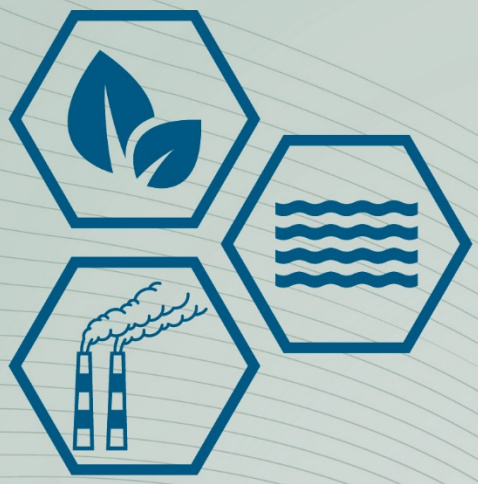


Toxicological Profile for 2-Butanone

October 2020

ATSDR
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.

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

Christopher M. Reh, Ph.D.
Associate Director
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

*Legislative Background

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

VERSION HISTORY

Date	Description
October 2020	Final toxicological profile released
May 2019	Draft for public comment toxicological profile released
December 2010	Addendum to the toxicological profile released
July 1992	Final toxicological profile released

CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

G. Daniel Todd, Ph.D.

ATSDR, Office of Innovation and Analytics, Toxicology Section, Atlanta, GA

Julie Melia, Ph.D., D.A.B.T.
Jenny S. Crisman, B.S.
Lisa D. Ingerman, Ph.D., D.A.B.T
David W. Wohlers, Ph.D.

SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:

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

Additional reviews for science and/or policy:

ATSDR, Office of Community Health and Hazard Assessment; ATSDR, Office of Capacity Development and Applied Prevention Science; ATSDR, Office of Science; NCEH, Division of Laboratory Science; NCEH, Division of Environmental Health Science and Practice.

PEER REVIEWERS

1. G.A. Shakeel Ansari, Ph.D.; Professor, Department of Pathology; University of Texas Medical Branch; Galveston, Texas

2. F. Peter Guengerich, Ph.D.; Tadashi Inagami Professor of Biochemistry; Department of Biochemistry; Vanderbilt University School of Medicine; Nashville, Tennessee

3. Dale Hattis, Ph.D.; Research Professor, George Perkins Marsh Institute; Clark University; Worcester, Massachusetts

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.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

2-Butanone, also referred to as methyl ethyl ketone or MEK, is a common industrial solvent. Examples of specific applications include its use as a solvent for paints, lacquers, rubber cement, printing inks, paint removers, vinyl films, resins, rosins, polystyrene, chlorinated rubber, polyurethane, acrylic coatings, and cleaning solutions (Neier and Strehlke 1985; NLM 2020; Papa and Sherman 1981; Sax and Lewis 1987). 2-Butanone is used in the production of synthetic leathers, transparent paper, and aluminum foil. It is also used in the degreasing of metals, as an extraction solvent, in dewaxing of lubricating oils, and as a solvent for the production of smokeless powders used as ammunition propellants.

2-Butanone is detected in environmental media, although usually at low levels. 2-Butanone is expected to rapidly volatilize from surface water and moist or dry soils and exists as a vapor in the atmosphere. 2-Butanone displays a high mobility in soil and leaches readily into groundwater. 2-Butanone does not adsorb strongly to soils and sediments or bioconcentrate in aquatic organisms. The most likely routes of 2-butanone exposure for the general public include ingestion of food, ingestion of contaminated drinking water, inhalation during household use of coating products, and dermal contact during the use of these products. High levels of occupational exposure to 2-butanone may occur by inhalation and dermal contact during the loading and unloading of large quantities of commercial coating materials during shipment. The application of commercial coatings containing 2-butanone without adequate protection may also lead to high levels of exposure, primarily by inhalation.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of 2-butanone comes primarily from inhalation studies in humans and laboratory animals and a limited number of oral studies in animals. The effects of 2-butanone in humans include neurological symptoms (headache, fatigue, feeling of intoxication) and mucous membrane irritation of the eyes, nose, and throat. Effects observed in animals include death, irritation of respiratory tissue, eyes, and skin, liver congestion, kidney congestion, corneal opacity, narcosis and incoordination, and fetotoxicity. As illustrated in Figure 1-1, clinical signs of neurotoxicity in humans (i.e., headache, fatigue, feeling of intoxication) and mucous membrane irritation (eyes, nose and throat) are the most sensitive effects in humans exposed by inhalation. Figure 1-2 illustrates that renal toxicity is the most sensitive effect following oral exposure in animals; however, studies of toxicity by the oral route are

Figure 1-1. Health Effects Found in Humans and Animals Following Inhalation Exposure to 2-Butanone

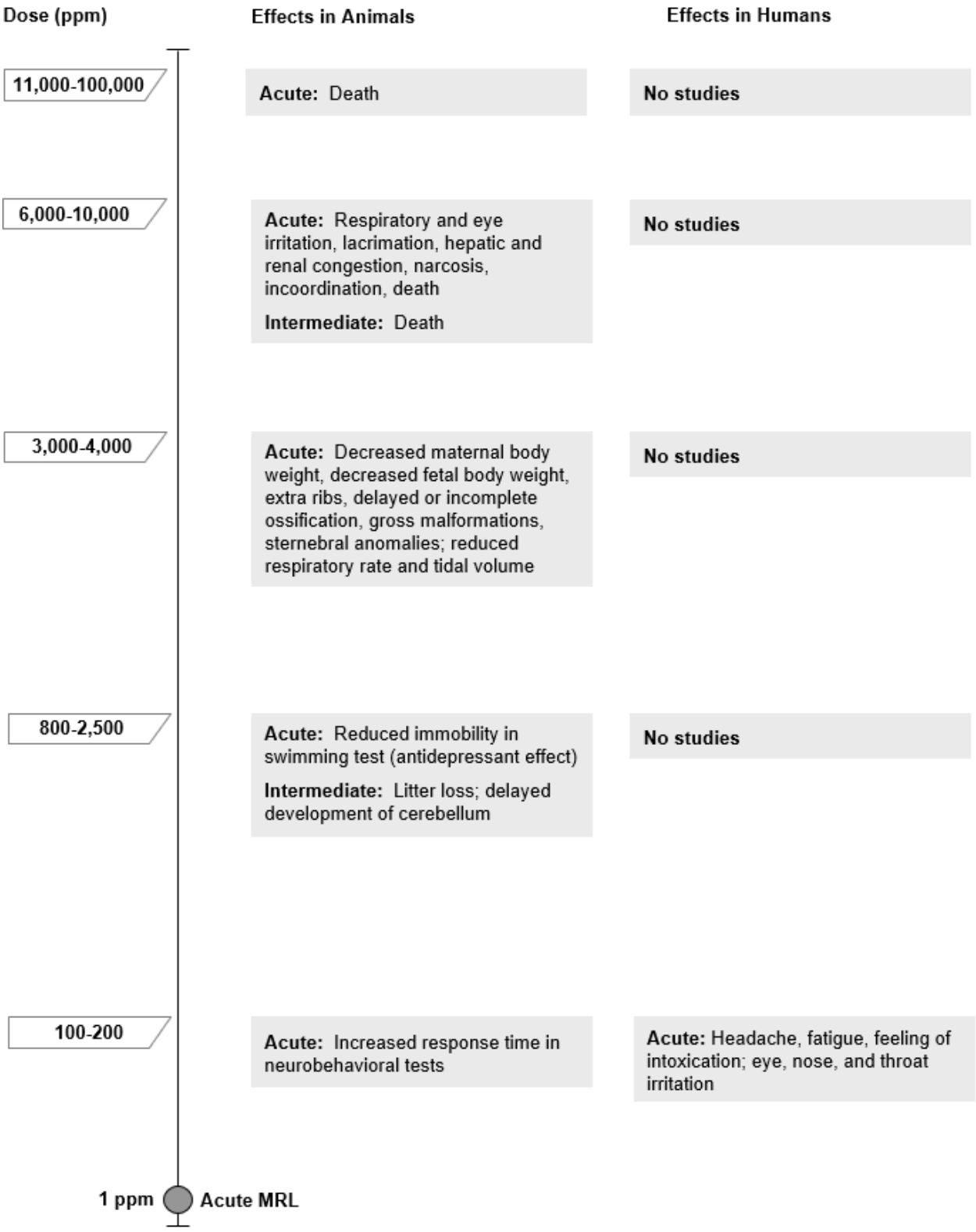
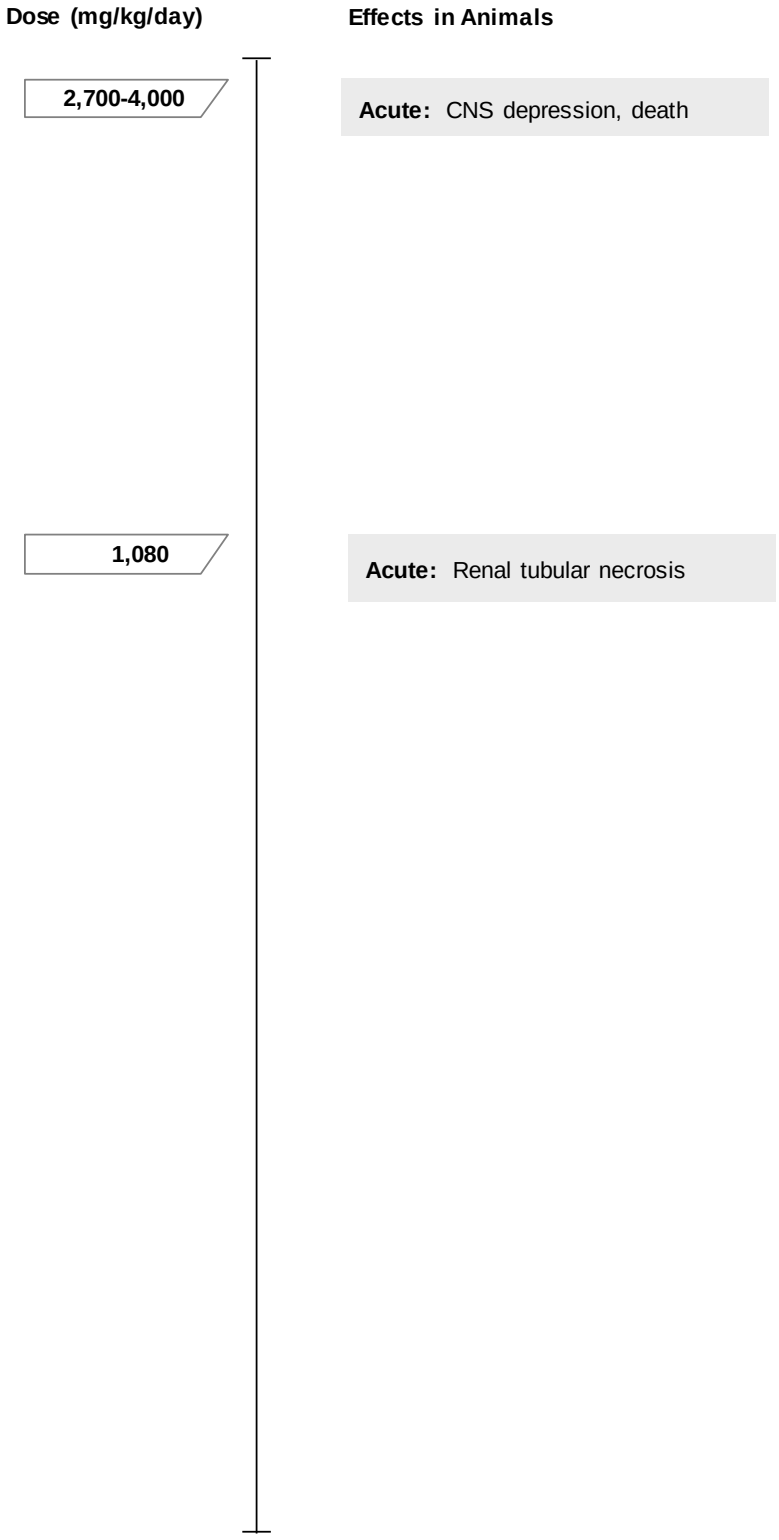


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 2-Butanone



generally lacking. Environmental exposure levels are typically lower than the concentrations used in animal studies.

Respiratory Effects. 2-Butanone is irritating to respiratory tissues. Upper respiratory tract irritation was noted in a case report of a patient with occupational 2-butanone exposure (concentration data were not reported) (Callender 1995). A clinical case report of three men exposed to 2-butanone fumes while removing paint from an airplane hangar noted mild respiratory symptoms but did not further describe the nature or extent of the symptoms (Berg 1971). Male and female volunteers exposed to 100 ppm 2-butanone complained of slight nose and throat irritation, which became objectionable at 350 ppm (Nelson et al. 1943). Tomicic et al. (2011) also reported nose and throat irritation during a 6-hour exposure to 100 ppm 2-butanone with female subjects reporting higher symptom ratings than male subjects. Other studies reported the absence of an irritation effect in volunteers at concentrations up to 200 ppm (Muttray et al. 2002; Seeber et al. 2002; van Thriel et al. 2002); however, these studies were conducted in male subjects only. Sensory irritation effects were seen in mice exposed to 2-butanone concentrations ≥3,809 ppm. A time- and concentration-dependent decrease in respiratory rate and tidal volume was observed (Hansen et al. 1992). Severe respiratory and eye irritation occurred in rats and guinea pigs exposed to 2-butanone concentrations ≥10,000 ppm (Altenkirch et al. 1978; Patty et al. 1935).

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation, oral, or dermal exposure to 2-butanone. Animal data indicate that hepatic effects after exposure to 2-butanone are minimal. Liver congestion was found in guinea pigs exposed acutely by inhalation to ≥10,000 ppm (Patty et al. 1935). Serum concentrations of hepatic enzymes were not changed in rats after 2-butanone exposures of 300–5,000 ppm for 1–12 weeks (Cavender et al. 1983; Li et al. 1986; Schwetz et al. 1974). No lesions that could be linked to 2-butanone exposure were found following histological examination, although a slight increase in absolute and relative liver weight was noted (Cavender et al. 1983).

Exposure of female rats to 3,000 ppm (but not 1,000 ppm) 2-butanone for 15 days increased absolute and relative liver weight, but did not affect serum chemistry parameters (alanine transaminase [ALT], aspartate transaminase [AST], urea, and creatinine) or liver histopathology (Saillenfait et al. 2006). Relative liver weight was also increased in male rats exposed to 800 ppm 2-butanone for 4 weeks (Toftgard et al. 1981) and pregnant mice exposed to 3,000 ppm 2-butanone on gestation days (GDs) 6–15 (NTP 1989; Schwetz et al. 1991). Liver weight increases in rodent studies may be related to induction of cytochrome P450 (CYP).

2-Butanone alone is not highly hepatotoxic, but has a well-documented role in potentiating the hepatotoxicity of haloalkane compounds including chloroform and carbon tetrachloride (Brown and Hewitt 1984; Dietz and Traiger 1979; Hewitt et al. 1983, 1986, 1987; Tanii et al. 1986).

Renal Effects. No studies were located regarding renal effects in humans after inhalation, oral, or dermal exposure to 2-butanone. Kidney congestion was found in guinea pigs exposed acutely by inhalation to ≥10,000 ppm (Patty et al. 1935). Cavender et al. (1983) assessed kidney function with measurements of blood urea nitrogen, urine volume, urine specific gravity, and pH after a 90-day exposure to 5,000 ppm 2-butanone. All values were within normal ranges, and no histopathological lesions attributable to 2-butanone exposure were found. Oral exposure of rats to a single gavage dose of 1,080 mg/kg caused mild renal tubule necrosis, but had no effect on renal organic ion transport or plasma creatinine; therefore, in spite of mild necrosis, normal kidney functions were not impaired. Kidney toxicity in rats exposed to chloroform, assessed by a decreased accumulation of *p*-aminohippuric acid in renal cortical slices, was potentiated in rats that were pretreated with 2-butanone for 3 days prior to chloroform exposure (Raymond and Plaa 1995a).

Neurological Effects. Neurological symptoms were reported in some volunteer studies, but the results of neurobehavioral testing were similar to unexposed controls. Headache, fatigue, and feeling of intoxication were noted in volunteer subjects exposed to 100 ppm 2-butanone for 4 hours, with females scoring higher on symptom questionnaires compared with men (Tomicic et al. 2011). Headache and nausea were also reported by male subjects 2 hours after exposure to 200 ppm, compared with pre-exposure ratings (Muttray et al. 2002). In four separate studies, volunteers underwent a single 4-hour exposure to 200 ppm 2-butanone (Dick et al. 1984, 1988, 1989, 1992). No differences were observed between exposed and control groups on neurobehavioral tests including psychomotor tests (choice reaction time, visual vigilance, dual task, and memory scanning), postural sway, and a profile of mood states. Regression analyses showed a significant linear relationship between blood concentrations of 2-butanone in females and a small increase in the number of incorrect responses on the auditory portion of the dual task test (Dick et al. 1992).

Narcosis and incoordination were also observed in guinea pigs exposed to ≥10,000 ppm 2-butanone in air for a few hours (Patty et al. 1935). Juvenile baboons exposed continuously to 100 ppm for 7 days showed delayed reaction times in neurobehavioral tests (Geller et al. 1979). The neurological effects observed in this study could have resulted from narcosis or it is also possible that the baboons were distracted during the testing due to the irritating effects of 2-butanone on the respiratory system. Rats continuously

exposed to 1,125 ppm for 5 months showed no signs of peripheral neuropathy on histological examination (Saida et al. 1976). Altenkirch et al. (1978) observed no clinical signs of neuropathy in rats exposed for 7 weeks to 6,000 ppm. No neurological effects were observed in rats exposed by inhalation to 5,000 ppm for 90 days (Cavender et al. 1983). No neurological effects were observed in rats after oral exposure to 1,725 mg/kg for 90 days (Ralston et al. 1985).

2-Butanone potentiates the neurotoxicity of ethanol, n-hexane, methyl-n-butyl ketone, and ethyl-n-butyl ketone (Altenkirch et al. 1977; Cunningham et al. 1989; King et al. 1985; Ralston et al. 1985; Robertson et al. 1989; Vallat et al. 1981). Glue formulations containing both 2-butanone and n-hexane caused "glue sniffers' neuropathy" (Altenkirch et al. 1977; King et al. 1985; Vallat et al. 1981). This neuropathy is characterized by motor nerve dysfunction, paresis, paralysis, muscular atrophy, and neural tissue morphology changes including paranodal axon swelling, neurofilamentous hyperplasia, and demyelination.

Ocular Effects. 2-Butanone is irritating to the eyes. Mild eye irritation was noted in some volunteers exposed to 200 ppm 2-butanone for 3–5 minutes (Nelson et al. 1943). Discomfort in the eyes was also reported in human subjects exposed to 100 ppm 2-butanone for 6 hours, with females scoring significantly higher on symptom questionnaires compared to male subjects (Tomicic et al. 2011). Eye irritation was not reported in male subjects exposed to 2-butanone vapor for 4 hours under constant (10 ppm) or changing exposure conditions (peaks up to 380 ppm; time-weighted average [TWA] of 189 ppm) (Seeber et al. 2002; van Thriel et al. 2002).

Guinea pigs exposed to 2-butanone concentrations ≥10,000 ppm had eye irritation and lacrimation (Patty et al. 1935). Exposure to 100,000 ppm for ≥30 minutes caused corneal opacity. This condition gradually improved in guinea pigs that lived to 8 days after exposure. No effects occurred when guinea pigs were exposed to 3,300 ppm. Ophthalmological examination of the eyes and histological examination of the skin revealed no effects in rats exposed to ≤5,000 ppm of 2-butanone for 90 days (Cavender and Casey 1981; Cavender et al. 1983).

Developmental Effects. No studies were located regarding developmental effects in humans following inhalation, oral, or dermal exposure to 2-butanone. Inhalation exposure of rats and mice to 3,000 or 4,000 ppm during gestation resulted in fetotoxic effects, such as reduced fetal weight, skeletal variations, and delayed or incomplete ossification (Deacon et al. 1981; NTP 1989; Saillenfait et al. 2006; Schwetz et al. 1974). Delayed brain development was also observed in offspring exposed continuously

(23 hours/day) throughout gestation (Stoltenburg-Didinger 1991). It is not known whether exposure of humans to 2-butanone by any route would result in fetotoxic effects, but the presence of these effects in two animal species suggests that such effects might occur in humans.

Cancer. Two retrospective epidemiological studies of industrial workers chronically exposed to 2-butanone in dewaxing plants reported that deaths due to cancer were less than expected (Alderson and Rattan 1980; Wen et al. 1985). An occupational cohort study of aircraft maintenance workers reported a statistically significant elevated rate ratio (RR) for multiple myeloma in females; however, the number of 2-butanone exposed cases in the cohort was very small (Blair et al. 1998; Radican et al. 2008; Spirtas et al. 1991). Two case-control studies evaluated the relationship between 2-butanone exposure and childhood leukemia (Gao et al. 2014; Infante-Rivard et al. 2005). One study demonstrated an increased odds ratio (OR) for the relationship between measured household 2-butanone exposure and the diagnosis of acute childhood leukemia (Gao et al. 2014). The Infante-Rivard et al. (2005) study determined that case mothers were more often exposed to 2-butanone than control mothers (exposure coding by job title and household exposure); however, the number of cases exposed to 2-butanone was very low. No other studies were located regarding cancer in humans or animals following inhalation exposure to 2-butanone.

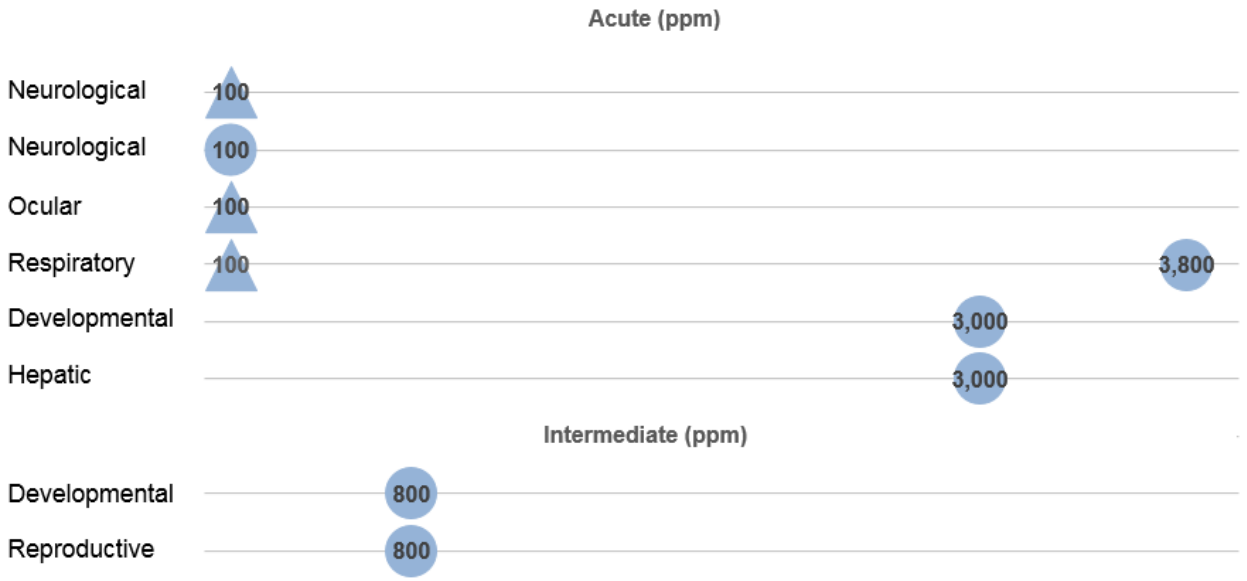
1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for derivation of an acute-duration MRL, but inadequate for derivation of intermediate- or chronic-duration MRLs. As presented in Figure 1-3, the available acute inhalation data for 2-butanone indicate that the neurological effects are sensitive targets of toxicity. Clinical signs of neurotoxicity in humans (i.e., headache, fatigue, feeling of intoxication) and neurobehavioral effects in primates were reported at low concentrations. Respiratory and ocular irritation are also sensitive targets of toxicity in humans. In the case of intermediate- and chronic-duration exposure, target organs have not been sufficiently identified. In addition, nose, throat and eye irritation occurred in humans at exposure levels that were much lower than no-observed-adverse-effect level (NOAEL) values in animals in intermediate-duration studies. No studies were located regarding toxic effects in humans or animals after chronic inhalation exposure, precluding the derivation of a chronic inhalation MRL.

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

Ocular, respiratory and neurological are the most sensitive targets of 2-butanone inhalation exposure.

Numbers in triangles and circles are the lowest LOAELs among health effects in humans and animals, respectively.

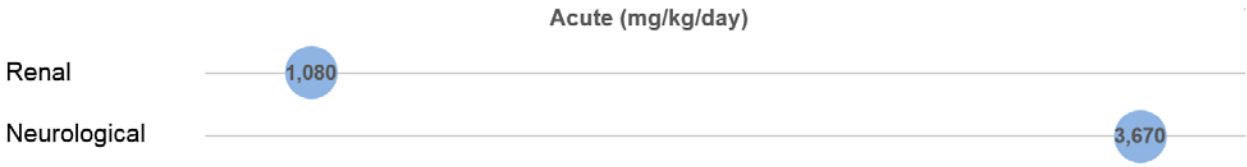


No acute, intermediate-, or chronic-duration oral MRLs were derived for 2-butanone. In the case of acute-duration oral exposure, target organs have not been sufficiently identified (see Figure 1-4). The paucity of information on toxic effects after intermediate- and chronic-duration oral exposure likewise precludes the derivation of MRLs for these durations.

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

Renal is the most sensitive target of 2-butanone oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.



The acute-duration inhalation MRL value is summarized in Table 1-1 and discussed in greater detail in Appendix A.

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

Exposure duration	MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty and modifying factor	Reference
Inhalation exposure (ppm)					
Acute	1	Neurological effects (headache, fatigue, feeling of intoxication)	LOAEL: 99.15	UF: 100	Tomicic et al. 2011
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	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

LOAEL = lowest-observed-adverse-effect level; 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-butanone. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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

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

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to 2-butanone, 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. Animal dermal studies are presented in Table 2-3.

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

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

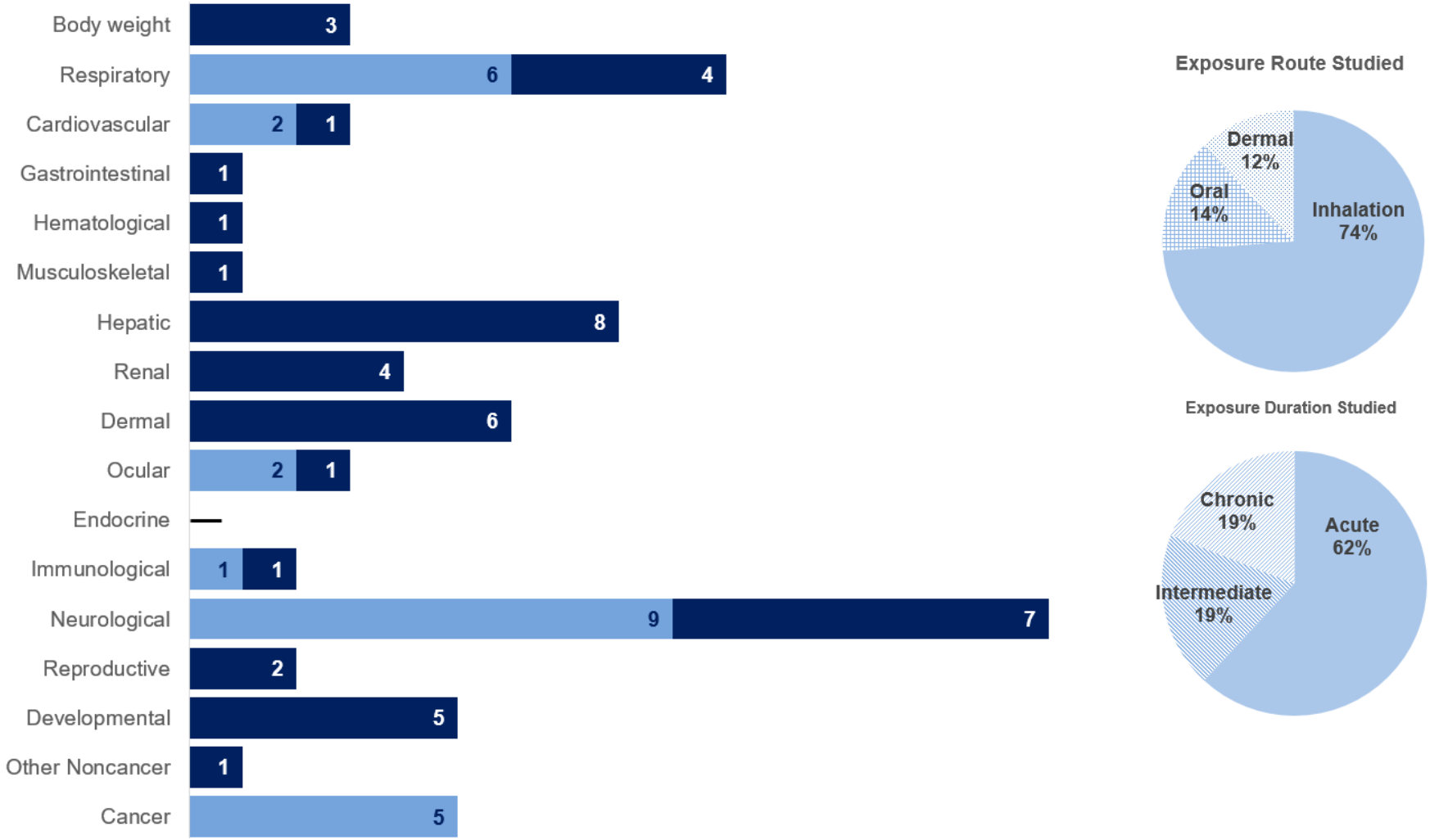
A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

Human and laboratory animal studies, primarily by the inhalation route, suggest potential associations between 2-butanone exposure and the following health outcomes:

- **Neurological endpoint:** Symptoms of neurotoxicity were reported in volunteers and neurobehavioral effects have been observed in laboratory animals.
- **Respiratory endpoint:** Nose and throat irritation were reported in volunteers exposed to 2-butanone. Respiratory irritation was also seen in laboratory animal studies at high concentrations.
- **Liver endpoint:** Liver congestion and increased organ weight were observed in laboratory animal studies only. No data are available in humans.
- **Kidney endpoint:** Kidney congestion, mild renal necrosis and increased organ weight were observed in laboratory animal studies only. No data are available in humans.
- **Ocular endpoint:** Eye irritation is observed following inhalation exposure in humans and laboratory animals.
- **Developmental endpoint:** 2-Butanone was fetotoxic in rats. No data are available in humans.

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

Most studies examined the potential respiratory, hepatic, dermal and neurological effects of 2-butanone
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 42 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
ACUTE EXPOSURE									
1	Human 16–143 M, F	1 day 4 hours/day	200	CS	Neuro	200			
Dick et al. 1984, 1988, 1989, 1992									
2	Human 24 M	1 day 4 hours	10–380	CS	Resp	189			
					Cardio	189			
					Ocular	189			
Haumann et al. 2003; Seeber et al. 2002; van Thriel et al. 2002, 2003; Wiesmuller et al. 2002									
3	Human 19 M	1 day 4 hours/day	200	BI, CS, OF	Resp	200			
					Immuno	200			
Muttray et al. 2002									
4	Human 10 M, F	1 day 5 minutes/day	0, 100, 200, 350	CS	Resp		100		Nose/throat irritation
					Ocular		200		Eye irritation
Nelson et al. 1943									
5	Human 10 M, 15 F	1 day 6 hours/day	0, 100	CS	Resp		100		Nose/throat irritation
					Ocular		100		Eye irritation
					Neuro		100[b]		Headache, fatigue, feeling of intoxication
Tomicic et al. 2011									
6	Monkey (baboon) 4 M	7 days 24 hours/day	100	CS	Neuro		100		Increased response time in neurobehavioral tests
Geller et al. 1979									
7	Rat (Wistar) 5 M	2–3 days 8 hour/day	10,000	CS	Resp		10,000		Respiratory irritation
Altenkirch et al. 1978									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
8	Rat (Sprague-Dawley) 25 F (35 F controls)	10 days GDs 6–15, 7 hours/day	0, 400, 10,00, 3,000	BW, OW, FI, WI, CS, FX, DX, MX, TG	Bd wt	1,000	3,000		Decreased maternal body weight
					Develop	1,000	3,000		Extra ribs, delayed ossification
Deacon et al. 1981									
9	Rat (NS) 3 M, F	1 day 3 hours/day	92,239	LE	Death			92,239	
Klimisch 1988									
10	Rat (albino) 8 M	1 day 4 hours/day	0, 7,850, 9,090, 9,060, 12,200, 13,150, 18,100, 20,200	LE	Death			11,700	LC_{50}
LaBelle and Brieger 1955									
11	Rat (Wistar) 6–7 F	7 days 8 hours/day	0, 300	BC, BI	Hepatic	300			
Li et al. 1986									
12	Rat (Sprague-Dawley) 19–23 F	GDs 6–20 6 hours/day	0, 1,000, 2,000, 4,000, 6,000	BW, DX, FI, FX, OW, MX, TG	Bd wt	2,000	4,000		Reduced food consumption (12%) and maternal body weight gain (52%)
					Develop	2,000	4,000		Decreased fetal body weight (15% in males); incomplete ossification of the sternebrae
Saillenfait et al. 2006									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
13	Rat (NS) 21–23 F (43 F controls)	GDs 6–15 7 hours/day	0, 1,000, 3,000	BW, OW, FI, FX, MX, DX, TG	Develop	1,000		3,000	Gross malformations and sternebral anomalies
Schwetz et al. 1974									
14	Rat (NS) 6 M	1 day 8 hours/ day	8,000	LE	Death			8,000	3/6 died
Smyth et al. 1962									
15	Mouse (NS) 50 M	1 day 4 hours/day	0, 1,602, 1,848, 2,050, 2,438	CS, OF	Neuro		1,602		Reduced immobility (anti-depressant effect)
De Ceaurriz et al. 1983									
16	Mouse Ssc:CF-1 4 M	1 day 0.5 hours	0, 3,809, 9,136, 12,771, 24,179, 26,416	OF	Resp		3,809		Reduced respiratory rate and tidal volume (sensory irritation effect)
Hansen et al. 1992									
17	Mouse (albino) 6 NS	43 minutes	103,000	LE	Death			103,000	
LaBelle and Brieger 1955									
18	Mouse (Swiss/ CD-1) 33 F	10 days GDs 6–15 7 hours/day	0, 400, 1,000, 3,000	BW, DX, FX, OW, MX, TG	Bd wt	3,000			
					Hepatic	1,000	3,000		Increased relative liver weight in dams (7%)
					Develop	1,000	3,000		Decreased fetal body weight (5% in males); misaligned sternebrae
NTP 1989; Schwetz et al. 1991									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
19	Guinea pig (NS) 6 NS	1 day 3–13.5 hours/ day	0, 3,300, 10,000, 3,3000, 100,000	GN, CS	Death			33,000	
					Resp	10,000		33,000	Gasping and death
					Hepatic	3,300	10,000		Congestion
					Renal	3,300	10,000		Congestions
					Ocular	3,300	10,000	100,000	Eye irritation, lacrimation (10,000 ppm); corneal opacity and death (100,000 ppm)
					Neuro	3,300		10,000	Narcosis, incoordination
Patty et al. 1935									
INTERMEDIATE EXPOSURE									
20	Rat (NS) 19 NS	7 weeks 7 days/week 8 hours/day	6,000	HP, CS, LE	Death			6,000	5/5 died
					Neuro	6,000			
Altenkirch et al. 1978, 1979									
21	Rat (Fischer) 15 M, F	90 days 5 days/week 6 hours/day	0, 1,250, 2,500, 5,000	BW, OW, FI, WI, GN, HP, BC, CS, BI, HE	Resp	5,000			
					Cardio	5,000			
					Gastro	5,000			
					Hemato	5,000			
					Musc/skel	5,000			
					Hepatic	5,000			
					Renal	5,000			
					Dermal	5,000			
					Immuno	5,000			
					Neuro	5,000			
					Repro	5,000			
					Other noncancer (not specified)	5,000			
Cavender et al. 1983; Cavender and Casey 1981									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
22	Rat (Sprague-Dawley) 12 M	5 months 7 days/week 24 hours/day	1,125	HP	Neuro	1,125			
Saida et al. 1976									
23	Rat (Sprague-Dawley) 6 F	15 days 6 hours/day	0, 1,000, 3,000	BC, HP, OW, UR	Hepatic	3,000			
					Renal	3,000			
Saillenfait et al. 2006									
24	Rat (Wistar) 8 F	GDs 1–21 23 hours/day	0, 800, 1,000–1,500	DX, MX	Develop			800	Delay in Purkinje cell outgrowth
					Develop			800	Complete litter loss
Stoltenburg-Didinger et al. 1990; Stoltenburg-Didinger 1991									

[a]The number corresponds to entries in Figure 2-2.
[b]An acute-duration Minimal Risk Level (MRL) of 1 ppm was derived for 2-butanone based on reported neurological symptoms (headache, fatigue, feeling of intoxication) in volunteers. The MRL is based on the LOAEL (not adjusted for continuous exposure) of 99.15 ppm and a total uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

BC = serum (blood) chemistry); Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; F = female(s); FI = food intake; FX = fetal toxicity; Gastro = gastrointestinal; GD = gestational day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LC_{50} = lethal concentration, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; TG = teratogenicity; UR = urinalysis; WI = water intake

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

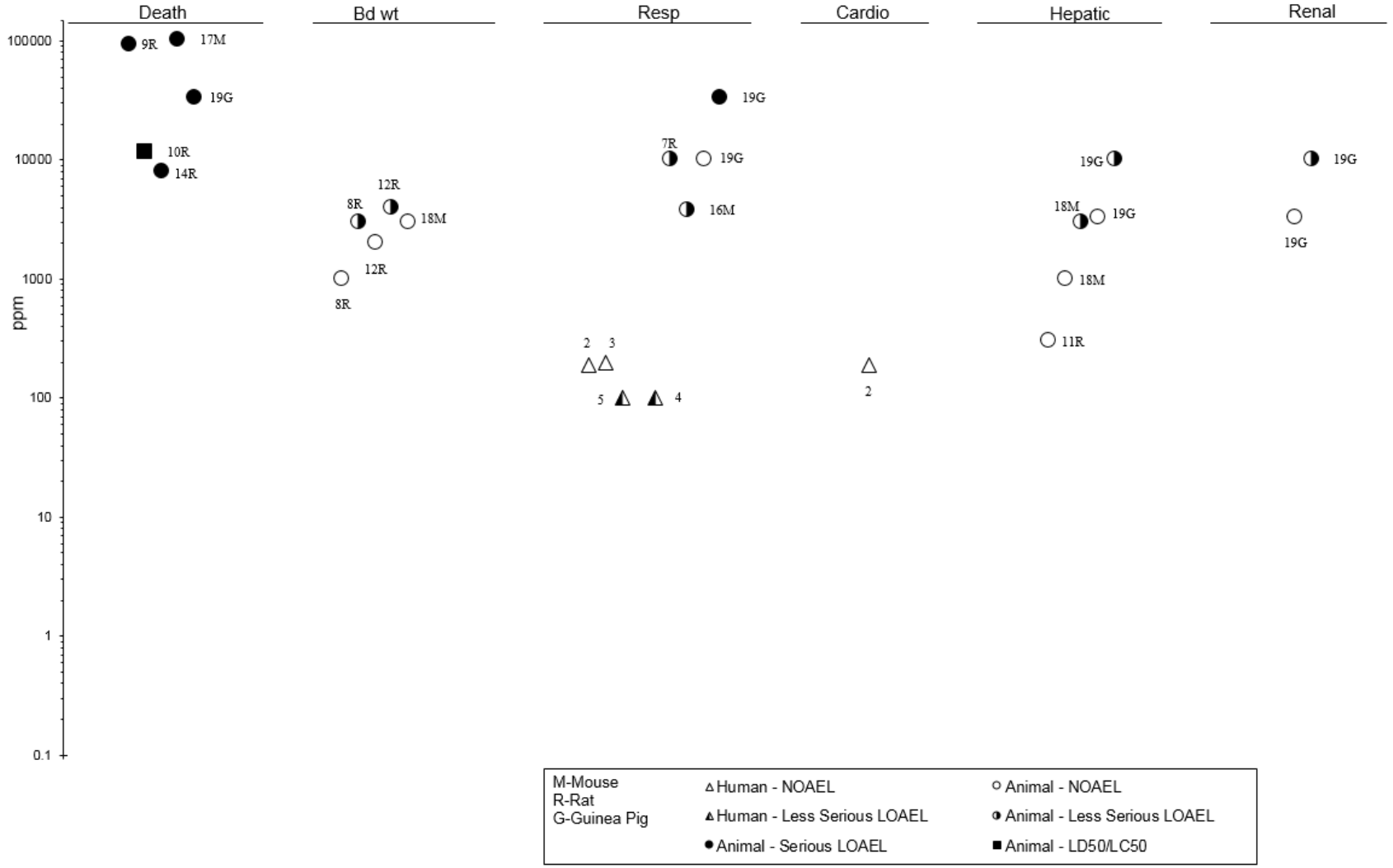


Figure 2-2. Levels of Significant Exposure to 2-Butanone – Inhalation
Acute (≤14 days)

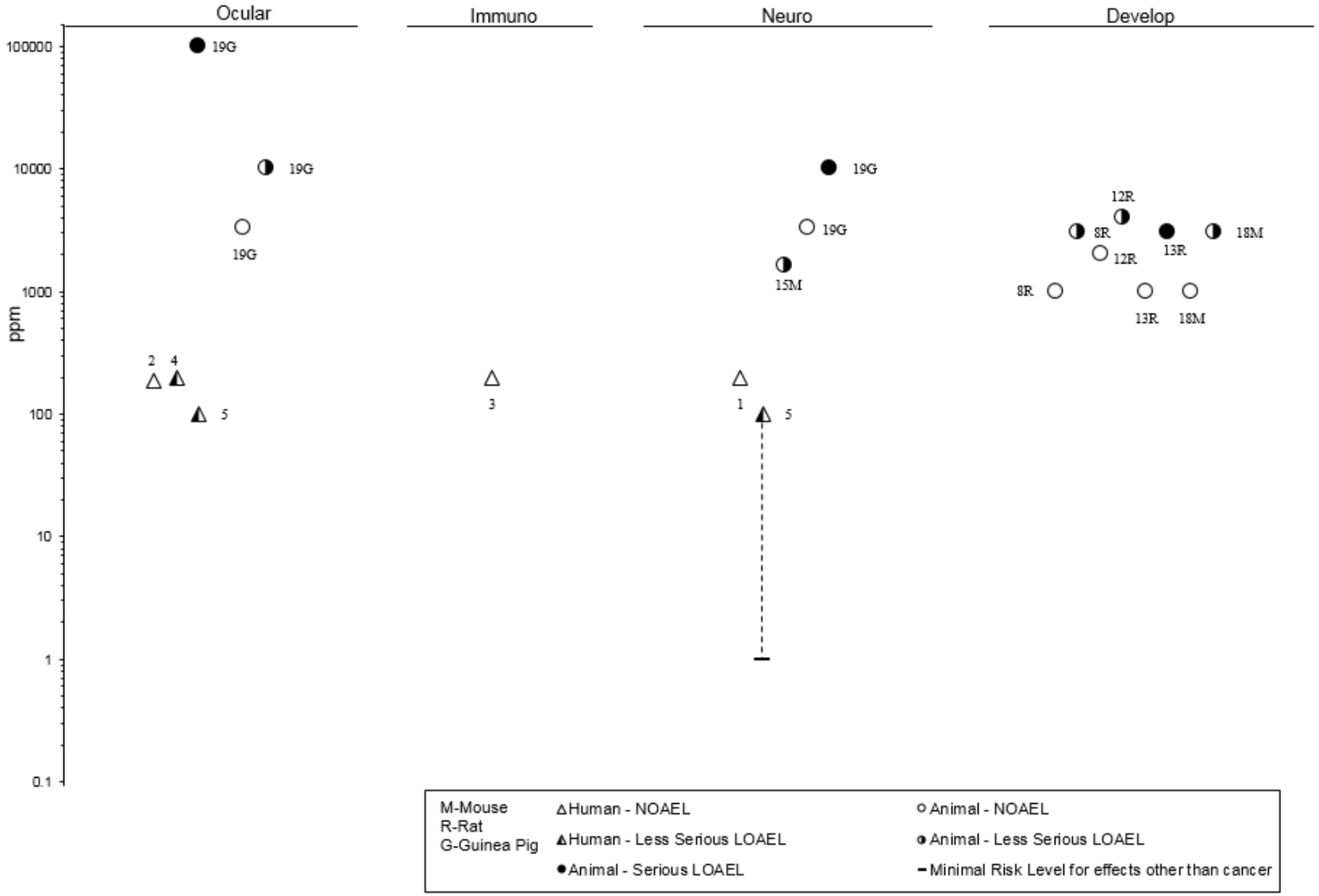


Figure 2-2. Levels of Significant Exposure to 2-Butanone – Inhalation
Intermediate (15-364)

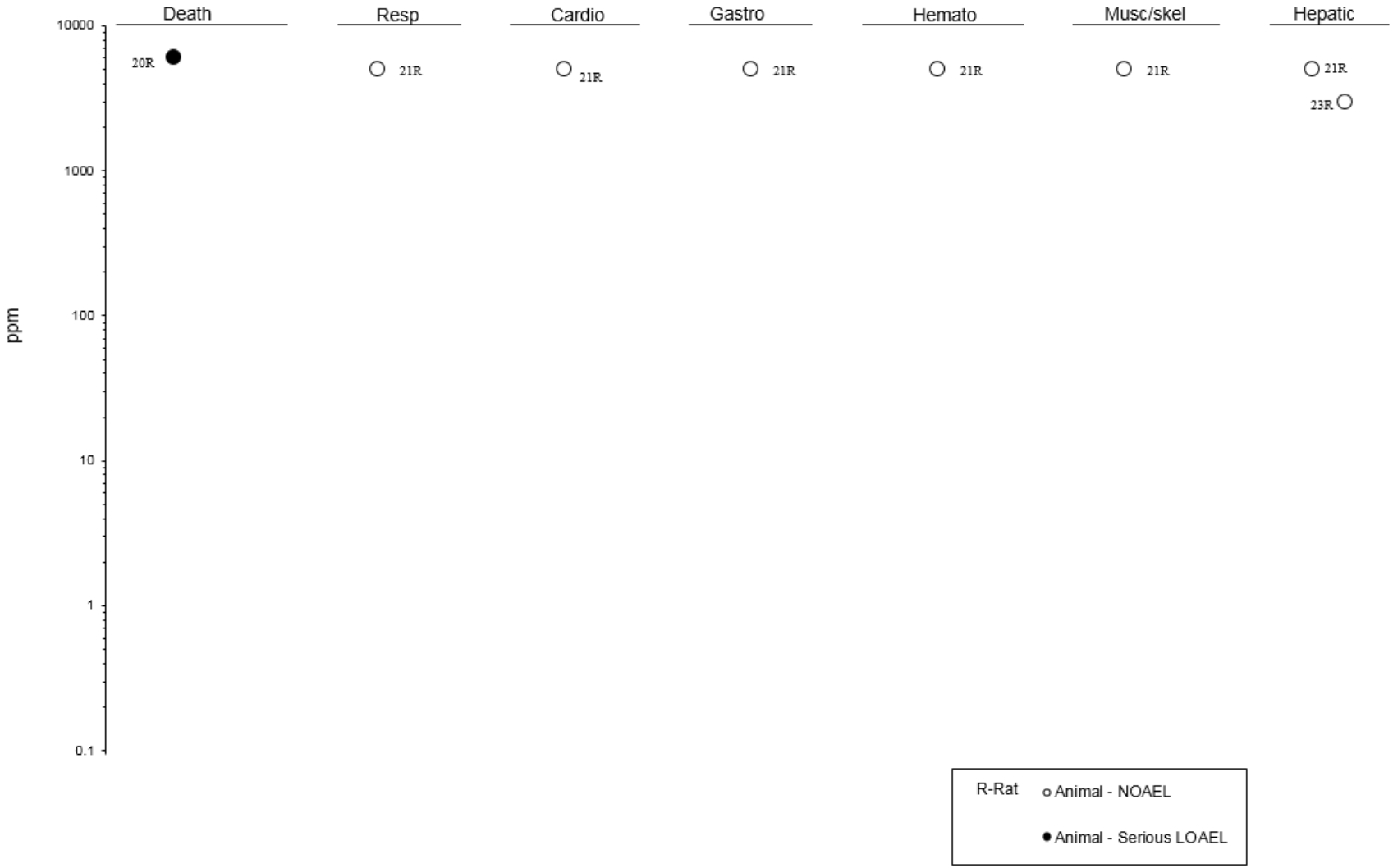


Figure 2-2. Levels of Significant Exposure to 2-Butanone – Inhalation
Intermediate (15-364)

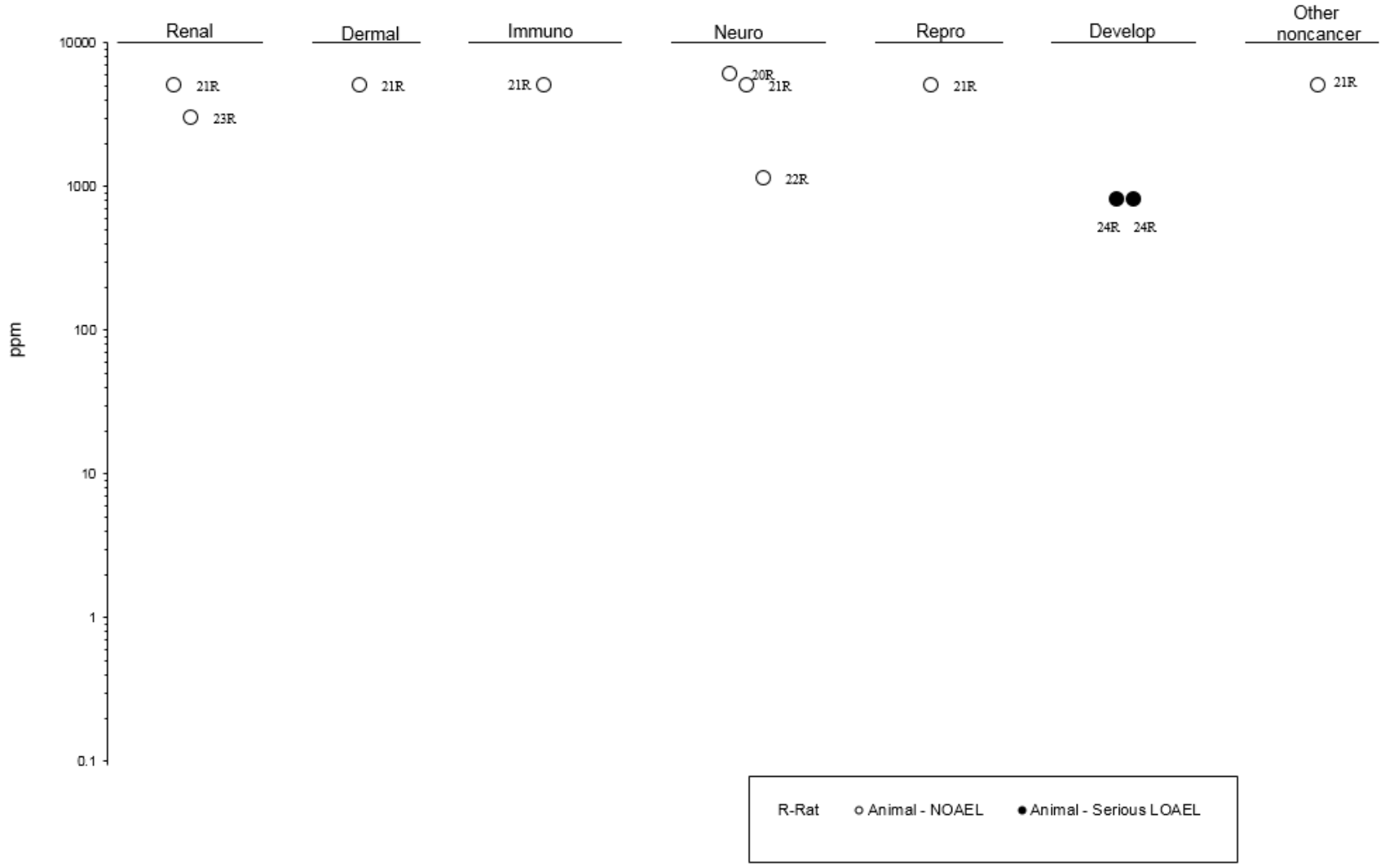


Table 2-2. Levels of Significant Exposure to 2-Butanone – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
ACUTE EXPOSURE									
1	Rat (Fischer) 6 M	1 day (G)	0, 1,080	GN, HP, OF	Hepatic	1,080			
					Renal		1,080		Tubular necrosis
Brown and Hewitt 1984									
2	Rat (Sprague-Dawley) 6 M	1 day 1 time/day (GO)	0, 1,080	BI	Hepatic	1,080			
Hewitt et al. 1990									
3	Rat (Sprague-Dawley) 6 M, 6–12 F	1 day (G)	2,737	LE	Death			2,737	LD_{50}
Kimura et al. 1971									
4	Rat (NS) 4 M	3 days 1 time/day (GW)	0, 1,130	BI	Hepatic	1,130			
Raunio et al. 1990									
5	Rat (F344) 3–4 M	1–7 days 1 time/day (GW)	0, 1,500	BI	Hepatic	1,500			
Robertson et al. 1989									
6	Rat (albino) 5 M, F	1 day (G)	0, 3670, 7,340, 14,680	BW	Death			3,670	8/10 died
					Neuro			3,670	CNS depression
Stillmeadow Inc. 1978									
7	Rat (NS) 56 M	1 day 1 time/day (G)	0, 1,500	BI	Hepatic	1,500			
Traiger et al. 1989									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
8	Mouse	1 day (G)			Death			4,044	LD_{50}
Tanii et al. 1986									
INTERMEDIATE EXPOSURE									
9	Rat (Fischer) 20 M	13 weeks 5 days/week (G)	0, 1,752	CS	Neuro	1,725			
Ralston et al. 1985									

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

BI = biochemical changes; BW = body weight; CNS = central nervous system; CS = clinical signs; F = female(s); (G) = gavage; GN = gross necropsy; (GO) = gavage in oil; (GW) = gavage in water; HP = histopathology; LD_{50} = lethal dose, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; Neuro = neurological; NS = not specified; OF = organ function

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

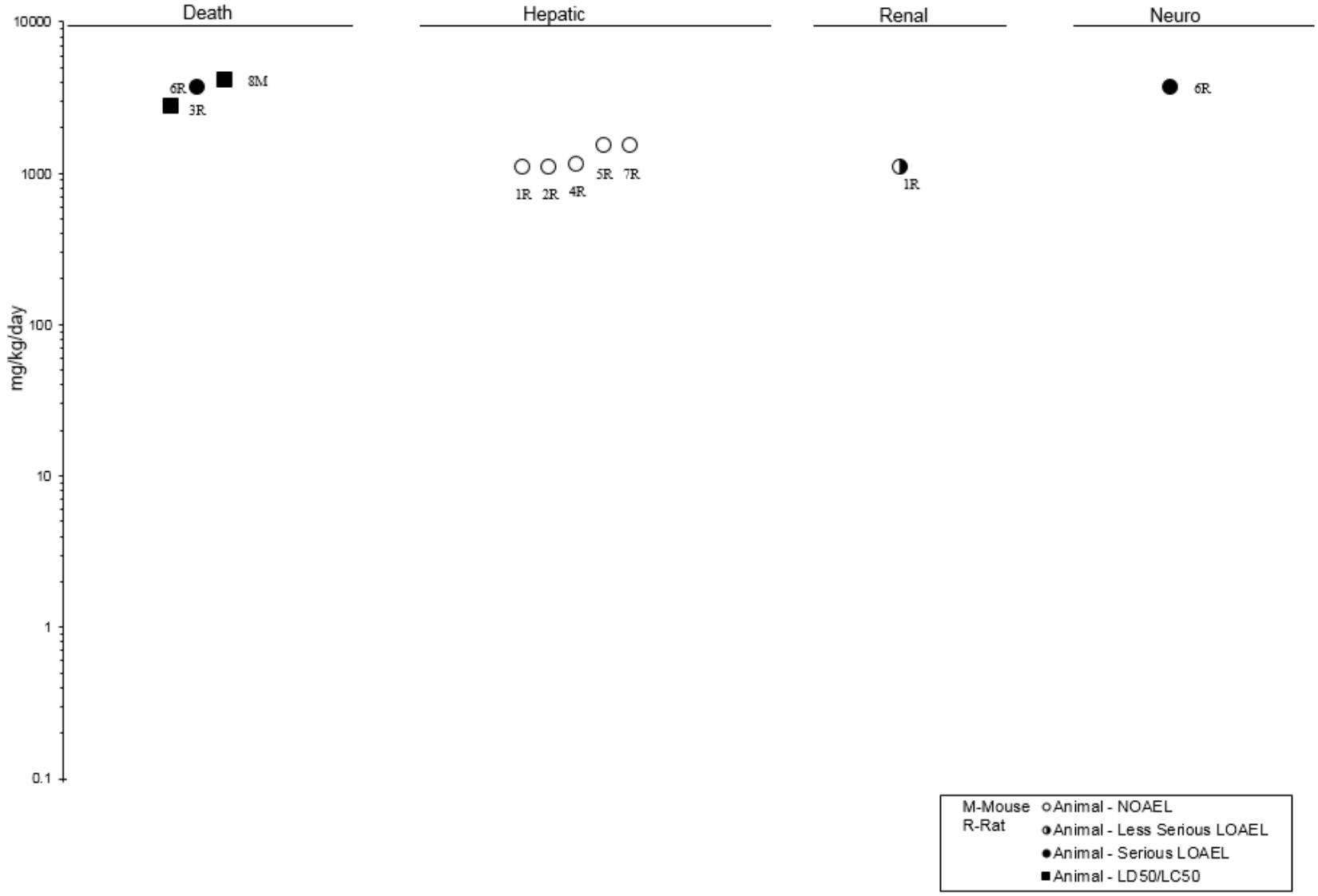


Figure 2-3. Levels of Significant Exposure to 2-Butanone – Oral
Intermediate (15-364 days)

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

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
ACUTE EXPOSURE								
Mouse BALB/c 5 F	1 day 24 hours	0.08 mL (undiluted)		Dermal		0.08		Skin irritation
Iyadomi et al. 2000								
Rabbit (albino) 12 NS	24 hours	0.5 mL		Dermal		0.5		Erythema
Hazelton Laboratories 1963a								
Guinea pig (Dunkin/Hartley) 10 F	3 days 3 times/day	10 µL/cm^2		Dermal		10		Erythema
Anderson et al. 1986								
Guinea pig (NS) 6–9 NS	10 days 1 time/day	0.1 mL		Dermal		0.1		Skin-fold thickening
Wahlberg 1984								
INTERMEDIATE EXPOSURE								
Human NS	18 days 1 time/day	0.1 mL		Dermal	0.1			
Wahlberg 1984								

F = female(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified

2.2 DEATH

No studies were located regarding death of humans following inhalation, oral, or dermal exposure to 2-butanone.

Acute inhalation exposure to ≥8,000 ppm 2-butanone resulted in death in rats, mice, and guinea pigs within a few hours (Klimisch 1988; LaBelle and Brieger 1955; Patty et al. 1935; Smyth et al. 1962). The 4-hour LC_{50} in rats was 11,700 ppm (LaBelle and Brieger 1955). Death was also observed in rats exposed daily (8 hours/day) to 6,000 ppm for 7 weeks (Altenkirch et al. 1978, 1979). The cause of death for all rats exposed to 2-butanone in this study was severe bronchopneumonia confirmed pathologically and histologically. A repeat of this study gave the same results (i.e., death within 7 weeks coincident with confirmed bronchopneumonia) (Altenkirch et al. 1979).

Oral LD_{50} values for 2-butanone were similar (approximately 2,737 mg/kg) in three groups of Sprague-Dawley rats: immature (14 days old), young adult (80–160 g), and older adult (300–470 g) (Kimura et al. 1971). Most of the Sprague-Dawley rats receiving 3,670, 7,340, or 14,680 mg/kg by gavage died within 1 hour at each dose, except one male and one female at the lowest dose; these rats survived until sacrifice at 14 days (Stillmeadow Inc. 1978). The data were insufficient for determination of an LD_{50}, but the authors estimated the acute oral LD_{50} to be <3,670 mg/kg, which is in agreement with the data reported in Kimura et al. (1971). Tanii et al. (1986) determined the oral LD_{50} for 2-butanone in mice as 4,044 mg/kg (95% confidence limits 3,200–5,111 mg/kg).

No studies were located regarding death in animals after dermal exposure to 2-butanone.

2.3 BODY WEIGHT

No studies were located regarding body weight changes in humans following inhalation, oral, or dermal exposure to 2-butanone.

Maternal body weight was decreased in rats exposed by inhalation to 3,000 ppm for 7 hours/day during GDs 6–15 (Deacon et al. 1981; magnitude of change not reported). Maternal body weight gain was reduced by 52% in rats exposed to 4,000 ppm for 6 hours/day during GDs 6–20 (Saillenfait et al. 2006). Mice appeared to less sensitive to maternal body weight effects than rats. No effect on maternal body weight was observed in mice exposed to 3,000 ppm for 7 hours/day during GDs 6–15 (NTP 1989;

Schwetz et al. 1991). No effect on rats exposed to ≤5,000 ppm of 2-butanone for 90 days (Cavender and Casey 1981; Cavender et al. 1983). Furthermore, no specific effects on body weight were found. Terminal body weight was similar to controls in rats exposed to ≤5,000 ppm 2-butanone for 13 weeks (Cavender and Casey 1981; Cavender et al. 1983).

No studies were located regarding body weight changes in animals after oral or dermal exposure to 2-butanone.

2.4 RESPIRATORY

2-Butanone is irritating to respiratory tissues. Upper respiratory tract irritation was noted in a case report of a patient with occupational 2-butanone exposure (concentration data were not reported) (Callender 1995). A clinical case report of three men exposed to 2-butanone fumes while removing paint from an airplane hangar noted mild respiratory symptoms but did not further describe the nature or extent of the symptoms (Berg 1971). An increased prevalence of upper respiratory tract irritation (statistical significance not reported) was observed in a group of 41 workers exposed to 2-butanone (concentrations ranging from 51 to 116 ppm) at a cable factory, compared with a control group of 63 workers (Mitran et al. 1997). It should be noted that concerns regarding the study design of the Mitran et al. (1997) study were raised in a letter to the editor (Graham 2000) concluding that the study results should not be used to derive or modify health guidance values.

Male and female volunteers (n=10) exposed to 100 ppm 2-butanone complained of slight nose and throat irritation, which became objectionable at 350 ppm (Nelson et al. 1943). Tomicic et al. (2011) also reported nose and throat irritation during a 6-hour exposure to 100 ppm 2-butanone with 15 female subjects reporting higher symptom ratings than 10 male subjects. Nasal irritation was not reported in 24 male subjects exposed to 2-butanone vapor for 4 hours under constant (10 ppm) or changing exposure conditions (peaks up to 380 ppm; TWA of 189 ppm) (Seeber et al. 2002; van Thriel et al. 2002). Symptoms were scored as “hardly at all” for male subjects with self-reported multiple chemical sensitivity and “not at all” for the other subjects. The median symptom score in 19 males exposed to 200 ppm for 4 hours was also 0 (no effect); however, a few of the subjects did report a significant increase in the severity of throat irritation after 4 hours of exposure (Muttray et al. 2002). Odor perception was reported by all subjects with the intensity influenced by concentration (10–380 ppm) and exposure duration (Seeber et al. 2002; van Thriel et al. 2002). Tomicic et al. (2011) reported that male subjects became tolerant to the odor of 2-butanone during the 6-hour exposure period (100 ppm), while

female subjects scored odor perception as high at the end of the exposure. The odor threshold for 2-butanone falls in the range 5.4–8.25 ppm (Amoore and Hautala 1983; Doty et al. 1988).

Nasal resistance was significantly increased in humans (12 males and 24 females) upon exposure to the odor threshold level of 2-butanone (5.4–8.25 ppm); this response reflects a nasopharyngeal reflex (Doty et al. 1988). A significant decrease in nasal flow was observed in anterior rhinomanometry of male subjects with self-reported multiple chemical sensitivity exposed to a TWA concentration of 189 ppm 2-butanone (Wiesmuller et al. 2002). This change was independent of the exposure concentration administered and may be related to odor perception. The nasal mucociliary transport time was increased in male subjects exposed to 200 ppm 2-butanone for 4 hours and the concentrations of IL-1β and IL-8 in nasal secretions were also increased (although not significantly) (Muttray et al. 2002). Concentrations of IL-8 and TNFα in nasal secretions were unchanged by 2-butanone exposure in this study (Muttray et al. 2002). Exposure of males to 2-butanone vapor for 4 hours under constant (10 ppm) or changing exposure conditions (peaks up to 380 ppm; TWA of 189 ppm) did not alter the concentrations of inflammatory biomarkers in nasal secretions (eosinophil cationic protein, myeloperoxidase, interleukin 1β, substance P, and neurokinin A) (van Thriel et al. 2003). Respiratory rate was not affected by 2-butanone exposure in these subjects (Haumann et al. 2003).

The respiratory tract irritation noted in humans at ≥100 ppm does not necessarily imply that humans are more sensitive to the respiratory effects of 2-butanone than other species tested (see Table 2-1). Another possible explanation is that humans are better able to communicate the early signs of irritation compared with the other species tested. At high concentrations, 2-butanone is also irritating to respiratory tissues of animals. Guinea pigs exposed to 33,000 ppm had gasping respiration after 180 minutes of exposure and died after 200–260 minutes of exposure (Patty et al. 1935). Their lungs were emphysematous. Severe upper respiratory tract irritation was found after a few days in rats exposed to 10,000 ppm, 8 hours/day (Altenkirch et al. 1978). Due to the irritation observed at 10,000 ppm in the study by Altenkirch et al. (1978), the exposure concentration was reduced to 6,000 ppm and the study continued. All of the rats died suddenly at 7 weeks with pathologically confirmed bronchopneumonia. This experiment was repeated and had the same results (Altenkirch et al. 1979). Furthermore, rats exposed to n-hexane or a combination of n-hexane and 2-butanone did not develop bronchopneumonia, suggesting that a factor other than poor animal maintenance precipitated the bronchopneumonia. The Wistar rats used in this study may possibly have been derived from a stock that was particularly susceptible to infection. The initial exposure to a high concentration of 2-butanone may have weakened their immune system, allowing infection to develop. No other studies were located that reported a link between 2-butanone exposure and

bronchopneumonia in humans or animals. Rats appeared to tolerate intermittent exposures up to 5,000 ppm. In a 90-day inhalation study, exposure of rats to 2-butanone concentrations of 0, 1,250, 2,500, or 5,000 ppm for 6 hours/day, 5 days/week caused no signs of upper respiratory tract irritation or other respiratory effects assessed by clinical signs and histopathology evaluation (Cavender et al. 1983). 2- Butanone produced a time- and concentration-dependent decrease in respiratory rate and tidal volume in mice exposed to 3,809, 9,136, 12,771, 24,179, or 26,416 ppm 2-butanone for 30 minutes followed by a 20-minute recovery (Hansen et al. 1992). These effects were consistent with sensory irritation and desensitization occurred at the lowest concentrations used.

One clinical report of oral exposure to 2-butanone in humans was located. A 47-year-old woman accidentally ingested an unknown volume of 2-butanone that had been stored in a rum bottle (Kopelman and Kalfayan 1983). She was admitted to an emergency ward unconscious and hyperventilating. Blood gases were 85 mmHg oxygen and 24 mmHg carbon dioxide. Analysis of her blood showed a 2-butanone plasma concentration of 95 mg/100 mL. Slow infusion of sodium bicarbonate reduced the hyper-ventilation, and blood gases improved to 78 mmHg oxygen and 25mmHg carbon dioxide. Within 12 hours, she had regained consciousness, made an uneventful recovery over the next few days, and was discharged after 1 week (Kopelman and Kalfayan 1983).

All albino rats receiving ≥3,670 mg/kg had labored breathing, and most of them died within 1 hour (Stillmeadow Inc. 1978). It is not clear whether the labored breathing represented a respiratory or a neurological response to a high dose. No other studies were located regarding respiratory effects after oral exposure to 2-butanone.

2.5 CARDIOVASCULAR

Heart rate was not affected in male volunteers exposed to 2-butanone vapor for 4 hours under constant (10 ppm) or changing exposure conditions (peaks up to 380 ppm; TWA of 189 ppm) (Haumann et al. 2003). Histological examination of the hearts and aorta of rats exposed to ≤5,000 ppm of 2-butanone for 90 days revealed no exposure-related lesions (Cavender and Casey 1981; Cavender et al. 1983).

Cardiovascular effects observed in a 47-year-old woman after accidental ingestion of 2-butanone were decreased blood pressure and increased pulse rate (Kopelman and Kalfayan 1983). No other reports were located regarding cardiovascular effects in humans or animals following exposure to 2-butanone.

2.6 GASTROINTESTINAL

A higher prevalence of gastrointestinal symptoms (including loss of appetite, hyperacidity, bad taste, and abdominal pains) was observed in 41 workers exposed to 51–117 ppm of 2-butanone, compared with 63 control workers (Mitran et al. 1997); statistical analysis of the prevalence data was not conducted. Concerns regarding the study design of the Mitran et al. (1997) study were raised in a letter to the editor (Graham 2000), which concluded that the study results should not be used to derive or modify health guidance values.

No histopathological lesions were found in the esophagus, salivary glands, ileum, duodenum, jejunum, cecum, large or small intestines, or pancreas of rats exposed to ≤5,000 ppm of 2-butanone for 90 days (Cavender and Casey 1981; Cavender et al. 1983). No other reports were located regarding gastrointestinal effects in humans or animals following exposure to 2-butanone.

2.7 HEMATOLOGICAL

Information regarding hematological effects of 2-butanone exposure in humans is limited to a case report in which a normal hematological profile and blood chemistry were found in an 18-year-old seaman exposed to 2-butanone while removing paint from an airplane hangar (Berg 1971). 2-Butanone exposure in this case was linked to retrobulbar neuritis and severely impaired vision. However, because methanol was found in the blood of the patient, consumption or exposure to methanol cannot be ruled out.

Studies in animals also indicate that 2-butanone does not produce hematological effects. No effect on hemoglobin concentration, or on red blood cell, white blood cell, neutrophil, lymphocyte, or monocyte populations were observed in rats exposed intermittently to 235 ppm 2-butanone for 12 weeks (LaBelle and Brieger 1955). Similarly, the hematological profile and serum chemistry of rats exposed to ≤5,000 ppm of 2-butanone for 90 days were normal (Cavender et al. 1983). No other reports were located regarding hematological effects in humans or animals following exposure to 2-butanone.

2.8 MUSCULOSKELETAL

Increased pain in the bones, joints, and vertebral column and diffuse muscular pain were reported by a majority of 41 cable factory workers exposed to 2-butanone, compared with 63 controls (Mitran et al. 1997). The exposure-level range throughout an 8-hour shift was 51–117 ppm. Concerns regarding the

study design of the Mitran et al. (1997) study were raised in a letter to the editor (Graham 2000), which concluded that the study results should not be used to derive or modify health guidance values.

Histological examination of skeletal muscle and bone of rats exposed to ≤5,000 ppm of 2-butanone for 90 days revealed no exposure-related lesions (Cavender and Casey 1981; Cavender et al. 1983). No other reports were located regarding musculoskeletal effects in humans or animals following exposure to 2-butanone.

2.9 HEPATIC

No studies were located regarding hepatic effects in humans after inhalation, oral and dermal exposure to 2-butanone.

Most of the hepatic effects of inhalation exposure to 2-butanone observed in animals are minimal and probably not adverse, although acute exposure of guinea pigs to a high concentration (10,000 ppm) caused liver congestion (Patty et al. 1935). Exposure to 3,300 ppm had no effects in guinea pigs from this study. Serum alkaline phosphatase activity was not altered in rats exposed 8 hours/day to 300 ppm 2-butanone for 7 days compared to nonexposed control rats (Li et al. 1986). A statistically significant increase in absolute and relative liver weights of male and female rats (13–27%), but no change in serum levels of hepatic enzymes (ALT, AST, gamma-glutamyl transferase [GGT], and alkaline phosphatase), was observed in male rats at an exposure level of 5,000 ppm for 90 days (Cavender et al. 1983). A significant increase only in alkaline phosphatase (41% above controls) was noted in the female rats. Histopathological examination did not reveal any hepatic lesion aside from those expected in Fischer rats of this age. Exposure to 2,500 ppm 2-butanone had no effect on any hepatic parameter (Cavender et al. 1983). In the absence of histopathological liver lesions, the mild liver effects observed at 5,000 ppm were probably not adverse. Exposure of female rats to 3,000 ppm (but not 1,000 ppm) 2-butanone 6 hours/day for 15 days increased absolute and relative liver weight by 13–16% (Saillenfait et al. 2006). Serum chemistry parameters (ALT, AST, urea, and creatinine) and liver histopathology were not affected by 2-butanone exposure in this study. Relative liver weight was also increased in male rats exposed to 800 ppm 2-butanone 6 hours/day for 4 weeks (6% increase over control) (Toftgard et al. 1981) and pregnant mice exposed to 3,000 ppm 2-butanone for 7 hours/day on GDs 6–15 (7% increase over controls) (NTP 1989; Schwetz et al. 1991). Liver weight increases in rodent studies may be related to induction of cytochrome P450 (CYP) (see Section 3.1).

2-Butanone had no effect on liver weight, ALT, or serum ornithine carbamyl transferase activities measured 42 hours after oral exposure of rats to a single gavage dose of 1,080 mg/kg (Hewitt et al. 1983). Similarly, Brown and Hewitt (1984) observed normal ALT activity in rats exposed orally to 1,080 mg 2-butanone/kg. Furthermore, oral treatment of rats with 1,080 mg/kg 2-butanone had no effect on the fragility of hepatic lysosomes or on the calcium uptake by mitochondria or microsomes (Hewitt et al. 1990).

2.10 RENAL

No studies were located regarding renal effects in humans following inhalation, oral or dermal exposure to 2-butanone.

Acute inhalation exposure of guinea pigs to 10,000 ppm 2-butanone resulted in congestion of the kidney (Patty et al. 1935). No effects were observed at 3,300 ppm. Minimal kidney effects were observed in rats exposed to ≤5,000 ppm for 6 hours/day, 5 days/week for 13 weeks (Cavender et al. 1983). Blood urea nitrogen determinations and urinalysis including urine volume, specific gravity, and pH showed that all values were within normal limits for male and female rats; the exception was that urine volume in the females was slightly, but significantly, increased. The kidney/body weight ratio in male rats and the kidney/brain weight ratio in female rats were slightly, but significantly, elevated (6–11% increase over controls). Histopathological examination did not reveal any treatment-related renal lesion. In the absence of histopathological lesions or decrements in kidney function, the mild kidney effects observed in this study do not appear to be adverse. Exposure of female rats to 1,000 or 3,000 ppm 2-butanone 6 hours/day for 15 days did not affect kidney weight or produce renal histopathological lesions (Saillenfait et al. 2006).

Acute oral exposure of rats to 1,080 mg/kg 2-butanone caused mild renal tubular necrosis but had no effect on renal organic ion transport (p-aminohippuric acid, tetraethylammonium) or plasma creatinine (Brown and Hewitt 1984). No other studies were located regarding renal effects in animals after exposure to 2-butanone.

2.11 DERMAL

A group of 41 workers exposed to 2-butanone reported a higher incidence of skin irritation, compared with a control group of 63 workers (Mitran et al. 1997). The exposure level range throughout an 8-hour

shift was 51–117 ppm. It should be noted that concerns regarding the study design of the Mitran et al. (1997) study were raised in a letter to the editor (Graham 2000) concluding that the study results should not be used to derive or modify health guidance values. Application of 0.1 mL undiluted 2-butanone once daily for 18 days to the forearm of volunteers did not result in erythema, an increase in skin-fold thickness, or edema over the 18-day exposure period (Wahlberg 1984). Further details regarding the number of volunteers were not reported.

In rabbits and guinea pigs, application of undiluted 2-butanone caused minimal skin irritation, erythema, and/or increase in skin-fold thickness (Anderson et al. 1986; Hazleton Laboratories 1963a; Wahlberg 1984). Slight desquamation occurred in guinea pigs after 31 weeks of dermal exposure to increasing amounts of 2-butanone (Eastman Kodak 1978). Abraded skin areas were slightly more sensitive to the application of 2-butanone (Hazleton Laboratories 1963a). Edema was detected in a mouse ear thickness test after application of 80 μL 2-butanone to the skin of the front and back of the ear (Iyadomi et al. 2000). Ear thickness was maximal 2 hours after application and decreased to control levels by 24 hours.

2.12 OCULAR

Two men exposed to 2-butanone while removing paint from an airplane hangar had conjunctival irritation (Berg 1971). A third man had severe loss of vision. Within 36 hours, the man's vision was completely restored. However, because methanol was found in the blood of the man with vision loss, exposure to methanol cannot be ruled out. A group of 41 workers exposed to 2-butanone reported a higher incidence of ocular symptoms compared with a control group of 63 workers (Mitran et al. 1997). The exposure-level range throughout an 8-hour shift was 51–117 ppm. It should be noted that concerns regarding the study design of the Mitran et al. (1997) study were raised in a letter to the editor (Graham 2000) concluding that the study results should not be used to derive or modify health guidance values.

Mild eye irritation was noted in some volunteers exposed to 200 ppm 2-butanone for 3–5 minutes (Nelson et al. 1943). Discomfort in the eyes was also reported in human subjects exposed to 100 ppm 2-butanone for 6 hours with females scoring significantly higher on symptom questionnaires compared to male subjects (Tomicic et al. 2011). Eye irritation was not reported in male subjects exposed to 2-butanone vapor for 4 hours under constant (10 ppm) or changing exposure conditions (peaks up to 380 ppm; TWA of 189 ppm) (Seeber et al. 2002; van Thriel et al. 2002).

Guinea pigs exposed to 2-butanone concentrations ≥10,000 ppm had eye irritation and lacrimation (Patty et al. 1935). Exposure to 100,000 ppm for ≥30 minutes caused corneal opacity. This condition gradually improved in guinea pigs that lived to 8 days after exposure. No effects occurred when guinea pigs were exposed to 3,300 ppm. Ophthalmological examination of the eyes and histological examination of the skin revealed no effects in rats exposed to ≤5,000 ppm of 2-butanone for 90 days (Cavender and Casey 1981; Cavender et al. 1983).

2-Butanone instilled into the conjunctival sac of rabbits caused irritation, corneal opacity, and conjunctivitis (Davis and Baker 1975; Haskell Laboratories 1971; Hazleton Laboratories 1963b; Kennah et al. 1989). These effects were generally reversible in 7–14 days. Hazleton Laboratories (1963b) reported that one of six rabbits had persistent corneal damage after 7 and 14 days. On the basis of Draize scores in these studies, 2-butanone was classified as moderately irritating.

2.13 ENDOCRINE

No studies were located regarding endocrine effects in humans following inhalation, oral, or dermal exposure to 2-butanone.

In rats, no histopathological lesions were found in the thyroid, parathyroid, pituitary gland, adrenal glands, ears, or Zymbal glands of rats exposed to ≤5,000 ppm of 2-butanone for 90 days (Cavender and Casey 1981; Cavender et al. 1983).

2.14 IMMUNOLOGICAL

Inflammatory biomarkers were not significantly elevated in nasal secretions of volunteers exposed to 2-butanone for 4 hours (Muttray et al. 2002 [200 ppm continuous]; van Thriel et al. 2003 [189 ppm TWA]). Although no specific tests for immunological effects were performed, histological examination of lymph nodes, thymus, spleen, and bone marrow of rats exposed to ≤5,000 ppm of 2-butanone for 90 days revealed no exposure-related lesions (Cavender and Casey 1981; Cavender et al. 1983).

One clinical report of 2-butanone-evoked contact urticaria was located. A 48-year-old man employed as a painter complained of severe irritation when he handled 2-butanone (Varigos and Nurse 1986). A small amount of 2-butanone applied to his forearm produced a bright red area at the site of application. The area became itchy, but no induration or edema was noted. After 15 minutes, the reaction subsided. Two

days later, the test was repeated with the same result. Five volunteers were later tested for sensitivity to 2-butanone by the same method, but no response was observed. No studies were located regarding immunological effects in animals after dermal exposure to 2-butanone.

An *in vitro* study using granulocytes and monocytes isolated from human peripheral blood showed a concentration-dependent decrease in phagocytosis of oponized zymosan particles (0.0005–0.05 mM 2-butanone). 2-Butanone also affected membrane integrity, glutathione homeostasis, and intracellular free calcium concentrations in an immortalized human T-lymphocyte cell line (>0.01 mM in Jurkat T cells) (McDermott et al. 2007).

2.15 NEUROLOGICAL

Neurotoxicity was reported in clinical case studies of occupational workers exposed to 2-butanone (exposure concentrations not reported). A worker exposed to 2-butanone fumes generated from burning fiberglass material (also occasionally to peroxides and acetone) reported severe chronic headache, dizziness, loss of balance, memory loss, fatigue, tremors, muscle twitches, visual disturbances, throat irritation, and tachycardia (exposure concentrations were not reported) (Callender 1995). Neurobehavioral tests revealed mild-to-moderate impairment of attention, psychomotor speed, short-term memory, and the ability to shift cognitive sets as processing demands increased, as well as significant mood disruption in the form of depression. Electroencephalography (EEG) and evoked potentials tests showed abnormalities that were consistent with behavioral effects. Additionally, motor and sensory polyneuropathy was found in nerve conduction velocity tests, and rotational and visual reflex testing results were consistent with peripheral labyrinthine dysfunction. The findings of a single-photon emission computerized tomography (SPECT) brain scan were consistent with small ischemic insults in both the right and left cerebral hemispheres. In another case report, a worker with inhalation and dermal exposure to solvents containing 100% 2-butanone for approximately 2 years reported dizziness, asthenia, anorexia, and weight loss (Orti-Pareja et al. 1996). Neurologic examination showed postural and action tremor in the hands, face, tongue, and voice; multifocal myoclonic jerks in the limbs; ocular flutter; and ataxic gait.

Increases in several neurological symptoms, including mood disorder, irritability, memory difficulties, sleep disturbances, and headaches, were also reported for 41 workers at a cable factory compared to 63 control workers (Mitran et al. 1997). The measured exposure-levels in this study ranged from 51 to 117 ppm during an 8-hour work shift. In motor nerve conduction velocity tests, significant increases in

proximal latency in the median, ulnar, and peroneal nerves and distal latency in the median and ulnar nerves were observed; significant decreases in nerve conduction velocity in median, ulnar, and peroneal nerves were also observed. It should be noted that concerns regarding the study design of the Mitran et al. (1997) study were raised in a letter to the editor (Graham 2000) concluding that the study results should not be used to derive or modify health guidance values. Specific concerns were raised regarding the lack of a detailed description of the experimental conditions maintained during electrodiagnostic testing.

Neurological symptoms were reported in some volunteer studies, but the results of neurobehavioral testing were similar to unexposed controls. Headache, fatigue, and feeling of intoxication were noted in volunteer subjects exposed to 100 ppm 2-butanone for 4 hours, with females scoring higher on symptom questionnaires compared with men (Tomicic et al. 2011). Headache and nausea were also reported by male subjects 2 hours after exposure to 200 ppm exposure, compared with pre-exposure ratings (Muttray et al. 2002). In four separate studies, groups of 16–25 volunteers underwent a single 4-hour exposure to 200 ppm 2-butanone (Dick et al. 1984, 1988, 1989, 1992). No differences were observed between exposed and control groups on neurobehavioral tests including psychomotor tests (choice reaction time, visual vigilance, dual task, and memory scanning), postural sway, and a profile of mood states. Regression analyses showed a significant linear relationship between blood concentrations of 2-butanone in females and a small increase in the number of incorrect responses on the auditory portion of the dual task test (Dick et al. 1992). In a study of 19 workers exposed to mixed solvents (2-butanone, cyclohexanone, tetrahydrofuran, and toluene), alterations in some neurobehavioral tests (Santa Ana dexterity test, digit span, and visual reproduction) were observed (Chia et al. 1993). However, there was no correlation between test score and mixed solvent exposure level.

Neurological effects have been observed in animals exposed by inhalation to 2-butanone. Exposure of mice to 2-butanone at concentrations ≥1,602 ppm for 4 hours caused a dose-related reduction in the duration of immobility in a "behavioral despair" swimming test (De Ceaurriz et al. 1983). The authors noted that the effect of 2-butanone was similar to that of antidepressants. In guinea pigs exposed acutely to 10,000 ppm 2-butanone, incoordination occurred within 90 minutes and unconsciousness occurred within 240–280 minutes (Patty et al. 1935). These signs occurred earlier at higher concentrations, but no neurological signs were observed at 3,300 ppm. Juvenile baboons exposed continuously to 100 ppm for 7 days showed early signs of narcosis, incoordination, and a loss of time perception in neurobehavioral tests (Geller et al. 1979). The neurological effects observed in this study could have resulted from narcosis. It is also possible that the baboons were distracted during the testing due to the irritating effects

of 2-butanone on the respiratory system. Furthermore, the effects of 2-butanone observed at 100 ppm in the baboons do not imply that baboons are more sensitive to 2-butanone than other species tested. Since the baboons were evaluated with a complex discriminant behavioral task, it is possible that subtle neurobehavioral effects could be observed. However, it should be noted that only one exposure level was tested, only one baboon of four tested showed consistently different results from the controls throughout the study, and no statistical tests were performed.

Intermediate-duration exposures to 2-butanone were not neurotoxic in rats. Male Sprague-Dawley rats exposed continuously to 1,125 ppm 2-butanone for periods of ≤5 months showed no signs of peripheral neuropathy following histological examination (Saida et al. 1976). The neurotoxicity of n-butyl ketone, however, was markedly potentiated by 2-butanone. No differences were observed in nerve fiber preparations from male and female Fischer 344 rats exposed to ≤5,000 ppm 2-butanone for 90 days (Cavender and Casey 1981; Cavender et al. 1983). Furthermore, no histopathological lesions were found in the brain, sciatic nerve, tibia1 nerve, spinal cord, or optic nerves. No effects were observed in posture, gait, tone, and symmetry of the facial muscles, or in the pupillary, palpebral, extensor thrust, and cross-extensor thrust reflexes. The only effect recorded was a slight, but statistically significant, increase in brain weight in female rats exposed to 5,000 ppm. No clinical signs and no histological evidence of neuropathy in peripheral nerves from the brachial plexus, sciatic nerve, spinal cord, and medulla were observed in rats exposed to 6,000 ppm for 7 weeks compared with rats exposed to n-hexane or a combination of n-hexane and 2-butanone (Altenkirch et al. 1978). In contrast, 2-butanone potentiated the neurotoxicity of n-hexane. No neuropathological changes were found on light microscope and electron microscope examination of teased tail nerves after exposure of a rat to 200 ppm 2-butanone for 24 weeks (Takeuchi et al. 1983). At 4 weeks, significant increases in motor nerve conduction velocity and mixed nerve conduction velocity were found, while distal motor latency was decreased. These changes in nerve conduction velocity were not seen beyond 4 weeks. The transient increase in nerve conduction velocity may have been due to an effect of 2-butanone on the axonal membrane (Takeuchi et al. 1983).

No studies were located regarding neurological effects in humans after oral or dermal exposure to 2-butanone.

In animals, clinical signs of central nervous system toxicity including lethargy, labored breathing, ptosis, lacrimation, exophthalmos, ataxia, salivation, and piloerection were observed in rats treated by gavage with 2-butanone at doses ≥3,670 mg/kg (Stillmeadow Inc. 1978). Most of these rats died. No effects were observed in neurobehavioral tests, including hindlimb grasp, hindlimb place, balance beam, and

rotorod, in rats treated by gavage with 2-butanone at a TWA dose of 173 mg/kg/day for 90 days (Ralston et al. 1985). No other studies were located regarding neurological effects in animals after oral exposure to 2-butanone.

In an intermediate study of dermal exposure, 1–2 mL of undiluted 2-butanone was applied in increasing amounts to shaved areas on the backs of guinea pigs 5 days/week for ≤31 weeks (Eastman Kodak 1978). No clinical signs of neurotoxicity were observed. No evidence of neurotoxicity was noted on examination of Epon sections of the medulla oblongata and tibia1 nerve by light microscopy (Eastman Kodak 1978). The details of 2-butanone application, however, were not clear in this report.

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans after inhalation, oral, or dermal exposure to 2-butanone.

Although no tests for reproductive function were performed, histological examination of the testes, epididymides, seminal vesicles, vaginas, cervices, uteri, oviducts, ovaries, or mammary glands of rats exposed to ≤5,000 ppm of 2-butanone for 90 days (6 hours/day, 5 days/week) revealed no exposure-related lesions (Cavender and Casey 1981; Cavender et al. 1983). Complete litter loss was observed in rats exposed throughout gestation (23 hours/day, GDs 1–21) to 800 ppm (3/8 dams) and 1,000–1,500 ppm (4/8 dams) (Stoltenburg-Didinger et al. 1990).

No studies were located regarding reproductive effects in animals after oral exposure to 2-butanone; however, Cox et al. (1975) describes a 2-generation drinking water study of 2-butanol in rats. 2-Butanol is metabolized to 2-butanone and its downstream metabolites within 16 hours following oral administration. In addition, peak blood concentrations of 2-butanone occurred within a similar time period following oral dosing of 2-butanol (7–8 hours) or 2-butanone (4–5 hours). The elimination kinetics for downstream urinary metabolites of both compounds (3-hydroxy-2-butanone and 2,3-butanediol) were also similar for 2-butanol and 2-butanone (EPA 2003). The findings of this reproductive toxicity study of n-butanol (Cox et al. 1975) are presented here due to the absence of available studies for 2-butanone. Male and female Wistar rats were exposed to 0, 0.3, 1, or 3% 2-butanol in the drinking water for 8 weeks prior to mating and during gestation and lactation. The premating doses were reported as 0, 538, 1,644, and 5,089 mg/kg/day in males and 0, 594, 1,771, and 4,571 mg/kg/day in females. High-dose dams were given control drinking water for 2 weeks after delivery of the F1A litter,

and treatment was resumed at 2% 2-butanol prior to mating and examination of the F1B litter on GD 20 (i.e., uterine contents examined after second mating). The F1 offspring used for mating and delivery of the F2 generation were also exposed to 2% 2-butanol as the highest drinking water concentration. Average daily doses were not reported for 2% 2-butanol in drinking water; however, EPA (2003) estimated doses of 3,384 mg/kg/day in males and 3,122 mg/kg/day in females based on a linear regression analysis of reported drinking water intake values. Body weight and body weight gain were reduced in male and female rats in the F0 generation following 8 weeks of exposure to 3% 2-butanol (12–16% decrease from controls). Maternal body weight on GD 20 was not affected by gestational exposure to concentrations $\leq$2% 2-butanol for the second mating (F1B generation). Reproductive parameters (e.g., pregnancy rate, implantations, resorptions, number of litters) were not altered at any treatment concentration in F0 or F1 rats (producing F1A, F1B, and F2 generations). Developmental effects observed in this study are described in Section 2.17.

2.17 DEVELOPMENTAL

No studies were located regarding developmental effects in humans after inhalation, oral, or dermal exposure to 2-butanone.

Several studies in rats and mice were located regarding developmental effects after inhalation exposure. Exposure of pregnant rats to 1,000 or 3,000 ppm 2-butanone during gestation resulted in a slight increase in the incidence of malformations at 3,000 ppm; acaudia and imperforate anus were found in two fetuses out of 21 litters, and brachygnathia was noted in two other fetuses (Schwetz et al. 1974). A low incidence of sternebral anomalies was also noted in the 3,000 ppm group. Although the incidence of malformations was not high enough to support a positive correlation, it may have indicated a slight teratogenic effect in rats. A second study by the same group supported the previous findings of skeletal anomalies (Deacon et al. 1981). No statistically significant differences in external or soft tissue abnormalities were found in the offspring of dams exposed to $\leq$3,000 ppm during gestation. No effect was observed on the number of live fetuses/litter or on fetal crown-rump length. Skeletal abnormalities, including delayed ossification of the cervical centra and extra ribs, were observed at 3,000 ppm. Decreased body weight gain and increased water consumption in the pregnant rats at 3,000 ppm 2-butanone indicated that some maternal toxicity may have occurred at this exposure level. Deacon et al. (1981) concluded 2-butanone was slightly fetotoxic, but not embryotoxic or teratogenic, at 3,000 ppm.

Groups of 33 pregnant Swiss mice were exposed to 0, 400, 1,000, or 3,000 ppm 2-butanone for 7 hours/day on GDs 6–15; weights were measured on GDs 0, 6, 9, 15, and 18 and dams were euthanized on GD 18 (NTP 1989; Schwetz et al. 1991). No significant alterations in maternal body weight gain were observed with 2-butanone exposure, but a significant 7% increase in relative liver weight was observed at 3,000 ppm. A small, but statistically significant, decrease in fetal body weight (approximately 5% lower than controls) was observed only in the male offspring of mice exposed to 3,000 ppm. A similar, but slightly smaller, decrease in fetal body weight was also observed in females, but the weights were not statistically significantly different from those of controls. No significant alterations in the number of fetuses or litters with malformations were found; however, a significant trend for increased incidence of misaligned sternebrae was observed at doses >400 ppm.

Groups of 19–23 pregnant Sprague-Dawley rats were exposed to 0, 1,000, 2,000, 4,000, or 6,000 ppm 2-butanone 6 hours/day on GDs 6–20 (Saillenfait et al. 2006). Significant decreases in maternal body weight gain (recorded on GDs 0, 6, 13, and 21) and food consumption (measured across GDs 6–13 and 13–21) were observed at exposure levels of 4,000 and 6,000 ppm. Decreases in fetal body weight were observed at ≥4,000 ppm; fetal body weights were 4.4, 15, and 20% lower than the weights of controls in the 2,000, 4,000, and 6,000 ppm groups, respectively. No significant alterations in the total number of external, visceral, or skeletal variations were observed at any level of 2-butanone exposure. However, the study reported statistically significant increases in the incidence of incomplete sternebrae ossification in the 4,000 and 6,000 ppm groups.

Following prenatal exposure to 2-butanone (23 hours/day GDs 1–21; 800 or 1,000–1,500 ppm), a delay was observed in the activity of succinic dehydrogenase and NADH tetrazolium reductase in the cerebellar cortex of offspring, suggesting a delay in the outgrowth of Purkinje cell apical dendritic tree (Stoltenburg-Didinger 1991). Histological examination of the cerebellar cortex showed a delay in the migration of the outer granular cells and a delay in the development of Purkinje cells (Stoltenburg-Didinger 1990). As discussed in Section 2.16, this exposure also resulted in an increase in the percentage of dams with complete litter loss.

No studies were located regarding developmental effects in animals after oral exposure to 2-butanone. The multigeneration drinking water study by Cox et al. (1975) (see study description in Section 2.16) reported decreased F1A and F2 pup body weights and decreased F1B fetal weights associated with 2-butanol exposure. Mean F1A pup body weights measured on postnatal days (PNDs) 4 and 21 were reduced by 22 and 39%, respectively in the high-dose group (3% 2-butanol in drinking water). Body

weight was reduced by 13% in F2 pups on PND 21 in the high-dose group (2% 2-butanol in drinking water). F1B fetal body weight was reduced by 10% following gestational exposure to 2% 2-butanol. The F1B fetuses in the 2% group also showed increases in skeletal variations (missing sternebrae, wavy ribs, and incomplete vertebrae ossification) when compared with the 1% dose group; however, no difference was observed in comparison to the control group.

2.18 OTHER NONCANCER

No studies were located regarding other systemic effects in humans or animals after inhalation, oral, or dermal exposure to 2-butanone.

2.19 CANCER

Two retrospective studies of industrial workers chronically exposed to 2-butanone in facilities involved in dewaxing lubricating oil reported that deaths due to cancer were less than expected. In a cohort of 446 males employed by Shell Chemical Company, 13 deaths were due to cancer, whereas 14.26 were expected; the standard mortality ratio (SMR) was 0.91 (Alderson and Rattan 1980). In the same cohort, 2 cases of buccal or pharyngeal neoplasms were found; 0.13 were expected to exist, and the SMR was 15.38. There were 4 cases of stomach, colon, or rectal cancer; 3.18 were expected, and the SMR was 1.28. The incidence of buccal or pharyngeal neoplasms was statistically significant, but was regarded by the authors as due to chance because of the small number of individuals affected and the number of separate comparisons made between observed and expected rates. Furthermore, the use of tobacco was not discussed in this study. The incidence of stomach, colon, or rectal cancer was not statistically significant. The authors concluded that there was no clear evidence of a cancer hazard at this dewaxing plant. A retrospective cohort study of 1,008 male oil refinery workers occupationally exposed to an estimated 1–4 ppm of 2-butanone in a dewaxing-lubricating oil plant was also conducted (Wen et al. 1985). The overall cancer-related mortality was less than expected. The increased incidence of buccal and pharyngeal neoplasms reported by Alderson and Rattan (1980) was not confirmed in this study. The decrease in cancer-related mortality from these studies (Alderson and Rattan 1980; Wen et al. 1985) may be due to the “healthy worker effect” because the mortality of workers (a population considered to have a lower overall death rate than the general population) was compared to that of the general population.

An occupational cohort study of >14,000 aircraft maintenance workers from Utah reported a statistically significant elevated rate ratio (RR) for multiple myeloma in females in the baseline study (Spirtas et al.

1991) and an extended follow-up study (Radican et al. 2008), but not the initial follow-up study (Blair et al. 1998). However, the number of 2-butanone-exposed cases in the cohort was very small (n=4; hazard ratio of 4.98 [95% confidence limits 1.24–19.93]).

Two case-control studies evaluated the relationship between 2-butanone exposure and childhood leukemia (Gao et al. 2014; Infante-Rivard et al. 2005). In a case-control study of acute childhood lymphoblastic leukemia diagnosis in Canada (790 cases, 790 controls), case mothers were more often exposed than were control mothers (exposure coding by job title and household exposure); however, the number of cases exposed to 2-butanone was very low (4 versus 0 in controls) (Infante-Rivard et al. 2005). A case-control study of acute childhood leukemia diagnosis in Shanghai (105 cases, 105 controls), demonstrated an elevated odds ratio (OR) for the relationship between measured household 2-butanone exposure and the diagnosis of acute childhood leukemia (OR 3.89, 95% confidence interval 1.55–9.78) (Gao et al. 2014).

No animal studies evaluating the carcinogenicity potential of 2-butanone were located.

EPA (IRIS 2003) concluded that the data are inadequate for an assessment of human carcinogenic potential of 2-butanone.

2.20 GENOTOXICITY

In vivo and *in vitro* studies regarding the genotoxicity of 2-butanone are summarized in Tables 2-4 and 2-5. Genotoxic effects including gene mutation, chromosome aberration, micronucleus frequency, deoxyribonucleic acid (DNA) damage, cell transformation, and unscheduled DNA synthesis were primarily negative. Three studies reported evidence for 2-butanone induction of chromosome effects in yeast, but the findings were inconsistent with other studies evaluating similar endpoints.

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

Species (exposure route)	Endpoint	Results	Reference
Mammals			
Mouse	Micronucleated erythrocytes	–	O'Donoghue et al. 1988
Hamster	Micronucleated erythrocytes	–	Basler 1986

– = negative result

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

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference
Prokaryotic organisms				
Salmonella typhimurium	Gene mutation	–	–	Thorpe 1982
S. typhimurium (TA102)	Gene mutation	–	–	Jung et al. 1992
S. typhimurium	Gene mutation	–	–	O'Donoghue et al. 1988
S. typhimurium (TA97, TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	Zeiger et al. 1992
Escherichia coli	Gene mutation	–	–	Thorpe 1982
Eukaryotic organisms				
Fungi				
Saccharomyces cerevisiae	Gene mutation	–	–	Thorpe 1982
S. cerevisiae	Chromosomal aberrations (malsegregation)	No data	+	Liu et al. 1997
S. cerevisiae (D61.M)	Mitotic chromosome loss	No data	–	Mayer and Groin 1994
S. cerevisiae (D61.M)	Gene mutation or recombination	No data	–	Mayer and Groin 1994
S. cerevisiae	Mitotic chromosome loss	No data	+	Whittaker et al. 1990; Zimmermann et al. 1989
S. cerevisiae	Aneuploidy	No data	+	Mayer and Goin 1987
Mammalian cells				
Rat liver cells (RL_4)	Chromosomal aberrations	No data	–	Thorpe 1982
Rat hepatocytes	Unscheduled DNA synthesis	No data	–	O'Donoghue et al. 1988
BALB/3T3	Morphological transformation	No data	–	O'Donoghue et al. 1988
Mouse lymphoma	Gene mutation	–	–	O'Donoghue et al. 1988
V79 Chinese hamster fibroblasts	Micronucleus frequency	No data	–	Kreja and Seidel 2002
V79 Chinese hamster fibroblasts	DNA damage (comet assay)	No data	–	Kreja and Seidel 2002
A549 cells	DNA damage (comet assay)	No data	–	Kreja and Seidel 2002

+ = positive results; – = negative results; DNA = deoxyribonucleic acid

In vivo, no induction of micronuclei was found in the erythrocytes of mice (O'Donoghue et al. 1988) or hamsters (Basler 1986) after intraperitoneal injection with 2-butanone. 2-Butanone was not mutagenic in bacteria (*Salmonella typhimurium* or *Escherichia coli*), yeast (*Saccharomyces cerevisiae*), or L5178Y mouse lymphoma cells with or without activation (O'Donoghue et al. 1988; Jung et al. 1992; Thorpe 1982; Zeiger et al. 1992). 2-Butanone also did not induce unscheduled DNA synthesis in rat primary hepatocytes, transform BALB/3T3cells, or increase the frequency of chromatid gaps, chromatid breaks, or total chromatid aberrations in rat liver cells (Thorpe 1982). Tests for micronuclei and DNA damage in v79 Chinese hamster fibroblasts or human lung A549 cells were also negative (Kreja and Seidel 2002). 2-Butanone produced mitotic chromosome loss in some (Liu et al. 1997; Whittaker et al. 1990; Zimmermann et al. 1989), but not all (Mayer and Groin 1994) studies. In both cases however, a positive induction of chromosome loss in the yeast cells was enhanced by coexposure to 2-butanone, and ethyl acetate, and propionitrile (Zimmermann et al. 1989), or with 2,5-hexanedione or 2-hexanone (Mayer and Groin 1994). Aneuploidy in *S. cerevisiae* (Mayer and Goin 1987) increased at high concentrations. The positive induction of aneuploidy was enhanced by coexposure to 2-butanone and nocodazole (Mayer and Goin 1987).

No studies were located regarding genotoxic effects in humans or animals after inhalation, oral, or dermal exposure to 2-butanone.

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

3.1 TOXICOKINETICS

Human studies of 2-butanone provide primarily qualitative information on absorption following inhalation exposure and limited quantitative data on urinary excretion kinetics following inhalation. 2-Butanone toxicokinetics have been studied in rats following oral and inhalation exposure. An overview of these data is summarized below.

- 2-Butanone is rapidly absorbed following inhalation and dermal exposure in humans. Experiments in rats indicate that 2-butanone is rapidly absorbed and eliminated after oral administration.
- Distribution has not been extensively studied following *in vivo* exposure; however, *in vitro* determinations of the 2-butanone tissue:air solubility ratios for human kidney, liver, muscle, lung, heart, fat, blood, and brain show similar solubility in all tissues. 2-Butanone did not accumulate in perirenal fat following repeat inhalation exposure in rats.
- Urinary metabolites of 2-butanone in humans include 3-hydroxy-2-butanone and 2,3-butanediol. In guinea pigs, 2-butanone was metabolized by both oxidative and reductive pathways. Oxidation produces 3-hydroxy-2-butanone, which is then reduced to 2,3-butanediol, and 2-butanone reduction produces 2-butanol. The metabolites of 2-butanone in guinea pigs were excreted in the urine as O-glucuronides or O-sulfates. 2-Butanone exposure induces CYP in the liver.
- 2-Butanone is removed rapidly from the blood and is excreted unchanged in expired air and urine. Metabolites of 2-butanone (3-hydroxy-2-butanone and 2,3-butanediol) with or without conjugation are also excreted in urine.

3.1.1 Absorption

2-Butanone is well absorbed during inhalation exposure in humans. Pulmonary uptake ranged from 41 to 56% of the inspired quantity (Liira et al. 1988a, 1988b, 1990a). Exercise increased the pulmonary uptake due to the greater ventilatory rate (Liira et al. 1988b). Several investigators have reported that exposure concentrations of 2-butanone are significantly correlated with blood concentrations in humans (Brown et al. 1986; Brugnone et al. 1983; Ghittori et al. 1987; Liira et al. 1988a, 1988b; Lowry 1987; Miyasaka et al. 1982; Perbellini et al. 1984; Tolos et al. 1987). Exposure of humans to 200 ppm 2-butanone for 4 hours resulted in blood concentrations of 3.5–7.2 μg/mL (Liira et al. 1988a, 1988b; Lowry 1987). In two subjects exposed to 25, 200, and 400 ppm on separate days for 4 hours/day (Liira et al. 1990b), blood levels increased continuously with increasing 2-butanone exposure. The increase in blood concentration

was steeper during exposure for 200 and 400 ppm compared to 25 ppm. Slower elimination from the blood after cessation of exposure was also seen at 400 ppm. These concentration-dependent changes in blood kinetics suggest that metabolic saturation may occur at higher exposure concentrations. Using physiologically based pharmacokinetic (PBPK) model simulations for 8-hour exposures, the investigators estimated that metabolic saturation may be approached at concentrations near 100 ppm at rest and 50 ppm during exercise (Liira et al. 1990b). Occupational concentrations are significantly correlated with blood and urine concentrations of unmetabolized 2-butanone (Brugnone et al. 1983; Ghittori et al. 1987; Miyasaka et al. 1982). Blood levels of 2-butanone are also significantly correlated with breath levels (Brown et al. 1986).

Information on the absorption of 2-butanone by animals after inhalation exposure is limited. Pulmonary and nasal uptake in dogs exposed to 500 ppm 2-butanone for 30 minutes was 25 and 36% of the total inhaled vapor concentration (Dahl et al. 1991). Rats that were exposed to 600 ppm 2-butanone for 6 hours on 1 day or for 6–10 hours/day for 8 days had blood concentrations of 1,041 μmol/L after a single exposure and 1,138 μmol/L after repeated exposure (Liira et al. 1991).

The high blood:air solubility ratio of 2-butanone also favors absorption (Saida et al. 1976; Perbellini et al. 1984). Blood:air partition coefficients determined for humans, rats and dogs ranged from 138 to 208 (Beliveau and Krishnan 2000; Dahl et al. 1991; Fisher et al. 1997; Mahle et al. 2007; Thrall et al. 2002). The human blood:air partition coefficient was 2–4% higher in male and female pediatric subjects compared with adults (Mahle et al. 2007). A similar age-related pattern was observed in rats with a 4–6% higher blood:air coefficient observed in PND 10 males compared with adult and aged male rats.

A woman who had metabolic acidosis after having accidentally ingested 2-butanone stored in a rum bottle had a blood concentration of 95 mg/100 mL (13.2 mM) (Kopelman and Kalfayan 1983). A man who intentionally ingested 100 mL of liquid cement containing a mixture of acetone (18%), 2-butanone (28% or about 37 mg/kg), and cyclohexanone (39%) had a plasma level of 2-butanone of about 110 μg/mL at 5 hours after ingestion (Sakata et al. 1989). These reports provide qualitative evidence that 2-butanone is absorbed following oral exposure in humans, but do not provide information regarding the extent of absorption. In the first case, the quantity ingested was unknown, while in the second case, the man was treated by gastric lavage at 2 hours after ingestion.

Experiments in rats indicate that 2-butanone is rapidly absorbed and eliminated after oral administration. Gavage administration of 1,690 mg/kg 2-butanone in rats resulted in a plasma concentration of

94 mg/100 mL at 4 hours (Dietz and Traiger 1979). Within 18 hours, the plasma concentration decreased to 6.2 mg/100 mL (Dietz and Traiger 1979). A second, similar experiment in rats showed that, after oral administration of 1,690 mg/kg 2-butanone, the plasma concentration was 95 mg/100 mL; the concentration decreased to 7 mg/100 mL by 18 hours (Dietz et al. 1981). The peak exhaled breath concentration of 2-butanone was measured within 1 hour of gavage dosing with 50 mg/kg (Thrall et al. 2002). Concentrations in expired breath decreased slowly over the next 3 hours.

2-Butanone was rapidly absorbed following dermal exposure to the forearm skin of volunteers and was detected in expired breath within 2–3 minutes of exposure (Munies and Wurster 1965; Wurster and Munies 1965). Dermal penetration was enhanced by hydration and was lower when applied to dry skin. In subjects exposed to 200 ppm airborne 2-butanone for 4 hours, dermal absorption contributed approximately 1.2–9.6% (mean of 3.10–3.5%) of absorbed dose (Brooke et al. 1998). A dermal permeability constant (Kp) of 53 g/m^2/hour was reported for 2-butanone across excised human skin (Ursin et al. 1995). Schenk et al. (2018) reported an *in vitro* steady-state flux of 0.00143 g/cm^2/hour (14.3 g/m^2/hour) and permeability coefficient of 0.00175 cm/hour for 2-butanone across pig skin.

3.1.2 Distribution

No studies were located regarding the distribution of 2-butanone following inhalation, oral, or dermal exposure in humans. *In vitro* determinations of the 2-butanone tissue:air solubility ratio for human kidney, liver, muscle, lung, heart, fat, and brain show that the solubility is similar in all tissues, and that the ratio is nearly equal to 200 (Perbellini et al. 1984). Blood:tissue solubility ratios are all near unity; therefore, 2-butanone is not expected to concentrate in any one tissue (Perbellini et al. 1984). In rats, tissue:air partition coefficients were similar for liver, kidney, fat, muscle, and brain (Mahle et al. 2007; Thrall et al. 2002). Tissue:air partition coefficients for muscle and brain were higher in PND 10 male rats compared with adult and aged male rats; however, older rats exhibited higher tissue:air partition coefficients for liver, kidney and fat (Mahle et al. 2007). 2-Butanone has been detected in human breast milk (Giroux et al. (1992).

Information regarding distribution of 2-butanone in animals after inhalation exposure is limited. Rats that were exposed to 600 ppm 2-butanone for 6 hours on 1 day or for 6–10 hours/day for 8 days had perirenal fat concentrations of 0.71 μmol/g after a single exposure and 0.70 μmol/g after repeated exposure. The similarity in fat concentrations after single and repeated intermittent exposure indicates that 2-butanone does not accumulate (Liira et al. 1991). Cosnier et al. (2018a) repeatedly exposed rats to 2-butanone by

inhalation at 20, 200, or 1,400 ppm. Similar blood levels of 2-butanone were observed following a single 6-hour exposure or repeated exposures for up to 1 month. Brain concentrations were only slightly increased by repeated exposures for 1 month.

3.1.3 Metabolism

Few studies exist regarding the metabolism of 2-butanone in humans. Two metabolites of 2-butanone have been identified in human urine after inhalation exposure. They are 3-hydroxy-2-butanone (Brugnone et al. 1983; Perbellini et al. 1984) and 2,3-butanediol (Liira et al. 1988a, 1988b, 1990a). The urinary concentrations of these metabolites, however, represent only about 0.1–2% of the absorbed 2-butanone. 2-Butanol was found in the blood of male volunteers exposed to 200 ppm 2-butanone for 4 hours (Liira et al. 1990a).

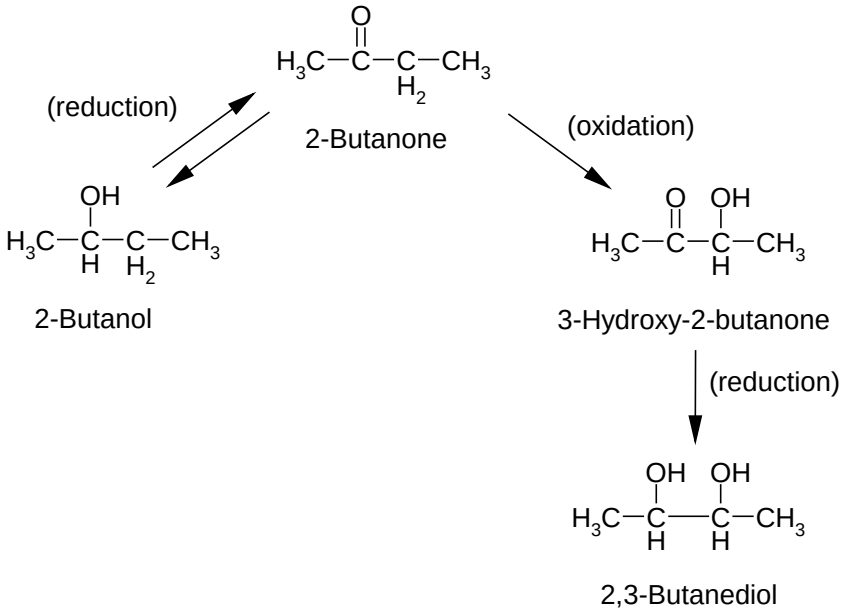
3-Hydroxy-2-butanone, 2,3-butanediol, and 2-butanol have also been found in the blood in guinea pigs (DiVincenzo et al. 1976) and rats (Dietz et al. 1981) exposed to 2-butanone. About 30% of the 2-butanone administered orally in rats was converted to 2,3-butanediol; 4% was converted to 2-butanol, and 4% was converted to 3-hydroxy-2-butanone (Dietz et al. 1981).

In guinea pigs, 2-butanone was metabolized by both oxidative and reductive pathways (Figure 3-1). Oxidation produces 3-hydroxy-2-butanone, which is then reduced to 2,3-butanediol (DiVincenzo et al. 1976). Reduction of 2-butanone produces 2-butanol. The metabolites of 2-butanone in guinea pigs were excreted in the urine as O-glucuronides or O-sulfates (DiVincenzo et al. 1976). Cosnier et al. (2018a) detected 2-butanone, 2-butanol, and 3-hydroxy-2-butanone in rat urine, but only at 2-butanone inhalation levels resulting in metabolic saturation. Thrall et al. (2002) demonstrated that 2-butanone metabolism in rats is not completely eliminated by inhibition of the oxidative pathway using pyrazole.

Several studies have shown that 2-butanone has the ability to induce microsomal liver enzymes. Acute oral treatment of rats with 2-butanone at doses of 1,080–1,500 mg/kg/day for 1–7 days resulted in increased levels of CYP protein, increased activities of CYP-dependent monooxygenases (Brady et al. 1989; Raunio et al. 1990; Robertson et al. 1989; Traiger et al. 1989), and proliferation of the smooth endoplasmic reticulum (Traiger et al. 1989). 2-Butanone also induced specific CYP isozymes in rat liver (CYP2B1 and CYP2B2) following daily intraperitoneal injections of 5 mmol/kg for 4 days (Imaoka and Funae 1991). Induction of microsomal enzymes did not occur in rats exposed to 2-butanone by inhalation. After exposure of rats to 800 ppm 2-butanone for 5 weeks (Toftgard et al. 1981) or 600 ppm

n-butanone for 8 days (Liira et al. 1991), no changes were observed in the content of hepatic CYP or in the CYP isozyme profile. However, Cosnier et al. (2018a) exposed rats to 2-butanone by inhalation and reported the exposure-related induction of both CYP1A2 and CYP2E1 enzymes, although total hepatic P450 enzyme concentration was not altered. Furthermore, exposure to 2-butanone at 1,400 ppm resulted in decreased hepatic glutathione concentration and glutathione S-transferase activity.

Figure 3-1. Proposed Metabolic Pathways for 2-Butanone



Source: DiVincenzo et al. 1976

3.1.4 Excretion

Urinary excretion of unchanged 2-butanone and its metabolites, 3-hydroxy-2-butanone and 2,3-butanediol, accounts for only 5% or less of the 2-butanone absorbed by inhalation in humans (Kawai et al. 2003; Liira et al. 1988a, 1990a; Perbellini et al. 1984) and rats (Cosnier et al. 2018a). Unchanged 2-butanone is excreted primarily through the lungs; the quantity eliminated by this route is an estimated 20–40% (Browning 1965; Riihimaki 1986); however, only about 3% of absorbed 2-butanone was excreted unchanged in the expired air of humans exposed to 200 ppm for 4 hours (Liira et al. 1988a, 1990a). 2-Butanone is rapidly cleared from the blood with a reported plasma half-life in humans of 49–96 minutes (Brown et al. 1986; Liira et al. 1988a; Lowry 1987) and an apparent clearance rate of 0.60 L/minute (Liira et al. 1990a). Therefore, 2-butanone would not be expected to accumulate with chronic exposure (Lowry 1987). Tomicic et al. (2011) measured urinary 2-butanone concentrations

before during and after a 6-hour exposure to 100 ppm 2-butanone. The urinary 2-butanone concentration was highest immediately following exposure and returned to pre-exposure levels by 6 hours after the cessation of exposure (urinary half-life was not determined). 2-Butanone concentrations were highest in women without hormonal contraceptives compared to women with hormonal contraceptives and men, suggesting an influence of sex hormones on 2-butanone metabolism.

Information regarding the excretion of 2-butanone after oral exposure in humans is limited. A man who intentionally ingested 100 mL of liquid cement containing a mixture of acetone (18%), 2-butanone (28% or about 37 mg/kg), and cyclohexanone (39%) had a plasma level of 2-butanone of about 110 µg/mL at 5 hours after exposure (Sakata et al. 1989). The plasma level declined to about 95 µg/mL at 12 hours and to <20 µg/mL at 18 hours, where it remained until about 25 hours and slowly declined to <5 µg/mL at 48 hours. Urine levels of 2-butanone decreased gradually from 123 µg/mL at 5 hours to 61 µg/mL at 19 hours. Disappearance from the urine then became more rapid with about 10 µg/mL excreted at 48 hours. While this study provided information on the elimination of 2-butanone from plasma and urine of a human orally exposed, coexposure to the other components of the cement could have influenced the elimination.

No studies were located regarding the rate or extent of excretion of 2-butanone in animals following inhalation or oral exposure.

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.

Several PBPK models of 2-butanone have been reported. These include human models simulating 2-butanone kinetics following inhalation exposure (Liira 1990b; Jongeneelen et al. 2013; Tomicic and Vernez 2014) and rat models using data from multiple exposure routes (Dietz et al. 1981; Thrall et al.

2002). Risk assessment applications of these models are limited by the small number of data sets available for testing and model calibration.

Liira et al. (1990b)

Liira et al. (1990b) developed a PBPK model using blood concentration data for two male subjects exposed to 25, 100, or 200 ppm 2-butanone for 4 hours. Blood samples were collected during exposure and for 8 hours after exposure. The pulmonary ventilation rate of the subjects was measured at rest and during exercise. 2-Butanone metabolism was assumed to occur in the liver only and followed Michaelis-Menten kinetics. The K_m (2 μM) and V_{max} (30 μmol/minute) were calculated from the best fit of the simulated blood concentrations. 2-Butanone was detected in blood (0.2–0.3 μM) prior to exposure suggesting some endogenous formation of this compound. This was treated as a continuous inhalation exposure in the PBPK model (1.25 ppm).

The elimination of 2-butanone from blood is slower at higher exposure concentrations, which is suggestive of metabolic saturation. The PBPK model was used to simulate blood concentrations for an 8-hour continuous exposure at rest and during exercise. Metabolic saturation was estimated to occur at 2-butanone concentrations of 100 ppm at rest and 50 ppm during exercise.

Tomicic and Vernez (2014); Jongeneelen et al. (2013)

Tomicic and Vernez (2014) and Jongeneelen et al. (2013) both utilized a generic PBPK model to evaluate human urinary biomarker data for 2-butanone obtained from volunteers exposed to 100 ppm for 6 hours (Tomicic et al. 2011). Tominic and Vernez (2014) used an inhalation model that describes absorption from air into a central compartment (representing the total body water) and distribution between the central compartment and a peripheral or storage compartment (representing fatty tissues). Absorption into the central compartment was calculated as a product of the mass concentration in air, the alveolar ventilation rate scaled to body weight, and the fraction absorbed by the lung (pulmonary retention of 0.56 from Liira et al. 1988a). Metabolism is described by Michaelis-Menten kinetics (K_m 45 mg/L and V_{max} 22 mg/(hour*$kg^{0.75}$) from Thrall et al. 2002) and elimination is represented by metabolism and excretion in expired air or urine.

The sensitivity analysis, obtained by increasing each toxicokinetic parameter of the PBPK model by 10% indicated that the urinary 2-butanone concentration was especially sensitive to metabolism parameters

(K_m and V_{max}), cardiac output, and liver blood flow. A comparison of experimental data and model simulations showed adequate goodness of fit during the 6 hours exposure with poorer fit during the urinary elimination phase. Predictive simulations done for a work week (8 hours/day, 5 days at the Threshold Limit Value [TLV] concentration of 200 ppm) showed an overestimation of urinary 2-butanone concentration for women without hormonal contraceptives compared to women with hormonal contraceptives and men.

Jongeneelen et al. (2013) used a generic model with 11 body compartments (lung, heart, brain, skin, adipose tissues, muscles, bone, bone marrow, stomach and intestines, liver, and kidney). This model used Michaelis-Menten kinetic constants for liver metabolism of 2-butanone (K_m 4 μmol/L, V_{max} 1,800 μmol/kg tissue/hour) and liver metabolism of 2,3-butanediol (K_m 50 μmol/L, V_{max} 300 μmol/kg tissue/hour). Model simulations for women were similar to the experimental data for women volunteers from the Tomicic et al. (2011) study. The model predicted higher urinary 2-butanone concentrations in men compared with experimental data.

Dietz et al. (1981)

A flow-limited PBPK model was used to describe blood concentrations of 2-butanol, 2-butanone, 3-hydroxy-2-butanone, and 2,3-butanediol in Sprague-Dawley rats after gavage administration of 2-butanol (1,776 mg/kg) or 2-butanone (1,776 mg/kg) or intravenous injection of 3-hydroxy-2-butanone (400 mg/kg) and 2,3-butanediol (800 mg/kg) were administered by intravenous injection. The model assumed distribution to liver and body water (including blood) and metabolism in liver only. Michaelis-Menten kinetics were used to describe metabolism, and rate constants for each metabolite were estimated by curve fitting of the experimental blood concentration data. The model was adjusted to account for the lower than expected concentration of 3-hydroxy-2-butanone in blood suggested to result from partitioning, binding, or decreased transport from the liver. The competitive inhibition of 2-butanone oxidation by 2-butanol was also accounted for. Model adjustments were shown to improve the fit of the simulation compared with the experimental data used to derive the model.

Thrall et al. (2002)

The PBPK model developed by Thrall et al. (2002) consisted of four tissue compartments (fat, liver, rapidly perfused tissues, and slowly perfused tissues) and a description of the exchange of 2-butanone between lung blood and alveolar air. Pulmonary uptake of 2-butanone was evaluated in Fisher 344 rats

exposed to concentrations ranging from 100 to 2,000 ppm. Exhaled breath concentration were considered a surrogate measure of blood concentration. Michaelis-Menten metabolic rate constants were obtained by model simulation of the gas uptake data (best fit values of K_m 0.63 mg/L, V_{max} 5.44 mg/hour/kg). The PBPK model was calibrated using experimental data for expired breath concentrations in rats exposed by intravenous injection (25 mg/kg), intraperitoneal injection (50 mg/kg), and gavage (50 mg/kg). Rate constants calculated for oral and intraperitoneal absorption were 1.9 and 0.91 $hours^{-1}$, respectively.

3.1.6 Animal-to-Human Extrapolations

The toxicokinetics of 2-butanone in humans are similar to those that have been observed in rats and guinea pigs. Metabolites of both oxidation and reduction reactions are found in all species.

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

The human blood:air partition coefficient was 2–4% higher in male and female pediatric subjects compared with adults and a similar age-related pattern was observed in rats, with a 4–6% higher blood:air coefficient observed in PND 10 males compared with adult and aged male rats (Mahle et al. 2007). These data suggest that pulmonary uptake following inhalation may be slightly higher in children compared to adults. Tomicic et al. (2011) suggested that individuals with a genetic polymorphism in the gene for

CYP2E1 (mutant allele CYP2E1*6) may exhibit enhanced oxidative metabolism of 2-butanone; however, the findings were limited by the small number of study participants (n=25). Experimental animal studies suggest that inhalation exposure to 2-butanone during pregnancy may lead to developmental effects; however, these effects were only seen at very high concentrations (>2,000 ppm).

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-butanone 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-butanone 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-butanone 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

Inhalation exposure to 2-butanone correlates well with blood, breath, and urinary concentrations of unchanged 2-butanone (Brown et al. 1986; Brugnone et al. 1983; Ghittori et al. 1987; Kawai et al. 2003; Miyasaka et al. 1982; Sia et al. 1991). Personal dosimetry was used to measure exposure to 2-butanone among 27 furniture makers (Kawai et al. 2003), 50 magnetic videotape factory workers (Sia et al. 1991), 62 printing plant workers (Miyasaka et al. 1982), 72 printing plant workers (Yoshikawa et al. 1995), and 659 workers in plastic boat, chemical, plastic button, paint, and shoe factories (Ghittori et al. 1987). The correlation between exposure levels and urinary concentration of unchanged 2-butanone was strong in each study (r values ranging from 0.774 to 0.889). Miyasaka et al. (1982) concluded, however, that estimating exposure from urinary levels was reliable on a group basis, but not an individual basis. In a study of eight aircraft maintenance workers, Lemasters et al. (1999) suggested that breath measurements were more sensitive than urine and blood measurements following low-level exposure to 2-butanone (<20 ppm).

A significant correlation between workroom and urinary 2-butanone concentrations was observed in shoe factory workers ($r=0.6877$, $p<0.001$) (Brugnone et al. 1983). In the same study, a more significant correlation was observed between workroom concentrations and a 2-butanone urinary metabolite, 3-hydroxy-2-butanone ($r=0.8179$, $p<0.001$). Another 2-butanone metabolite, 2,3-butanediol, has also been identified in the urine of humans (Liira et al. 1988a, 1988b); however, no studies have examined the correlation between exposure to 2-butanone and urinary levels of this metabolite. A third metabolite, 2-butanol, was identified in guinea pig blood; however, no attempt was made to correlate 2-butanol blood levels with exposure to 2-butanone (DiVincenzo et al. 1976). Metabolism of alcohols, hydrocarbons, and other ketones may also yield 2-butanone, 3-hydroxy-2-butanone, and 2,3-butanediol (Dietz and Traiger 1979; Tsukamoto et al. 1985); therefore, these compounds may confound assessment of exposure to 2-butanone. The urinary concentration of 2-butanone measured immediately after a 6-hour exposure to 100 ppm 2-butanone was similar in women using hormonal contraceptives and men of similar age, but was higher in women not using hormonal contraceptives (Tomicic et al. 2011). This finding suggests that the presence of sex hormones may increase 2-butanone metabolism by CYP2E1; however, interpretation of study findings is limited by the small number of study participants (n=25). Creatinine adjustment of

this exposure biomarker was not necessary due to the passive process of elimination by the kidney (i.e., dependent on urine flow rate only).

Blood and breath levels of 2-butanone were significantly correlated ($r=0.78$, $p<0.001$) in volunteers exposed to 200 ppm 2-butanone for 4 hours (Brown et al. 1986). Measurements of tissue, blood, and excreta levels may not be an accurate indication of past exposure to 2-butanone. Accumulation in target tissues does not occur because tissue/blood solubility ratios are all near unity; therefore, 2-butanone will not concentrate in specific tissues (Perbellini et al. 1984). The serum half-life of 2-butanone in humans is very short; estimates range from 49 to 96 minutes (Liira et al. 1988a; Lowry 1987). Furthermore, 2-butanone was not detectable in blood or breath measurements reported the morning after a 4-hour exposure to 200 ppm (Brown et al. 1987).

2-Butanone is endogenously produced during the catabolism of isoleucine and is considered a normal constituent of urine (Tsao and Pfeiffer 1957). A study of National Health and Nutrition Examination Survey (NHANES) participants found an association between daily consumption of >20 mL alcohol and blood 2-butanone levels (Churchill et al. 2001).

3.3.2 Biomarkers of Effect

2-Butanone induces hepatic microsomal enzymes in rats after oral exposure (Brady et al. 1989; Raunio et al. 1990; Robertson et al. 1989; Traiger et al. 1989), but this enzyme induction has not been associated with more severe liver effects. No other subtle biochemical effects of 2-butanone have been identified that would be useful as biomarkers to characterize effects of 2-butanone.

3.4 INTERACTIONS WITH OTHER CHEMICALS

The neurological and hepatic effects of 2-butanone alone are minimal (Altenkirch et al. 1978; Saida et al. 1976). This compound, however, is frequently mixed with other chemicals such as n-hexane or methyl-n-butyl ketone for various commercial and industrial applications, which can then lead to serious toxic effects. Exposure to mixed solvents is most likely to occur in occupational settings or at a hazardous waste site. Clinical reports, animal studies, and some *in vitro* tests have shown that 2-butanone potentiates or enhances the neurotoxicity of ethanol, n-hexane, and methyl-n-butyl ketone, ethyl-n-butyl ketone, and toluene; the hepatotoxicity of carbon tetrachloride, chloroform, n-hexane, and

dimethylformamide; and the renal toxicity of methanol, and chloroform. These studies emphasize the potential public health hazard of mixed solvent exposure including 2-butanone.

Interactions Potentially Influencing Neurotoxicity. Based on several case studies and clinical case reports, there is some evidence to suggest an interaction between 2-butanone and n-hexane and 2-butanone and methyl-n-butyl ketone, which potentiates neurotoxic effects. Altenkirch et al. (1977) investigated a large outbreak of toxic polyneuropathies in a group of West Berlin "glue sniffers." Until the fall of 1975, the major constituents of the glue were n-hexane, toluene, ethyl acetate, and benzene. The development of neuropathies (muscular atrophy, paresthesia, paresis, quadriplegia) coincided with the addition of 2-butanone to the mixture. Similar outcomes were described in a clinical case report of three men exhibiting “glue sniffing neuropathy” following the addition of 2-butanone to the glue formulation (King et al. 1985), and also in workers from a coated fabrics plant who exhibited peripheral nephropathy when a methyl-n-butyl ketone solvent was introduced that contained high concentrations of 2-butanone (Allen et al. 1975; Billmaier et al. 1974). In another case, a 39-year-old woman who had worked for several years gluing shoes using a glue containing 20% 2-butanone and 8% n-hexane, developed polyneuropathy after a few weeks of work in a poorly ventilated shop (Vallat et al. 1981).

Laboratory animal studies demonstrated 2-butanone potentiation of n-hexane, methyl-n-butyl ketone, and ethyl-n-butyl ketone neurotoxicity (Altenkirch et al. 1978, 1982; O'Donoghue et al. 1984; Saida et al. 1976; Schmidt et al. 1984). A study exposing rats to either 10,000 ppm n-hexane or a combination of 1,000 ppm 2-butanone and 9,000 ppm n-hexane reported that the co-exposed animals developed paresis more rapidly and in greater numbers than rats exposed to n-hexane only (Altenkirch et al. 1978). In the same study, rats exposed to 6,000 ppm 2-butanone alone showed no signs of neurotoxicity up to 7 weeks, when all of the rats in this group died suddenly of bronchopneumonia. These results were confirmed in a second study; mixtures of 500 ppm n-hexane and 2-butanone (4:1 or 3:2) or 700 ppm (5:2) caused clinical signs of neuropathy 1–5 weeks earlier than 500 ppm n-hexane alone (Altenkirch et al. 1982). Histological examination revealed morphological changes in the rats similar to those found in youths suffering from glue sniffing neuropathy, including paranodal axon swelling, accumulation of neurofilaments in the cytoplasm, and demyelination. Takeuchi et al. (1983) observed a significant decrease in motor nerve and mixed nerve conduction velocity in rats exposed to 300 ppm n-hexane:2-butanone (1:2) compared with rats exposed to 200 ppm 2-butanone alone or 100 ppm n-hexane alone (measured after 20 and 24 weeks of exposure). Finally, male Wistar rats exposed to n-hexane or a combination of n-hexane and 2-butanone developed ultrastructural changes in the intrapulmonary nerves characteristic of hexacarbon neurotoxicity (Schmidt et al. 1984).

A marked potentiation of peripheral neurotoxicity was reported when rats were exposed to methyl-n-butyl ketone:2-butanone (225:1,125 ppm) (Saida et al. 1976). Rats exposed to methyl-n-butyl ketone alone developed paralysis by 66 days. The combination caused paralysis in 25 days, while 2-butanone alone had no effect up to 5 months. Histological examination of neurons revealed morphological changes similar to those reported by Altenkirch et al. (1982), which included paranodal axon swelling, accumulation of neurofilaments, and demyelination. Subcutaneous injection of methyl-n-butyl ketone alone increased distal motor latency and decreased motor fiber conduction velocity in male Donryu strain rats; these effects were enhanced with concomitant exposure to 2-butanone (Misumi and Nagano 1985). Oral administration of ethyl-n-butyl ketone in rats for several weeks caused paranodal axon swelling and neurofilamentous hyperplasia characteristic of n-hexane and methyl-n-butyl ketone neurotoxicity (O'Donoghue et al. 1984). Oral administration of 2-butanone potentiated the development of clinical and histological signs of ethyl-n-butyl ketone neurotoxicity.

In vitro studies support the hypothesis that 2-butanone potentiates both n-hexane and methyl-n-butyl ketone neurotoxicity. Veronesi et al. (1984) observed that, in tissues cultured from fetal mouse spinal cord, dorsal root ganglia, and muscle, the combination of 2-butanone and n-hexane produced giant axonal swellings more rapidly than cultures treated with n-hexane alone. Furthermore, cultures exposed to nontoxic concentrations of n-hexane also developed giant axonal swellings when 2-butanone was administered concomitantly.

The precise mechanisms behind 2-butanone potentiation of n-hexane and methyl-n-butyl ketone neurotoxicity remain unclear; however, several studies suggest that 2-butanone alters the metabolism and elimination kinetics of these compounds. Biotransformation of n-hexane, methyl-n-butyl ketone, and ethyl-n-butylketone can produce the neurotoxic metabolite, 2,5-hexanedione (2,5-HD) (Couri et al. 1978; DiVincenzo et al. 1976; Robertson et al. 1989). The concentrations of the n-hexane metabolites, 2,5-HD and 2,5-dimethylfuran, were significantly higher in the blood and sciatic nerves of rats pretreated by gavage with 2-butanone before inhalation exposure to n-hexane, compared to concentrations in rats exposed to n-hexane alone (Robertson et al. 1989). Shibata et al. (1990a, 1990b) observed changes in urine n-hexane metabolite profiles in rats co-exposed to 2-butanone for 8 hours, indicating an overall decrease in both the production and clearance of 2,5-HD. Similar urine metabolite changes were seen in a controlled, acute 2-butanone/n-hexane co-exposure inhalation study in four human subjects (Shibata et al. 2002). In other acute single-dose studies in laboratory animals, concomitant oral administration of 2-butanone and 2,5-HD in rats reduced blood 2,5-HD clearance (Ralston et al. 1985). In Wistar rats co-

exposed interperitoneally to 2,5-HD and 2-butanone, reductions in of 2,5-HD clearance was observed in all tissues examined including serum, urine, and sciatic nerve tissue (Aoki et al. 1996; Yasui et al. 1995; Zhao et al. 1998a, 1998b). Concomitant inhalation exposure to ethyl-n-butyl ketone and 2-butanone (700:700 ppm) for 4 consecutive days caused a 2.6-fold increase in the serum concentration of 2,5-heptanedione, which can be further metabolized to 2,5-HD (O'Donoghue et al. 1984). A metabolic study *in vitro* was done to evaluate the effect of 2-butanone on n-hexane metabolism in rat liver S9 fractions using a head-space vial equilibration technique (Mortensen et al. 1998). Liver S9 fractions were isolated from rats orally exposed (pretreated) *in vivo* to a vehicle control or to 2-butanone. S9 fractions where then exposed in closed test tubes to either *n*-hexane vapors alone or to an n-hexane:2-butanone mixture. Consistent with metabolism studies done *in vivo*, the total amount of n-hexane metabolized from the head space was higher in 2-butanone pretreated liver S9 fractions than in untreated fractions, and the levels of the n-hexane metabolite, 2,5-HD, was approximately 3.5 times higher. 2,5-HD levels increased further with increasing concentrations of 2-butanone vapors added *in vitro* (Mortensen et al. 1998).

The impact of reduced 2,5-HD clearance on neurotoxicity becomes more evident in longer studies. A 20-week subchronic inhalation study in rats exposed to n-hexane and 2-butanone reported a biphasic response, and an initial decrease in 2,5-HD concentrations in urine, similar to the observations from acute studies, was followed by an overall increase in 2,5-HD over time (Ichihara et al. 1998). The rise in 2,5-HD coincided with decreased motor nerve velocity and increased distal latency of the tail nerve, measures of n-hexane neurotoxicity (Ichihara et al. 1998). Collectively, these studies indicate that the potentiating effects of 2-butantone on n-hexane, methyl-n-butyl ketone, and ethyl-n-butyl ketone neurotoxicity may be mediated by increased persistence of the 2,5-HD metabolite.

2-Butanone has also been found to potentiate the neurotoxicity of ethanol (Cunningham et al. 1989). Mice pretreated intraperitoneally with 2-butanone followed by intraperitoneal injection of ethanol 30 minutes later showed prolonged loss of righting reflex induced by ethanol. 2-Butanone decreased the rate of ethanol elimination in mice *in vivo* and inhibited the *in vitro* activity of alcohol dehydrogenase, the primary mechanism for ethanol elimination. These results suggest that 2-butanone may potentiate the neurotoxicity of ethanol by inhibiting its metabolism by alcohol dehydrogenase.

Cosnier et al. (2014) reported significant increases in blood toluene levels at both 1 and 5 days after exposure by inhalation to binary mixtures of toluene and 2-butanone, compared to those exposed to toluene alone. Cosnier et al. (2018b) found that toluene inhibited 2-butanone metabolism and that

2-butanone inhibited toluene metabolism in rats exposed by inhalation to both substances. However, the studies of Cosnier and coworkers did not include evaluation of neurological endpoints.

Interactions Potentially Influencing Liver Toxicity. 2-Butanone alone is not highly hepatotoxic but has a well-documented role in potentiating haloalkane-induced hepatotoxicity (Brown and Hewitt 1984; Dietz and Traiger 1979; Hewitt et al. 1983, 1986, 1987; Tanii et al. 1986). Intraperitoneal injection of chloroform (0.5 mL/kg) alone caused a 9-fold increase in rat ALT activity (Brown and Hewitt 1984). In contrast, chloroform injection caused a 195-fold increase in rat ALT activity if administered 18 hours after oral administration of 2-butanone. Similarly, intraperitoneal injection of chloroform increased rat plasma ornithine carbamyl transferase activity 215-fold if given 18 hours after oral administration of 2-butanone (Hewitt et al. 1983). The severity of hepatotoxicity appears to be dependent on dose and the length of time between 2-butanone pretreatment and subsequence chloroform exposure (Hewitt et al. 1987). 2-Butanone also potentiates carbon tetrachloride-induced hepatotoxicity in the rat (Dietz and Traiger 1979; Raymond and Plaa 1995a; Traiger et al. 1989). Significant increases in rat plasma ALT activity and hepatic triglyceride content, both suggestive of liver damage, were observed following the administration of 2-butanone either for 16 hours (Traiger et al. 1989) or for a duration of 3 days (Raymond and Plaa 1995a) before intraperitoneal injection of carbon tetrachloride. An *in vitro* study by Kim et al. (2014) suggests a possible interaction between 2-butanone and dimethylformamide (DMF) in HepG2 cells. Additional studies will be needed to determine what effect this interaction, if any, will have on DMF-mediated liver toxicity *in vivo*.

The potentiation of liver toxicity by ketones like 2-butanone is thought to be due to CYP induction. The maximal potentiation of carbon tetrachloride-induced hepatic injury by pretreatment with 2-butanone coincided with increased microsomal enzyme activity within the same time frame following exposure to 2-butanone alone (Traiger et al. 1989). This strongly suggests that 2-butanone potentiates the hepatotoxicity of carbon tetrachloride by enhancing its metabolism to toxic intermediates. Liver microsomes extracted from rats pretreated with 2-butanone, however, did not have increased CYP content compared with controls (Raymond and Plaa 1995b). Additionally, the mechanism of 2-butanone potentiation of chloroform-induced hepatotoxicity apparently does not involve biotransformation of chloroform to a reactive intermediate, an alteration of the CYP system, or depletion of liver glutathione (Hewitt et al. 1987). To explore other possibilities, Raymond and Plaa (1996) tested whether 2-butantone altered the adverse impacts of carbon tetrachloride treatment on liver membrane integrity. Purified liver membranes from controls or rats pretreated with 2-butanone were monitored for membrane fluidity and measured for membrane enzymes including 5’-nucleotidase, leucine aminopeptidase, and alkaline

phosphatase (Raymond and Plaa 1996). 2-Butanone had no significant impact on the membrane integrity status influenced by carbon tetrachloride; therefore, increased membrane sensitivity is not likely a mechanism contributing to 2-butanone potentiation of carbon tetrachloride hepatotoxicity.

Another hypothesis is that the observed 2-butanone potentiation of chloroform and carbon tetrachloride hepatotoxicity may be related to biotransformation of the 2-butanone to its metabolite, 2,3-butanediol. Carbon tetrachloride increased rat ALT 164-fold when injected 16 hours after oral administration of 2,3-butanediol. Replacement of 2,3-butanediol with 2-butanone increased the transaminase 66-fold. Hepatic triglyceride content was potentiated to a similar degree by both 2-butanone and 2,3-butanediol (Traiger et al. 1989).

Interactions Potentially Influencing Kidney Toxicity. Few studies have evaluated the impact of 2-butanone interactions on kidney toxicity. In a case-report, a 42-year-old male who ingested a cleaning solution that contained methanol and 2-butanone became tachycardic, with a hyperosmolar coma without anion gap metabolic acidosis. The study authors suggested that the osmolar gap, in the absence of metabolic acidosis, could be due to 2-butanone inhibition of methanol metabolism (Price et al. 1994).

Kidney toxicity, assessed by a decreased accumulation of *p*-aminohippuric acid in renal cortical slices in rats exposed to chloroform, was potentiated in rats that were pretreated with 2-butanone for 3 days prior to chloroform exposure (Raymond and Plaa 1995a). Unlike in the liver, total CYP content and aniline hydroxylase levels were increased in kidney microsomes extracted from rats pretreated with 2-butanone, compared to controls. These data suggest a role for CYP induction in the potentiation of chloroform kidney toxicity by 2-butanone (Raymond and Plaa 1995b).

Interactions Potentially Influencing Other Toxicity. Pretreatment of ddY mice with carbon tetrachloride 24 hours before oral administration of 2-butanone reduced the 2-butanone LD_{50} about 20% (Tanii et al. 1986). The mechanism of this effect was not investigated.

Exposure of pregnant rats continuously to n-hexane alone (1,000–1,500 ppm) or n-hexane and 2-butanone (1,200 ppm n-hexane, 300 ppm 2-butanone) throughout gestation and/or during the postnatal period resulted in reduced birth weight of pups, and weight gain reduction persisted during the postnatal exposure period (Stoltenburg-Didinger et al. 1990). The effect was more pronounced with the mixture of solvents. In addition, hindlimb weakness in one dam during the gestational exposure period progressing

to quadriplegia in all dams during the postpartum exposure period was observed with the solvent mixture, while only hindlimb weakness was observed in the dams exposed to n-hexane alone.

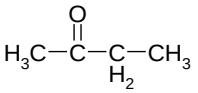
Coexposure of *S. cerevisiae* to 2-butanone, ethyl acetate, and propionitrile enhanced the induction of chromosome loss caused by 2-butanone (Zimmermann et al. 1989). Coexposure of *S. cerevisiae* to 2-butanone and nocodazole enhanced the induction of aneuploidy caused by 2-butanone alone (Mayer and Goin 1987).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of 2-butanone are listed in Table 4-1.

Table 4-1. Chemical Identity of 2-Butanone

Characteristic	Information	Reference
Chemical name	2-Butanone	CAS 1989
Synonym(s) and registered trade name(s)	Methyl ethyl ketone; MEK; ethyl methyl ketone; methyl acetone; and others; Meetco	CAS 1989; SANSS 1989; Chemline 1989; OHM/TADS 1989
Chemical formula	C_4H_8O	CAS 1989
Chemical structure		
CAS Registry Number	78-93-3	CAS 1989

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of 2-butanone are presented in Table 4-2.

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

Property	Information	Reference
Molecular weight	72.11	Weast et al. 1988
Color	Colorless	Sax and Lewis 1987
Physical state	Liquid	Sax and Lewis 1987
Melting point	-86.3°C	Weast et al. 1988
Boiling point	79.6°C	Weast et al. 1988
Density (liquid) at 20°C	0.8054	Weast et al. 1988
Odor	Acetone-like	Sax and Lewis 1987
Odor threshold:		
Water	8.4 ppm	Amoore and Hautala 1983
Air	5.4 ppm	Amoore and Hautala 1983

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

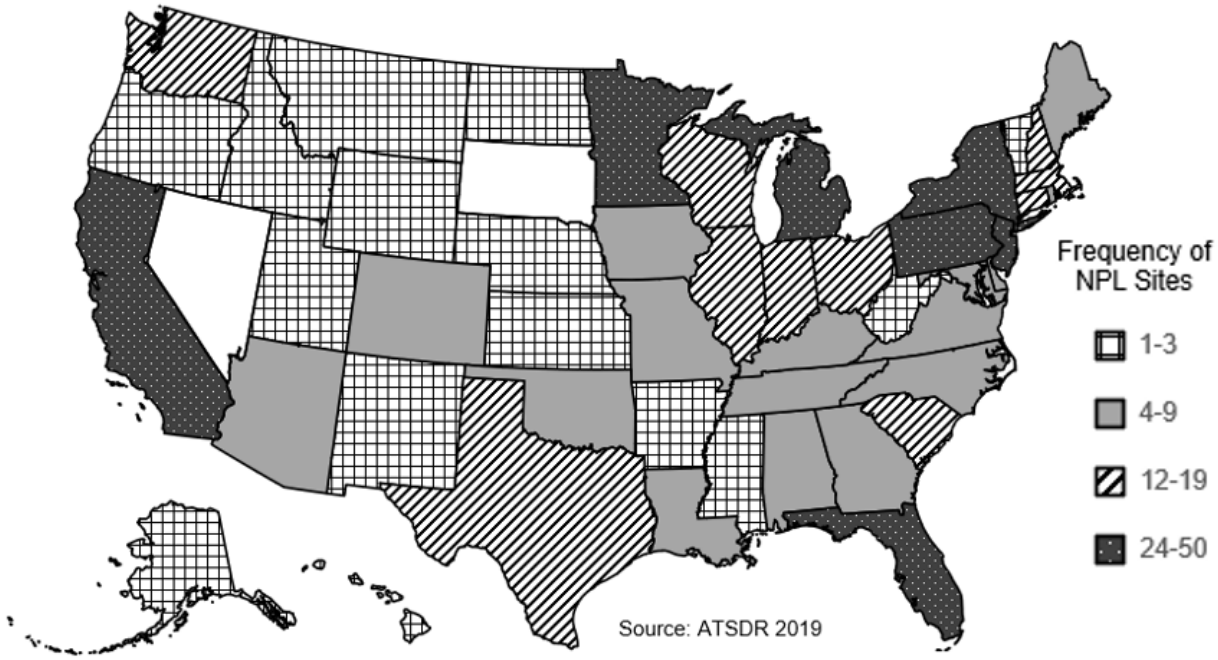
Property	Information	Reference
Solubility:		
Water at 25°C	136,000 mg/L	Tewari et al. 1982
Organic solvents	Benzene, alcohol, ether, oils, most organic solvents	Sax and Lewis 1987; Neier and Strehlke 1985
Partition coefficients:		
Log K_{ow}	0.29	Hansch et al. 1995
Log K_{oc}	0.55	Roy and Griffin 1985
Vapor pressure at 25°C	90.6 mmHg	Riddick et al. 1986
Henry's law constant at 25°C	5.77×10^{-5} atm m^3/mol	Rathbun and Tai 1987
Autoignition temperature	515°C	Sax and Lewis 1987
Flashpoint:		
Closed cup	-2°C	Riddick et al. 1986
Open cup	1°C	Riddick et al. 1986
Flammability limits in air	2–10%	Sax and Lewis 1987
Conversion factors:		
ppm (v/v) to mg/m^3 in air (20°C)	1 ppm=2.95 mg/m^3	
mg/m^3 to ppm (v/v) in air (20°C)	1 mg/m^3=0.339 ppm	
Bioconcentration factor	0.98 (calculated from K_{ow})	Lyman et al. 1982
Explosive limits	1.4–11.4% at 200°F	NIOSH 2019

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

2-Butanone has been identified in at least 526 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which 2-butanone has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 523 are located within the United States and 3 are located in Puerto Rico (not shown).

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



- The most likely routes of 2-butanone exposure for the general public include ingestion of food, ingestion of contaminated drinking water, inhalation during household use of coating products, and dermal contact during the use of these products. High levels of occupational exposure to 2-butanone may occur by inhalation and dermal contact during the loading and unloading of large quantities of commercial coating materials during shipment. The application of commercial coatings containing 2-butanone without adequate protection may also lead to high levels of exposure, primarily by inhalation.

- 2-Butanone is detected in environmental media, although usually at low levels. 2-Butanone is expected to rapidly volatilize from surface water and moist or dry soils and exists as a vapor in the atmosphere. 2-Butanone displays a high mobility in soil and leaches readily into groundwater. 2-Butanone does not adsorb strongly to soils and sediments or bioconcentrate in aquatic organisms.

- 2-Butanone undergoes degradation in the atmosphere although the mechanisms responsible for this process are not known. Biodegradation is expected to occur in soil and water under both aerobic and anaerobic conditions.

2-Butanone may be released to the atmosphere in fugitive emissions during its production, transport, and use. In urban areas, it can exist in the atmosphere as a result of automobile exhaust, the decomposition of other organic compounds, and from natural sources.

The release of 2-butanone to water or soil is not well documented. Release of 2-butanone to surface water may occur via industrial wastewater emissions. 2-Butanone may also be released to soil or water from a spill or other catastrophic event. The leachate of landfills and hazardous waste sites may result in 2-butanone contamination of soil and groundwater.

2-Butanone is expected to rapidly volatilize from surface water and moist or dry soils to the atmosphere. In the atmosphere, this compound is expected to exist predominantly in the vapor phase. Wet deposition may return 2-butanone to the earth's surface.

In soil, 2-butanone is expected to display very high mobility, and it has the potential to leach into groundwater. This characteristic also suggests that it does not significantly adsorb to sediment and suspended organic matter in surface waters. 2-Butanone is not expected to bioconcentrate in fish or aquatic organisms.

Although the degradation of 2-butanone in the environment is understood on a theoretical level, data are not available to quantify all conclusions. In the atmosphere, 2-butanone is expected to undergo a vapor-phase reaction with photochemically produced hydroxyl radicals; the half-life for this process is approximately 1 day. However, laboratory experiments have suggested that the atmospheric half-life of 2-butanone is much shorter.

In water, 2-butanone is expected to undergo microbial degradation under both aerobic and anaerobic conditions. Chemical oxidation, direct photolysis, and hydrolysis of 2-butanone under environmental conditions are not expected to occur to any significant extent. Data on the fate of 2-butanone in soil are not available.

Various data are available regarding the concentration of 2-butanone in environmental media. It has been qualitatively detected in U.S. drinking water supplies and as a naturally occurring constituent of foods. It has also been detected in the air.

The general population is exposed to 2-butanone by drinking contaminated water or by the ingestion of food containing it. Members of the general population living near hazardous waste sites may be exposed to contaminated drinking water if their household water source is well water. The general population is also expected to be exposed to 2-butanone by inhalation, especially in urban areas. The use of commercial coatings containing 2-butanone also results in exposure by inhalation, and possibly by dermal contact as well. High levels of exposure may occur for members of the general population if these coatings are used in an enclosed, unventilated area. Occupational exposure to 2-butanone may occur by inhalation during the production, formulation, use, or transport of this compound.

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-butanone because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005).

According to the most recent edition of U.S. Chemical Data Reporting on chemical production and use in the United States (EPA 2020), the National Aggregate Production Volume of 2-butanone in 2015 was 100,000,000–250,000,000 pounds. The National Aggregate Production Volumes of 2-butanone were 282,480,991, 100,000,000–250,000,000, 100,000,000–250,000,000, and 50,000,000–100,000,000 pounds in 2011, 2012, 2013, and 2014, respectively. U.S. facilities that produced, processed, or used 2-butanone in 2015 are included in Table 5-1.

Table 5-1. Facilities that Produce, Process, or Use 2-Butanone

State	Number of facilities
Alabama	1
Arkansas	1
California	2
Delaware	1
Florida	3
Illinois	2
Indiana	2
Kentucky	2
Louisiana	1
Massachusetts	1
Minnesota	1
Missouri	1
New Jersey	8
New York	2
Ohio	6
Oregon	2
Pennsylvania	2
South Carolina	1
Texas	9
Washington	1
Wisconsin	3

Source: EPA 2020

2-Butanone is produced on a commercial scale by one of two processes. The catalytic dehydrogenation of 2-butanol in the gas-phase accounts for 92% of 2-butanone production (2006). The remaining 8% of 2-butanone is produced by a process in which liquid n-butane is oxidized catalytically to produce acetic acid and 2-butanone as a byproduct (Hoell et al. 2012).

5.2.2 Import/Export

No publicly accessible data were located to indicate the amount of 2-butanone exported or imported from or to the United States.

5.2.3 Use

2-Butanone is an important solvent with properties similar to those of acetone. 2-Butanone exhibits a very high power of dissolution. Some natural substances, plastics, and resins can be dissolved in 2-butanone. Areas of application are production of paints, lacquers, varnishes, paint thinners and removers, adhesives, cements, sealants, magnetic tapes, artificial leather, transparent paper, printing inks, cleaner for electronic equipment, cosmetics, pharmaceuticals; degreasing of metal surfaces; extraction of fats, oils, waxes, natural resins; and dewaxing of mineral oils or lube oils. Additionally, it is used as a synthetic flavoring agent in foods and pharmaceuticals and as a sterilizer for bacterial spores on surgical instruments, hypodermic needles and syringes, and dental instruments. It is also used in the manufacturing of smokeless powders (Hoell et al. 2012), which are ammunition propellants.

5.2.4 Disposal

Incineration can be used to dispose of 2-butanone by spraying into incinerators or burning in paper packaging (NLM 2020). 2-Butanone has been reported to be amenable to biological degradation in sewage treatment plants (Babeu and Vaishnav 1987; Bridie et al. 1979; Gaudy et al. 1963; Price et al. 1974; Urano and Kato 1986; Vaishnav et al. 1987; Young et al. 1968). No data are available regarding the amount disposed by each of these methods, nor is any information available regarding the trends in the disposal of 2-butanone.

5.3 RELEASES TO THE ENVIRONMENT

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).

5.3.1 Air

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

2-Butanone may be emitted to the atmosphere during its production, formulation, storage, or use in commercial products. 2-Butanone may also be released to the atmosphere as a result of its use as a solvent in commercial products. It was identified as an emission from a variety of indoor building materials: latex caulk, particle board, latex paint, and polyurethane floor finish (EPA 1987a; Tichenor and Mason 1988). Since 2-butanone is prevalent in adhesives and coatings (Papa and Sherman 1981), it may be released to the atmosphere during the curing of these products.

2-Butanone is present in the exhaust of automobiles (Seizinger and Dimitriades 1972). In a Swedish study, 2-butanone was detected in automobile exhaust, although the ambient air levels measured in Stockholm did not correlate with these emissions (Jonsson et al. 1985). Thus, the prevalence of other sources is indicated, as the air levels of 2-butanone were higher than could be explained solely by automobile emissions. Other potential sources of 2-butanone in the atmosphere include the burning of polyethylene (Hodgkin et al. 1982) and the photochemical degradation of hydrocarbons (Grosjean 1982), especially those emitted from motor vehicles. 2-Butanone was reported in the emissions of common household wastes (Wilkins and Larsen 1995, 1996) and in aerobic composting at a rate of 22 g/ton of waste, 0.8 g/ton in phase I of combined anaerobic/aerobic composting processes, and 0.1 g/ton in phase II (Smet et al. 1999). 2-Butanone is also emitted to the atmosphere from such natural sources as European firs, junipers, cedars, cypress trees, and ferns (Isidorov et al. 1985) and ant secretions (Cammaerts et al. 1978).

5.3.2 Water

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

Limited data are available regarding the release of 2-butanone to surface and groundwaters. It has been detected in wastewater effluents from commercial processes (Dunovant et al. 1986; Hawthorne and Sievers 1984; Jungclaus et al. 1978; Pellizzari et al. 1979). 2-Butanone may also be present in water from

the microbial oxidation of butane (Phillips and Perry 1974). Its relatively high water solubility, 136,000 mg/L at 25°C (Tewari et al. 1982), suggests that wet deposition of atmospheric 2-butanone results in the contamination of surface water. Evidence for this comes from the fact that 2-butanone has been detected in rainwater (Grosjean and Wright 1983).

The contamination of groundwater with 2-butanone has occurred at hazardous waste sites (Francis et al. 1980; Sawhney and Kozloski 1984) and landfills (Sabel and Clark 1984) due to infiltration of contaminated leachate. 2-Butanone is also likely to enter groundwater as a result of a spill to soil during a catastrophic event, such as a tanker spill (Halvorsen and Ohneck 1985).

2-Butanone may also enter water from natural sources. It has been detected in various species of macroalgae at concentrations as high as 2,600 ng/g (Whelan et al. 1982).

5.3.3 Soil

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

Limited data are available regarding the release of 2-butanone to soil. The presence of this compound in the groundwater at hazardous waste sites and landfills (Francis et al. 1980; Sabel and Clark 1984; Sawhney and Kozloski 1984) suggests that leachate at these facilities will be a source of 2-butanone release to soil. Wet deposition of atmospheric 2-butanone may also result in its contamination of soil. 2-Butanone may enter soil during a catastrophic event, such as a tanker spill (Halvorsen and Ohneck 1985).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. In the atmosphere, 2-butanone is expected to exist predominantly in the vapor phase (Eisenreich et al. 1981; Riddick et al. 1986). This is consistent with experimental data, which demonstrated that the gas-phase concentration of 2-butanone in Los Angeles, California was 220–3,000 times greater than the particulate phase concentration (Grosjean 1982). The relatively high water solubility of 2-butanone, 136,000 mg/L at 25°C (Tewari et al. 1982), suggests that wet deposition may remove 2-butanone from the

atmosphere. 2-Butanone has been identified in rainwater (Grosjean and Wright 1983). The absence of significant amounts of particulate 2-butanone indicates that dry deposition to the earth's surface is not an important fate process. The short residence time expected for 2-butanone in the atmosphere, <1 day, suggests that it is not transported long distances from its original point of release.

Water. If 2-butanone is released to water, it is expected to rapidly volatilize to the atmosphere. Based on its Henry's law constant, an estimated volatilization half-life from a model river 1 m deep, flowing at 1 m/second with a wind velocity of 3 m/second, is approximately 15 hours (Lyman et al. 1982).

Sediment and Soil. Based on an experimental soil adsorption coefficient (K_{oc}) of 3.55 (Roy and Griffin 1985), 2-butanone is expected to display very high mobility in soil (Swann et al. 1983). 2-Butanone was found in groundwater samples shortly after a tanker spill (Halvorsen and Ohneck 1985) and in the groundwater underneath hazardous waste sites and public landfills (Francis et al. 1980; Sabel and Clark 1984; Sawhney and Kozloski 1984). The vapor pressure of 2-butanone, 90.6 mmHg at 25°C (Riddick et al. 1986), and the Henry's law constant, 5.77×10^{-5} atm m^3/mol at 25°C, suggest that volatilization from either dry or moist soil to the atmosphere will be an important environmental process.

2-Butanone is not expected to significantly adsorb to sediment and suspended organic matter. It is also not expected to bioconcentrate in fish and aquatic organisms (Lyman et al. 1982). These conclusions are based on an experimental K_{oc} of 3.55 (Roy and Griffin 1985) and a calculated bioconcentration factor of 0.98 obtained from its octanol/water partition coefficient, 0.29 (Hansch et al. 1995), and an appropriate regression equation (Lyman et al. 1982).

5.4.2 Transformation and Degradation

Air. 2-Butanone is expected to undergo atmospheric destruction by the gas phase reaction with photochemically produced hydroxyl radicals. Rate constants for this reaction ranging from 1.85×10^{-11} to 9.8×10^{-13} atm/molecule-second in the temperature range of 22–32°C have appeared in the literature (Cox et al. 1980, 1981; EPA 1986; Edney et al. 1986; Darnall et al. 1976; Gusten et al. 1984; Wallington and Kurylo 1987; Wallington et al. 1988). Using a recommended rate constant of 1.85×10^{-11} atm/molecule-second at 25°C and an average atmospheric hydroxyl radical concentration of 5×10^5 molecule/cm^3 (Atkinson 1985), a half-life of 21 hours for this reaction can be calculated. However, experiments performed under simulated atmospheric conditions in the laboratory have shown that 2-butanone has a half-life of only 9.8 hours for photo-initiated processes (Dilling et al. 1976). The rate of its destruction

increased in the presence of other anthropogenic compounds. The atmospheric destruction of 2-butanone as a result of direct irradiation is not expected to be significant under atmospheric conditions (Cox et al. 1980). Therefore, direct photolysis cannot account for the enhanced rate of atmospheric destruction observed in the laboratory. However, the data suggest that other mechanisms are responsible for the destruction of 2-butanone in the atmosphere, which are yet to be defined.

Water. 2-Butanone is expected to be removed from environmental waters by microbial degradation under both aerobic and anaerobic conditions. Limited data specific to the chemical degradation of 2-butanone in water are available; however, it is not expected to occur to any significant extent.

Numerous investigations have concluded that 2-butanone undergoes biological degradation under aerobic conditions. At an initial concentration of 1 ppm, 2-butanone completely degraded in aerated water obtained from a deep Florida aquifer within 14 days after a 5-day lag period (Delfino and Miles 1985). Screening studies using a microbial seed from domestic waste treatment plants have indicated that 2-butanone has a 5-day biological oxygen demand (BOD5), which is between 59 and 74% of the theoretical amount after a short lag period (Babeu and Vaishnav 1987; Bridie et al. 1979; Gaudy et al. 1963; Price et al. 1974; Urano and Kato 1986; Vaishnav et al. 1987; Young et al. 1968). A pure culture study indicated that propionate is produced as a result of the microbial oxidation of 2-butanone (Phillips and Perry 1974).

2-Butanone has been listed as a compound amenable to degradation by anaerobic biotechnology (Speece 1983). At an initial concentration of 500 ppm, 2-butanone was completely reduced to methane within 8 days in a fermenter using a domestic sludge inoculum that had been adapted to acetate (Chou et al. 1978).

An experimentally determined rate constant of 5.4×10^{8} L/mol-second has been determined for the reaction of 2-butanone with hydroxyl radicals in water (Anbar and Neta 1967). This value corresponds to a half-life of 4 years for this reaction, given a hydroxy radical concentration of 1×10^{-17} M (Mill et al. 1980). Hydrolysis of ketones is generally not believed to be an environmentally important process (Lyman et al. 1982; Mill 1982). A rate constant of 0 L/mol-year was listed for the hydrolysis of 2-butanone under neutral, acidic, and basic conditions at 25°C (EPA 1987b), indicating that this process does not occur in the environment. By analogy to the gas phase photolysis of 2-butanone (Cox et al. 1980), direct photochemical breakdown of 2-butanone in water is not expected. Therefore, the chemical degradation of 2-butanone in environmental waters is not expected to occur to any significant extent.

The chemical alteration of 2-butanone in rainwater has been postulated. In acid rain, hydroxy sulfonates may be formed by their action with bisulfite, and ammonia adducts may be formed in ammoniated rain (Grosjean and Wright 1983). The concentration of these reactive species is likely to be much higher in rainwater than in surface water; therefore, a more rapid rate of reaction would be expected in rain.

Sediment and Soil. No specific data concerning the fate of 2-butanone in soil were available. By analogy to the experimental results on the microbial degradation of 2-butanone in water, this compound may degrade in soil under aerobic and anaerobic conditions given suitable time for adaptation of the microbial population. Again by using an analogy to the fate of 2-butanone in aqueous systems, it is not expected to hydrolyze, photolyze on the surface, or undergo chemical degradation in soil.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to 2-butanone depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of 2-butanone 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-butanone 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 5-2 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 5-3.

Table 5-2. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	4 µg	NIOSH 1996
Air	8 ppb	Jonsson et al. 1985
Drinking water	No data	Wallace et al. 1984
Surface water and groundwater	10 ppb	EPA 1988
Soil	10 ppb	EPA 1988

Table 5-2. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Sediment	10 ppb	EPA 1988
Whole blood	0.01 ppm	Van Doorn et al. 1989

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

Table 5-3. Summary of Environmental Levels of 2-Butanone

Media	Low	High	Mean
Outdoor air (ppb)	0.5	14	2.8
Indoor air (ppb)	No data	No data	No data
Surface water (ppb)	No data	No data	11
Groundwater (ppb)	No data	No data	302
Drinking water (ppb)	No data	No data	1.6
Soil (ppb)	No data	No data	87

Detections of 2-butanone in air, water, and soil at NPL sites are summarized in Table 5-4.

Table 5-4. 2-Butanone 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)	200	401	26.9	158	94
Soil (ppb)	550	1,700	65.7	119	93
Air (ppbv)	15.9	16.8	21.4	33	20

[a]Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). 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

2-Butanone has been detected in a limited number of sites in rural, urban, and indoor locations. It was detected in 17 samples taken in Tucson, Arizona, in 1982 at an average concentration of 2.8 ppb. In the mountains of Arizona, the concentration was 0.50 ppb (Snider and Dawson 1985). The range of 2-butanone measured in Los Angeles air in 1980 was 0–14 ppb in 70 samples (Grosjean 1982). An

average concentration of 0.638 ppb of 2-butanone was obtained from 714 atmospheric samples in the United States (EPA 1988). The average concentration of 2-butanone at 25 urban locations in the United States was 1.4 μg/m^3 (0.48 ppb) (Kelly et al. 1993). 2-Butanone was found in one-third of samples taken downwind of a solvent recycling facility in Maryland in 1970, at a maximum concentration of 94 ppm (Smoyer et al. 1971). Although it has been detected in the exhaust of gasoline engines, 2-butanone was not found in the air of a highway mountain tunnel (Hampton et al. 1982).

2-Butanone was detected in the air of the Kin-But chemical waste site, located in New Jersey, at concentrations ranging from trace to 1.5 pg/m^3 (0.51 ppb); in samples surrounding the site, concentrations were 0.5–33 μg/m^3 (0.17–11.3 ppb) (Pellizzari 1982). It was qualitatively detected in the air at four of four hazardous waste sites and one landfill in New Jersey (LaRegina et al. 1986).

In a survey of 36 homes taken in Chicago, Illinois, 2-butanone was detected in the indoor air at 3 residences (Jarke et al. 1981). It was also found in three outdoor samples in this survey. It is not clear, however, if the positive indoor and outdoor samples were collected at the same location. In a compilation and analysis of ambient monitoring data collected from 1970 to 1987, the daily concentration of 2-butanone was 0 ppb in urban, suburban, and rural areas (EPA 1988). 2-Butanone has been qualitatively detected in the indoor air of homes in Chicago (Jarke et al. 1981) and in Canadian residential and office buildings (Tsuchiya 1987).

The sporadic ambient air monitoring data available for 2-butanone suggest that the average background concentration of this compound may be very low. However, the available data also suggest that there are dramatic, temporal, and diurnal variations in its concentration.

5.5.2 Water

From water quality data collected across the United States, 2-butanone was found at <2.0 μg/L (detection limit) in 1 of 107 samples of finished water (NWQMC 2020). 2-Butanone was identified as an ozone disinfection byproduct in drinking water (Richardson et al. 1999). 2-Butanone was detected in tap water 8 months after the installation of new polyvinyl chloride (PVC) pipes at a concentration ranging from 0.4 to 4.5 ppm (Wang and Bricker 1979). It resulted from the glue used to cement the water pipes together. The concentration of 2-butanone in the water increased with the amount of time the water sat in the pipes.

2-Butanone has been qualitatively detected in rainwater and the clouds of Henninger, California, at 0.04 ppb, and in the mist of Long Beach, California (Grosjean and Wright 1983). Trace amounts have also been found in the ice in Fairbanks, Alaska (Grosjean and Wright 1983).

Water quality data compiled from the STORET Data Warehouse and the U.S. Geological Survey (USGS) National Water Information System (NWIS) reports are summarized in Table 5-5. These data are comprised of water quality data from water resource management groups across the country.

Table 5-5. 2-Butanone Detected in Samples Collected Throughout the United States from 2010 to 2020

Type	Number of samples	Number of positive	Concentration range
Groundwater	21,395	3,072	0.09–5000 ppb
Surface water	1,093	66	0.3–<50 ppb
Storm water	9	9	<1.9–<50 ppb
Leachate	60	60	<50–2,450 ppb
Municipal waste	2	0	1.5 ppb (detection limit)
Sediment	37	0	0.89–4.30 ppb (detection limit)
Soil	18	0	1.1–330 ppb (detection limit)
Drinking water[a]	107	1	<2.0 ppb (detection limit)

[a]Samples taken 1998–2009; no results were reported for 2010–2020.

Source: NWQMC (2020).

2-Butanone has been detected in the effluent of various industrial processes. It was found in six of seven wastewater samples from energy-related processes at a concentration up to 645 ppb (Pellizzari et al. 1979). 2-Butanone was detected in the wastewater of a specialty chemical manufacturing plant at a concentration of 8–20 ppm, but not in the receiving river water or its sediment (Jungclaus et al. 1978). It was also detected in the wastewater from shale oil processing at a concentration of 0.4–18 ppm (Hawthorne and Sievers 1984). In 1982, 2-butanone was detected at concentrations of ≤83 ppb in the wastewater entering Cincinnati treatment plants (Dunovant et al. 1986).

2-Butanone was qualitatively detected in the Black Warrior River, located in Tuscaloosa, Alabama (Bertsch et al. 1975) and in Newark Bay, New Jersey (Gunster et al. 1993). It was also detected in

seawater from the straits of Florida at 0–22 ppb in 1968 (Corwin 1969) and in the Potomac River at <40 μg/L (Hall et al. 1987).

5.5.3 Sediment and Soil

2-Butanone has been reported in soil samples collected from various mines and waste disposal facilities in the United States at concentrations ranging from 32 to 38,000 μg/kg (EPA 1987c, 1987d, 1988b, 1989).

5.5.4 Other Media

2-Butanone has been detected as a natural component of numerous types of foods. It has been qualitatively identified as a volatile constituent in raw chicken breast muscle, milk, roasted filberts (nuts), Beaufort (Gruyere) and cheddar cheese, bread dough, and intact tree-ripened nectarines (Dumont and Adda 1978; Gordon and Morgan 1972; Grey and Shrimpton 1967; Keen et al. 1974; Kinlin et al. 1972; Sosulski and Mahmoud 1979; Takeoka et al. 1988). The mean concentrations of 2-butanone in dried beans, split peas, and lentils were 148, 110, and 50 ppm, respectively (Lovegren et al. 1979). 2-Butanone has been detected in southern peas at a median concentration of 120 ppb (Fisher et al. 1979), and it has been qualitatively detected in winged beans and soybeans (Del Rosario et al. 1984). 2-Butanone is a constituent of plant families including Lamiaceae, Solanaceae, Myrtaceae, and Grossulariaceae (USDA 2020). It has also been detected in cigarette smoke (Higgins et al. 1983; Osborne et al. 1956).

5.6 GENERAL POPULATION EXPOSURE

Available monitoring data suggest that the general population is exposed to 2-butanone. In the early stages of the Total Exposure Assessment Methodology (TEAM) study, 2-butanone was qualitatively detected in 3 of 8 personal air samples, 5 of 12 breath samples, and 1 of 1 drinking water sample obtained from 12 volunteers living in urban areas of New Jersey or North Carolina (Wallace et al. 1984). 2-Butanone has also been detected in the expired air of 206 of 387 samples (53.2%) taken from 54 adult, nonsmoking, urban-dwelling subjects, at an average concentration of 3.6 ng/L (Krotoszynski et al. 1979). It was detected in the expired air of six of eight male volunteers, three of whom were smokers (Conkle et al. 1975). 2-Butanone was found in 5 of 12 samples of human mothers' milk from subjects in four different U.S. urban areas (Pellizzari et al. 1982). It has been qualitatively detected in the indoor air of homes in Chicago (Jarke et al. 1981) and in Canadian residential and office buildings (Tsuchiya 1987).

Exposure to 2-butanone by the general population may occur by ingestion of contaminated drinking water. This compound has been identified in U.S. drinking water supplies (Bertsch et al. 1975; Coleman et al. 1976; EPA 1974, 1975; Kopfler et al. 1977; Ogawa and Fritz 1985; Scheiman et al. 1974). However, in 107 finished water samples collected across the United States from 1990 to 2020, 2-butanone was detected in only one sample at <2 ppb (NWQMC 2020). Inhalation is also a likely route of exposure to 2-butanone, especially during the household use of commercial coatings that use 2-butanone as a solvent. Exposure by dermal contact may also occur during the use of such coatings.

2-Butanone in water is expected to rapidly volatilize; thus, there is potential for inhalation exposure during showering and bathing. ATSDR's three-compartment Shower and Household-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day by estimating the contribution from showering or bathing and the contribution from other water sources in the house, such as the dishwasher, clothes washer, and faucets. This information along with human activity patterns are used to calculate a daily time-weighted average exposure concentration via inhalation exposure and from dermal uptake from skin contact. ATSDR's SHOWER model is available by sending a request to showermodel@cdc.gov. The SHOWER model predicts 40% volatilization of 2-butanone while showering and about 30% from taking a tub bath.

Vapor intrusion may also be a potential source of 2-butanone exposure, as vapor intrusion has been observed for several volatile organic chemicals (VOCs) with similar properties. EPA's compilation of four studies of background indoor air concentrations found a 79–91% detection rate for 2-butanone in 802 U.S. resident samples between 1990 and 2005 (EPA 2011). The background medians ranged from 2.7 to 6.5 µg/m^3, 95th percentiles ranged from 21 to 39 µg/m^3, and maximum values ranged from 76 to 890 µg/m^3. ATSDR extracted environmental data from 135 ATSDR reports evaluating the vapor intrusion pathway at 121 sites published between 1994 and 2009 (Burk and Zarus 2013). The data set contained the maximum measured 2-butanone indoor air data at 11 vapor intrusion sites and ranged from 0.06 to 96 µg/m^3 (ATSDR 2005a, 2005b). ATSDR's findings for 2-butanone from the 121 vapor intrusion sites generally fell within EPA's background ranges, although the 95th percentile was about 2 times greater than background, indicating some potential vapor intrusion impact on indoor air concentrations.

2-Butanone is a naturally occurring constituent in a variety of common foods (Del Rosario et al. 1984; Dumont and Adda 1978; Gordon and Morgan 1972; Grey and Shrimpton 1967; Keen et al. 1974; Kinlin et al. 1972; Lovegren et al. 1979; Takeoka et al. 1988). Ingestion of these foods will result in exposure to

2-butanone. Exposure to 2-butanone may also occur while smoking (Higgins et al. 1983; Osborne et al. 1956). Students taking undergraduate general chemistry laboratory courses may be also exposed to 2-butanone (Kolb 1988).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Exposure to both 2-butanone and n-hexane or methyl-n-butyl ketone is possible in occupational settings and at hazardous waste sites; thus, neurological effects of n-hexane and methyl-n-butyl ketone may be greater with coexposure to 2-butanone. Likewise, occupational exposure or exposure at hazardous waste sites to a combination of 2-butanone and the haloalkanes, carbon tetrachloride, or chloroform, presents a greater risk for liver damage.

For the general population, high levels of exposure to 2-butanone may occur for those living near commercial settings where this compound is used. For example, the downwind 2-butanone concentration near a solvent recycling facility was measured at concentrations up to 94 ppm (Smoyer et al. 1971). High levels of exposure may also occur during the use of commercial coatings containing 2-butanone, especially when working in enclosed, unventilated spaces. Members of the general population living near hazardous waste sites and drawing their drinking water from groundwater sources may be exposed to high levels of 2-butanone through ingestion of contaminated water, although no information on the size of the population can be provided.

Occupational exposure to 2-butanone is expected to occur by inhalation and dermal contact. High levels of occupational exposure could occur during the loading and unloading of large quantities of this material during shipment and during the application of commercial coatings containing 2-butanone without adequate protection. According to the National Occupational Exposure Survey (NOES) conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1980 and 1983, 1,221,587 workers, of which 201,308 were women, were potentially exposed to 2-butanone during that time period (NIOSH 1989). Of these workers, 84% (80% for the women) were exposed during the use of trade name products containing 2-butanone. More recent occupational survey data were not identified.

Similarly, recent occupational monitoring data were not identified for 2-butanone. A study of three companies involved in spray painting and spray gluing operations reported that, for 89 workers exposed to 2-butanone, the mean air concentration was 0.3 ppm (Whitehead et al. 1984). 2-Butanone was detected in the air of Cincinnati wastewater treatment plants in 1982; 3 of 17 samples were positive at

concentrations ≤5.7 ppb (Dunovant et al. 1986). It has also been detected in the air above shale oil wastewaters (Hawthorne and Sievers 1984). The breathing zone air for workers at an organic solvent recycling plant averaged 11 ppm during drum decantation operations and 10 ppm during all other work activities (Kupferschmid and Perkins 1986). The ambient concentration was not greater than exposure limits of 200 ppm in any of these examples (NIOSH 1984). The concentrations of 2-butanone in air samples obtained from the Skylab, 1973–1974, ranged from 2.4 to 1,505 ppb (Liebich et al. 1975). Personal exposure to 2-butanone at a waste solvent incineration facility ranged from <0.01 to 1.2 ppm (Decker et al. 1983).

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-butanone 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-butanone.

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.

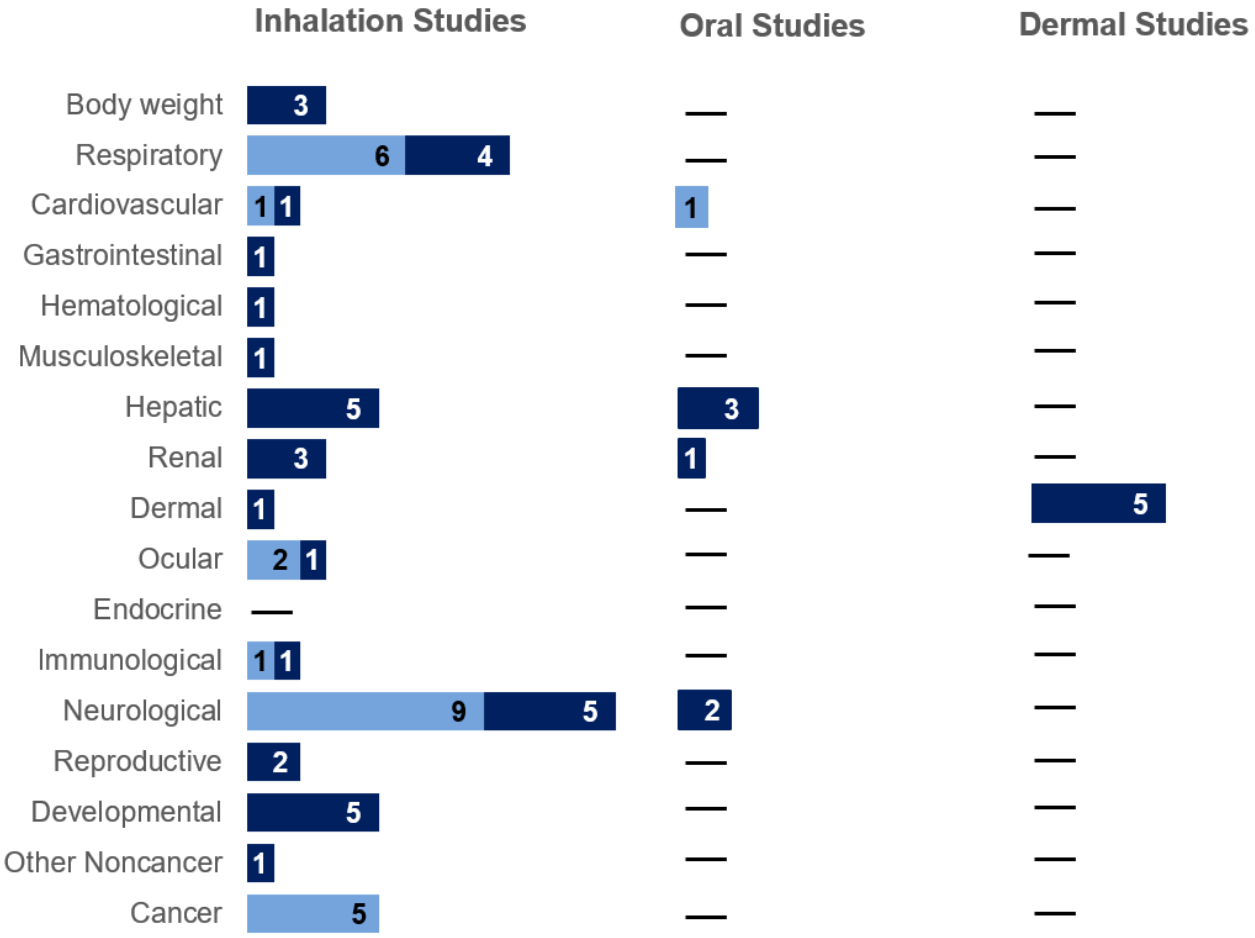
6.1 INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to 2-butanone 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-butanone. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

As illustrated in Figure 6-1, most of the data on the toxicity of 2-butanone come from inhalation studies in humans and laboratory animals. The most commonly examined endpoints were respiratory and neurological effects. Developmental effects and liver toxicity were also studied in animals only. A small number of oral studies in animals evaluated hepatic, renal, and neurological effects. No reports of systemic toxicity are available for dermal exposure.

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

Potential respiratory, hepatic, and neurological effects were the most studied endpoints
The majority of the studies examined inhalation exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2. The number of studies include those finding no effect; many studies examined more than one endpoint.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. A number of studies have evaluated the acute-duration toxicity of inhaled 2-butanone in humans, primates, rats, mice, and guinea pigs. The data were considered adequate for derivation of an acute-duration inhalation MRL. The acute oral toxicity of 2-butanone was evaluated in rats; most of these studies involved a single gavage exposure. An acute-duration oral MRL was not derived because the oral database was considered inadequate to identify target organs or establish dose-response relationships.

Intermediate-Duration MRLs. A comprehensive 90-day inhalation study in rats showed that 2-butanone did not have adverse effects in the respiratory, cardiovascular, gastrointestinal, musculoskeletal, hematological, hepatic, renal, or dermal/ocular systems (Cavender and Casey 1981; Cavender et al. 1983). The most serious effect was slightly increased liver weight at the highest concentration tested, 5,000 ppm. Occupational exposures to concentrations this high are unlikely since humans find 350 ppm 2-butanone intolerable (Nelson et al. 1943). No signs of neurotoxicity, either clinical or histological, were observed in several studies of intermediate exposures to high concentrations of 2-butanone up to 6,000 ppm (Altenkirch et al. 1978, 1979; Cavender and Casey 1981; Cavender et al. 1983). Therefore, most organs and tissues in humans probably would not be adversely affected by intermediate 2-butanone exposures either occupationally or near toxic waste sites. An intermediate-duration inhalation MRL was not derived because neurological symptoms (i.e., headache, fatigue, feeling of intoxication) and nose and throat irritation occurred in humans at acute inhalation exposure levels lower than the NOAEL values for intermediate-duration inhalation exposure in animals. No intermediate oral or dermal studies investigated the systemic toxicity of 2-butanone by these routes, and the available pharmacokinetic data are not sufficient to predict whether target organs would be similar by the various routes of exposure. 2-Butanone has been detected in air, water, food, and soil (see Section 5.5); therefore, exposures by the inhalation, oral, and dermal routes are possible. From a public health perspective, exposure to solvent mixtures is more likely than exposure to a single pure chemical. Therefore, intermediate exposure studies of 2-butanone mixed with other solvents (hexacarbons and haloalkanes),

the toxicity of which is potentiated by 2-butanone, would provide valuable information on neurotoxicity and systemic toxicity. This information is important since these chemicals are often found together in solvents used occupationally, and they might be stored together at hazardous waste sites where surrounding populations could be exposed for intermediate durations.

Chronic-Duration MRLs. No studies were located regarding the health effects of chronic exposure to 2-butanone by any route in humans or animals. Pharmacokinetic data are insufficient to predict the possible target organs of chronic exposure by any route. Since 2-butanone has been detected in air, water, food, and soil (see Section 5.5), exposures by the inhalation, oral, and dermal routes are possible. 2-Butanone is often found in formulations with other chemicals, such as chloroform, carbon tetrachloride, n-hexane, and methyl-n-butyl ketone, the toxicities of which 2-butanone potentiates. These chemicals may be stored together at hazardous waste sites. Chronic inhalation, oral, and dermal studies in which animals are administered these chemicals in combination with 2-butanone may provide dose-response information for the potentiation of the neurotoxicity and hepatotoxicity of these chemicals by 2-butanone. This information is important because there are populations surrounding hazardous waste sites that might be exposed to these chemicals for similar durations.

Although no cancer bioassays were available, preliminary epidemiological studies suggest that occupational exposure to 2-butanone does not increase the development of neoplasms. Furthermore, genotoxic effects including gene mutation, chromosome aberration, micronucleus frequency, DNA damage, cell transformation, and unscheduled DNA synthesis were primarily negative (see Section 2.20). Three studies reported evidence for 2-butanone induction of chromosome effects in yeast, but the findings were inconsistent with other studies evaluating similar endpoints. On the basis of this information, 2-butanone does not appear to be carcinogenic.

Health Effects.

Reproductive Toxicity. No studies were located regarding effects on reproductive capacity or reproductive organs and tissues in humans following exposure to 2-butanone. The authors of a health hazard evaluation report for NIOSH concluded that a perceived increase in the number of spontaneous abortions among female workers believed to result from exposure to 2-butanone and several other volatile chemicals at a shoe factory was not related to exposure (NIOSH 1982). No histopathological lesions were found in male or female reproductive organs of rats exposed to 5,000 ppm 2-butanone for 90 days (Cavender and Casey 1981; Cavender et al. 1983), but reproductive function was not assessed. Further studies of the reproductive function of

2-butanone by all durations and routes would provide valuable information, particularly if the studies include histological examination of the organs and tissues of the reproductive system. If reproductive organs were identified as targets of 2-butanone toxicity, single or multigeneration reproductive studies probably would be warranted. Since 2-butanone potentiates the neurotoxicity or hepatotoxicity of certain chemicals, it would be valuable to investigate the reproductive effects of mixed solvent exposures that include 2-butanone. This investigation would be useful because 2-butanone is often found in mixtures with other solvents in occupational settings, and these mixtures may be found together at or near hazardous waste sites.

Developmental Toxicity. Information regarding developmental toxicity of 2-butanone in humans was not located. 2-Butanone was slightly fetotoxic in rats (Deacon et al. 1981; Saillenfait et al. 2006; Schwetz et al. 1974) and mice (NTP 1989; Schwetz et al. 1991) following inhalation exposure of pregnant rats and mice to 3,000 or 4,000 ppm. The fetotoxicity was related to delayed development. Furthermore, five of eight pregnant rats exposed continuously to 800 ppm throughout gestation failed to deliver litters and brain development was delayed in offspring of rats that delivered pups (Stoltenburg-Didinger 1991; Stoltenburg-Didinger 1990). In addition, developmental effects were more pronounced in pups born to rat dams exposed to a mixture of n-hexane and 2-butanone than in pups born to dams exposed to n-hexane alone (Stoltenburg-Didinger et al. 1990). This study, however, was very poorly reported, with very little information provided on exposure to 2-butanone alone. No developmental or distribution studies have been conducted by the oral route, but there is no reason to believe that 2-butanone or its metabolites could not cross the placenta after administration by the oral route. Therefore, it is likely that orally administered 2-butanone would be fetotoxic in these species. Determination of the doses needed to produce the fetotoxicity by the oral route would provide valuable information. Since 2-butanone potentiates the neurotoxicity or hepatotoxicity of certain chemicals, it would be valuable to further investigate the developmental effects of mixed solvent exposures that include 2-butanone. Such a study would be useful because 2-butanone is often found in mixtures with other solvents in occupational settings, and these mixtures may be found at or near hazardous waste sites.

Immunotoxicity. There are limited data on the potential immunotoxicity of 2-butanone. A case report of an individual reported 2-butanone-induced contact urticaria (Varigos and Nurse 1986). Studies in rats reported no histological alterations of immune and lymphoreticular tissues following intermediate-duration inhalation exposure (Cavender and Casey 1981; Cavender et al.

1983). Because these studies did not evaluate immune function, they are not considered adequate for evaluating potential immunotoxicity of 2-butanone. Studies evaluating potential impairment of immune function (thymus, lymph nodes, peripheral blood lymphocytes, etc.) would provide valuable information regarding the immunotoxicity of 2-butanone.

Neurotoxicity. 2-Butanone was not neurotoxic at a concentration of 200 ppm in several acute inhalation exposure studies in male volunteers (Dick et al. 1984, 1988, 1989, 1992). However, symptoms of neurotoxicity (headache, fatigue, feeling of intoxication) were reported by subjects exposed to 100 ppm (Tomicic et al. 2011). Neurobehavioral effects have been observed in mice (1,602 ppm) (De Ceaurriz et al. 1983) and baboons (100 ppm) (Geller et al. 1979) exposed acutely by inhalation. Guinea pigs displayed narcosis and incoordination after acute inhalation exposure to high concentrations (Patty et al. 1935). Clinical signs of neurotoxicity were also observed in rats treated acutely by gavage with a high dose of 2-butanone (Stillmeadow Inc. 1978). Most of the available information on the neurotoxicity of 2-butanone is derived from studies conducted over 30 years ago when neurobehavioral screening tests were not as sensitive as currently available tests. Additional studies using sensitive measures could provide information on potential subtle neuropathological alterations. 2-Butanone is not generally regarded as being highly neurotoxic when administered alone. In acute and intermediate exposure studies, 2-butanone markedly potentiated the neurotoxicity of n-hexane and methyl-n-butyl ketone both in humans and animals. A comprehensive study of acute, intermediate, and chronic exposures to mixtures of 2-butanone, n-hexane, and methyl-n-butyl ketone by inhalation, oral, and dermal routes would provide valuable information regarding the neurotoxicity of these compounds. Such a study would be particularly valuable because 2-butanone is often found occupationally in mixtures containing n-hexane and methyl-n-butyl ketone, and these chemicals would probably be found together at hazardous waste sites.

Epidemiology and Human Dosimetry Studies. Studies with male and female volunteers determined that inhalation exposure to 100 ppm produced neurological symptoms (i.e., headache, fatigue, feeling of intoxication) (Tomicic et al. 2011) and was irritating to the eyes, nose, and throat (Nelson et al. 1943; Tomicic et al. 2011). Other studies reported the absence of neurological and irritation effects in volunteers at concentrations up to 200 ppm (Muttray et al. 2002; Seeber et al. 2002; van Thriel et al. 2002); however, these studies were conducted in male subjects only. Female subjects were reported to be more sensitive than males to neurological symptoms and the respiratory and eye irritation effects of 2-butanone (Tomicic et al. 2011). In four separate studies, volunteers exposed to 200 ppm had no

neurobehavioral effects (Dick et al. 1984, 1988, 1989, 1992). Several epidemiological studies of occupational workers exposed to 2-butanone showed inconclusive results regarding increased risk of cancer (Alderson and Rattan 1980; Blair et al. 1998; Radican et al. 2008; Wen et al. 1985). Two case-control studies evaluating the relationship between 2-butanone exposure and childhood leukemia were also inconclusive (Gao et al. 2014; Infante-Rivard et al. 2005). No epidemiological studies regarding other health effects of 2-butanone exposure were located. Therefore, valuable epidemiological information could be obtained from further studies of cancer and other health effects, particularly neurotoxicity and reproductive and developmental toxicity.

Biomarkers of Exposure and Effect. The only known biomarkers of 2-butanone exposure are blood, breath, and urinary concentrations of 2-butanone and its metabolites (Brown et al. 1986; Brugnone et al. 1983; Ghittori et al. 1987; Miyasaka et al. 1982). 2-Butanone is rapidly cleared from the body, and existing studies show that accumulation of 2-butanone in tissues does not occur to a significant extent. Furthermore, 2-butanone alone is relatively free of adverse health effects. Therefore, development of biomarkers of exposure to a battery of solvents often used occupationally in combination with 2-butanone would be more valuable than development of biomarkers for 2-butanone alone.

2-Butanone exposure has no specific effects that can be used as biomarkers for exposure by any route or for any duration of exposure.

Absorption, Distribution, Metabolism, and Excretion. 2-Butanone is absorbed by inhalation (Liira et al. 1988a, 1988b, 1990a, 1991) and oral exposure (Brown and Hewitt 1984; Dietz and Traiger 1979; Dietz et al. 1981; Hewitt et al. 1983; Sakata et al. 1989). Net retention of inhaled 2-butanone is approximately 50% in humans (Liira et al. 1988a, 1988b). Studies of absorption after dermal exposure would provide valuable information on this occupationally significant route of entry. Available data regarding the relative rates or extent of absorption, metabolism, distribution, and excretion by the three routes of exposure are not sufficient to draw meaningful conclusions. 2-Butanone is equally soluble in all tissues and organs measured (Perbellini et al. 1984). Therefore, 2-butanone is probably evenly distributed throughout the body. The primary route of excretion appears to be the lungs. The metabolic pathways for 2-butanone have been thoroughly studied in rats (Dietz and Traiger 1979; Dietz et al. 1981) and guinea pigs (DiVincenzo et al. 1976). Similar metabolites have been identified in humans (Liira et al. 1988a, 1988b; Miyasaka et al. 1982). In rats, 30% of an oral dose of 2-butanone was converted to 2,3-butanediol (Dietz et al. 1981). Potentiation of the neurotoxicity of ethanol, n-hexane, and methyl-n-butyl ketone and the hepatotoxicity of haloalkanes by 2-butanone may involve interactions in the biotransformation of

these compounds (Brady et al. 1989; Cunningham et al. 1989; Raunio et al. 1990; Robertson et al. 1989; Traiger et al. 1989). Further studies regarding the interaction of hexacarbons, haloalkanes, and 2-butanone at the metabolic level may provide valuable information.

Comparative Toxicokinetics. Available human data show that 2-butanone is metabolized primarily to 2,3-butanediol and 3-hydroxy-2-butanone, but the extent of metabolism appears to be small (Liira et al. 1988a, 1988b). In an occupational exposure study of 2-butanone, only 3-hydroxy-2-butanone was observed (Brugnone et al. 1983). In rats and guinea pigs, a third metabolite, 2-butanol, was observed (Dietz et al. 1981; DiVincenzo et al. 1976). About 30% of an oral dose of 2-butanone in rats later appeared in plasma as 2,3-butanediol (Dietz et al. 1981). 2-Butanol is also a product of 2-butanone metabolism in humans (Liira et al. 1990a). 2-Butanone potentiates the neurotoxicity of n-hexane and methyl-n-butyl ketone and the hepatotoxicity of haloalkanes. The 2-butanone metabolite, 2,3-butanediol, may be more efficacious for potentiating the hepatotoxicity of the haloalkanes than 2-butanone. Therefore, valuable information would be gained by toxicokinetic studies of 2-butanone and its metabolites as they pertain to the toxicity of the hexacarbons and haloalkanes.

Children's Susceptibility. The human blood:air partition coefficient was 2–4% higher in male and female pediatric subjects compared with adults and a similar age-related pattern was observed in rats with a 4–6% higher blood:air coefficient observed in PND 10 males compared with adult and aged male rats (Mahle et al. 2007). These data suggest that pulmonary uptake following inhalation may be slightly higher in children compared to adults. Although several animal studies have evaluated the potential developmental toxicity of 2-butanone, no studies were identified that evaluated potential age-related differences. Additional studies in young animals would be useful to address potential concerns that children may be more susceptible to the toxicity of 2-butanone than adults.

Physical and Chemical Properties. The physical and chemical properties of 2-butanone are well documented. The environmental fate of 2-butanone can be predicted from these properties and compared to experimental results once they are obtained in areas where deficiencies exist.

Production, Import/Export, Use, Release, and Disposal. The significant amounts of 2-butanone produced in the United States, combined with its prevalence in commercial and household products, suggest that large numbers of citizens are potentially exposed to anthropogenic sources of this compound. The production, use, and international trading of 2-butanone is well described in the available literature (Kavaler 1987; Neier and Strehlke 1985; Papa and Sherman 1981; USITC 1987, 1988, 1989). Methods

for the disposal of 2-butanone are established (OHM/TADS 1989), but the amounts processed by each method cannot be ascertained. Therefore, disposal of 2-butanone cannot be compared to the regulations controlling this practice. Knowing the amount of 2-butanone released to the environment and its disposal pattern will aid in determining routes and levels of exposure to the general population by indicating which media should be monitored carefully.

Environmental Fate. There is sufficient predictive information to indicate that 2-butanone is not likely to partition from water (Hansch et al. 1995; Lyman et al. 1982; Roy and Griffin 1985); yet, there are few field studies to verify these predictions. Similarly, 2-butanone's transport, transformation, and degradation in the environment can be predicted (Atkinson 1985; Babeu and Vaishnav 1987; Cox et al. 1980; Delfino and Miles 1985), but has not yet been experimentally substantiated in all areas. Experimental studies in this area would allow the determination of 2-butanone's lifetime in the environment and aid in determining levels and routes of human exposure.

Bioavailability from Environmental Media. Numerous toxicokinetic and toxicity studies in humans and animals have demonstrated the bioavailability of 2-butanone from air, ingestion of food and water, and dermal contact. Absorption of 2-butanone after inhalation is well-established, and it appears to be adsorbed after ingestion. These mechanisms are consistent with what one would expect, based on 2-butanone's physical and chemical properties (Lyman et al. 1982). Given the potential for exposure to 2-butanone because of its prevalence in commercial products available to the public, further research on the bioavailability of this compound will allow the quantification of human exposure and risk.

Food Chain Bioaccumulation. 2-Butanone is not believed to appreciably bioconcentrate in fish and aquatic organisms (Hansch et al. 1995; Lyman et al. 1982). It is also not expected to biomagnify in the food chain. Quantitative data supporting these conclusions are not available in the literature. Additional information on bioconcentration and biomagnification would be useful in confirming the predicted behavior of this compound.

Exposure Levels in Environmental Media. Data are available regarding the level of 2-butanone in environmental media (Grosjean and Wright 1983; EPA 1988) and foods (Dumont and Adda 1978; Grey and Shrimpton 1967; Kinlin et al. 1972; Lovegren et al. 1979; Takeoka et al. 1988); however, the data available are often qualitative and only generalized trends regarding the occurrence of this compound can be derived. Quantitative determination of the levels of 2-butanone in environmental media and foods will allow the estimation of human intake levels of this compound from each media. Studies evaluating

potential exposure via vapor intrusion or volatilization during showering/bathing would provide valuable information regarding potential human exposure pathways.

Exposure Levels in Humans. 2-Butanone has been found in the human blood samples of urban dwellers, but the observed levels have not been correlated with personal activities. Studies on the level of 2-butanone in human tissues near hazardous waste sites are not complete. A study is needed to evaluate the levels of 2-butanone in humans with their personal activities or the areas where they live will allow an assessment of potential exposure to the general population. Similarly, correlations of occupational exposure by profession will aid in the determination of human exposure levels.

Exposures of Children. No studies are available to assess whether children are at a higher exposure risk than adults to 2-butanone. Studies examining potential exposure sources for children would be useful.

6.3 ONGOING STUDIES

No ongoing studies of 2-butanone were identified by the National Institutes of Health (NIH) (RePORTER 2020).

CHAPTER 7. REGULATIONS AND GUIDELINES

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

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

Agency	Description	Information	Reference
	Air		
EPA	RfC	5 mg/m^3 (1.7 ppm)	IRIS 2003
WHO	Air quality guidelines	Not listed	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018a
	1-Day health advisory (10-kg child)	75 mg/L	
	10-Day health advisory (10-kg child)	7.5 mg/L	
	DWEL	20 mg/L	
	Lifetime health advisory	4 mg/L	
	10^{-4} Cancer risk	No data	
	National primary drinking water regulations	Not listed	EPA 2009
	RfD	0.6 mg/kg/day	IRIS 2003
WHO	Drinking water quality guidelines	Not listed	WHO 2017
FDA	Substances Added to Food[a]	Approved under food additive and GRAS regulations	FDA 2020
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	Data are inadequate for an assessment of human carcinogenic potential	IRIS 2003
IARC	Carcinogenicity classification	No data	IARC 2020
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	200 ppm	OSHA 2019a, 2019b, 2019c
NIOSH	REL (up to 10-hour TWA)	200 ppm	NIOSH 2019
	STEL (15-minute TWA)	300 ppm	
	IDLH	3,000 ppm	NIOSH 1994

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

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air		EPA 2018b
	AEGL 1[b]		
	10-minute, 30-minute, 60-minute, 4-hour, and 8-hour	200 ppm	
	AEGL 2[b]		
	10-minute	4,900 ppm[c]	
	30-minute	3,400 ppm[c]	
	60-minute	2,700 ppm[c]	
	4-hour	1,700 ppm	
	8-hour	1,700 ppm	
	AEGL 3[b]		
	10-minute	10,000 ppm[d]	
	30-minute	10,000 ppm[d]	
	60-minute	4,000 ppm[c]	
	4-hour	2,500 ppm[c]	
	8-hour	2,500 ppm[c]	
DOE	PACs-air		DOE 2018a
	PAC-1[e]	200 ppm	
	PAC-2[e]	2,700 ppm	
	PAC-3[e]	4,000 ppm	

[a]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".
[b]Definitions of AEGL terminology are available from U.S. Environmental Protection Agency (EPA 2018c).
[c]Concentration is ≥10% of the Lower Explosive Limit (LEL) of 18,000 ppm for methyl ethyl ketone. Safety considerations against the hazard of explosion must be taken into account.
[d]Concentration is ≥50% of the LEL of 18,000 ppm for methyl ethyl ketone. Extreme safety considerations against the hazard of explosion must be taken into account.
[c]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO 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; STEL = short-term exposure limit; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

Alderson MR, Rattan NS. 1980. Mortality of workers on an isopropyl alcohol plant and two MEK dewaxing plants. Br J Ind Med 37(1):85-89. http://doi.org/10.1136/oem.37.1.85.

Allen N, Mendell JR, Billmaier DJ, et al. 1975. Toxic polyneuropathy due to methyl n-butyl ketone. An industrial outbreak. Arch Neurol 32(4):209-218. http://doi.org/10.1001/archneur.1975.00490460025001.

Altenkirch H, Stoltenburg G, Wagner HM. 1978. Experimental studies on hydrocarbon neuropathies induced by methyl-ethyl-ketone (MEK). J Neurol 219(3):159-170. http://doi.org/10.1007/BF00314531.

Altenkirch H, Stoltenburg-Didinger G, Wagner H. 1979. Experimental data on the neurotoxicity of methyl-ethyl-ketone. Experentia 35(4):503-504. http://doi.org/10.1007/BF01922732.

Altenkirch H, Mager J, Stoltenburg G, et al. 1977. Toxic polyneuropathies after sniffing a glue thinner. J Neurol 214(2):137-152. http://doi.org/10.1007/BF02430351.

Altenkirch H, Wagner HM, Stoltenburg G, et al. 1982. Nervous system responses of rats to subchronic inhalation of N-hexane and N-hexane + methyl-ethyl-ketone mixtures. J Neurol Sci 57(2-3):209-219. http://doi.org/10.1016/0022-510x(82)90028-4.

Amoore JE, Hautala E. 1983. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 3(6):272-290. http://doi.org/10.1002/jat.2550030603.

Anbar M, Neta P. 1967. A compilation of specific bimolecular rate constant for the reactions of hydrated electrons, hydrogen atoms and hydroxyl radical with inorganic and organic compounds in aqueous solution. Int J Appl Radiat Isot 18(7):493-523. http://doi.org/10.1016/0020-708X(67)90115-9.

Anderson C, Sundberg K, Groth O. 1986. Animal model for assessment of skin irritancy. Contact Dermatitis 15(3):143-151. http://doi.org/10.1111/j.1600-0536.1986.tb01315.x.

Aoki K, Zhao W, Misumi J, et al. 1996. Changes in 2,5-hexanedione concentration in the Sciatic Nerve, serum and urine of rats induced by combined administration of 2,5-hexanedione with acetone or methyl ethyl ketone. J Occup Health 38(1):30-35.

Atkinson R. 1985. Kinetics and mechanisms of the gas-phase reactions of hydroxyl radical with organic compounds under atmospheric conditions. Chem Rev 85:69-201.

ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Agency for Toxic Substances and Disease Registry. Fed Regist 54(174):37618-37634.

ATSDR. 2005a. Health consultation: State of Arizona Silver Creek Subdivision. Atlanta, GA: Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/hac/PHA/StateOfArizona-SilverCreekSudv/SilverCreekHCFinal060305.pdf. August 12, 2020.

ATSDR. 2005b. Health consultation: Evaluation of potential soil gas migration in residences adjacent to the Pemaco Superfund site Maywood, Los Angeles County, California. Atlanta, GA: Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/HAC/pha/PemacoSuperfundSite042905/PemacoHC042505.pdf. August 12, 2020.

ATSDR. 2019. 2-Butanone. Full SPL data. Substance priority list (SPL) resource page. Agency for Toxic Substances and Disease Registry.

Babeu L, Vaishnav DD. 1987. Prediction of biodegradability for selected organic chemicals. J Ind Microbiol 2(2):107-115. http://doi.org/10.1007/BF01569509.

Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8(4):471-486.

Basler A. 1986. Aneuploidy-inducing chemicals in yeast evaluated by the micronucleus test. Mutat Res 174(1):11-13. http://doi.org/10.1016/0165-7992(86)90070-9.

8. REFERENCES

Beliveau M, Krishnan K. 2000. Estimation of rat blood:air partition coefficients of volatile organic chemicals using reconstituted mixtures of blood components. Toxicol Lett 116(3):183-188. http://doi.org/10.1016/s0378-4274(00)00219-8.

Berg EF. 1971. Retrobulbar neuritis. A case report of presumed solvent toxicity. Ann Ophthalmol 3(12):1351-1253.

Bertsch W, Anderson E, Holzer G. 1975. Trace analysis of organic volatiles in water by gas chromatography-mass spectrometry with glass capillary columns. J Chromatogr 112:701-718. http://doi.org/10.1016/s0021-9673(00)99998-9.

Billmaier D, Allen N, Craft B, et al. 1974. Peripheral neuropathy in a coated fabrics plant. J Occup Med 16(10):665-671.

Blair A, Hartge P, Stewart PA, et al. 1998. Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow up. Occup Environ Med 55(3):161-171. http://doi.org/10.1136/oem.55.3.161.

Brady JF, Li D, Ishizaki H, et al. 1989. Induction of cytochromes P450IIE1 and P450IIB1 by secondary ketones and the role of P450IIE1 in chloroform metabolism. Toxicol Appl Pharmacol 100(2):342-349. http://doi.org/10.1016/0041-008x(89)90320-7.

Bridie AL, Wolff CJM, Winter M. 1979. BOD and COD of some petrochemicals. Water Res 13(7):627-630. http://doi.org/10.1016/0043-1354(79)90011-3.

Brooke I, Cocker J, Delic JI, et al. 1998. Dermal uptake of solvents from the vapour phase: An experimental study in humans. Ann Occup Hyg 42(8):531-540. http://doi.org/10.1016/s0003-4878(98)00064-7.

Brown EM, Hewitt WR. 1984. Dose-response relationships in ketone-induced potentiation of chloroform hepato- and nephrotoxicity. Toxicol Appl Pharmacol 76(3):437-453. http://doi.org/10.1016/0041-008x(84)90348-x.

Brown W, Setzer J, Dick R, et al. 1986. Body burden profiles of single and mixed exposure to solvents. In: The changing nature of work and workforce, Proceedings of the Third Joint US-Finnish Science Symposium, Frankfort, Kentucky. Cincinnati, OH: National Institute for Occupational Safety and Health, 111-114.

Brown WD, Setzer JV, Dick RB, et al. 1987. Body burden profiles of single and mixed solvent exposures. J Occup Med 29(11):877-883.

Browning E. 1965. Ketones. In: Toxicity and metabolism of industrial solvents. New York, NY: Elsevier Publishing Co., 412-462.

Brugnone F, Perbellini L, Apostoli P, et al. 1983. Environmental and biological monitoring of occupational methylethyl ketone exposure. Dev Toxicol Environ Sci 11:571-574.

Burk T, Zarus G. 2013. Community exposures to chemicals through vapor intrusion: a review of past agency for toxic substances and Disease Registry public health evaluations. J Environ Health 75(9):36-41.

Callender TJ. 1995. Neurotoxic impairment in a case of methylethyl-ketone exposure. Arch Environ Health 50(5):392.

Cammaerts MC, Inwood MR, Morgan ED, et al. 1978. Comparative study of the pheromones emitted by workers of the ants Myrmica rubra and Myrmica scabrinodis. J Insect Physiol 24(3):207-214. http://doi.org/10.1016/0022-1910(78)90036-7.

CAS. 1989. Chemical Abstracts Registry File. September 19, 1989. Chemical Abstracts Service.

Cavender FL, Casey HW. 1981. 90-Day vapor inhalation toxicity study of methyl ethyl ketone in albino rats. Chemical Industrial Institute of Toxicology. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS84003A. 878212064. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0205953.xhtml. May 7, 2020.

Cavender FL, Casey HW, Salem H, et al. 1983. A 90-day vapor inhalation toxicity study of methyl ethyl ketone. Fundam Appl Toxicol 3(4):264-270. http://doi.org/10.1016/s0272-0590(83)80138-9.

Chia SE, Ong CN, Phoon WH, et al. 1993. Neurobehavioural effects on workers in a video tape manufacturing factory in Singapore. Neurotoxicology 14(1):51-56.

8. REFERENCES

Chemline. 1989. National Library of Medicine Chemline Database. September 19, 1989.

Chou WL, Speece RE, Siddiqi RH. 1978. Acclimation and degradation of petrochemical wastewater components by methane fermentation. Biotechnol Bioeng Symp 8:391-414.

Churchill JE, Ashley DL, Kaye WE. 2001. Recent chemical exposures and blood volatile organic compound levels in a large population-based sample. Arch Environ Health 56(2):157-166. http://doi.org/10.1080/00039890109604068.

Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131. http://doi.org/10.1177/074823378500100408.

Coleman WE, Lingg RD, Melton RG, et al. 1976. The occurrence of volatile organics in five drinking water supplies using gas chromatography/mass spectrometry. In: Keith L, ed. Analysis and identification of organic substances in water. Ann Arbor, MI: Ann Arbor Science, 305-327.

Conkle JP, Camp BJ, Welch BE. 1975. Trace composition of human respiratory gas. Arch Environ Health 30(6):290-295. http://doi.org/10.1080/00039896.1975.10666702.

Corwin JF. 1969. Volatile oxygen-containing organic compounds in seawater: Determination. Bull Mar Sci 19:504-559.

Cosnier F, Nunge H, Brochard C, et al. 2014. Impact of coexposure on toluene biomarkers in rats. Xenobiotica 44(3):217-228. http://doi.org/10.3109/00498254.2013.830204.

Cosnier F, Grossmann S, Nunge H, et al. 2018a. Metabolism of inhaled methylethylketone in rats. Drug Chem Toxicol 41(1):42-50. http://doi.org/10.1080/01480545.2017.1289220.

Cosnier F, Nunge H, Bonfanti E, et al. 2018b. Toluene and methylethylketone: effect of combined exposure on their metabolism in rat. Xenobiotica 48(7):684-694. http://doi.org/10.1080/00498254.2017.1362604.

Couri D, Abdel-Rahman MS, Hetland LB. 1978. Biotransformation of n-hexane and methyl n-butyl ketone in guinea pigs and mice. Am Ind Hyg Assoc J 39(4):295-300. http://doi.org/10.1080/0002889778507761.

Cox GE, Bailey DE, Morgareidge K. 1975. Toxicity studies in rats with 2-butanol including growth, reproduction, and teratologic observations. Food and Drug Research Laboratories, Inc. Submitted to the U.S. Environmental Protection Agency under TSCA section 8E. OTS0571256. 88-920009599. 8EHQ-1092-11318. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0571256.xhtml. May 7, 2020.

Cox RA, Derwent RG, Williams MR. 1980. Atmospheric photooxidation reactions. Rates, reactivity, and mechanism for reaction of organic compounds with hydroxyl radicals. Environ Sci Technol 14(1):57-61. http://doi.org/10.1021/es60161a007.

Cox RA, Patrick KF, Chant SA. 1981. Mechanism of atmospheric photooxidation of organic compounds. Reactions of alkoxy radicals in oxidation of n-butane and simple ketones. Environ Sci Technol 15(5):587-592. http://doi.org/10.1021/es00087a011.

Cunningham J, Sharkawi M, Plaa GL. 1989. Pharmacological and metabolic interactions between ethanol and methyl n-butyl ketone, methyl isobutyl ketone, methyl ethyl ketone, or acetone in mice. Fundam Appl Toxicol 13(1):102-109. http://doi.org/10.1016/0272-0590(89)90310-2.

Dahl AR, Snipes MB, Gerde P. 1991. Sites for uptake of inhaled vapors in beagle dogs. Toxicol Appl Pharmacol 109(2):263-275. http://doi.org/10.1016/0041-008x(91)90174-d.

Darnall KR, Lloyd AC, Winer AM, et al. 1976. Reactivity scales for atmospheric hydrocarbons based on reaction with hydroxyl radical. Environ Sci Technol 10(7):692-696. http://doi.org/10.1021/es60118a008.

Davis T, Baker R. 1975. Eye irritation tests with four samples of methyl ethyl ketone in albino rabbits. Celanese Chemical Corporation, Inc. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0206023. 878211195. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0206023.xhtml. May 7, 2020.

De Ceaurriz J, Desiles J, Bonnet P, et al. 1983. Concentration-dependent behavioral changes in mice following short-term inhalation exposure to various industrial solvents. Toxicol Appl Pharmacol 67:383-389. http://doi.org/10.1016/0041-008x(83)90322-8.

Deacon M, Pilny M, John J, et al. 1981. Embryotoxicity and fetotoxicity of inhaled methyl ethyl ketone in rats. Toxicol Appl Pharmacol 59:620-622. http://doi.org/10.1016/0041-008X(81)90317-3.

Decker DW, Clark CS, Elia VJ, et al. 1983. Worker exposure to organic vapors at a liquid chemical waste incinerator. Am Ind Hyg Assoc J 44(4):296-300. http://doi.org/10.1080/15298668391404833.

Del Rosario R, De Lumen BO, Habu T, et al. 1984. Comparison of headspace volatiles from winged beans and soybeans. J Agric Food Chem 32(5):1011-1015. http://doi.org/10.1021/jf00125a015.

Delfino JJ, Miles CJ. 1985. Aerobic and anaerobic degradation of organic contaminants in Florida groundwater. Soil Crop Sci Soc 44:9-12.

Dick RB, Setzer JV, Wait R, et al. 1984. Effects of acute exposure of toluene and methyl ethyl ketone on psychomotor performance. Int Arch Occup Environ Health 54(2):91-109. http://doi.org/10.1007/BF00378512.

Dick RB, Brown WD, Setzer JV, et al. 1988. Effects of short duration exposures to acetone and methyl ethyl ketone. Toxicol Lett 43(1-3):31-49. http://doi.org/10.1016/0378-4274(88)90019-7.

Dick RB, Setzer JV, Taylor BJ, et al. 1989. Neurobehavioural effects of short duration exposures to acetone and methyl ethyl ketone. Br J Ind Med 46(2):111-121. http://doi.org/10.1136/oem.46.2.111.

Dick RB, Krieg EF, Setzer J, et al. 1992. Neurobehavioral effects from acute exposures to methyl isobutyl ketone and methyl ethyl ketone. Fundam Appl Toxicol 19(3):453-473. http://doi.org/10.1016/0272-0590(92)90185-k.

Dietz FK, Traiger GJ. 1979. Potentiation of CCl4 hepatotoxicity in rats by a metabolite of 2-butanone: 2,3-butanediol. Toxicology 14(3):209-215. http://doi.org/10.1016/0300-483x(79)90003-9.

Dietz FK, Rodriguez-Giaxola M, Traiger GJ, et al. 1981. Pharmacokinetics of 2-butanol and its metabolites in the rat. J Pharmacokinet Biopharm 9(5):553-576. http://doi.org/10.1007/BF01061026.

Dilling WL, Bredeweg CJ, Tefertiller NB. 1976. Organic photochemistry. XIII. Simulated atmospheric photo decomposition rates of methylene chloride, 1,1,1-trichlcroethane, trichloroethylene, tetrachloroethylene, and other compounds. Environ Sci Technol 10(4):351-356. http://doi.org/10.1021/es60115a006.

DiVincenzo G, Kaplan C, Dedinas J. 1976. Characterization of the metabolites of methyl n-butyl ketone, methyl iso-butyl ketone, and methyl ethyl ketone in guinea pig serum and their clearance. Toxicol Appl Pharmacol 36:511-522. http://doi.org/10.1016/0041-008x(76)90230-1.

DOE. 2018a. Table 3: Protective Action Criteria (PAC) Rev. 29a based on applicable 60-minute AEGLs, ERPGs, or TEELs. The chemicals are listed by CASRN. June 2018. Oak Ridge, TN: U.S. Department of Energy. https://edms.energy.gov/pac/docs/Revision_29A_Table3.pdf. April 12, 2020.

DOE. 2018b. Protective Action Criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 29A, June 2018. Oak Ridge, TN: U.S. Department of Energy. https://edms.energy.gov/pac/. April 12, 2020.

Doty RL, Deems DA, Frye RE, et al. 1988. Olfactory sensitivity, nasal resistance, and autonomic function in patients with multiple chemical sensitivities. Arch Otolaryngol Head Neck Surg 114(12):1422-1427. http://doi.org/10.1001/archotol.1988.01860240072027.

Dumont JP, Adda J. 1978. Occurrence of sesquiterpenes in mountain cheese volatiles. J Agric Food Chem 26(2):364-367. http://doi.org/10.1021/jf60216a037.

Dunovant VS, Clark CS, Que Hee SS, et al. 1986. Volatile organics in the wastewater and airspaces of three wastewater plants. J Water Pollut Control Fed 58(9):886-895.

Eastman Kodak. 1978. Chronic skin application of MnBK, MEK, MiBK, MEK/MiBK and MEK/MnBK. Eastman Kodak Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0206514. 878214321. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0206514.xhtml. May 7, 2020.

Edney EO, Kleindienst TE, Corse EW. 1986. Room temperature rate constants for the reaction of OH with selected chlorinated and oxygenated hydrocarbons. Int J Chem Kinet 18(12):1355-1371. http://doi.org/10.1002/kin.550181207.

8. REFERENCES

Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 15(1):30-38. http://doi.org/10.1021/es00083a002.

EPA. 1974. Draft analytical report: New Orleans Water supply study. Dallas, TX: U.S. Environmental Protection Agency. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=9101WZ63.txt. May 7, 2020.

EPA. 1975. Preliminary assessment of suspected carcinogens in drinking water Interim report to Congress. Washington, DC: U.S. Environmental Protection Agency. EPA560475005. PB250961. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=91012F6P.txt. May 7, 2020.

EPA. 1986. Validation of OH radical reaction rate constant test protocol. Washington, DC: U.S. Environmental Protection Agency. PB86166758. EPA68024033.

EPA. 1987a. Organic emission measurements via small chamber testing. Washington, DC: U.S. Environmental Protection Agency. PB87199154XAB. EPA600D87187. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB87199154.xhtml. May 7, 2020.

EPA. 1987b. Hydrolysis rate constants, partition coefficients, and their water solubilities for 129 chemicals. A summary of fate constants provided for the concentration-based listing program, 1987. Athens, GA: U.S. Environmental Protection Agency.

EPA. 1987c. Superfund record of decision: Galloway Ponds Site, Galloway, TN. U.S. Environmental Protection Agency. USEPARODR0486013. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=91002B7W.txt. June 30, 2020.

EPA. 1987d. Superfund record of decision: Lang Property Pemberton Township, NJ. Washington, DC: U.S. Environmental Protection Agency. EPARODR0286031. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=9100SALM.txt. October 1, 2020.

EPA. 1988. National ambient volatile organic compounds (VOCS) database update. U.S. Environmental Protection Agency. EPA600388010A. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100SS3R.txt. May 7, 2020.

EPA. 2003. Toxicological review of methyl ethyl ketone. In support of summary information on the Integrated Risk Information System (IRIS). Washington, DC: U.S. Environmental Protection Agency. EPA635R03009. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0071tr.pdf. May 7, 2020.

EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency. EPA260B05001. https://19january2017snapshot.epa.gov/sites/production/files/documents/ry2004rfi.pdf. May 7, 2020.

EPA. 2009. National primary drinking water regulations. Washington, DC: U.S. Environmental Protection Agency. EPA816F090004. https://www.epa.gov/sites/production/files/2016-06/documents/npwdr_complete_table.pdf. September 7, 2017.

EPA. 2011. Background indoor air concentrations of volatile organic compounds in North American residences (1990–2005): A compilation of statistics for assessing vapor intrusion. Washington, DC: U.S. Environmental Protection Agency. EPA530R10001. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100GL6W.txt. August 12, 2020.

EPA. 2018a. 2018 Edition of the drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency. EPA822S12001. https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf. July 25, 2018.

EPA. 2018b. Acute Exposure Guideline Levels (AEGLs) values. U.S. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2018-08/documents/compiled_aegls_update_27jul2018.pdf. April 12, 2020.

EPA. 2018c. About Acute Exposure Guideline Levels (AEGLs). U.S. Environmental Protection Agency. https://www.epa.gov/aegl/about-acute-exposure-guideline-levels-aegls. July 26, 2018.

EPA. 2020. Chemical data reporting: 2-butanone. U.S. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2020-02/csv_data_file.zip. May 6, 2020.

8. REFERENCES

FDA. 2020. 2-Butanone. Substances added to food. Washington, DC: U.S. Food and Drug Administration. https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=FoodSubstances&id=BUTANONE. May 1, 2020.

Fisher GS, Legendre MG, Lovgren NV, et al. 1979. Volatile constituents of southern pea seed [Vigna unguiculata (L.) Walp.]. J Agric Food Chem 27(1):7-11. http://doi.org/10.1021/jf60221a040.

Fisher J, Mahle D, Bankston L, et al. 1997. Lactational transfer of volatile chemicals in breast milk. Am Ind Hyg Assoc J 58(6):425-431. http://doi.org/10.1080/15428119791012667.

Francis AJ, Iden CR, Nine BJ, et al. 1980. Characterization of organics in leachates from low-level radioactive waste disposal sites. Nucl Technol 50(2):158-163. http://doi.org/10.13182/NT80-A32541.

Gao Y, Zhang Y, Kamijima M, et al. 2014. Quantitative assessments of indoor air pollution and the risk of childhood acute leukemia in Shanghai. Environ Pollut 187:81-89. http://doi.org/10.1016/j.envpol.2013.12.029.

Gaudy AF, Turner BG, Pusztaszeri S. 1963. Biological treatment of volatile waste components. J Water Pollut Control Fed 35(1):75-93.

Geller I, Gause E, Kaplan H, et al. 1979. Effects of acetone, methyl ethyl ketone and methyl isobutyl ketone on a match-to-sample task in the baboon. Pharmacol Biochem Behav 11(4):401-406. http://doi.org/10.1016/0091-3057(79)90115-1.

Ghittori S, Imbriani M, Pezzagno G, et al. 1987. The urinary concentration of solvents as a biological indicator of exposure: proposal for the biological equivalent exposure limit for nine solvents. Am Ind Hyg Assoc J 48(9):786-790.

Giroux D, Lapointe G, Baril M. 1992. Toxicological index and the presence in the workplace of chemical hazards for workers who breast-feed infants. Am Ind Hyg Assoc J 53(7):471-474. http://doi.org/10.1080/15298669291359960.

Gordon DT, Morgan ME. 1972. Principal volatile compounds in feed flavored milk. J Dairy Sci 55(7):905-912. http://doi.org/10.3168/jds.S0022-0302(72)85595-4.

Graham DG. 2000. Critical analysis of Mitran et al. (1997). Neurotoxicity associated with occupational exposure to acetone. Methyl ethyl ketone, and cyclohexanone. Environ. Res. 73, 181-188. Environ Res 82(2):181-185. http://doi.org/10.1006/enrs.1999.3988.

Grey TC, Shrimpton DH. 1967. Volatile components of raw chicken breast muscle. Br Poult Sci 8(1):23-33. http://doi.org/10.1080/00071666708415646.

Grosjean D. 1982. Formaldehyde and other carbonyls in Los Angeles ambient air. Environ Sci Technol 16(5):254-262. http://doi.org/10.1021/es00099a005.

Grosjean D, Wright B. 1983. Carbonyls in urban fog, ice fog, cloudwater and rainwater. Atmos Environ 17(10):2093-2096. http://doi.org/10.1016/0004-6981(83)90368-2.

Gunster DG, Gillis CA, Bonnevie NL, et al. 1993. Petroleum and hazardous chemical spills in Newark Bay, New Jersey, USA from 1982 to 1991. Environ Pollut 82(3):245-253. http://doi.org/10.1016/0269-7491(93)90126-9.

Güsten H, Klasinc L, Marić D. 1984. Prediction of the abiotic degradability of organic compounds in the troposphere. J Atmos Chem 2(1):83-93. http://doi.org/10.1007/bf00127264.

Hall LW, Scott Hall W, Bushong SJ, et al. 1987. In situ striped bass (Morone saxatilis) contaminant and water quality studies in the Potomac River. Aquat Toxicol 10(2-3):73-99. http://doi.org/10.1016/0166-445x(87)90016-6.

Halvorsen F, Ohneck R. 1985. MEK groundwater decontamination. In: Hazardous wastes and environmental emergencies. Silver Springs, MD: Hazardous Materials Control Research Institute, 193-195.

Hampton CV, Pierson WR, Harvey TM, et al. 1982. Hydrocarbon gases emitted from vehicles on the road. 1. A qualitative gas chromatography/mass spectrometry survey. Environ Sci Technol 16(5):287-298. http://doi.org/10.1021/es00099a011.

8. REFERENCES

Hansch C, Leo A, Hoekman D. 1995. Methyl ethyl ketone. In: Heller SR, ed. Exploring QSAR, hydrophobic, electronic, and steric constants. Washington, DC: American Chemistry Society, 9.

Hansen LF, Knudsen A, Nielsen GD. 1992. Sensory irritation effects of methyl ethyl ketone and its receptor activation mechanism. Pharmacol Toxicol 71(3 Pt 1):201-208. http://doi.org/10.1111/j.1600-0773.1992.tb00546.x.

Haskell Laboratory. 1971. Federal hazardous substances act tests - rabbit eye irritation. E.I. du Pont de Nemours and Company, Inc. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0215038. 8878220418. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0215038.xhtml. May 7, 2020.

Hawthorne SB, Sievers RE. 1984. Emission of organic air pollutants from shale oil wastewaters. Environ Sci Technol 18(6):483-490. http://doi.org/10.1021/es00124a016.

Hazleton Laboratories. 1963a. Primary skin irritation - rabbits. Exxon Chemical Americas. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0206264. 878210453. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0206264.xhtml. May 7, 2020.

Hazleton Laboratories. 1963b. Acute eye irritation - rabbits. Exxon Chemical Americas. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0206264. 878210454. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0206264.xhtml. May 7, 2020.

Hewitt W, Brown E, Plaa G. 1983. Relationship between the carbon skeleton length of ketonic solvents and potentiation of chloroform-induced hepatotoxicity in rats. Toxicol Lett 16:297-304. http://doi.org/10.1016/0378-4274(83)90190-x.

Hewitt L, Ayotte P, Plaa G. 1986. Modifications in rat hepato biliary function following treatment with acetone, 2-butanone, 2-hexanone, mirex or chlordecone and subsequently exposed to chloroform. Toxicol Appl Pharmacol 83:465-473. http://doi.org/10.1016/0041-008x(86)90229-2.

Hewitt LA, Valiquette C, Plaa GL. 1987. The role of biotransformation-detoxication in acetone-, 2-butanone-, and 2-hexanone-potentiated chloroform-induced hepatotoxicity. Can J Physiol Pharmacol 65(11):2313-2318. http://doi.org/10.1139/y87-367.

Hewitt LA, Palmason C, Masson S, et al. 1990. Evidence for the involvement of organelles in the mechanism of ketone-potentiated chloroform-induced hepatotoxicity. Liver 10(1):35-48. http://doi.org/10.1111/j.1600-0676.1990.tb00433.x.

Higgins CE, Griest WH, Olerich. 1983. Application of Tenax trapping to analysis of gas phase organic compounds in ultra-low tar cigarette smoke. J AOAC Int 66(5):1074-1083. http://doi.org/10.1093/jaoac/66.5.1074.

Hodgkin JH, Galbraith MN, Chong YK. 1982. Combustion products from burning polyethylene. J Macromol Sci Chem 17(1):35-43. http://doi.org/10.1080/00222338208056463.

Hoell D, Mensing T, Roggenbuck R, et al. 2012. 2-Butanone. In: Ullmann's encyclopedia of industrial chemistry. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co., 1-14. http://doi.org/10.1002/14356007.a04_475.pub2.

IARC. 2020. Agents classified by the IARC Monographs , Volumes 1–125. Lyon, France: International Agency for Research on Cancer. https://monographs.iarc.fr/list-of-classifications. April 30, 2020.

Ichihara G, Saito I, Kamijima M, et al. 1998. Urinary 2,5-hexanedione increases with potentiation of neurotoxicity in chronic coexposure to n-hexane and methyl ethyl ketone. Int Arch Occup Environ Health 71(2):100-104. http://doi.org/10.1007/s004200050255.

Imaoka S, Funae Y. 1991. Induction of cytochrome P450 isozymes in rat liver by methyl n-alkyl ketones and n-alkylbenzenes. Effects of hydrophobicity of inducers on inducibility of cytochrome P450. Biochem Pharmacol 42(Suppl):S143-150. http://doi.org/10.1016/0006-2952(91)90404-s.

Infante-Rivard C, Siemiatycki J, Lakhani R, et al. 2005. Maternal exposure to occupational solvents and childhood leukemia. Environ Health Perspect 113(6):787-792. http://doi.org/10.1289/ehp.7707.

IRIS. 2003. Methyl ethyl ketone (MEK). Integrated Risk Information System. Chemical assessment summary. Washington, DC: U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0071_summary.pdf. November 16, 2017.

8. REFERENCES

Isidorov VA, Zenkevich IG, Ioffe BV. 1985. Volatile organic compounds in the atmosphere of forests. Atmos Environ 19(1):1-8. http://doi.org/10.1016/0004-6981(85)90131-3.

Iyadomi M, Ichiba M, Zhang J, et al. 2000. Evaluation of skin irritants caused by organic solvents by means of the mouse ear thickness measurement method. J Occup Health 42(1):44-46. http://doi.org/10.1539/joh.42.44.

Jarke FH, Dravnieks A, Gordon SM. 1981. Organic contaminants in indoor air and their relation to outdoor contaminants. ASHRAE Trans 87(1):153-166.

Jongeneelen F, Berge WT, Boogaard P. 2013. Interpretation of human biological monitoring data using a newly developed generic physiological-based toxicokinetic model: examples of simulations with carbofuran and methyl ethyl ketone. In: Fowler BA, ed. Computational toxicology: Methods and applications for risk assessment. Boston, MA: Elsevier, Inc., 137-150. http://doi.org/10.1016/B978-0-12-396461-8.00010-5.

Jonsson A, Persson KA, Grigoriadis V. 1985. Measurements of some low molecular-weight oxygenated, aromatic and chlorinated hydrocarbons in ambient air and in vehicle emissions. Environ Int 11(2-4):383-392. http://doi.org/10.1016/0160-4120(85)90033-9.

Jung R, Engelhart G, Herbolt B, et al. 1992. Collaborative study of mutagenicity with Salmonella typhimurium TA102. Mutat Res 278(4):265-270. http://doi.org/10.1016/s0165-1218(10)80006-0.

Jungclaus GA, Lopez-Avila V, Hites RA. 1978. Organic compounds in an industrial waste water: A case study of their environmental impact. Environ Sci Technol 12(1):88-96. http://doi.org/10.1021/es60137a015.

Kavaler AR. 1987. Chemical profile methyl ethyl ketone. Chem Mark Rep 232(8):50.

Kawai T, Zhang ZW, Takeuchi A, et al. 2003. Methyl isobutyl ketone and methyl ethyl ketone in urine as biological markers of occupational exposure to these solvents at low levels. Int Arch Occup Environ Health 76(1):17-23. http://doi.org/10.1007/s00420-002-0374-9.

Keen AR, Walker NJ, Peberdy MF. 1974. The formation of 2-butanone and 2-butanol in cheddar cheese. J Dairy Res 41(2):249-257. http://doi.org/10.1017/S002202990001966X.

Kelly TJ, Callahan PJ, Pleil J, et al. 2002. Method development and field measurements for polar volatile organic compounds in ambient air. Environ Sci Technol 27(6):1146-1153. http://doi.org/10.1021/es00043a014.

Kennah HE, Hignet S, Laux PE, et al. 1989. An objective procedure for quantitating eye irritation based upon changes of corneal thickness. Fundam Appl Toxicol 12(2):258-268. http://doi.org/10.1016/0272-0590(89)90043-2.

Kim KW, Won YL, Park DJ, et al. 2014. Comparative study on the EC50 value in single and mixtures of dimethylformamide, methyl ethyl ketone, and toluene. Toxicol Res 30(3):199-204. http://doi.org/10.5487/tr.2014.30.3.199.

Kimura ET, Ebert DM, Dodge PW. 1971. Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol Appl Pharmacol 19(4):699-704. http://doi.org/10.1016/0041-008x(71)90301-2.

King PJ, Morris JG, Pollard JD. 1985. Glue sniffing neuropathy. Aust N Z J Med 15(3):293-299. http://doi.org/10.1111/j.1445-5994.1985.tb04039.x.

Kinlin TE, Muralidhara R, Pittet AO, et al. 1972. Volatile components of roasted filberts. J Agric Food Chem 20(5):1021-1028. http://doi.org/10.1021/jf60183a013.

Klimisch H. 1988. The inhalation hazard test; principle and method. Arch Toxicol 61:411-416.

Kolb DK. 1988. Teratogenic chemicals in undergraduate general chemistry laboratories. Stud Environ Sci 31:247-255. http://doi.org/10.1016/S0166-1116(09)70070-6.

Kopelman PG, Kalfayan PY. 1983. Severe metabolic acidosis after ingestion of butanone. Br Med J 286(6358):21-22. http://doi.org/10.1136/bmj.286.6358.21-a.

Kopfler FC, Melton RG, Mullaney JL, et al. 1977. Human exposure to water pollutants. In: Lloyd AC, ed. Advances in Environmental Science and Technology. Vol. 8. John Wiley & Sons Inc, 419-433.

Kreja L, Seidel HJ. 2002. Evaluation of the genotoxic potential of some microbial volatile organic compounds (MVOC) with the comet assay, the micronucleus assay and the HPRT gene mutation assay. Mutat Res 513(1-2):143-150. http://doi.org/10.1016/s1383-5718(01)00306-0.

Krishnan K, Anderson ME, Clewell HJ, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures. Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

Krotoszynski NK, Bruneau GM, O'Neill HJ. 1979. Measurement of chemical inhalation exposure in urban population in the presence of endogenous effluents. J Anal Toxicol 3(6):225-234. http://doi.org/10.1093/jat/3.6.225.

Kupferschmid LL, Perkins JL. 1986. Organic solvent recycling plant exposure levels. Appl Ind Hyg 1(3):122-131. http://doi.org/10.1080/08828032.1986.10390494.

Labelle CW, Brieger H. 1955. The vapor toxicity of a composite solvent and its principal components. AMA Arch Ind Health 12(6):623-627.

LaRegina J, Bozzelli JW, Harkov R, et al. 1986. Volatile organic compounds at hazardous waste sites and a sanitary landfill in New Jersey. An up-to-date review of the present situation. Environ Prog 5(1):18-27. http://doi.org/10.1002/ep.670050109.

Lemasters GK, Lockey JE, Olsen DM, et al. 1999. Comparison of internal dose measures of solvents in breath, blood and urine and genotoxic changes in aircraft maintenance personnel. Drug Chem Toxicol 22(1):181-200. http://doi.org/10.3109/01480549909029731.

Li GL, Yin SN, Watanabe T, et al. 1986. Benzene-specific increase in leukocyte alkaline phosphatase activity in rats exposed to vapors of various organic solvents. J Toxicol Environ Health 19(4):581-589. http://doi.org/10.1080/15287398609530954.

Liebich HM, Bertsch W, Zlatkis A, et al. 1975. Volatile organic components in the Skylab 4 spacecraft atmosphere. Aviat Space Environ Med 46(8):1002-1007.

Liira J, Riihimaki V, Pfaffli P. 1988a. Kinetics of methyl ethyl ketone in man: absorption, distribution and elimination in inhalation exposure. Int Arch Occup Environ Health 60(3):195-200. http://doi.org/10.1007/BF00378697.

Liira J, Riihimaki V, Engstrom K, et al. 1988b. Co-exposure of man to m-xylene and methyl ethyl ketone: Kinetics and metabolism. Scand J Work Environ Health 14:322-327. http://doi.org/10.5271/sjweh.1912.

Liira J, Riihimaki V, Engstrom K. 1990a. Effects of ethanol on the kinetics of methyl ethyl ketone in man. Br J Ind Med 47(5):325-330. http://doi.org/10.1136/oem.47.5.325.

Liira J, Johanson G, Riihimaki V. 1990b. Dose-dependent kinetics of inhaled methylethylketone in man. Toxicol Lett 50(2-3):195-201. http://doi.org/10.1016/0378-4274(90)90011-a.

Liira J, Elovaara E, Raunio H, et al. 1991. Metabolic interaction and disposition of methyl ethyl ketone and m-xylene in rats at single and repeated inhalation exposures. Xenobiotica 21(1):53-63. http://doi.org/10.3109/00498259109039450.

Liu M, Grant SG, Macina OT, et al. 1997. Structural and mechanistic bases for the induction of mitotic chromosomal loss and duplication ('malsegregation') in the yeast Saccharomyces cerevisiae: relevance to human carcinogenesis and developmental toxicology. Mutat Res 374(2):209-231. http://doi.org/10.1016/s0027-5107(96)00236-9.

Lovegren NV, Fisher GS, Legendre MG, et al. 1979. Volatile constituents of dried legumes. J Agric Food Chem 27(4):851-853. http://doi.org/10.1021/jf60224a055.

Lowry L. 1987. The biological exposure index: Its use in assessing chemical exposures in the workplace. Toxicology 47:55-69. http://doi.org/10.1016/0300-483x(87)90160-0.

Lyman WJ, Reehl WF, Rosenblatt DH. 1982. Methyl ethyl ketone. In: Handbook of chemical property estimation methods. New York, NY: McGraw Hill Book Co., Chapters 4, 7, 15.

Mahle DA, Gearhart JM, Grigsby CC, et al. 2007. Age-dependent partition coefficients for a mixture of volatile organic solvents in Sprague-Dawley rats and humans. J Toxicol Environ Health 70(20):1745-1751. http://doi.org/10.1080/15287390701458991.

Mayer VW, Goin CJ. 1987. Effects of chemical combinations on the induction of aneuploidy in Saccharomyces cerevisiae. Mutat Res 187(1):21-30. http://doi.org/10.1016/0165-1218(87)90072-3.

Mayer VW, Goin CJ. 1994. Induction of chromosome loss in yeast by combined treatment with neurotoxic hexacarbons and monoketones. Mutat Res 341(2):83-91. http://doi.org/10.1016/0165-1218(94)90090-6.

McDermott C, Allshire A, van Pelt FN, et al. 2007. Sub-chronic toxicity of low concentrations of industrial volatile organic pollutants in vitro. Toxicol Appl Pharmacol 219(1):85-94. http://doi.org/10.1016/j.taap.2006.12.004.

Mill T. 1982. Hydrolysis and oxidation processes in the environment. Environ Toxicol Chem 1(2):135-141. http://doi.org/10.1002/etc.5620010204.

Mill T, Hendry DG, Richardson H. 1980. Free-radical oxidants in natural waters. Science 207(4433):886-887. http://doi.org/10.1126/science.207.4433.886.

Misumi J, Nagano M. 1985. Experimental study on the enhancement of the neurotoxicity of methyl n-butyl ketone by non-neurotoxic aliphatic monoketones. Br J Ind Med 42(3):155-161. http://doi.org/10.1136/oem.42.3.155.

Mitran E, Callender T, Orha B, et al. 1997. Neurotoxicity associated with occupational exposure to acetone, methyl ethyl ketone, and cyclohexanone. Environ Res 73(1-2):181-188. http://doi.org/10.1006/enrs.1997.3703.

Miyasaka M, Kumai M, Koizumi A, et al. 1982. Biological monitoring of occupational exposure to methyl ethyl ketone by means of urinalysis for methyl ethyl ketone itself. Int Arch Occup Environ Health 50(2):131-137. http://doi.org/10.1007/BF00378075.

Mortensen B, Zahlsen K, Nilsen OG. 1998. Metabolic interaction of n-hexane and methyl ethyl ketone in vitro in a head space rat liver S9 vial equilibration system. Pharmacol Toxicol 82(2):67-73. http://doi.org/10.1111/j.1600-0773.1998.tb01400.x.

Munies R, Wurster DE. 1965. Investigation of some factors influencing percutaneous absorption. III. Absorption of methyl ethyl ketone. J Pharm Sci 54(9):1281-1284. http://doi.org/10.1002/jps.2600540912.

Muttray A, Jung D, Klimek L, et al. 2002. Effects of an external exposure to 200 ppm methyl ethyl ketone on nasal mucosa in healthy volunteers. Int Arch Occup Environ Health 75(3):197-200. http://doi.org/10.1007/s00420-001-0291-3.

NAS/NRC. 1989. Report of the oversight committee. Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences. National Research Council. 15-35. https://www.ncbi.nlm.nih.gov/books/NBK218924/. May 7, 2020.

Neier W, Strehlke G. 1985. Methyl ethyl ketone. In: Ullman's encyclopedia of industrial chemistry. Deerfield Beach, FL: Wiley-VCH Verlag GmbH & Co. KGaA, 475-481.

Nelson KW, Ege JF, Ross M, et al. 1943. Sensory Response to certain Industrial Solvent Vapors. J Ind Hyg Toxicol 25(7):282-285.

NIOSH. 1982. Health hazard evaluation report: Red Wing Shoe Company, Red Wing, Minnesota. Cincinnati, OH: National Institute for Occupational Safety and Health. HETA814551229. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB84172592.xhtml. May 7, 2020.

NIOSH. 1984. Method 2500. NIOSH manual of analytical methods. Cincinnati, OH: National Institute for Occupational Safety and Health. 2500-l to 2500-2503.

NIOSH. 1989. National occupational exposure survey (NOES). Cincinnati, OH: National Institute for Occupational Safety and Health.

NIOSH. 1994. 2-Butanone. Immediately dangerous to life or health concentrations (IDLH). Atlanta, GA: National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/idlh/78933.html. November 16, 2017.

NIOSH. 1996. Method 2500: Methyl ethyl ketone. National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/docs/2003-154/pdfs/2500.pdf. September 23, 2020.

NIOSH. 2019. Methyl ethyl ketone. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/npg/npgd0069.html. May 1, 2020.

8. REFERENCES

NLM. 2020. Pubchem data: Methyl ethyl ketone. National Library of Medicine. https://pubchem.ncbi.nlm.nih.gov/compound/6569. August 12, 2020.

NTP. 1989. Inhalation developmental toxicology studies: Teratology study of methyl ethyl ketone in mice. National Toxicology Program. PNL6833. DE89009563. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/DE89009563.xhtml. May 7, 2020.

NTP. 2016. Report on carcinogens, fourteenth edition. CASRN Index in MS Excel. Research Triangle Park, NC: National Toxicology Program. https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html#P. March 1, 2017.

NWQMC. 2020. 2-Butanone sample results. National Water Quality Monitoring Council. https://www.waterqualitydata.us/portal/#characteristicName=Methyl%20ethyl%20ketone&mimeType=csv. May 6, 2020.

O'Donoghue J, Krasavage W, DiVincenzo G, et al. 1984. Further studies on ketone neurotoxicity and interactions. Toxicol Appl Pharmacol 72:201-209. http://doi.org/10.1016/0041-008x(84)90304-1.

O'Donoghue JL, Haworth SR, Curren RD, et al. 1988. Mutagenicity studies on ketone solvents: methyl ethyl ketone, methyl isobutyl ketone, and isophorone. Mutat Res 206(2):149-161. http://doi.org/10.1016/0165-1218(88)90154-1.

Ogawa I, Fritz JS. 1985. Determination of low concentrations of low-molecular-weight aldehydes and ketones in aqueous samples. J Chromatogr 329:81-89. http://doi.org/10.1016/S0021-9673(01)81897-5.

Orti-Pareja M, Jimenez-Jimenez FJ, Miquel J, et al. 1996. Reversible myoclonus, tremor, and ataxia in a patient exposed to methyl ethyl ketone. Neurology 46(1):272. http://doi.org/10.1212/wnl.46.1.272.

Osborne JS, Adamek S, Hobbs ME. 1956. Some components of gas phase of cigarette smoke. Anal Chem 28(2):211-215. http://doi.org/10.1021/ac60110a020.

OSHA. 2019a. Occupational safety and health standards for shipyard employment. Subpart Z - Toxic and hazardous substances. Air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000. https://www.osha.gov/laws-regs/regulations/standardnumber/1915/1915.1000. October 25, 2019.

OSHA. 2019b. Occupational safety and health standards. Subpart Z - Toxic and hazardous substances. Air contaminants. Table Z-1: Limits for air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000. https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.1000TABLEZ1. October 25, 2019.

OSHA. 2019c. Safety and health regulations for construction. Subpart D - Occupational health and environment controls. Gases, vapors, fumes, dusts, and mists. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55 Appendix A. https://www.osha.gov/laws-regs/regulations/standardnumber/1926/1926.55AppA. October 25, 2019.

Papa AJ, Sherman PD. 1981. Ketones. In: Kirk-Othmer Encyclopedia of chemical technology. Vol. 13. 3rd ed. New York, NY: John Wiley and Sons, Inc, 894-941.

Patty F, Schrenk H, Yant W. 1935. Acute response of guinea pigs to vapours of some new commercial organic compounds. US Treasury Publ Health Rep 50:1217.

Pellizzari ED. 1982. Analysis for organic vapor emissions near industrial and chemical waste disposal sites. Environ Sci Technol 16(11):781-785. http://doi.org/10.1021/es00105a010.

Pellizzari ED, Castillo NP, Willis S, et al. 1979. Identification of organic components in aqueous effluents from energy-related processes. In: Van Hall CE, ed. Measurement of organic pollutants in water and wastewater. West Conshohocken, PA: ASTM International, 256-274. http://doi.org/10.1520/STP686-EB.

Pellizzari ED, Hartwell TD, Harris BS, et al. 1982. Purgeable organic compounds in mother's milk. Bull Environ Contam Toxicol 28(3):322-328. http://doi.org/10.1007/BF01608515.

Perbellini L, Brugnone F, Mozzo P, et al. 1984. Methyl ethyl ketone exposure in industrial workers. Uptake and kinetics. Int Arch Occup Environ Health 54(1):73-81. http://doi.org/10.1007/BF00378730.

Phillips WE, Perry JJ. 1974. Metabolism of n-butane and 2-butanone by Mycobacterium vaccae. J Bacteriol 120(2):987-989.

Price KS, Waggy GT, Conway RA. 1974. Brine shrimp bioassay and seawater BOD of petrochemicals. J Water Pollut Control Fed 46(1):63-77.

Price EA, D'Alessandro A, Kearney T, et al. 1994. Osmolar gap with minimal acidosis in combined methanol and methyl ethyl ketone ingestion. J Toxicol Clin Toxicol 32(1):79-84. http://doi.org/10.3109/15563659409000434.

Radican L, Blair A, Stewart P, et al. 2008. Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: extended follow-up. J Occup Environ Med 50(11):1306-1319. http://doi.org/10.1097/JOM.0b013e3181845f7f.

Ralston WH, Hilderbrand RL, Uddin DE, et al. 1985. Potentiation of 2,5-hexanedione neurotoxicity by methyl ethyl ketone. Toxicol Appl Pharmacol 81(2):319-327. http://doi.org/10.1016/0041-008x(85)90169-3.

Rathbun RE, Tai DY. 1987. Vapor pressures and gas-film coefficients for ketones. Chemosphere 16(1):69-78. http://doi.org/10.1016/0045-6535(87)90110-x.

Raunio H, Liira J, Elovaara E, et al. 1990. Cytochrome P450 isozyme induction by methyl ethyl ketone and m-xylene in rat liver. Toxicol Appl Pharmacol 103(1):175-179. http://doi.org/10.1016/0041-008x(90)90273-w.

Raymond P, Plaa GL. 1995a. Ketone potentiation of haloalkane-induced hepato- and nephrotoxicity. I. Dose-response relationships. J Toxicol Environ Health 45(4):465-480. http://doi.org/10.1080/15287399509532009.

Raymond P, Plaa GL. 1995b. Ketone potentiation of haloalkane-induced hepato- and nephrotoxicity. II. Implication of monooxygenases. J Toxicol Environ Health 46(3):317-328. http://doi.org/10.1080/15287399509532038.

Raymond P, Plaa GL. 1996. Ketone potentiation of haloalkane-induced hepatotoxicity: CCl4 and ketone treatment on hepatic membrane integrity. J Toxicol Environ Health 49(3):285-300. http://doi.org/10.1080/00984108.1996.11667602.

RePORTER. 2020. 2-Butanone. National Institutes of Health, Research Portfolio Online Reporting Tools. http://projectreporter.nih.gov/reporter.cfm. April 30, 2020.

Richardson SD, Thruston AD, Caughran TV, et al. 1999. Identification of new ozone disinfection byproducts in drinking water. Environ Sci Technol 33(19):3368-3377. http://doi.org/10.1021/es981218c.

Riddick JA, Bunger WB, Sakano TK. 1986. Organic solvents. In: Physical properties and methods of purification techniques of chemistry. 4th ed. New York, NY: Wiley-Interscience, 338-339.

Riihimaki V. 1986. Metabolism and excretion of organic solvents. In: Ulfvarson U, ed. Progress in clinical and biological research. Vol. 220. New York, NY: Alan R Liss, Inc., 61-72.

Robertson P, White EL, Bus JS. 1989. Effects of methyl ethyl ketone pretreatment on hepatic mixed-function oxidase activity and on in vivo metabolism of n-hexane. Xenobiotica 19(7):721-729. http://doi.org/10.3109/00498258909042310.

Roy WR, Griffin RA. 1985. Mobility of organic solvents in water-saturated soil materials. Environ Geol Water Sci 7(4):241-247. http://doi.org/10.1007/BF02509925.

Sabel GV, Clark TP. 1984. Volatile organic compounds as indicators of municipal solid waste leachate contamination. Waste Manag Res 2(2):119-130. http://doi.org/10.1016/0734-242X(84)90135-6.

Saida K, Mendell JR, Weiss HS. 1976. Peripheral nerve changes induced by methyl n-butyl ketone and potentiation by methyl ethyl ketone. J Neuropathol Exp Neurol 35(3):207-225. http://doi.org/10.1097/00005072-197605000-00001.

Saillenfait AM, Gallissot F, Sabate JP, et al. 2006. Developmental toxicity of combined ethylbenzene and methylethylketone administered by inhalation to rats. Food Chem Toxicol 44(8):1287-1298. http://doi.org/10.1016/j.fct.2006.02.006.

Sakata M, Kikuchi J, Haga M, et al. 1989. Disposition of acetone, methyl ethyl ketone and cyclohexanone in acute poisoning. J Toxicol Clin Toxicol 27(1-2):67-77. http://doi.org/10.3109/15563658909038570.

SANSS. 1989. Structure and Nomenclature Search System. September 1, 1989.

Sawhney BL, Kozloski RP. 1984. Organic pollutants in leachates from landfill sites. J Environ Qual 13(3):349-352. http://doi.org/10.2134/jeq1984.00472425001300030005x.

Sax NI, Lewis RJ. 1987. Metyhl ethyl ketone. In: Hawley's condensed chemical dictionary. 11th ed. New York, NY: Van Nostrand Reinhold Co, 769.

Scheiman MA, Saunders RA, Saalfeld FE. 1974. Organic contaminants in the District of Columbia water supply. Biomed Mass Spectrom 1(4):209-211. http://doi.org/10.1002/bms.1200010402.

Schenk L, Rauma M, Fransson MN, et al. 2018. Percutaneous absorption of thirty-eight organic solvents in vitro using pig skin. PLoS ONE 13(10):e0205458. http://doi.org/10.1371/journal.pone.0205458.

Schmidt R, Schnoy N, Altenkirch H, et al. 1984. Ultrastructural alteration of intrapulmonary nerves after exposure to organic solvents. A contribution to 'sniffers disease'. Respiration 46(4):362-369. http://doi.org/10.1159/000194713.

Schwetz BA, Leong BK, Gehring PJ. 1974. Embryo- and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. Toxicol Appl Pharmacol 28(3):452-464. http://doi.org/10.1016/0041-008x(74)90230-0.

Schwetz BA, Mast TJ, Weigel RJ, et al. 1991. Developmental toxicity of inhaled methyl ethyl ketone in Swiss mice. Fundam Appl Toxicol 16(4):742-748. http://doi.org/10.1016/0272-0590(91)90160-6.

Seeber A, van Thriel C, Haumann K, et al. 2002. Psychological reactions related to chemosensory irritation. Int Arch Occup Environ Health 75(5):314-325. http://doi.org/10.1007/s00420-002-0316-6.

Seizinger DE, Dimitriades B. 1972. Oxygenates in exhaust from simple hydrocarbon fuels. J Air Pollut Control Assoc 22(1):47-51. http://doi.org/10.1080/00022470.1972.10469608.

Shibata E, Huang J, Ono Y, et al. 1990a. Changes in urinary n-hexane metabolites by co-exposure to various concentrations of methyl ethyl ketone and fixed n-hexane levels. Arch Toxicol 64(2):165-168.

Shibata E, Huang J, Hisanaga N, et al. 1990b. Effects of MEK on kinetics of n-hexane metabolites in serum. Arch Toxicol 64(3):247-250. http://doi.org/10.1007/BF02010732.

Shibata E, Johanson G, Lof A, et al. 2002. Changes in n-hexane toxicokinetics in short-term single exposure due to co-exposure to methyl ethyl ketone in volunteers. Int Arch Occup Environ Health 75(6):399-405. http://doi.org/10.1007/s00420-002-0325-5.

Sia GL, Ong CN, Chia SE, et al. 1991. Environmental and biological monitoring of methyl ethyl ketone (MEK). Environ Monit Assess 19(1-3):401-411. http://doi.org/10.1007/BF00401328.

Smet E, Van Langenhove H, De Bo I. 1999. The emission of volatile compounds during the aerobic and the combined anaerobic/aerobic composting of biowaste. Atmos Environ 33(8):1295-1303. http://doi.org/10.1016/s1352-2310(98)00260-x.

Smoyer JC, Shaffer DE, Dewitt IL. 1971. A program to sample and analyze air pollution in the vicinity of a chemical reclamation plant. In: Institute of Environmental Sciences, 1971: Annual technical meeting proceedings. Mt. Prospect, IL: Institute of Environmental Sciences, 339-345.

Smyth HF, Carpenter CP, Weil CS, et al. 1962. Range-finding toxicity data: List VI. Am Ind Hyg Assoc J 23:95-107. http://doi.org/10.1080/00028896209343211.

Snider JR, Dawson GA. 1985. Tropospheric light alcohols, carbonyls, and acetonitrile: Concentrations in the southwestern United States and Henry's Law data. J Geophys Res 90(D2):3797. http://doi.org/10.1029/JD090iD02p03797.

Sosulski F, Mahmoud RM. 1979. Effects of protein supplements on carbonyl compounds and flavor in bread. Cereal Chem 56(6):533-536.

Speece RE. 1983. Anaerobic biotechnology for industrial wastewater treatment. Environ Sci Technol 17(9):416A-427A. http://doi.org/10.1021/es00115a725.

Spirtas R, Stewart PA, Lee JS, et al. 1991. Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. Br J Ind Med 48(8):515-530. http://doi.org/10.1136/oem.48.8.515.

Stillmeadow Inc. 1978. Rat acute oral toxicity. Shell Oil Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0206206. 878210023. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0206206.xhtml. May 7, 2020.

Stoltenburg-Didinger G. 1991. The effect of pre- and postnatal exposure to organic solvents on the development of the cerebellar cortex in the rat. Prog Histochem Cytochem 23(1-4):227-234. http://doi.org/10.1016/s0079-6336(11)80189-0.

Stoltenburg-Didinger G, Altenkirch H, Wagner M. 1990. Neurotoxicity of organic solvent mixtures: embryotoxicity and fetotoxicity. Neurotoxicol Teratol 12(6):585-589. http://doi.org/10.1016/0892-0362(90)90066-l.

Swann RL, Laskowski DA, McCall PJ, et al. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio and water solubility. Residue Rev 85:17-28. http://doi.org/10.1007/978-1-4612-5462-1_3.

Takeoka GR, Flath RA, Guentert M, et al. 1988. Nectarine volatiles: Vacuum steam distillation versus headspace sampling. J Agric Food Chem 36(3):553-560. http://doi.org/10.1021/jf00081a037.

Takeuchi Y, Ono Y, Hisanaga N, et al. 1983. An experimental study of the combined effects of n-hexane and methyl ethyl ketone. Br J Ind Med 40(2):199-203. http://doi.org/10.1136/oem.40.2.199.

Tanii H, Tsuji H, Hashimoto K. 1986. Structure-toxicity relationship of monoketones. Toxicol Lett 30(1):13-17. http://doi.org/10.1016/0378-4274(86)90173-6.

Tewari YB, Miller MM, Wasik SP, et al. 1982. Aqueous solubility and octanol/water partition coefficient of organic compounds at 25.0.degree.C. J Chem Eng Data 27(4):451-454. http://doi.org/10.1021/je00030a025.

Thorpe E. 1982. Toxicity studies with chemical solvents Short-term in vitro tests for genotoxic activity with methyl ethyl ketone. Shell Oil Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0206206. 978210097. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0206206.xhtml. June 30, 2020.

Thrall KD, Soelberg JJ, Weitz KK, et al. 2002. Development of a physiologically based pharmacokinetic model for methyl ethyl ketone in F344 rats. J Toxicol Environ Health 65(13):881-896. http://doi.org/10.1080/00984100290071207.

Tichenor BA, Mason MA. 1988. Organic emissions from consumer products and building materials to the indoor environment. JAPCA 38(3):264-268. http://doi.org/10.1080/08940630.1988.10466376.

Toftgard R, Nilsen O, Gustafsson JA. 1981. Changes in rat liver microsomal cytochrome P-450 and enzymatic activities after the inhalation of n-hexane, xylene, methyl ethyl ketone and methyl chloroform for four weeks. Scand J Work Environ Health 7(1):31-37. http://doi.org/10.5271/sjweh.2569.

Tolos W, Setzer J, MacKenzie B, et al. 1987. Biological monitoring of experimental human inhalation exposures of methyl ethyl ketone and toluene. In: Ho M, Dillon H, eds. Biological monitoring of exposure to chemicals, organic compounds. New York, NY: John Wiley and Sons, 133-142.

Tomicic C, Vernez D. 2014. Sex differences in urinary levels of several biological indicators of exposure: a simulation study using a compartmental-based toxicokinetic model. J Occup Environ Hyg 11(6):377-387. http://doi.org/10.1080/15459624.2013.875180.

Tomicic C, Berode M, Oppliger A, et al. 2011. Sex differences in urinary levels of several biological indicators of exposure: a human volunteer study. Toxicol Lett 202(3):218-225. http://doi.org/10.1016/j.toxlet.2011.01.032.

Traiger GJ, Bruckner JV, Jiang WD, et al. 1989. Effect of 2-butanol and 2-butanone on rat hepatic ultrastructure and drug metabolizing enzyme activity. J Toxicol Environ Health 28(2):235-248. http://doi.org/10.1080/15287398909531343.

Tsao MU, Pfeiffer EL. 1957. Isolation and identification of a new ketone body in normal human urine. Proc Soc Exp Biol Med 94(4):628-629. http://doi.org/10.3181/00379727-94-23031.

Tsuchiya Y. 1987. Volatile organic compounds in indoor air. Am Chem Soc Div Environ Chem Preprint 27:183-185.

Tsukamoto S, Chiba S, Muto T, et al. 1985. Study on the metabolism of volatile hydrocarbons in mice--propane, n-butane, and iso-butane. J Toxicol Sci 10(4):323-332. http://doi.org/10.2131/jts.10.323.

Urano K, Kato Z. 1986. Evaluation of biodegradation ranks of priority organic compounds. J Hazard Mater 13(2):147-159. http://doi.org/10.1016/0304-3894(86)80015-2.

Ursin C, Hansen CM, Van Dyk JW, et al. 1995. Permeability of commercial solvents through living human skin. Am Ind Hyg Assoc J 56(7):651-660. http://doi.org/10.1080/15428119591016665.

USDA. 2020. Dr. Duke's phytochemical and ethnobotanical databases: 2-butanone. U.S. Department of Agriculture. https://phytochem.nal.usda.gov/phytochem/chemicals/show/1109?qlookup=2-butanone&offset=0&max=20&et=. May 6, 2020.

USITC. 1987. Synthetic organic chemicals, United States Production and Sales, 1986. Washington, DC: U.S. International Trade Commission. 210, 226, 238-239. USITC Publication 2009.

USITC. 1988. Synthetic organic chemicals, United States Production and Sales, 1987. Washington, DC: U.S. International Trade Commission. 15-15, 15-22, 1536, 1515-1537. USITC Publication 2118.

USITC. 1989. Synthetic organic chemicals, United States Production and Sales, 1988. Washington, DC: U.S. International Trade Commission. 15-15, 15-23, 15-36 to 15-38. USITC Publication 2219.

Vaishnav DC, Boethling RS, Babeu L. 1987. Quantitative structure - Biodegradability relationships for alcohols, ketones and alicyclic compounds. Chemosphere 16(4):695-703. http://doi.org/10.1016/0045-6535(87)90005-1.

Vallat JM, Leboutet MJ, Loubet A, et al. 1981. N-Hexane- and methylethylketone-induced polyneuropathy. Abnormal accumulation of glycogen in unmyelinated axons. Report of a case. Acta Neuropathol (Berl) 55(4):275-279. http://doi.org/10.1007/BF00690990.

Van Doorn JE, De Cock J, Kezic S, et al. 1989. Determination of methyl ethyl ketone in human urine after derivatization with o-nitrophenylhydrazine, using solid-phase extraction and reversed-phase high-performance liquid chromatography and ultraviolet detection. J Chromatogr 489(2):419-424. http://doi.org/10.1016/s0378-4347(00)82924-2.

van Thriel C, Haumann K, Kiesswetter E, et al. 2002. Time courses of sensory irritations due to 2-butanone and ethyl benzene exposure: influences of self-reported multiple chemical sensitivity (sMCS). Int J Hyg Environ Health 204(5-6):367-369. http://doi.org/10.1078/1438-4639-00112.

van Thriel C, Wiesmuller GA, Blaszkewicz M, et al. 2003. Intranasal effects in chemically sensitive volunteers: an experimental exposure study. Environ Toxicol Pharmacol 14(3):129-137. http://doi.org/10.1016/S1382-6689(03)00047-4.

Varigos GA, Nurse DS. 1986. Contact urticaria from methyl ethyl ketone. Contact Dermatitis 15(4):259-260. http://doi.org/10.1111/j.1600-0536.1986.tb01362.x.

Veronesi B, Lington AW, Spencer PS. 1984. A tissue culture model of methyl ethyl ketone's potentiation of n-hexane neurotoxicity. Neurotoxicology 5(2):43-52.

Wahlberg JE. 1984. Edema-inducing effects of solvents following topical administration. Derm Beruf Umwelt 32(3):91-94.

Wallace LA, Pellizzari E, Hartwell T, et al. 1984. Personal exposure to volatile organic compounds. I. Direct measurements in breathing-zone air, drinking water, food, and exhaled breath. Environ Res 35(1):293-319. http://doi.org/10.1016/0013-9351(84)90137-3.

Wallington TJ, Kurylo MJ. 1987. Flash photolysis resonance fluorescence investigation of the gas-phase reactions of hydroxyl radicals with a series of aliphatic ketones over the temperature range 240-440 K. J Phys Chem 91(19):5050-5054. http://doi.org/10.1021/j100303a033.

Wallington TJ, Dagaut P, Kurylo MJ. 1988. Correlation between gas-phase and solution-phase reactivities of hydroxyl radicals towards saturated organic compounds. J Phys Chem 92(17):5024-5028. http://doi.org/10.1021/j100328a039.

Wang TC, Bricker JL. 1979. 2-Butanone and tetrahydrofuran contamination in the water supply. Bull Environ Contam Toxicol 23(4-5):620-623. http://doi.org/10.1007/BF01770014.

8. REFERENCES

Weast RC, Astle MJ, Beyer WH. 1988. Methyl ethyl ketone. In: O'Neil MJ, ed. CRC handbook of chemistry and physics. 69th ed. Boca Raton, FL: CRC Press, Inc., C-170.

Wen CP, Tsai SP, Weiss NS, et al. 1985. Long-term mortality study of oil refinery workers. IV. Exposure to the lubricating-dewaxing process. J Natl Cancer Inst 74(1):11-18.

Whelan JK, Tarafa ME, Hunt JM. 1982. Volatile C1-C8 organic compounds in macroalgae. Nature 299:50-52.

Whitehead LW, Ball GL, Fine LJ, et al. 1984. Solvent vapor exposures in booth spray painting and spray glueing, and associated operations. Am Ind Hyg Assoc J 45(11):767-772. http://doi.org/10.1080/15298668491400584.

Whittaker SG, Zimmermann FK, Dicus B, et al. 1990. Detection of induced mitotic chromosome loss in Saccharomyces cerevisiae--an interlaboratory assessment of 12 chemicals. Mutat Res 241(3):225-242. http://doi.org/10.1016/0165-1218(90)90020-3.

WHO. 2010. Guidelines for indoor air quality: Selected pollutants. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf. April 25, 2012.

WHO. 2017. Guidelines for drinking-water quality. Fourth edition incorporating the first addendum. Geneva, Switzerland: World Health Organization. http://apps.who.int/iris/bitstream/10665/254637/1/9789241549950-eng.pdf?ua=1. February 28, 2017.

Wiesmuller GA, Van Thriel C, Steup A, et al. 2002. Nasal function in self-reported chemically intolerant individuals. Arch Environ Health 57(3):247-254. http://doi.org/10.1080/00039890209602944.

Wilkins CK, Larsen K. 1995. Identification of volatile (micro) biological compounds from household waste and building materials by thermal desorption-capillary gas chromatography-mass spectroscopy. J High Resolut Chromatogr 18(6):373-377. http://doi.org/10.1002/jhrc.1240180610.

Wilkins K, Larsen K. 1996. Volatile organic compounds from garden waste. Chemosphere 32(10):2049-2055. http://doi.org/10.1016/0045-6535(96)00113-0.

Wurster DE, Munies R. 1965. Factors influencing percutaneous absorption. II. Absorption of methyl ethyl ketone. J Pharm Sci 54(4):554-556. http://doi.org/10.1002/jps.2600540412.

Yasui T, Zhao W, Misumi J, et al. 1995. Influence of different doses of methyl ethyl ketone on 2,5-hexanedione concentrations in the sciatic nerve, serum, and urine of rats. Sangyo Eiseigaku Zasshi 37(1):19-24. http://doi.org/10.1539/sangyoeisei.37.19.

Yoshikawa M, Kawamoto T, Murata K, et al. 1995. Biological monitoring of occupational exposure to methyl ethyl ketone in Japanese workers. Arch Environ Contam Toxicol 29(1):135-139. http://doi.org/10.1007/BF00213098.

Young RH, Ryckman DW, Buzzell JC. 1968. An improved tool for measuring biodegrability. J Water Pollut Control Fed 40(8):R354-R368.

Zeiger E, Anderson B, Haworth S, et al. 1992. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ Mol Mutagen 19 (Suppl 21):2-141. http://doi.org/10.1002/em.2850190603.

Zhao W, Misumi J, Yasui T, et al. 1998a. Relationship between 2,5-hexanedione concentrations in nerve, serum, and urine alone or under co-treatment with different doses of methyl ethyl ketone, acetone, and toluene. Neurochem Res 23(6):837-843. http://doi.org/10.1023/a:1022402810695.

Zhao W, Misumi J, Yasui T, et al. 1998b. Effects of methyl ethyl ketone, acetone, or toluene coadministration on 2,5-hexanedione concentration in the sciatic nerve, serum, and urine of rats. Int Arch Occup Environ Health 71(4):236-244. http://doi.org/10.1007/s004200050275.

Zimmermann FK, Scheel I, Resnick MA. 1989. Induction of chromosome loss by mixtures of organic solvents including neurotoxins. Mutat Res 224(2):287-303. http://doi.org/10.1016/0165-1218(89)90168-7.

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 Office of Innovation and Analytics, Toxicology Section, 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 Office of Innovation and Analytics, Toxicology Section, 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-Butanone
CAS Numbers: 78-93-3
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL 1 ppm
Critical Effect: Neurological (headache, fatigue, feeling of intoxication)
Reference: Tomicic et al. 2011
Point of Departure: LOAEL of 99.15 ppm
Uncertainty Factor: 100
LSE Graph Key: 5
Species: Humans

MRL Summary: An acute-duration inhalation MRL of 1 ppm was derived for 2-butanone based on reported neurological symptoms (headache, fatigue, feeling of intoxication) in volunteers. The MRL is based on the LOAEL (not adjusted for continuous exposure) of 99.15 ppm and a total uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

Selection of the Critical Effect: Clinical signs of neurotoxicity in humans (i.e., headache, fatigue, feeling of intoxication) are a sensitive effect of 2-butanone exposure (Tomicic et al. 2011). Neurobehavioral effects in primates (Geller et al. 1979) were also reported at low concentrations (increased response time in match-to-sample tasks).

Selection of the Principal Study: Tomicic et al. (2011) was selected as the principal study because neurological effects were reported in volunteers exposed to 100 ppm.

Summary of the Principal Study:

Tomicic C, Berode M, Oppliger A, et al. 2011. Sex differences in urinary levels of several biological indicators of exposure: A human volunteer study. Toxicol Lett 202:218-225.

Volunteers (10 males and 10 females using hormonal contraceptives and 5 females without hormonal contraceptives) were exposed to 100 ppm 2-butanone for 6 hours (measured concentration 99.15±5.29 ppm). Urinary 2-butanone concentrations were measured every 2 hours before, during, and after exposure (24 hours total). A symptom questionnaire was administered every 2 hours during exposure. The symptoms rated on a visual analog scale (graded from “not at all” to “almost unbearable”) included headache, fatigue, nausea, dizziness, feeling of intoxication, discomfort in the eyes, in the nose, or in the throat or airways, breathing difficulty, and solvent smell. The quantitative symptom ratings were not reported; however, a statistically significant difference between men and women was indicated for neurological effects and irritation symptoms (eyes, nose, and throat) with females giving higher ratings than males. Specific ratings that were described as higher in females compared to males included headache after 4 and 6 hours, fatigue and feeling of intoxication after 6 hours and discomfort in the eyes after 2 and 4 hours.

Selection of the Point of Departure for the MRL: The LOAEL of 100 ppm for neurological effects (headache, fatigue, feeling of intoxication) was selected as the point of departure (POD) for the acute-duration inhalation MRL.

Calculations: Not applicable.

Intermittent Exposure: Because of the reversible nature of mucous membrane irritation, adjustment for intermittent exposure was not necessary.

Human Equivalent Concentration: The POD was derived from human exposure studies (no conversion required).

Uncertainty Factor: The LOAEL is divided by a total uncertainty factor of 100:

- 10 for use of a LOAEL
- 10 for human variability

MRL = LOAEL ÷ UFs
99.15 ppm ÷ (10x10) = 1 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Neurobehavioral testing was conducted in four baboons exposed to 100 ppm 2-butanone 24 hours/day for 7 days (Geller et al. 1979). A decrease in the mean response time for a match-to-sample task was observed. Nelson et al. (1943) exposed 10 subjects (both male and female) to 2-butanone at concentrations of 100, 200, or 350 ppm for 3–5 minutes. Symptom classifications were no reaction, slightly irritating, and very irritating. At 100 ppm, slight nose and throat irritation were reported. At 200 ppm, mild eye irritation appeared in some subjects. Exposure to 350 ppm was conclusively rejected as not tolerable for an 8-hour workday. No further details were reported. Sensory irritation effects were seen in mice exposed to 2-butanone concentrations ≥3,809 ppm. A time- and concentration-dependent decrease in respiratory rate and tidal volume was observed (Hansen et al. 1992). Severe respiratory and eye irritation occurred in rats and guinea pigs exposed to 2-butanone concentrations ≥10,000 ppm (Altenkirch et al. 1978; Patty et al. 1935).

Agency Contacts (Chemical Managers): G. Daniel Todd

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Butanone
CAS Numbers: 78-93-3
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Intermediate

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

Rational for Not Deriving an MRL: Target organs have not been sufficiently identified. In addition, clinical signs of neurotoxicity (i.e., headache, fatigue, feeling of intoxication) and nose, throat, and eye irritation occurred in humans at exposure levels that were much lower than NOAEL values in animals in intermediate-duration studies.

Agency Contacts (Chemical Managers): G. Daniel Todd

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Butanone
CAS Numbers: 78-93-3
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Chronic

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

Rational for Not Deriving an MRL: No chronic-duration studies examining noncarcinogenic effects following inhalation exposure were identified.

Agency Contacts (Chemical Managers): G. Daniel Todd

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Butanone
CAS Numbers: 78-93-3
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Acute

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

Rational for Not Deriving an MRL: Target organs have not been sufficiently identified and dose-response data are lacking.

Agency Contacts (Chemical Managers): G. Daniel Todd

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Butanone
CAS Numbers: 78-93-3
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Intermediate

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

Rational for Not Deriving an MRL: Target organs have not been sufficiently identified and dose-response data are lacking.

Agency Contacts (Chemical Managers): G. Daniel Todd

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Butanone
CAS Numbers: 78-93-3
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Chronic

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

Rational for Not Deriving an MRL: No chronic-duration studies examining noncarcinogenic effects following oral exposure were identified.

Agency Contacts (Chemical Managers): G. Daniel Todd

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR 2-BUTANONE

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-butanone.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for 2-butanone. 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-butanone 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-butanone 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-butanone released for public comment in May 2019. The following main databases were searched in October 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-butanone. 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-butanone 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	
10/2019	(78-93-3[rn] AND 2017:3000[mhda]) OR (("2 butanone"[tw] OR "2-butanon"[tw] OR "2-butanone"[tw] OR "3-butanone"[tw] OR "acetone, methyl-"[tw] OR "butan-2-one"[tw] OR "butanon"[tw] OR "butanona"[tw] OR "butanone"[tw] OR "ethyl methyl ketone"[tw] OR "ethylmethyl ketone"[tw] OR "ketone, ethyl methyl"[tw] OR "methyl acetone"[tw] OR " methyl ethyl ketone"[tw] OR "methylethyl ketone"[tw] OR "methylethylketone"[tw] OR "metyl ethyl ketone"[tw]) AND (2017:3000[crdat] OR 2017:3000[edat]))
Toxline	
10/2019	(78-93-3 [rn] OR "2 butanone" OR "2-butanon" OR "2-butanone" OR "3-butanone" OR "acetone methyl-" OR "butan-2-one" OR "butanon" OR "butanona" OR "butanone" OR "ethyl methyl ketone" OR "ethylmethyl ketone" OR "ketone ethyl methyl" OR "methyl acetone" OR " methyl ethyl ketone" OR "methylethyl ketone" OR "methylethylketone" OR "metyl ethyl ketone") AND 2017:2019 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HAPAB [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] Limited to: YEAR of PUBLICATION of 2017-2019; and unchecked: synonyms, include pubmed
Toxcenter	
10/2019	FILE 'TOXCENTER' ENTERED AT 08:01:10 ON 18 OCT 2019 CHARGED TO COST=EH038.06.01.OD L1 9677 SEA FILE=TOXCENTER 78-93-3 L2 9423 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 6574 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 358 SEA FILE=TOXCENTER L3 AND ED>=20170101 ACTIVATE TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)

Table B-2. Database Query Strings

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

Table B-2. Database Query Strings

Database search date	Query string
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L37 QUE L35 OR L36 --------- L38 150 SEA FILE=TOXCENTER L4 AND L37 L39 10 SEA FILE=TOXCENTER L38 AND MEDLINE/FS L40 14 SEA FILE=TOXCENTER L38 AND BIOSIS/FS L41 126 SEA FILE=TOXCENTER L38 AND CAPLUS/FS L42 0 SEA FILE=TOXCENTER L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L43 147 DUP REM L39 L40 L41 (3 DUPLICATES REMOVED) L*** DEL 10 S L38 AND MEDLINE/FS L*** DEL 10 S L38 AND MEDLINE/FS L44 10 SEA FILE=TOXCENTER L43 L*** DEL 14 S L38 AND BIOSIS/FS L*** DEL 14 S L38 AND BIOSIS/FS L45 12 SEA FILE=TOXCENTER L43 L*** DEL 126 S L38 AND CAPLUS/FS L*** DEL 126 S L38 AND CAPLUS/FS L46 125 SEA FILE=TOXCENTER L43 L47 137 SEA FILE=TOXCENTER (L44 OR L45 OR L46) NOT MEDLINE/FS SAVE TEMP L47 BUTANONE/A D SCAN L47

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
10/2019	Compounds searched: 78-93-3
NTP	
10/2019	"78-93-3" "methyl ethyl ketone" "2 butanone" "2-butanone" "acetone, methyl-" "methylethyl ketone" "methylethylketone" "methyl acetone" "methylethyl ketone" "methylethylketone" "metyl ethyl ketone" "2-butanon" "butan-2-one" "butanon" "butanona" "butanone" "ethyl methyl ketone" "ethylmethyl ketone" "ketone, ethyl methyl" "methyl acetone"
NIH RePORTER	
04/2020	Search Criteria: Text Search: "2 butanone" OR "2-butanon" OR "2-butanone" OR "3-butanone" OR "acetone methyl-" OR "butan-2-one" OR "butanon" OR "butanona" OR "butanone" OR "ethyl methyl ketone" OR "ethylmethyl ketone" OR "ketone ethyl methyl" OR "methyl acetone" OR " methyl ethyl ketone" OR "methylethyl ketone" OR "methylethylketone" OR "metyl ethyl ketone" (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): 740
- Number of records identified from other strategies: 47
- Total number of records to undergo literature screening: 787

B.1.2 Literature Screening

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

- 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.

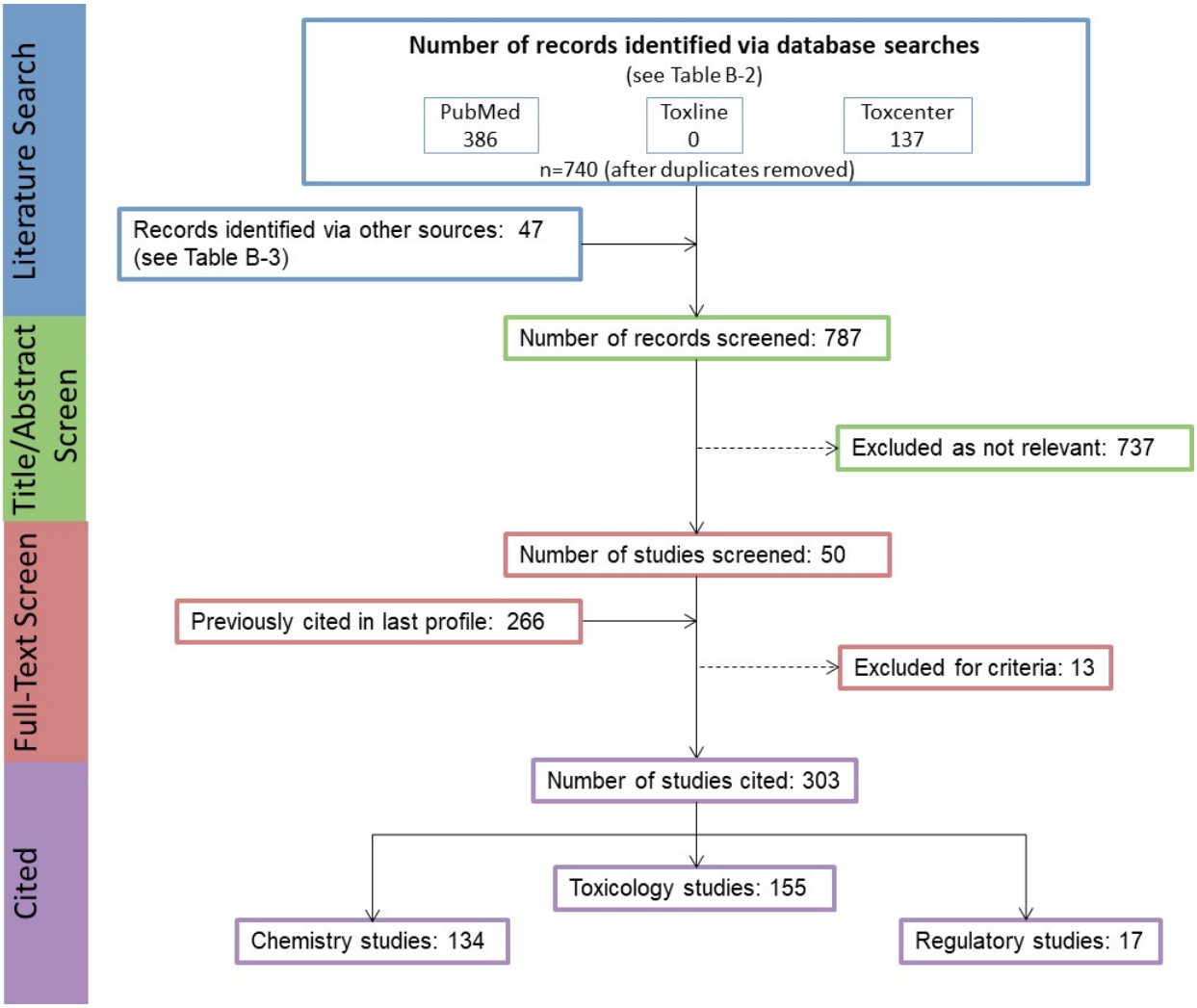
- Number of titles and abstracts screened: 787
- Number of studies considered relevant and moved to the next step: 50

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: 50
- Number of studies cited in the pre-public draft of the toxicological profile: 266
- Total number of studies cited in the profile: 303

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

Figure B-1. October 2019 Literature Search Results and Screen for 2-Butanone



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] (4)	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 (3)	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									

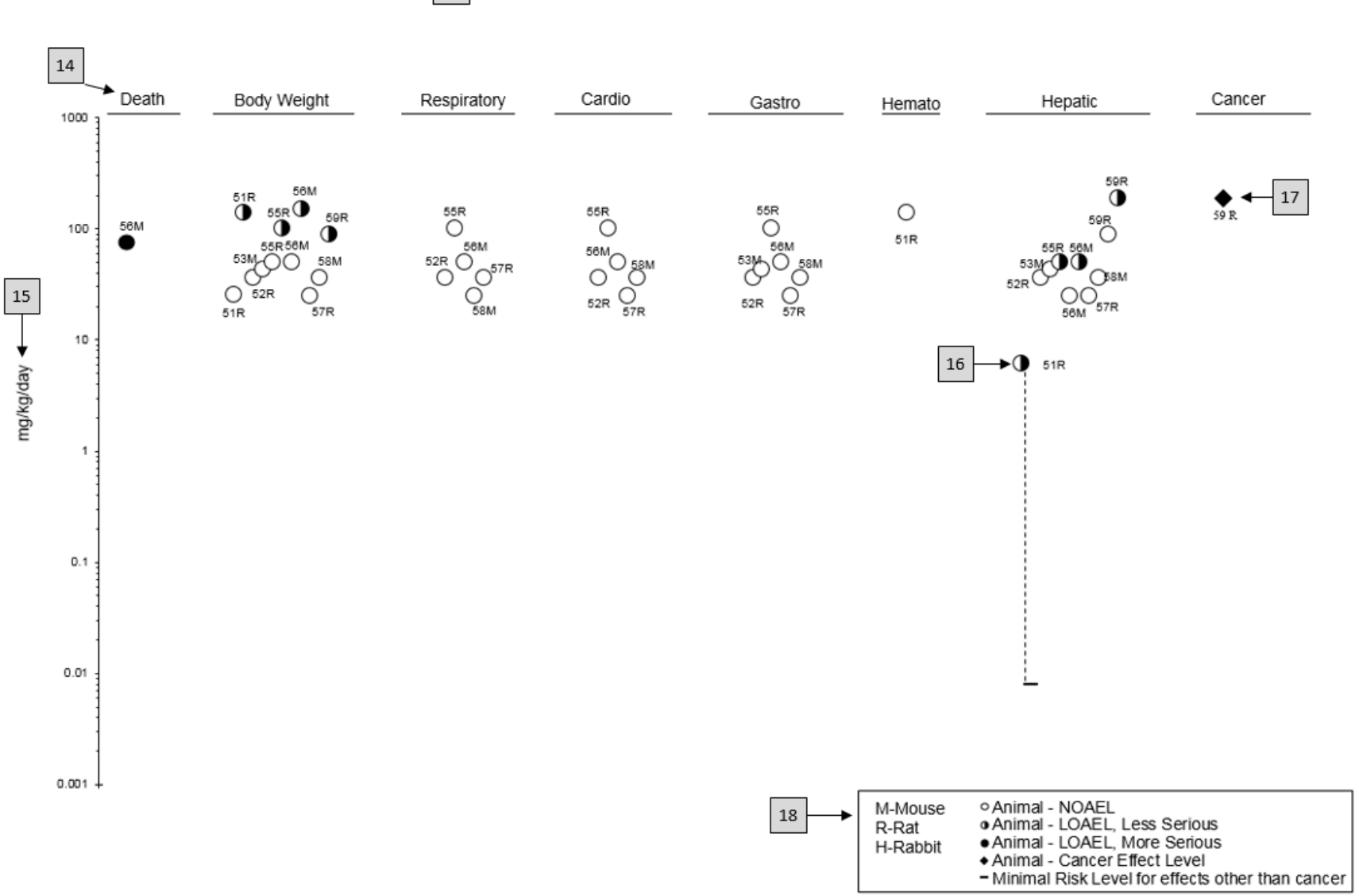
[a]The number corresponds to entries in Figure 2-x.

(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