Toxicological Profile for 2-Butanone

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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 and EPA.

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 and the associated acute, intermediate, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures; 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. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
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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.

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 is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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VERSION HISTORY

Date	Description
May 2019	Update of data in Chapters 2, 3, and 7
December 2010	Addendum to the toxicological profile released
July 1992	Final toxicological profile released

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

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

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

ATSDR's *Toxicological Profile for Substance 2-Butanone* was released in 1992. In order to update the literature in this profile, ATSDR conducted a literature search focused on health effects information as described in Appendix B. Chapters 2, 3, and 7 were revised to reflect the most current health effects and regulations/guidelines data. In some cases, other sections of the profile were updated as needed or for consistency with the updated health effects data. However, the focus of the update to this profile is on health effects information.

2-Butanone, also referred to as methyl ethyl ketone or MEK, is a common industrial solvent. Uses of 2-butanone can be broken down into the following categories: coatings solvent, 50%; adhesives, 13%; magnetic tapes, 8%; lube oil dewaxing, 4%; printing inks, 3%; exports, 16%; and miscellaneous, 6% (Chemical Marketing Reporter 1987). Examples of specific applications include its use as a solvent for nitrocellulose, lacquers, rubber cement, printing inks, paint removers, vinyl films, resins, rosins, polystyrene, chlorinated rubber, polyurethane, acrylic coatings, and cleaning solutions (Neier and Strehlke 1985; 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.

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 sorb 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 generally lacking. Environmental exposure levels are 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. 1978a; 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).

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

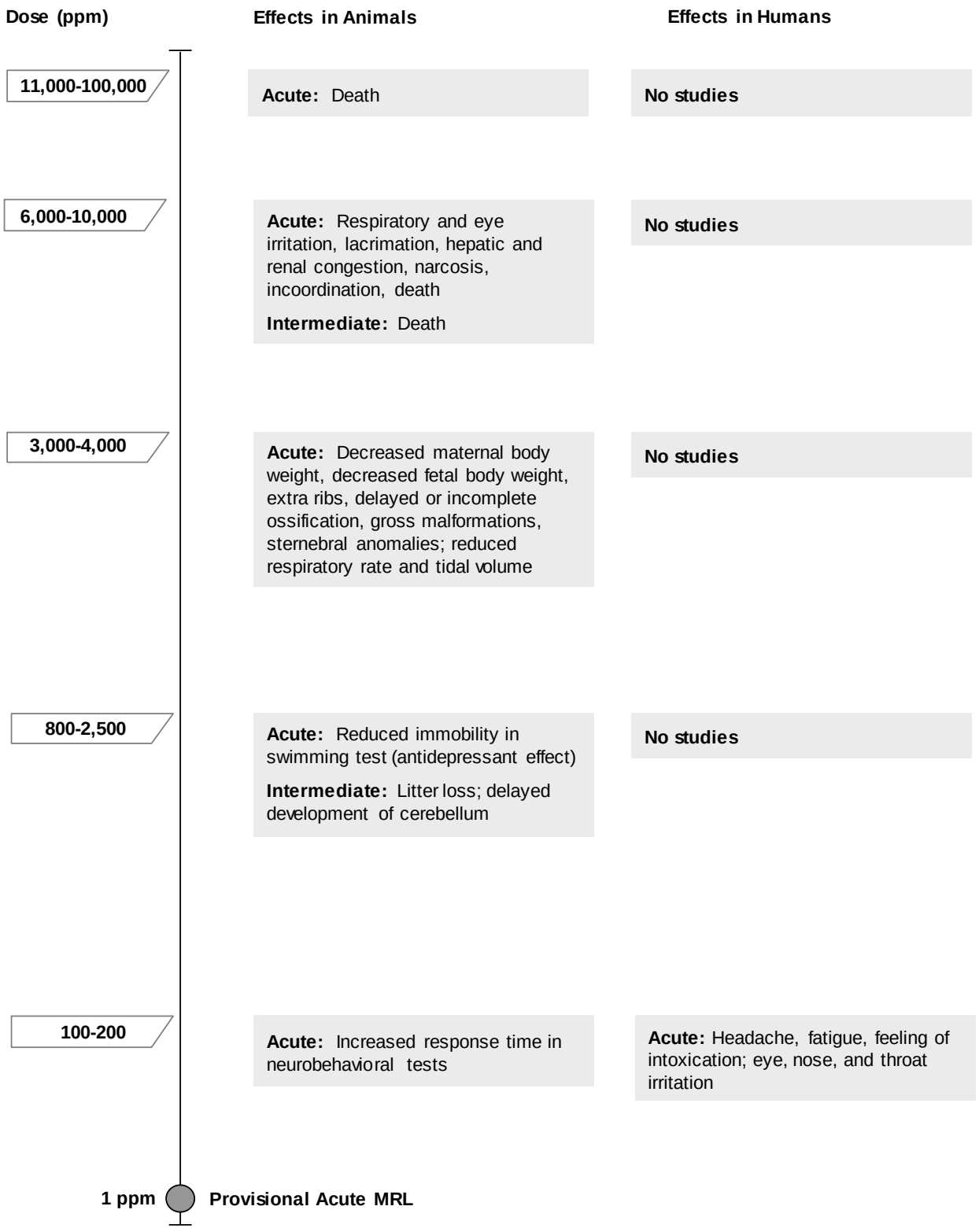
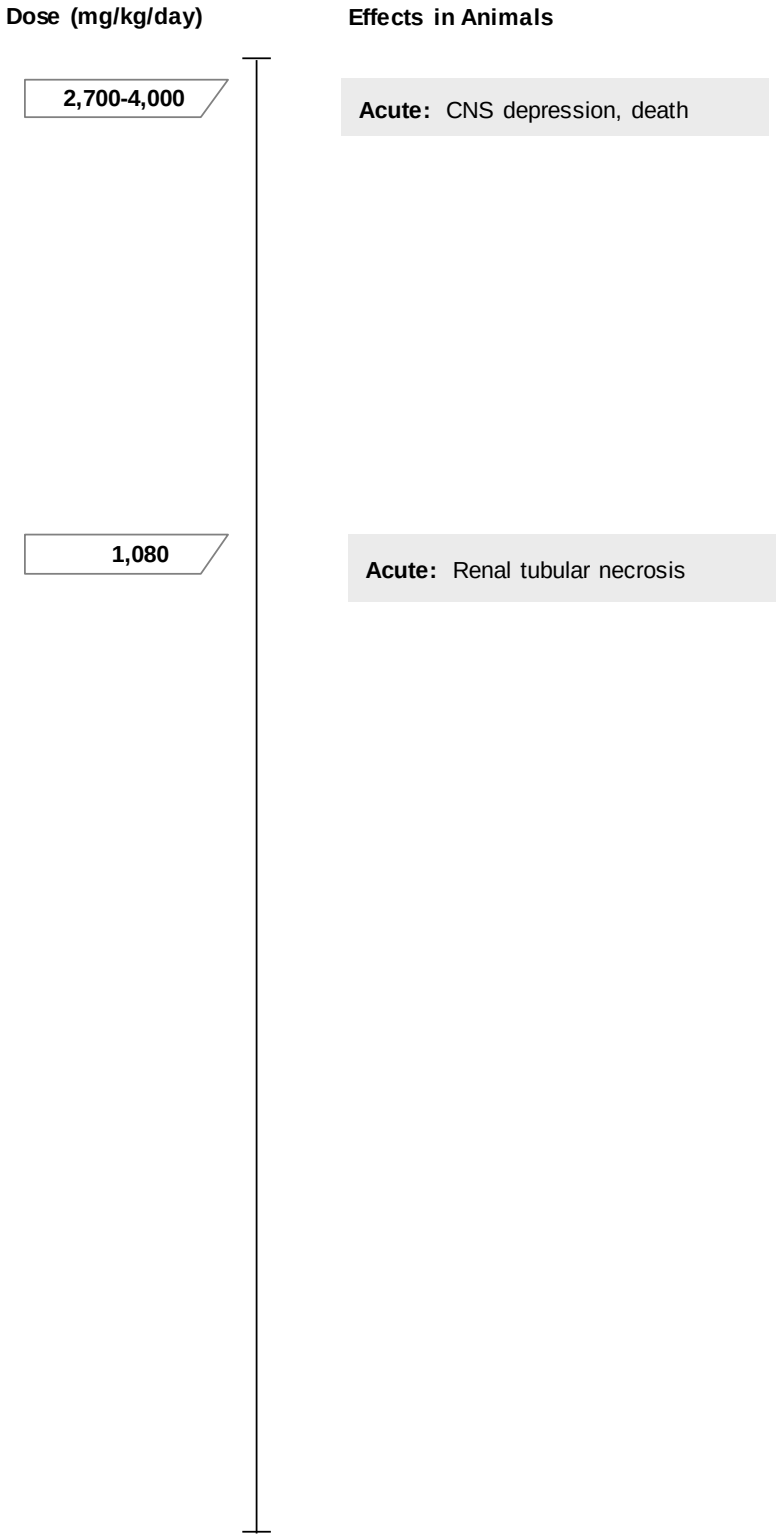


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 2-Butanone



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 (Mast et al. 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 pre-treated with 2-butanone for 3 days prior to chloroform exposure (Raymond et al. 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. (1978a) 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 markedly 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; Mast et al. 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). 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 were 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 a provisional 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.

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.

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

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.

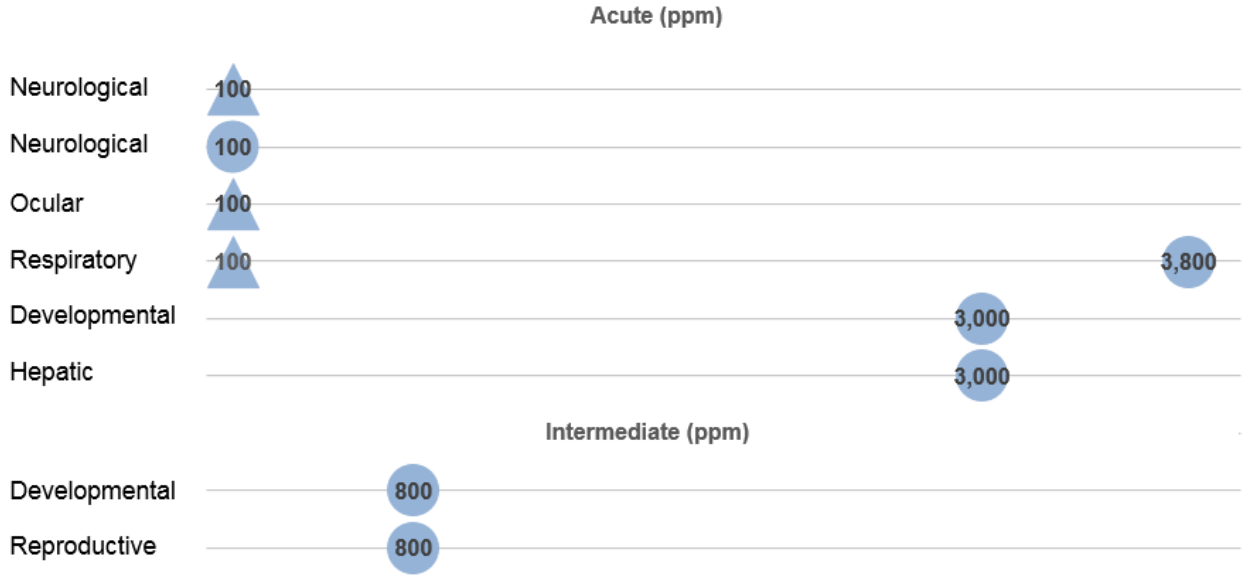


Figure 1-4. Summary of Sensitive Targets of 2-Butanone – Oral

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.

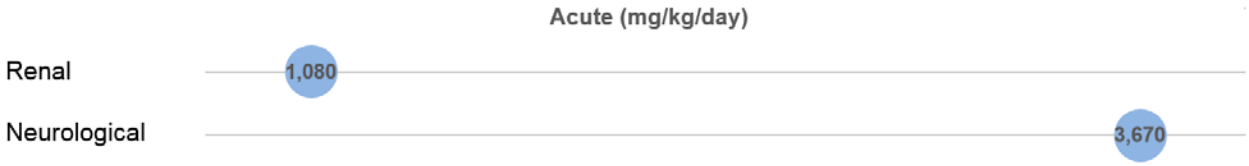


Table 1-1. Minimal Risk Levels (MRLs) for 2-Butanone[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute (provisional)	1	Neurological effects (headache, fatigue, feeling of intoxication)	99.15 (LOAEL)	100[b]	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]The respective exposure durations for acute, intermediate, and chronic MRLs are ≤14 days, 15–364 days, and ≥1 year.
[b]10 for human variability and 10 for use of a LOAEL.

LOAEL = lowest-observed-adverse-effect level

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 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.

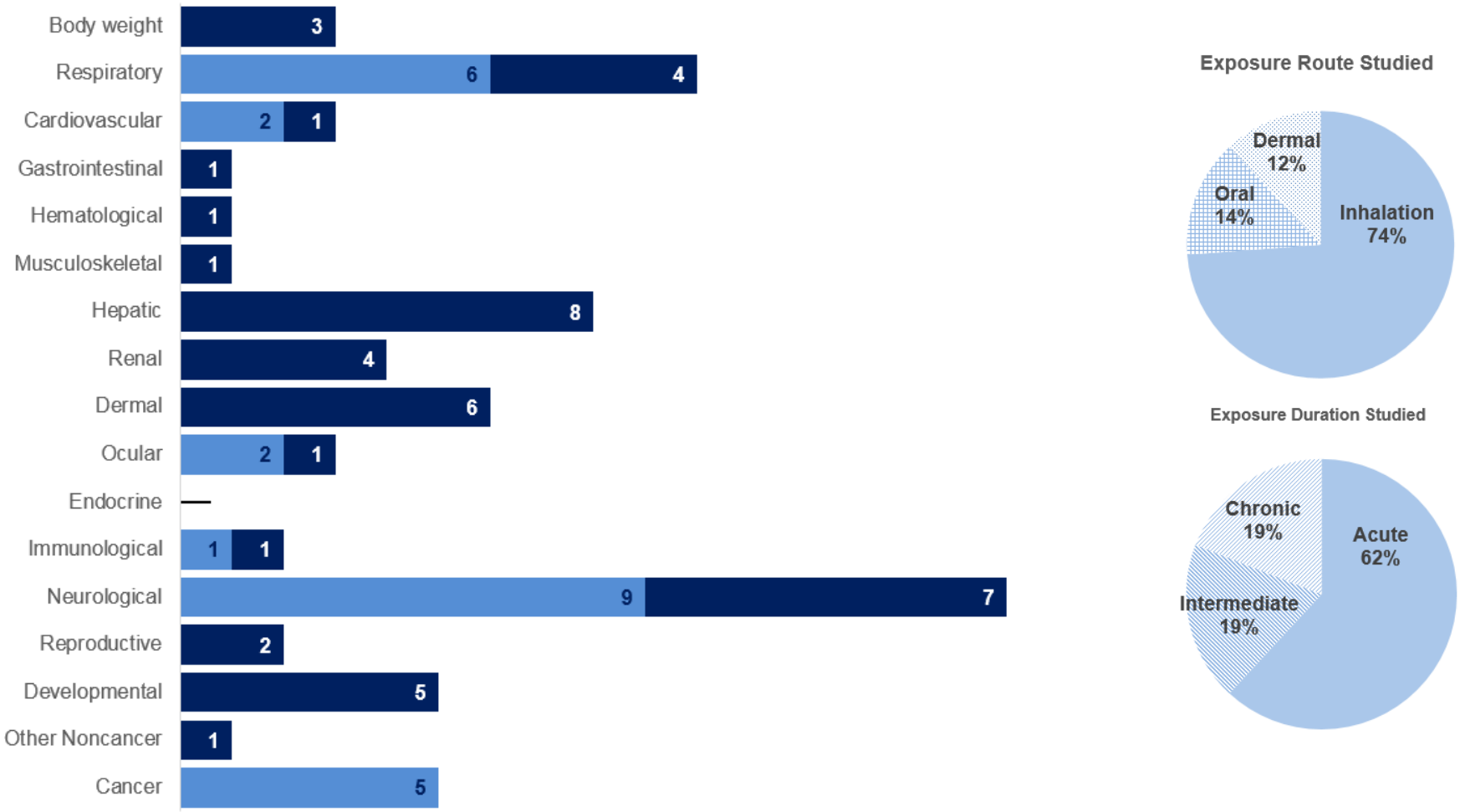
A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

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 slightly 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; Wismuller 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. 1978a									

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
Mast et al. 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. 1978a, 1978b									
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 Renal	3,000 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 Develop			800 800	Delay in Purkinje cell outgrowth Complete litter loss
Stoltenburg-Didinger et al. 1990, 1991									

[a]The number corresponds to entries in Figure 2-2.
[b]A provisional 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 provisional 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)

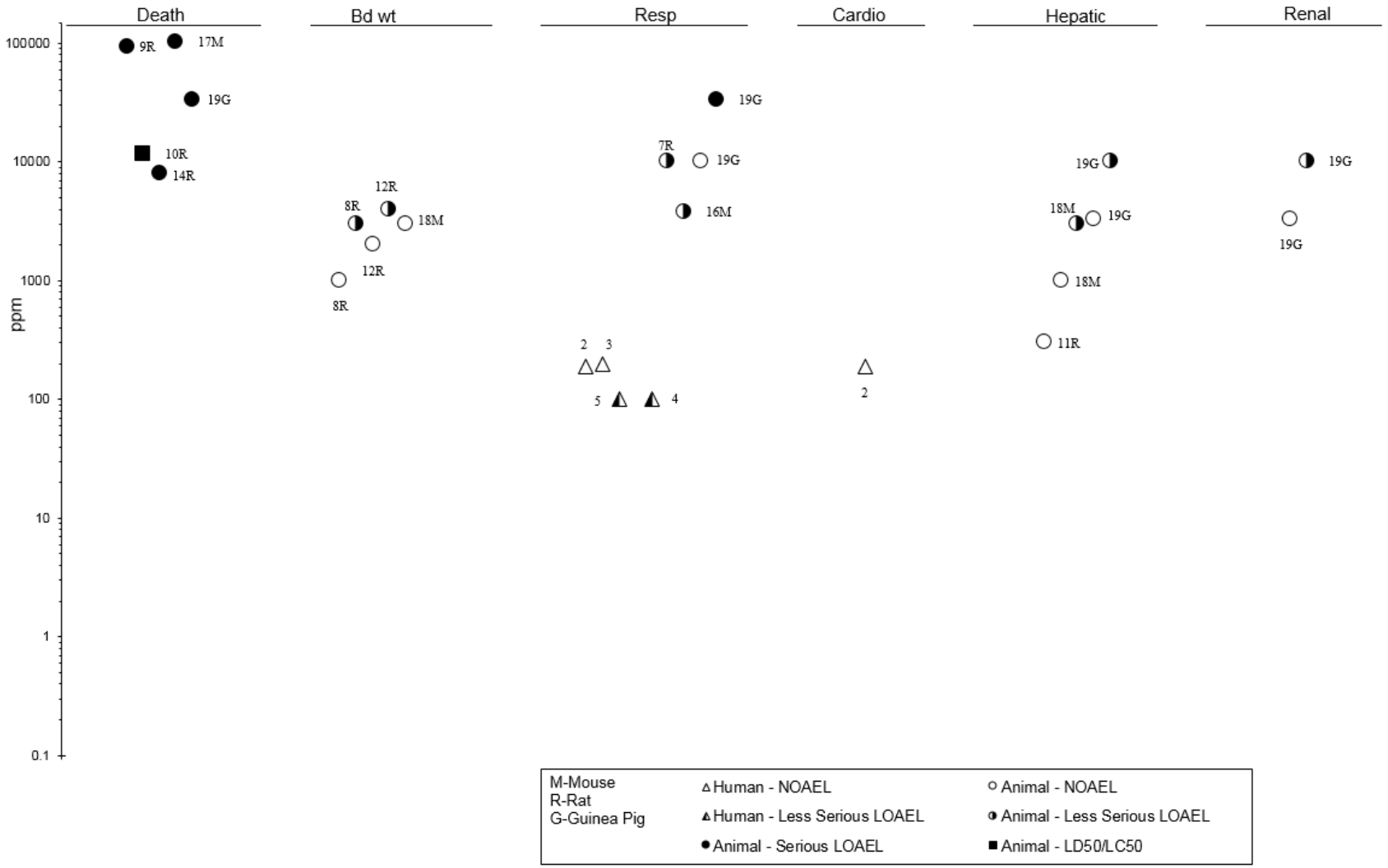


Figure 2-2. Levels of Significant Exposure to 2-Butanone – Inhalation
Acute (≤14 days)

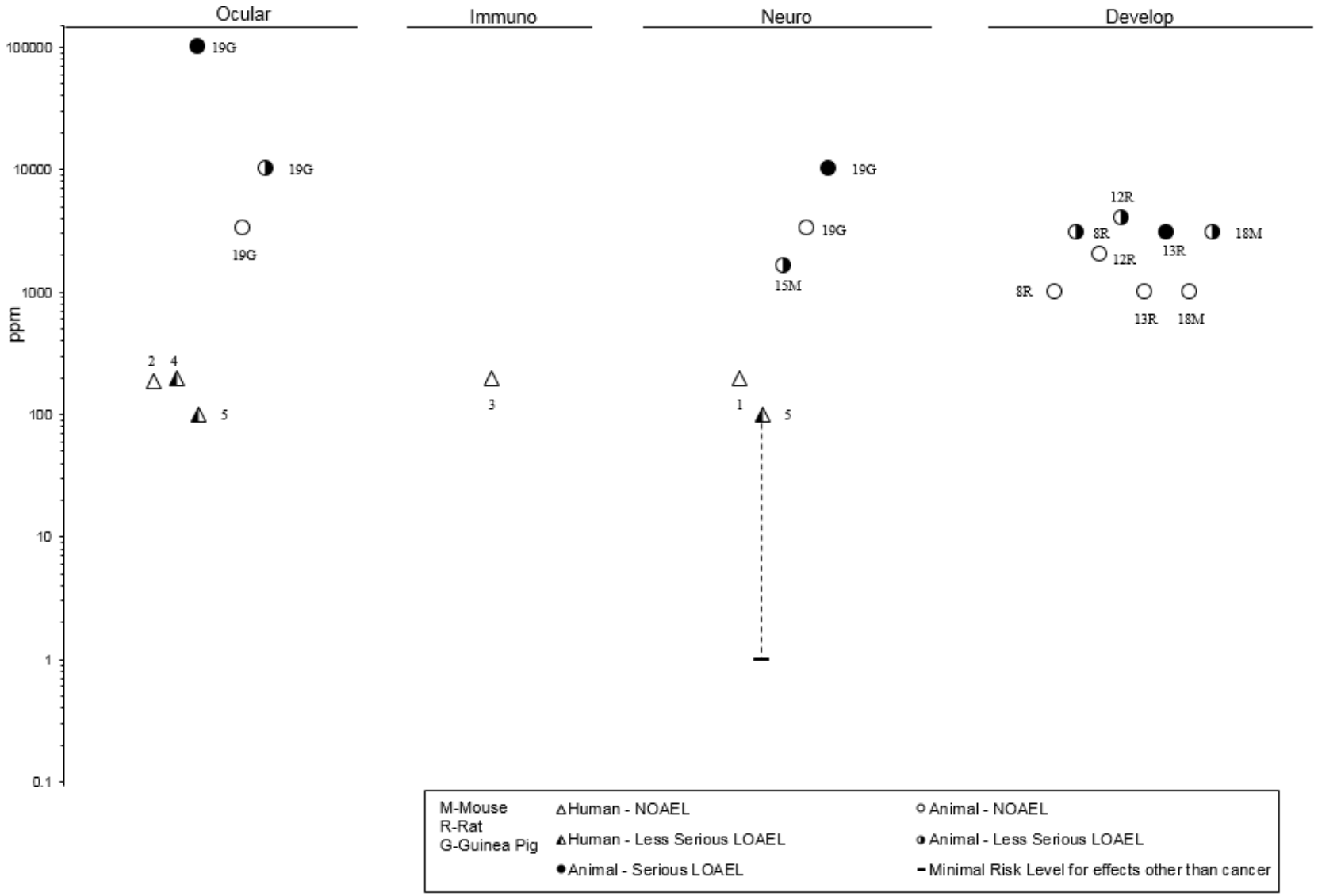


Figure 2-2. Levels of Significant Exposure to 2-Butanone – Inhalation
Intermediate (15-364)

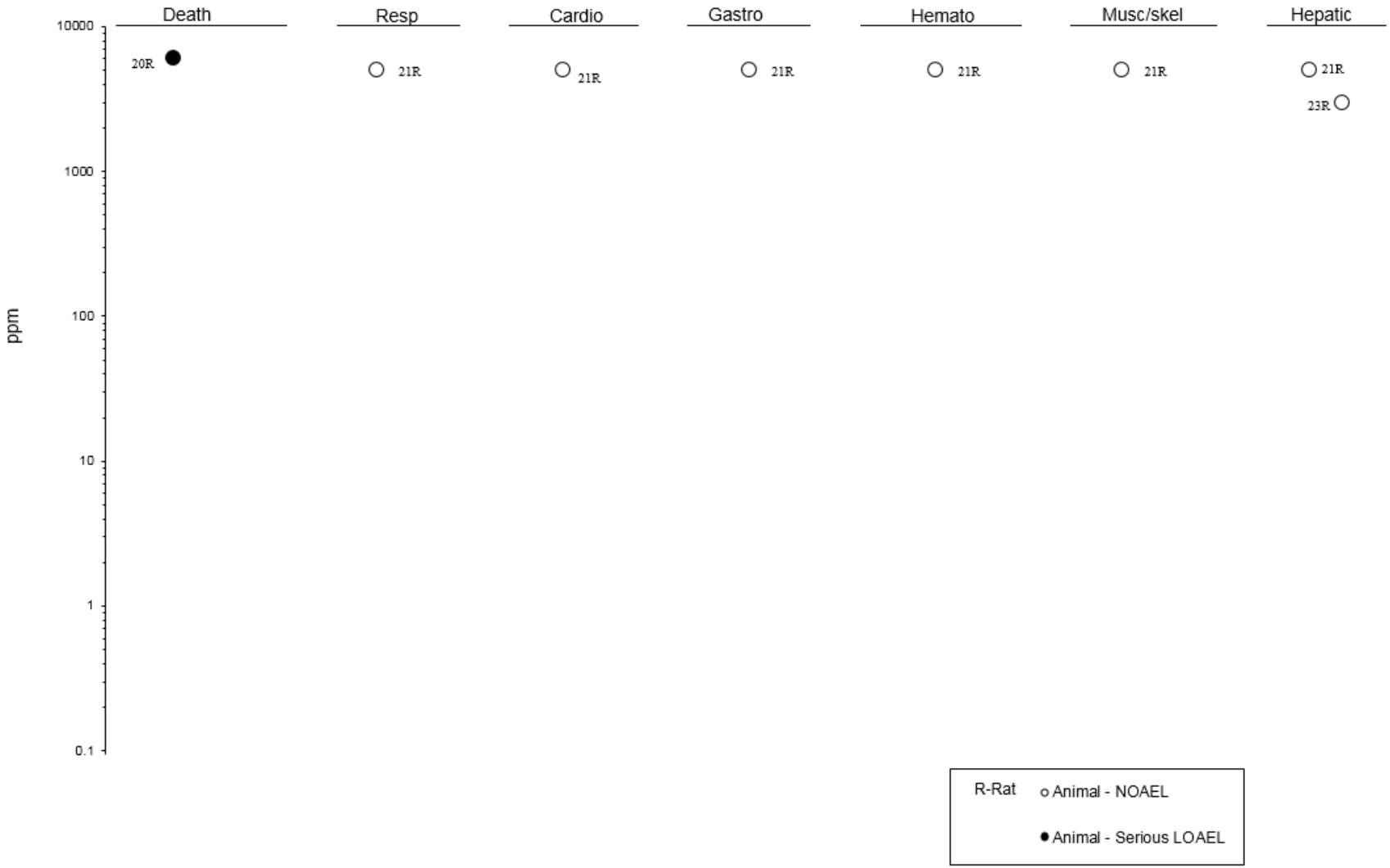


Figure 2-2. Levels of Significant Exposure to 2-Butanone – Inhalation
Intermediate (15-364)

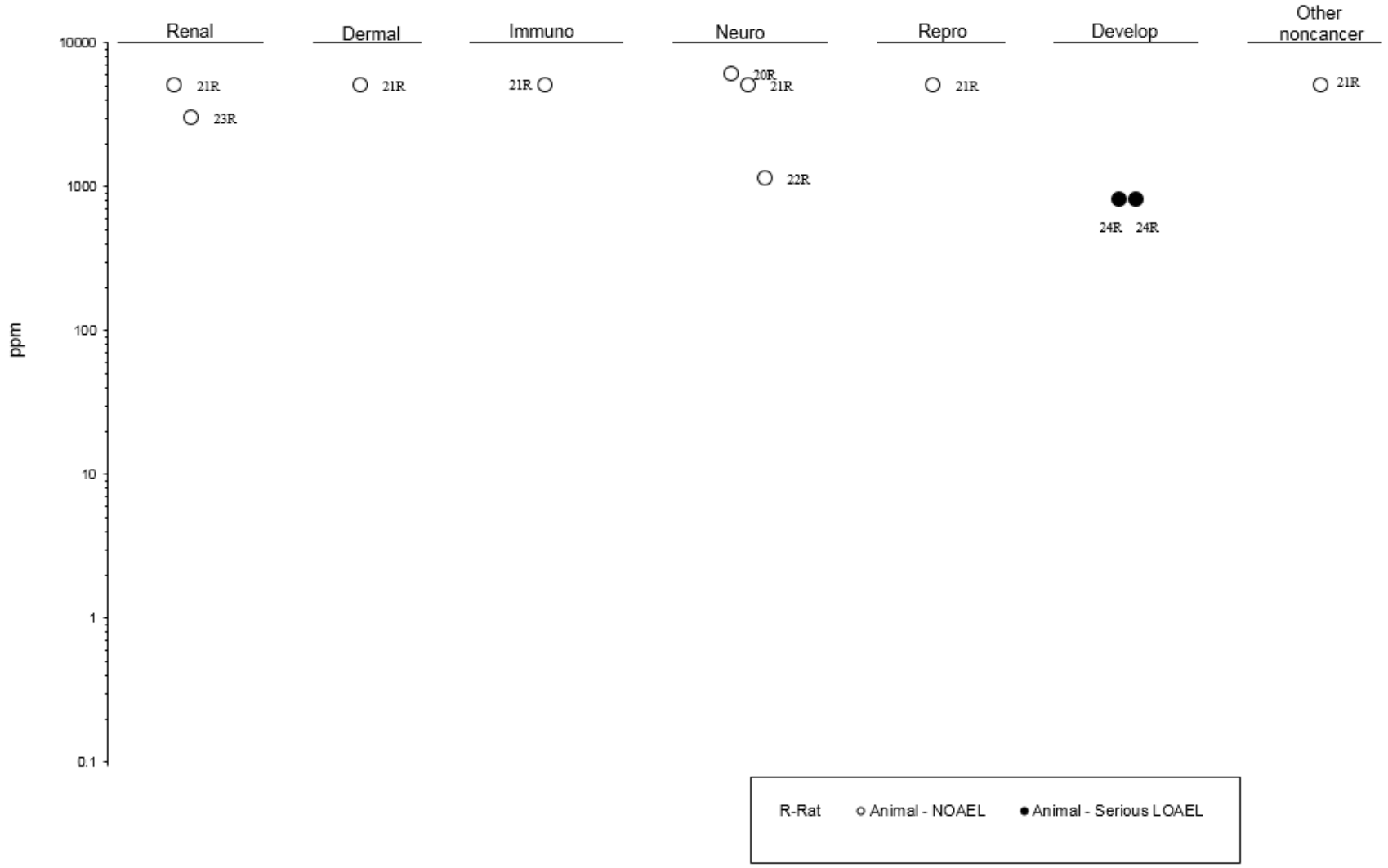


Table 2-2. Levels of Significant Exposure to 2-Butanone – Oral

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)

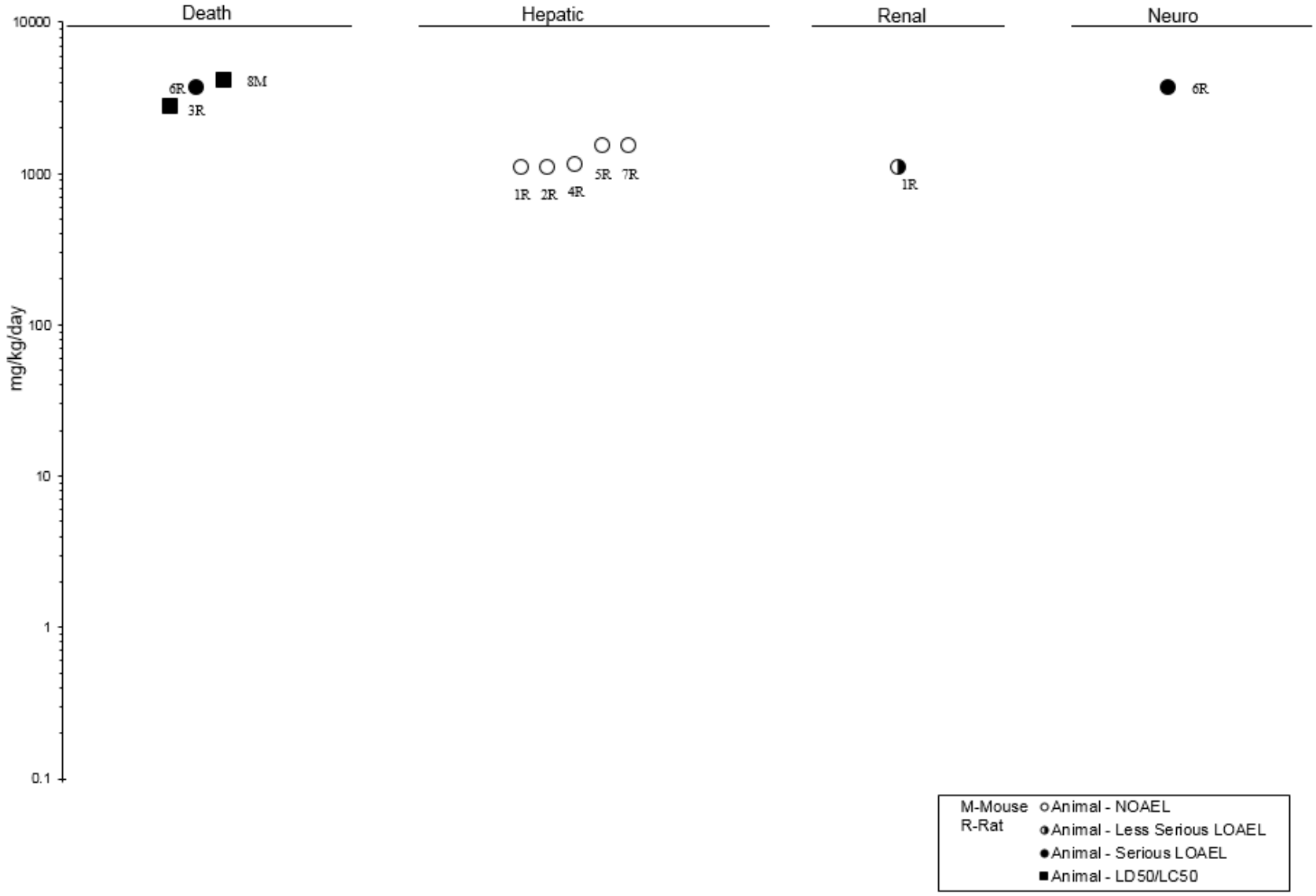


Figure 2-3. Levels of Significant Exposure to 2-Butanone – Oral
Intermediate (15-364 days)

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. 1978a, 1978b). 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. 1978b).

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 (Mast et al. 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 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 time-weighted average 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 Triel 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. 1978a). Due to the irritation observed at 10,000 ppm in the study by Altenkirch et al. (1978a), 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. 1978b). 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; time-weighted average 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 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 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) (Mast et al. 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 ornithinecarbamyl 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 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 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 Triel 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 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, 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).

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. 1978a). 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 roto-rod, 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, l–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 to 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 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 ≤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 ≤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 per day on GDs 6–15; weights were measured on GDs 0, 6, 9, 15, and 18 and the dams were euthanized on GD 18 (Mast et al. 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).

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 dewaxing plants 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 more than 14,000 aircraft maintenance workers from Utah reported a statistically significant elevated rate ratio (RR) for multiple myeloma in females in an extended followup study (Radican et al. 2008) that was not observed/reported in the baseline 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 studies were located regarding cancer in animals following inhalation exposure to 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 report 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*

		Results		
		Activation		
Species (test system)	Endpoint	With	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

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

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae	Gene mutation	–	–	Thorpe 1982
S. cerevisiae	Chromosomal aberrations (malsegregation)	No data	+	Liu et al. 1997 (as reported by Albtertini et al. 1991)
S. cerevisiae (D61.M)	Mitotic chromosome loss	No data	–	Mayer et al. 1994
S. cerevisiae (D61.M)	Gene mutation or recombination	No data	–	Mayer et al. 1994
S. cerevisiae	Mitotic chromosome loss	No data	+	Whittaker et al. 1990; Zimmerman 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 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 (Krejo 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 et al. 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 et al. 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 viv*o 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

Inhalation Exposure. 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.

Oral Exposure. 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.

Dermal Exposure. 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. The dermal permeability constant (Kp) reported for 2-butanone in excised human skin was 58 g/m^2/hour (Ursin et al. 1995).

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 of 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).

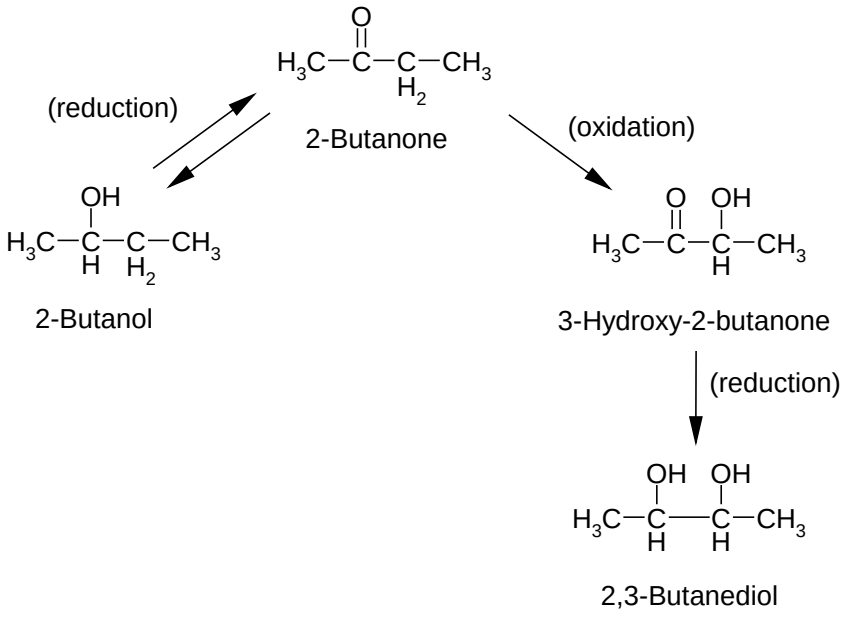
Inhalation Exposure. Information regarding distribution of 2-butanone in animals after inhalation exposure is limited. Rats that were exposed to 600 ppm 2-butanone for 6 hours on 1 day or for 6–10 hours/day for 8 days had perirenal fat concentrations of 0.71 μmol/g after a single exposure and 0.70 μmol/g 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).

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). Thrall et al. (2002) demonstrated the 2-butanone metabolism in rats is not completely eliminated by inhibition of the oxidative pathway using pyrazole.

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



Source: DiVincenzo et al. 1976

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 l–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.

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). 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 (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/h/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 postnatal day (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. 1985a); 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).

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. 1978a; 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. 1978a, 1982a; 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. 1978a). In the same study, rats exposed to 6,000 ppm 2-butanone only 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 l–5 weeks earlier than 500 ppm n-hexane alone (Altenkirch et al. 1982a). 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 only 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. (1982a), which included paranodal axon swelling, accumulation of neurofilaments, and demyelination. Subcutaneous injection of methyl-n-butyl ketone with 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 ethyl-n-butyl ketone of in rats for several weeks caused the 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 ppm: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 (pre-treated) *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 pre-treated liver S9 fractions that 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 reported a bi-phasic 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 in animals co-exposed to high levels of 2-butanone (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 potentiated 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, although measures of toluene neurotoxicity were not evaluated in this study.

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 et al. 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 16 hours (Traiger et al. 1989) or for a duration of 3 days (Raymond et al. 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 et al. 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 pre-treated 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 pre-treated with 2-butanone for 3 days prior to chloroform exposure (Raymond et al. 1995a). Unlike in the liver, total CYP content and aniline hydroxylase levels were increased in kidney microsomes extracted from rats pre-treated with 2-butanone,

compared to controls. These data suggest a role for CYP induction in the potentiation of kidney chloroform kidney toxicity by 2-butanone (Raymond et al. 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 evident for the solvent mixture, while only hindlimb weakness was observed in the dams exposed observed n-hexane alone.

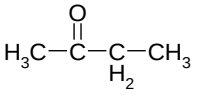
Coexposure of *S. cerevisiae* to 2-butanone, ethyl acetate, and propionitrile enhanced the induction of chromosome loss caused by 2-butanone (Zimmermann et al. 1989). Coexposure of *S. cerevisiae* to 2-butanone and nocodazole enhanced the induction of aneuploidy caused by 2-butanone alone (Mayer and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

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

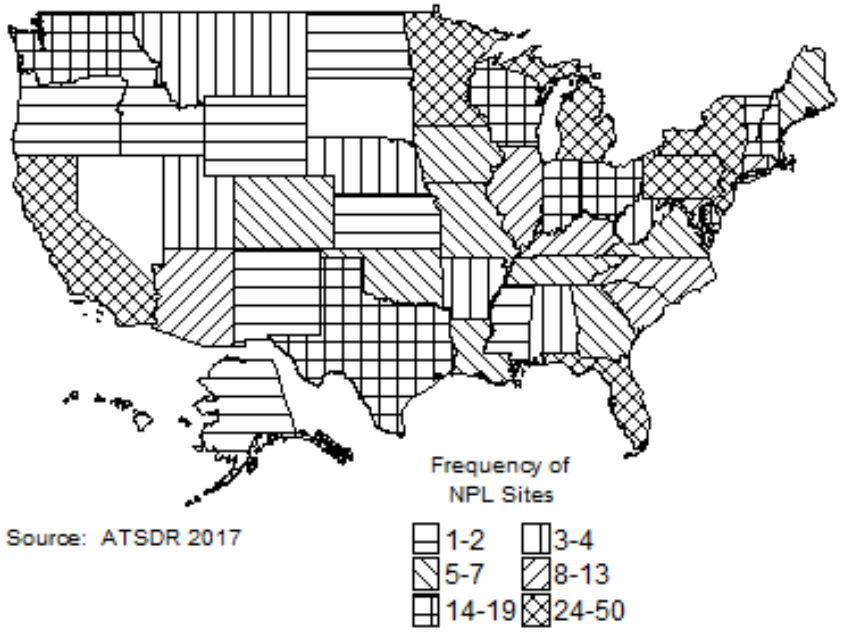
Property	Information	Reference
Partition coefficients:		
Log K_{ow}	0.29	Hansch and Leo 1985
Log K_{oc}	0.55	Roy and Griffin 1985
Vapor pressure at 25°C	90.6 mmHg	Riddick et al. 1986
Henry's law constant at 25°C	5.77×10^{-5} atm m^3/mol	Rathburn and Tai 1987
Autoignition temperature	515°C	Sax and Lewis 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=2.93 mg/m^3	
mg/m^3 to ppm (v/v) in air (20°C)	1 mg/m^3=0.341 ppm	
Bioconcentration factor	0.98 (calculated from K_{ow})	Lyman et al. 1982
Explosive limits	No data	

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

2-Butanone has been identified in at least 526 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which 2-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 sorb 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. It is widely used in coating systems where its volatilization to the atmosphere is an intended outcome of its 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 waste water 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. International Trade Commission (USITC 1989), 482,028,000 pounds of 2-butanone were produced in the United States in 1988. The production volumes for 1986 and 1987 were 600,440,000 and 671,859,000 pounds, respectively (USITC 1987, 1988). Total U.S. capacity for 1989 was estimated at 622 million pounds (SRI 1989). Production of 2-butanone was flat in the early 1980s, but it was expected to grow at 2–3% through 1991 (Chemical Marketing Reporter 1987). Manufacturers of 2-butanone in 1989 are included in Table 5-1.

Table 5-1. Manufacturers of 2-Butanone in 1989

Company	Location
ARCO Chemical Company	Channelview, Texas
Exxon Corporation	Baton Rouge, Louisiana
Hoechst Celanese Corporation	Pampa, Texas
Shell Oil Company	Norco, Louisiana
Union Carbide Corporation	No data

Sources: SRI 1989; USITC 1989

2-Butanone is produced on a commercial scale by one of two processes. The vapor-phase dehydrogenation of sec-butanol (2-butanol), itself obtained from the hydrolysis of butene, accounts for 88% 2-butanone production (Neier and Strehlke 1985; Papa and Sherman 1981). In the other commercially significant process, 2-butanone is obtained as a byproduct of acetic acid production. In this methodology, liquified butane is subjected to catalytic oxidation.

5.2.2 Import/Export

Approximately 16% of the total U.S. production of 2-butanone is exported to other countries (Chemical Marketing Reporter 1987). Imports into the United States amounted to about 52 million pounds in 1986.

5.2.3 Use

2-Butanone exhibits outstanding solvent properties, and combined with its low cost, it is often the choice solvent for various coating systems (Neier and Strehlke 1985; Papa and Sherman 1981). Uses of 2-butanone can be broken down into the following categories: coatings solvent, 50%; adhesives, 13%; magnetic tapes, 8%; lube oil dewaxing, 4%; printing inks, 3%; exports, 16%; and miscellaneous, 6% (Chemical Marketing Reporter 1987). Examples of specific applications include its use as a solvent for nitrocellulose, lacquers, rubber cement, printing inks, paint removers, vinyl films, resins, rosins, polystyrene, chlorinated rubber, polyurethane, acrylic coatings, and cleaning solutions (Neier and Strehlke 1985; 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 applications, and as a solvent for the production of smokeless powders.

5.2.4 Disposal

Dilute solutions of 2-butanone can be discharged directly into sewage treatment facilities, sprayed into incinerators, or burned in paper packaging (OHM/TADS 1989). It can be destroyed in fluidized-bed incinerators, rotary kiln incinerators, or liquid injection incinerators using short residence times of a few seconds for either liquids or gases, and longer residence times for contaminated solids, if applicable (HSDB 1989). 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

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

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 (Tichenor 1987; 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 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 waste water 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 rain water (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 rain water (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 and Leo 1985), 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; Edney and Corse 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. 1979).

An experimentally determined rate constant of $5.4x10^{8}$ 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 $1x10^{-17}$ 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 (Kollig et al. 1987), 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 rain water 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 rain water 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 1984
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
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
Ground water (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	26,900	158	94
Soil (ppb)	550	1,700	65,700	119	93
Air (ppbv)	15.5	16.33	7059	33	20

[a]Concentrations found in ATSDR site documents from 1981 to 2017 for 1,854 NPL sites (ATSDR 2017). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

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). 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 $\mu g/m^3$ (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 (Shah and Heyerdahl 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

Numerous studies have qualitatively detected 2-butanone in drinking water supplies (Kool et al. 1982). It has been found in drinking water from the District of Columbia; Cincinnati, Ohio; Miami, Florida; Ottumwa, Iowa; Philadelphia, Pennsylvania; Seattle, Washington; Tuscaloosa, Alabama; and New Orleans, Louisiana (Bertsch et al. 1975; Coleman et al. 1976; EPA 1974, 1975; Kopfler et al. 1977; Scheiman et al. 1974). It was detected in Des Moines, Iowa, drinking water samples at an estimated concentration of 1.6 ppb (Ogawa and Fritz 1985). 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 rain water 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).

2-Butanone was listed as being detected in <5% of U.S. groundwater supplies (Dyksen and Hess 1982). At U.S. hazardous waste sites, 2-Butanone was listed as being frequently detected in the groundwater (Garman et al. 1987). This statement should be interpreted with caution, as "frequently" was defined as >0.1%, of the samples. Examples of the presence of 2-butanone at hazardous waste sites and landfills can be found in Table 5-5. It was detected in groundwater samples underneath a tanker truck spill at concentrations up to 2,200 ppm (Halvorsen and Ohneck 1985). Interpretation of the concentration of 2-butanone found in groundwater samples should be made carefully, and should take into account the experimental methods used in the determinations; results may be skewed due to the presence of 2-butanone in the adhesives used to cement PVC well pipes together (Sosebee et al. 1983).

Table 5-5. Detection of 2-Butanone in the Groundwater of Hazardous Waste Sites and Landfills

Type/location	Sampling dates	Number of samples	Number of positive	Concentration	Reference
Waste sites, groundwater Connecticut Low-level radioactive	1982–1983	5	1	4,800 ppm	Sawhney and Kozloski 1984
Waste sites, surface water Valley of the Drums, Kentucky	No data	No data	No data	≤690 ppb	Stonebraker and Smith 1980
Landfills, groundwater Municipal solid waste	No data	13	7	6.8–6,200 ppb	Sabel and Clark 1984
Landfills, leachate Municipal solid waste	No data	6	6	110–27,000 ppb	Sabel and Clark 1984

2-Butanone has been detected in the effluent of various industrial processes. It was found in six of seven waste water samples from energy-related processes at a concentration up to 645 ppb (Pellizzari et al. 1979). 2-Butanone was detected in the waste water 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 waste water 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 waste water 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 seawater from the straits of Florida at 0–22 ppb in 1968 (Corwin 1969).

5.5.3 Sediment and Soil

Limited data are available on the detection of 2-butanone in soil samples.

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 1979; 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). 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). 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 is a naturally occurring constituent in a variety of common foods (Del Rosario et al. 1984; Dumont and Adda 1978; Gordon and Morgan 1979; 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).

According to the National Occupational Exposure Survey (NOES) conducted by 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. Occupational exposure is expected to occur by inhalation and dermal contact.

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 waste water 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 waste waters (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).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

No studies were located that identified populations that are unusually susceptible to adverse health effects after exposure to 2-butanone. The very young and the very old are typically more susceptible to chemical toxicity than are older children, adolescents, and healthy adults. Individuals who are alcoholics and those with existing liver disease would be expected to metabolize 2-butanone differently than the general population. Persons with existing neuropathies may also be more susceptible. 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.

High levels of occupational exposure to 2-butanone may occur by inhalation and dermal contact during the loading and unloading of large quantities of this material during shipment. The application of commercial coatings containing 2-butanone without adequate protection may also lead to high levels of exposure, primarily by inhalation.

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.

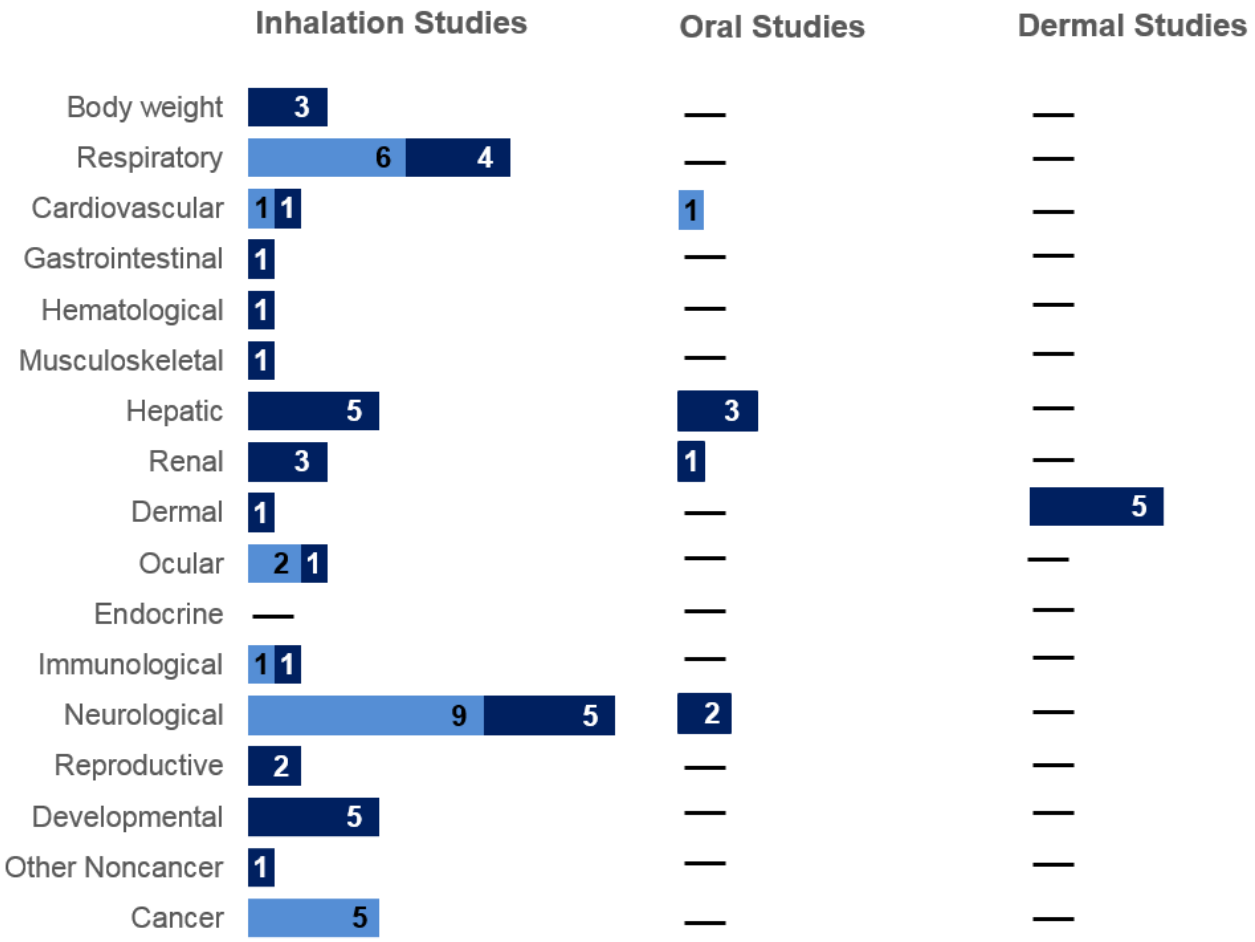
As illustrated in Figure 6-1, most of the data on the toxicity of 2-butanone come from inhalation studies in humans and laboratory animals. The most commonly examined endpoints were respiratory and neurological effects. Developmental effects and liver toxicity were also studied in animals only. A small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

6.2 Identification of Data Needs

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

Figure 6-1. Summary of Existing Health Effects Studies on 2-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.

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. 1978a, 1978b; 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 by 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 (Tharr et al. 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 Casey1981; 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 of 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 (Mast et al. 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. No studies were located regarding immunotoxicity after oral exposure to 2-butanone. A clinical report of contact urticaria in a 47-year-old painter exposed occupationally to 2-butanone (Varigos and Nurse 1986) suggests that skin sensitivity requires more study. Altenkirch et al. (1978a) reported that 19/19 rats died suddenly of pathologically confirmed bronchopneumonia after 7 weeks of inhalation exposure to 6,000 ppm 2-butanone. 2-Butanone may weaken the immune system, thus predisposing humans and animals to infection. No histopathological lesions were found in the thymus, lymph nodes, spleen, or bone marrow of rats exposed to ≤5,000 ppm of 2-butanone for 90 days (Cavender and Casey 1981; Cavender et al. 1983), but tests for immune function were not performed. Therefore, a study of the effects of 2-butanone on 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 in female subjects exposed to 100 ppm (Tomicic et al. 2011). Neurobehavioral effects have been observed in mice (1,602 ppm) (DeCeaurriz 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). However, 2-butanone is not generally regarded as being highly neurotoxic when administered alone. In acute and intermediate exposure studies in animals, 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, 1990, 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. 1990). 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. 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). Developmental effects have not been evaluated in oral studies and no studies of early postnatal exposure are available by any exposure route. 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 (Chemical Marketing Reporter 1987; Neir and Strehlke 1985; Papa and Sherman 1981; USITC 1987, 1988, 1989). Methods for the disposal of 2-butanone are established (HSDB 1989; 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 and Leo 1985; Lyman et al. 1982; Roy and Griffen 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 (Lyma et al. 1982). Given the potential for exposure to 2-butanone because of its prevalence in commercial products available to the public (Neier and Strehlke 1985), 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 and Leo 1985; 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; Shah and Heyerdahl 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.

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 correlation of 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 in the National Institutes of Health (NIH) Reporter (2017).

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	IRIS 2003
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2012
	1-Day health advisory (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	No data	EPA 2009
	RfD	0.6 mg/kg/day[a]	IRIS 2003
WHO	Drinking water quality guidelines	No data	WHO 2017
FDA	EAFUS	Yes[b]	FDA 2013
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	No data	IRIS 2003
IARC	Carcinogenicity classification	No data	IARC 2017
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards and construction	200 ppm (590 mg/m^3)	OSHA 2016a, 2016b, 2017
NIOSH	REL (up to 10-hour TWA)	200 ppm (590 mg/m^3)	NIOSH 2016
	STEL	300 ppm (885 mg/m^3)	
	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	No data	EPA 2016
	AEGL 1		
	10-minute	200 ppm	
	30-minute	200 ppm	
	60-minute	200 ppm	
	4-hour	200 ppm	
	8-hour	200 ppm	
	AEGL 2		
	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		
	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 2016b
	PAC-1[e]	200 ppm	
	PAC-2[e]	2,700 ppm	
	PAC-3[e]	4,000 ppm	

[a]RfD is based on data for 2-butanol (a metabolic precursor of 2-butanone).
[b]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[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.
[e]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2016b).

AEGL = acute exposure guideline level; 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; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	2-Butanone
CAS Numbers:	78-93-3
Date:	May 2019
Profile Status:	Final, Draft for Public Comment
Route:	Inhalation
Duration:	Acute
MRL	1 ppm (provisional)
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: A provisional acute duration MRL of 1 ppm was derived for 2-butanone based on reported neurological symptoms (headache, fatigue, feeling of intoxication) in volunteers. The provisional 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 provisional acute-duration inhalation MRL.

Calculations: Not applicable.

Intermittent Exposure: 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 human variability
- 10 for use of a LOAEL

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 work day. 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. 1978a; Patty et al. 1935).

Agency Contacts (Chemical Managers): G. Daniel Todd

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Butanone
CAS Numbers: 78-93-3
Date: July, 1992
April, 2017—Updated literature search
Profile Status: Final, Draft for Public Comment
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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Butanone
CAS Numbers: 78-93-3
Date: July, 1992
April, 2017—Updated literature search
Profile Status: Final, Draft for Public Comment
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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Butanone
CAS Numbers: 78-93-3
Date: July, 1992
April, 2017—Updated literature search
Profile Status: Final, Draft for Public Comment
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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Butanone
CAS Numbers: 78-93-3
Date: July, 1992
April, 2017—Updated literature search
Profile Status: Final, Draft for Public Comment
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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Butanone
CAS Numbers: 78-93-3
Date: July, 1992
April, 2017—Updated literature search
Profile Status: Final, Draft for Public Comment
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, and chemical interactions 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
Cancer

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

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

B.1.1 Literature Search

The current literature search was intended to update the health effects sections of the existing toxicological profile for 2-butanone (ATSDR 1992), thus, the literature search was restricted to studies published between January 1990 to April 2017. The following main databases were searched in April 2017:

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

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, and Medical Subject Headings (MeSH) terms 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	
04/2017	(("methylethyl ketone"[supplementary concept] OR "methylethyl ketone"[nm] OR 6PT9KLV9IO[rn] OR 78-93-3[rn]) AND (1990/01/01 : 3000[dp] OR 1990/01/01 : 3000[mhda])) OR ((("2-Butanone"[tw] OR "3-Butanone"[tw] OR "Aethylmethylketon"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"Butanone 2"[tw] OR "Ethyl methyl cetone"[tw] OR "Ethyl methyl ketone"[tw] OR "Ethylmethylcetone"[tw] OR "Ethylmethylketon"[tw] OR "Meetco"[tw] OR "Methyl acetone"[tw] OR "Methyl ethyl ketone"[tw] OR "Methylethyl ketone"[tw] OR "Methylethylketone"[tw] OR "Metiletilcetona"[tw] OR "Metiletilchetone"[tw] OR "Metyl ethyl ketone"[tw] OR "Metyloetyloketon"[tw] OR ("Butanone"[tw] NOT "1-butanone"[tw])) NOT medline[sb]) AND (1990/01/01 : 3000[dp] OR 1990/01/01 : 3000[crdat] OR 1990/01/01 : 3000[edat]))
Toxline	
04/2017	("2-butanone" OR "3-butanone" OR "aethylmethylketon" OR "butanone 2" OR "ethyl methyl cetone" OR "ethyl methyl ketone" OR "ethylmethylcetone" OR "ethylmethylketon" OR "meetco" OR "methyl acetone" OR "methyl ethyl ketone" OR "methylethyl ketone" OR "methylethylketone" OR "metiletilcetona" OR "metiletilchetone" OR "metyl ethyl ketone" OR "metyloetyloketon" OR ("butanone" NOT "1-butanone") OR 78-93-3 [rn]) AND 1990:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
04/2017	(FILE 'HOME' ENTERED AT 11:15:08 ON 06 APR 2017) FILE 'TOXCENTER' ENTERED AT 11:15:34 ON 06 APR 2017 CHARGED TO COST=EH011.13.01.01 L1 8642 SEA 78-93-3 L2 8388 SEA L1 NOT TSCATS/FS L3 6086 SEA L2 NOT PATENT/DT L4 4588 SEA L3 AND PY>=1990 ACTIVATE TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)

Table B-2. Database Query Strings

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

	L38 1853 SEA L4 AND L37
	L39 111 SEA L38 AND MEDLINE/FS
	L40 180 SEA L38 AND BIOSIS/FS
	L41 1524 SEA L38 AND CAPLUS/FS
	L42 38 SEA L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L43 1659 DUP REM L39 L40 L42 L41 (194 DUPLICATES REMOVED)
	L*** DEL 111 S L38 AND MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	L*** DEL 111 S L38 AND MEDLINE/FS L44 111 SEA L43 L*** DEL 180 S L38 AND BIOSIS/FS L*** DEL 180 S L38 AND BIOSIS/FS L45 123 SEA L43 L*** DEL 1524 S L38 AND CAPLUS/FS L*** DEL 1524 S L38 AND CAPLUS/FS L46 1390 SEA L43 L*** DEL 38 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 38 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L47 35 SEA L43 L48 1548 SEA (L44 OR L45 OR L46 OR L47) NOT MEDLINE/FS D SCAN L48

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
04/2017	Compound searched: 78-93-3
NTP	
04/2017	78-93-3 2-Butanone 3-Butanone Ethyl methyl ketone Methyl acetone Methyl ethyl ketone
NIH RePORTER	
11/2017	Text Search: "78-93-3" OR "2-Butanone" OR "3-Butanone" OR "Aethylmethylketon" OR "Butanone 2" OR "Ethyl methyl cetone" OR "Ethyl methyl ketone" OR "Ethylmethylcetone" OR "Ethylmethylketon" OR "Meetco" OR "Methyl acetone" OR "Methyl ethyl ketone" OR "Methylethyl ketone" OR "Methylethylketone" OR "Metiletilcetona" OR "Metiletilchetone" OR "Metyl ethyl ketone" OR "Metyloetyloketon" OR ("butanone" NOT "1-butanone") (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

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

The 2017 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 2,629
- Number of records identified from other strategies: 27
- Total number of records to undergo literature screening: 2,656

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.

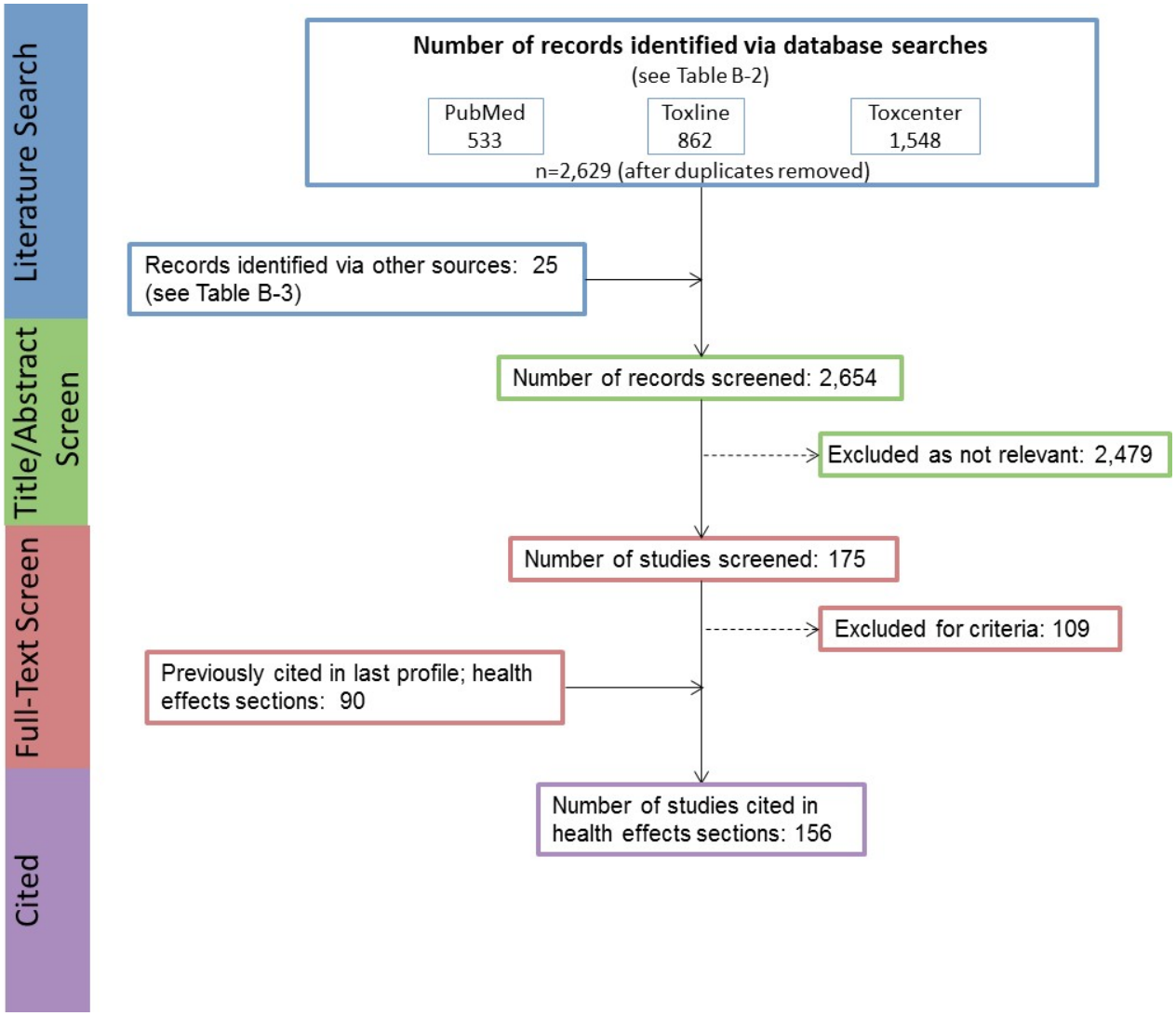
- Number of titles and abstracts screened: 2,654
- Number of studies considered relevant and moved to the next step: 175

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: 175
- Number of studies cited in the health effects sections of the existing toxicological profile (July, 1992): 90
- Total number of studies cited in the health effects sections of the updated profile: 156
- Number of new studies cited in the updated profile: 66

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

Figure B-1. April 2017 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.

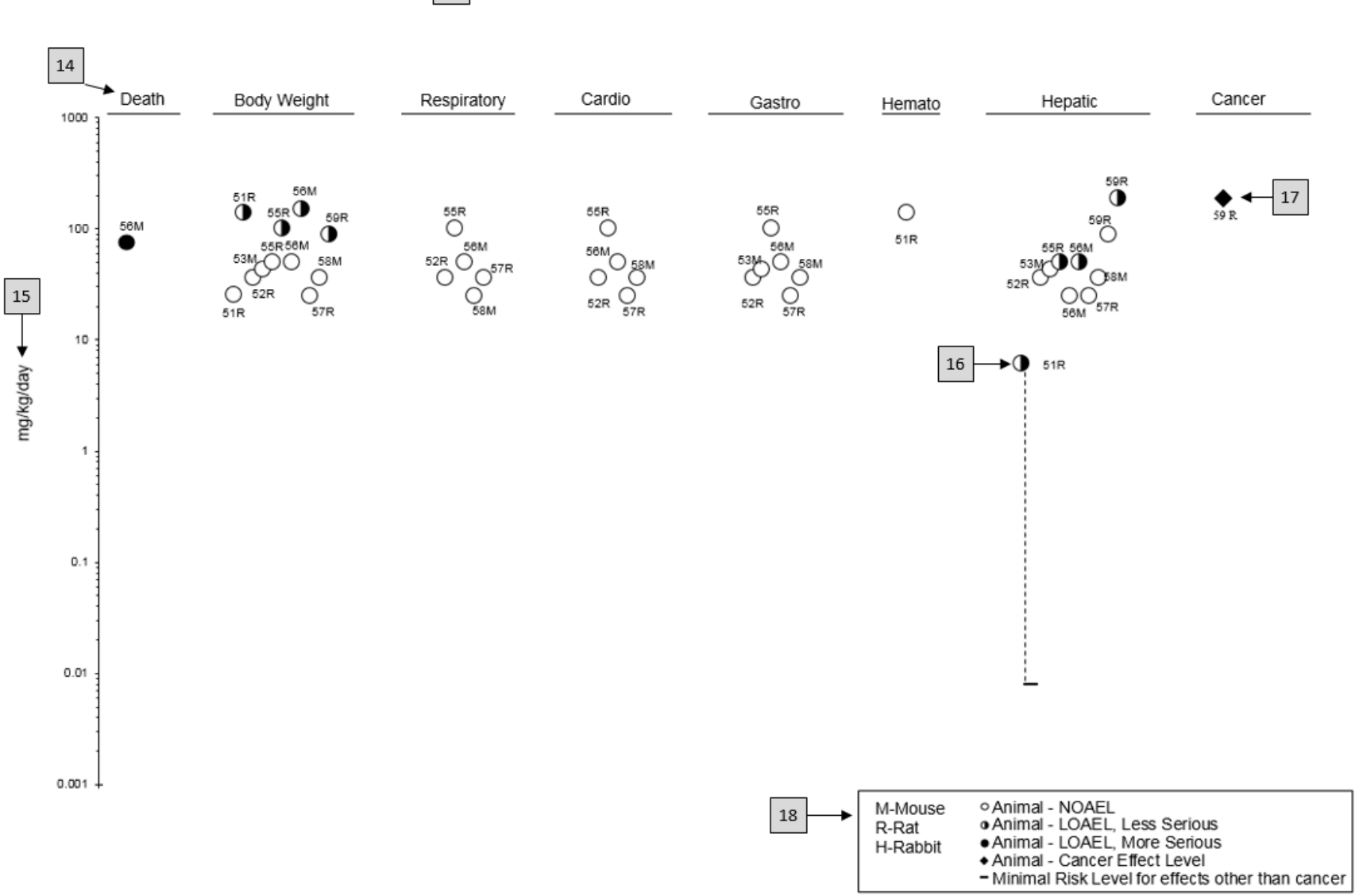
APPENDIX C

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

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

[a]The number corresponds to entries in Figure 2-x.
[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). (11)
[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).

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
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act

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

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

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result