels of the spinal cord, medulla, and cerebellum from five rats per group were embedded in plastic for microscopic examination. Most tissues and organs from the highest dose group and target organs from lower dose groups were embedded in paraffin for light microscopy examination.

Clinical signs were restricted to neurological effects and reduced body weight. Final body weights were reduced approximately 6, 14, and 30% in the 143, 266, and 560 mg/kg/day dose groups, respectively. No information was provided regarding food consumption. Clinical neurological signs were seen in the 266 and 560 mg/kg/day groups. Signs first appeared on day 42 in the 560 mg/kg/day group and on day 77 in the 266 mg/kg/day group. All rats in the 560 mg/kg/day group showed severe deficits. Signs included decreased extension of hindlimbs, hindlimb weakness, waddling gait, dragging of hind paws, and loss of tone in hindlimb musculature with grossly observable atrophy of hindlimb musculature and axial muscles of the lumbar area. Weakness of the forelimbs was seen in three out of nine rats in the 560 mg/kg/day group by the end of the study. No clinical progression was apparent in the 266 mg/kg/day group. Histological examination showed that rats from all treated groups had "giant" axonal neuropathy. Axonal swelling and giant axonopathy were common in peripheral nerves and spinal cord from 560 mg/kg/day rats, less common in dorsal root ganglia, and rare in the brain. Sections embedded in plastic showed clumping of axonal organelles. Myelin alterations were also seen in peripheral nerves. Neurogenic skeletal muscle atrophy occurred in proximal and distal hindlimb musculature. Alterations in the 266 mg/kg/day group were similar but less severe. Less severe changes were seen in peripheral nerves from 143 mg/kg/day rats; fewer giant axons were evident, but myelin changes were more common. Spinal lesions and neurogenic muscle atrophy were minimal. Relevant incidence data are shown in Table A-1. No treatment-related gross or microscopic alterations were reported in tissues other than the nervous system and skeletal muscle.

Table A-1. Incidence Data for Neuropathological Lesions in Rats exposed to 2-Hexanone for 13 Months

	Axonal swelling				Myofibrillar atrophy	
Dose (mg/kg/day)	Brain	Spinal cord	Dorsal root ganglia	Peripheral nerve	Quadriceps muscle	Calf muscle
0	0/10	0/5	0/5	0/10	0/10	0/10
143	2/10	7/10[a]	0/7	8/10[a]	1/10	2/10
266	4/10[a]	5/5[a]	0/5	10/10[a]	5/10[a]	6/10[a]
560	8/10[a]	5/5[a]	3/5	10/10[a]	10/10[a]	10/10[a]

[a]p<0.05 per Fisher Exact Test conducted by SRC, Inc.

Source: O'Donoghue et al. 1978

Selection of the Point of Departure for the MRL: Benchmark dose (BMD) modelling of the incidence data for axonal swelling in peripheral nerve of rats in the O'Donoghue et al. (1978) study was considered and rejected because a nearly maximum response level (80%) was reached with the lowest dose tested. In such cases, there is great uncertainty because the BMD may be just below the first dose or orders of magnitude lower (EPA 2012b). Therefore, the NOAEL/LOAEL approach was used to derive a chronic-duration oral MRL for 2-hexanone.

Calculations: Conversion of drinking water concentrations to daily doses (mg/kg/day) was done by the investigators.

Uncertainty Factor (UF) and Modifying Factor (MF):

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

- 3 MF to account for an 80% response rate at the lowest dose

  MRL = LOAEL ÷ (UFs x MF)
  0.05 mg/kg/day = 143 mg/kg/day ÷ (1,000 x 3)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: 2-Hexanone is well-known as a neurotoxic chemical that has been tested in a variety of animal species. Neurotoxicity, including hind limb weakness, paralysis, decreased locomotor activity, and peripheral neuropathy, was observed in intermediate-duration oral exposure studies reported in rats and guinea pigs (Abdel-Rahman et al. 1978; Eben et al. 1979; Krasavage et al. 1980; Union Carbide 1977). Although no studies examining oral exposure of 2-hexanone in humans were identified, case reports and studies in workers also provide evidence that 2-hexanone produces neurotoxicity in humans following inhalation exposure (Allen et al. 1975; Billmaier et al. 1974; Davenport et al. 1976; Mallov 1976). Inhalation studies in animals also demonstrate that 2-hexanone is neurotoxic, with adverse neurological effects following acute exposure of guinea pigs (Schrenk et al. 1936), intermediate exposure of monkeys, rats, and cats (Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Mendell et al. 1974; Saida et al. 1976; Spencer et al. 1975), and chronic exposure of rats and cats (Krasavage and O' Donoghue 1977, 1979). Because the toxic chemical form of 2-hexanone is the metabolite, 2,5-hexanedione, and 2,5-hexanedione is also a metabolite of *n*-hexane, additional relevant information can be found in documents on *n*-hexane (i.e., ATSDR 1999).

Agency Contacts (Chemical Managers): Nickolette Roney

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR 2-HEXANONE

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 2-hexanone.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for 2-hexanone. 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 2-hexanone 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 2-hexanone 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

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

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for 2-hexanone released for public comment in April 2018. The following main databases were searched in March 2019:

- 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 2-hexanone. 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 2-hexanone 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	
03/2019	((591-78-6[rn] OR "Methyl n-Butyl Ketone"[mh] OR "2-Hexanone"[tw] OR "2-Oxohexane"[tw] OR "Butyl methyl ketone"[tw] OR "Butylmethyl Ketone"[tw] OR "Hexan-2-one"[tw] OR "Hexanone-2"[tw] OR ("MBK"[tw] AND (ketone OR hexanone)) OR "Methyl butyl ketone"[tw] OR "Methyl n-butyl ketone"[tw] OR "n-Butyl methyl ketone"[tw] OR "Propylacetone"[tw]) AND (2014/12/01 : 3000[dp] OR 2015/12/01 : 3000[mhda] OR 2015/12/01 : 3000[crdat] OR 2015/12/01 : 3000[edat])) OR ("2-HEXANON"[tw] OR "Hexan-2-on"[tw] OR "hexan-2-ona"[tw] OR "hexane-2-one"[tw] OR "Ketone, butyl methyl"[tw] OR "MnBK"[tw])
Toxline	
03/2019	Year of Publication 2014 through 2019 (591-78-6[rn] OR "2-Hexanone" OR "2-Oxohexane" OR "Butyl methyl ketone" OR "Butylmethyl Ketone" OR "Hexan-2-one" OR "Hexanone-2" OR "Methyl butyl ketone" OR "Methyl n-butyl ketone" OR "n-Butyl methyl ketone" OR "Propylacetone" OR "2-HEXANON" OR "Hexan-2-on" OR "hexan-2-ona" OR "hexane-2-one" OR "Ketone, butyl methyl") 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] Year of Publication 2014 through 2019 ("MBK" AND (ketone OR hexanone)) 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] ("2-HEXANON" OR "Hexan-2-on" OR "hexan-2-ona" OR "hexane-2-one" OR "Ketone, butyl methyl" OR "MnBK") 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	
03/2019	L1 1426 SEA FILE=TOXCENTER 591-78-6 L2 1286 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 1253 SEA FILE=TOXCENTER L2 NOT TSCATS/FS L4 82 SEA FILE=TOXCENTER L3 AND ED>=20151201 L5 116 SEA FILE=TOXCENTER L3 AND PY>2014 L6 116 SEA FILE=TOXCENTER L4 OR L5 ANSWERS '1-115' FROM FILE TOXCENTER

Table B-2. Database Query Strings

Database search date	Query string
	ACT TOXQUERY/Q

	L11 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L12 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L13 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L14 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L15 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L16 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L17 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L18 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L19 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L20 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L21 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L22 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L23 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L24 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L25 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L26 QUE (ENDOCRIN? AND DISRUPT?)
	L27 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L28 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L29 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L30 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L31 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L32 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L33 QUE (NEPHROTOX? OR HEPATOTOX?)
	L34 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L35 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L36 QUE 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

Table B-2. Database Query Strings

Database search date	Query string
	L28 OR L29 OR L30 OR L31 OR L32 OR L33 OR L34 OR L35
	L37 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?)
	L38 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L39 QUE L36 OR L37 OR L38
	L40 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L41 QUE L39 OR L40

	L42 47 SEA FILE=TOXCENTER L6 AND L41
	L43 46 DUP REM L42 (1 DUPLICATE REMOVED)
	ANSWERS '1-46' FROM FILE TOXCENTER
	D SCAN L43

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
03/2019	Compounds searched: 591-78-6
NTP	
03/2019	"591-78-6" "2-Hexanone" "Butylmethyl Ketone" "Methyl butyl ketone" "Methyl n-butyl ketone" "n-Butyl methyl ketone" "Hexan-2-one" "Hexanone-2" "Butyl methyl ketone" "2-Oxohexane" "Propylacetone" "Ketone, butyl methyl" "MBK" "mnbk" "2-HEXANON" "Hexan-2-on" "hexan-2-ona" "hexane-2-one"
DTIC	
05/2019	**Synonyms in all fields search box** "591-78-6" OR "2-Hexanone" OR "2-Oxohexane" OR "Butyl methyl ketone" OR "Hexanone-2" OR "Methyl butyl ketone" OR "Methyl n-butyl ketone" OR "Propylacetone" OR "n-Butyl methyl ketone" OR "Butylmethyl Ketone" OR "Hexan-2-one" OR "2-Hexanone Methyl n-butyl ketone" OR "2-hexanon" OR "hexan-2-on" OR "hexan-2-ona" OR "hexane-2-one" OR "ketone, butyl methyl" OR "MnBK" OR ("MBK" AND ("ketone" OR "hexanone")) **Keywords in citation terms box** "toxicity" OR "toxicology" OR "poisoning" OR "cancer" OR "carcinogens" OR "carcinogen" OR "neoplasms" OR "neoplasm" OR "oncogenesis" OR "teratogenic compounds" OR "lethality" OR "death" OR "body weight" OR "immunology" OR "genotoxicity" OR "mutagenicity" OR "mutagens" OR "mutations" OR "oral" OR "gavage" OR "inhalation" OR "dermal" OR "metabolism" OR "pharmacokinetics" OR

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"pharmacokinetic" OR "PBPK" OR "pharmacology" OR "organs" OR "skin" OR "tissues" OR "body fluids" OR "toxic agents" OR "rats" OR "mice" OR "mouse" OR "rat"
NIH RePORTER	
09/2019	"2-Hexanone" OR "2-Oxohexane" OR "Butyl methyl ketone" OR "Butylmethyl Ketone" OR "Hexan-2-one" OR "Hexanone-2" OR ("MBK" AND (ketone OR hexanone)) OR "Methyl butyl ketone" OR "Methyl n-butyl ketone" OR "n-Butyl methyl ketone" OR "Propylacetone" OR "2-HEXANON" OR "Hexan-2-on" OR "hexan-2-ona" OR "hexane-2-one" OR "Ketone, butyl methyl" OR "MnBK" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

The 2019 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 86
- Number of records identified from other strategies: 23
- Total number of records to undergo literature screening: 109

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on 2-hexanone:

- 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.

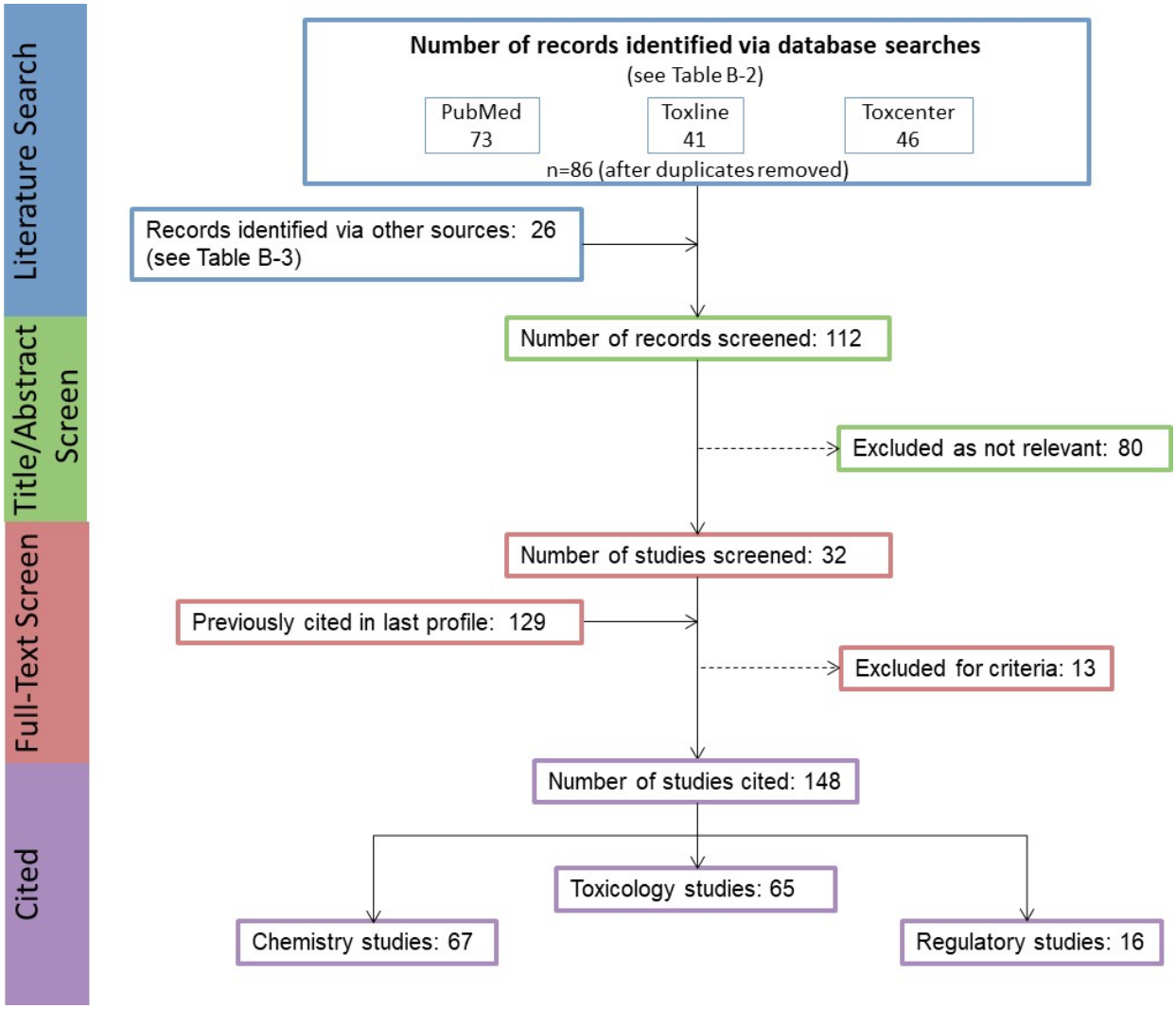
- Number of titles and abstracts screened: 112
- Number of studies considered relevant and moved to the next step: 32

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: 32
- Number of studies cited in the pre-public draft of the toxicological profile: 129
- Total number of studies cited in the profile: 148

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

Figure B-1. March 2019 Literature Search Results and Screen for 2-Hexanone



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.

APPENDIX C

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									

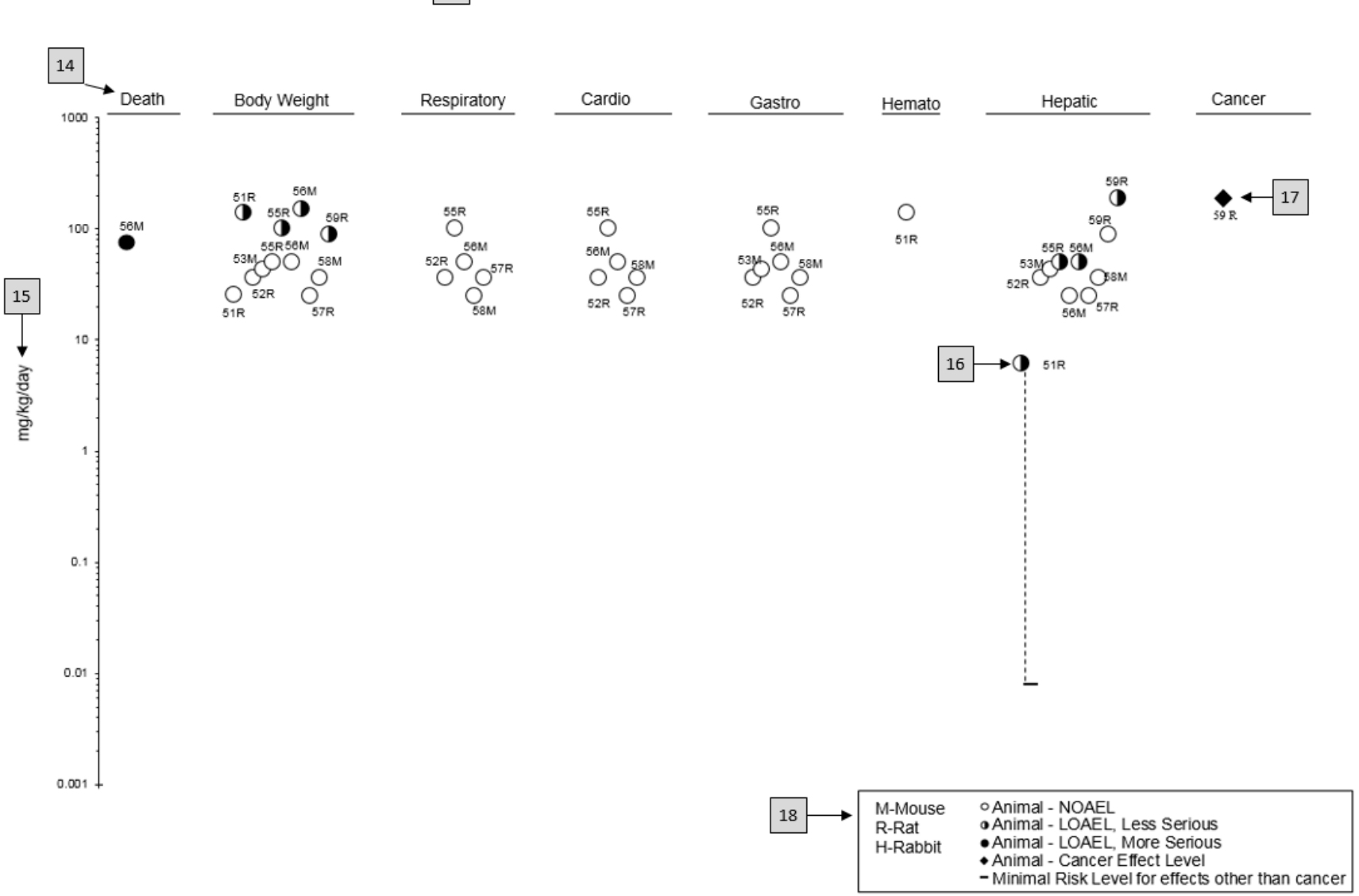
[a]The number corresponds to entries in Figure 2-x.

(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) ≥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
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