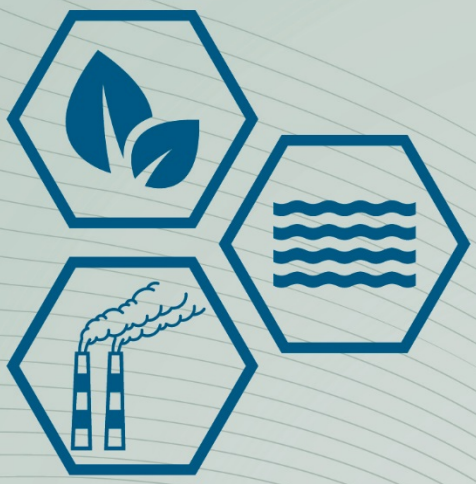

Toxicological Profile for Acetone

June 2022

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

CS274127-A

DISCLAIMER

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

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

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

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, intermediate, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

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

VERSION HISTORY

Date	Description
June 2022	Final toxicological profile released
July 2021	Draft for public comment toxicological profile released
August 2011	Addendum to the toxicological profile released
May 1994	Final toxicological profile released

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

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

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

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Acetone is a colorless volatile liquid at room temperature. It is water soluble and will volatize from soil and water. Acetone is used primarily as an intermediate in chemical production and as a solvent (ICIS 2017). It is used in many products, including paints and coatings, cleaning products, personal care products, and industrial products such as lubricants and plastics (CDR 2012, 2016).

In addition to its anthropogenic sources, acetone occurs naturally in the environment. Plants, trees, insects, and microbes emit acetone (Graedel et al. 1986; Isidorov et al. 1985; Khalil and Rasmussen 1992). Acetone is produced during human-made and natural combustion such as volcanic eruptions (Isidorov et al. 1990), forest fires (Graedel et al. 1986), vehicular exhaust (Graedel et al. 1986), trash incineration (Graedel et al. 1986), and smoking tobacco (Manning et al. 1983). Acetone is also formed endogenously in the human body as a byproduct of metabolism. Baseline levels of acetone vary from person to person. Children and adolescents tend to produce more endogenous acetone than adults due to their relatively high metabolic rates (Johanson 2012). People with diabetes may produce high levels of endogenous acetone in the process of metabolizing fatty acids in blood (Johanson 2012).

As a result of its emission during combustion, acetone is present in the air, leaving the general population susceptible to inhalation exposure. However, acetone levels in ambient air in the United States are low, ranging from less than 1 ppb (volume per volume) in remote areas (Cavanagh et al. 1969) to 6.9 ppb in urban air (Shah and Singh 1988). The low levels of acetone in ambient air reduce the concern for inhalation exposure in the general population. Individuals who smoke cigarettes, frequently use acetone-containing products in their home, or work in certain occupations may have higher risk of exposure.

Oral exposure to acetone may occur when people eat foods that contain acetone or drink water contaminated with acetone. Acetone has been detected in the volatile components of several fruits and vegetables (Bartley and Schwede 1989; Lovegren et al. 1979). No information on average dietary intake was found. Disulfiram, a medicine commonly used in alcohol aversion therapy, has been found to induce endogenous acetone production in humans and animals (DeMaster and Stevens 1988; Stowell et al. 1980). While acetone may already be present in water in low levels due to atmospheric deposition, landfill leaching and discharges from manufacturers can lead to increased levels of acetone in drinking water. Well water may be especially susceptible to acetone pollution due to acetone’s mobility in soil.

Dermal exposures may occur when individuals use products that contain acetone such as personal care (e.g., nail polish remover) or cleaning products or come into contact with water or soil containing acetone.

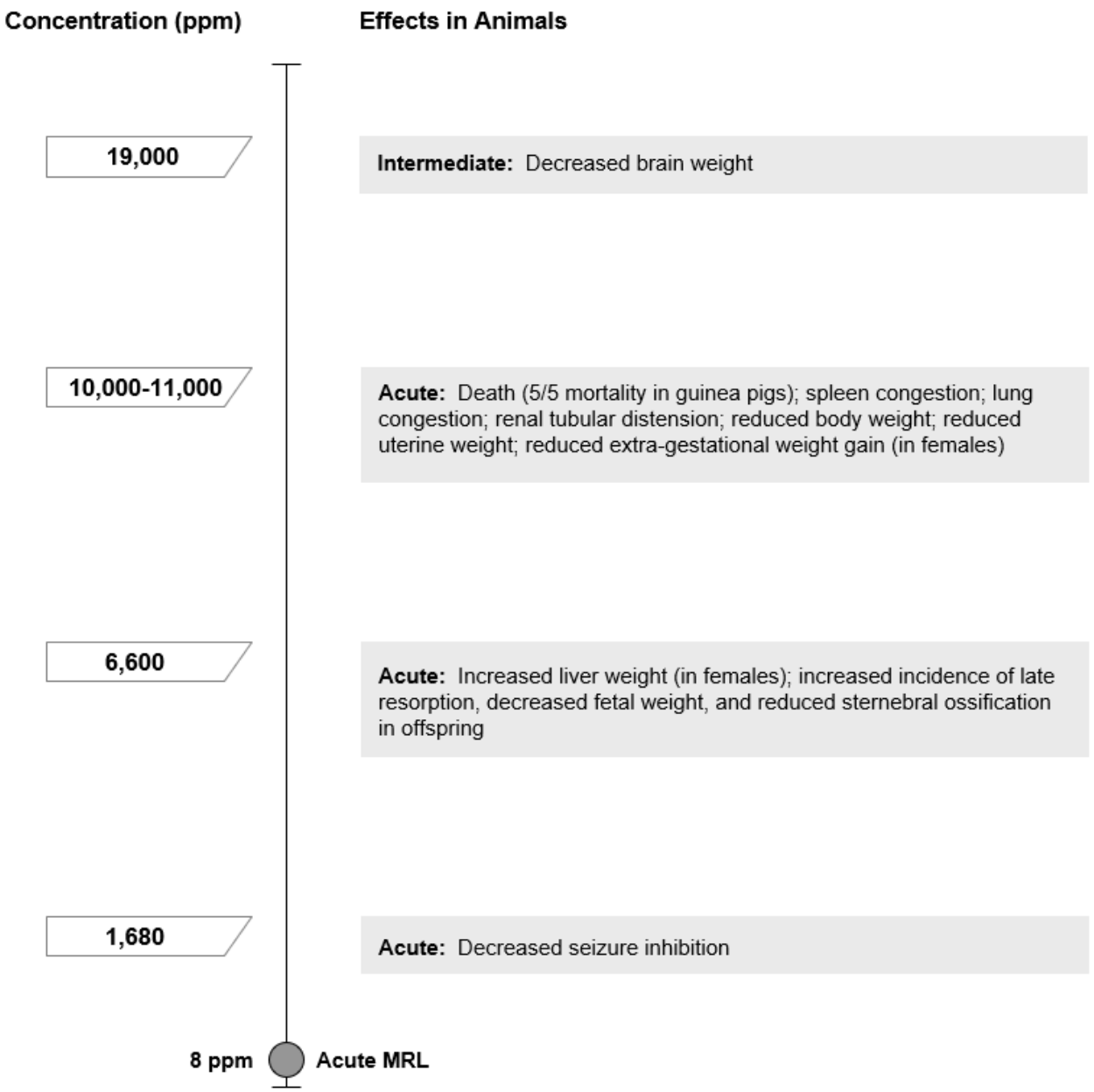
Acetone is produced endogenously by the human body, and this production varies from human to human. Therefore, baseline levels of acetone in the human body may also vary from person to person. Acetone in the body can be detected in exhaled breath, urine, blood, and breastmilk. However, because acetone is eliminated within 1–3 days, these biomarkers should only be used to monitor recent acetone exposure. While biomarkers are useful for assessing exposure to high levels of acetone found in, for example, occupational exposure studies, they are less accurate for the lower acetone levels found in the general population.

1.2 SUMMARY OF HEALTH EFFECTS

The health effects of acetone have been evaluated in epidemiology studies, controlled human trials, and experimental animal studies. Most studies examined acute inhalation or oral exposure to acetone. Both human and animal studies were located for the majority of the endpoints evaluated in this profile. However, body weight was only evaluated in animal studies, and no studies were located on the endocrine effects of acetone. Figures 1-1, 1-2, and 1-3 show the lowest-observed-adverse-effect levels (LOAELs) of acetone for various endpoints. The current body of literature suggests the following six main endpoints that are sensitive to acetone exposure:

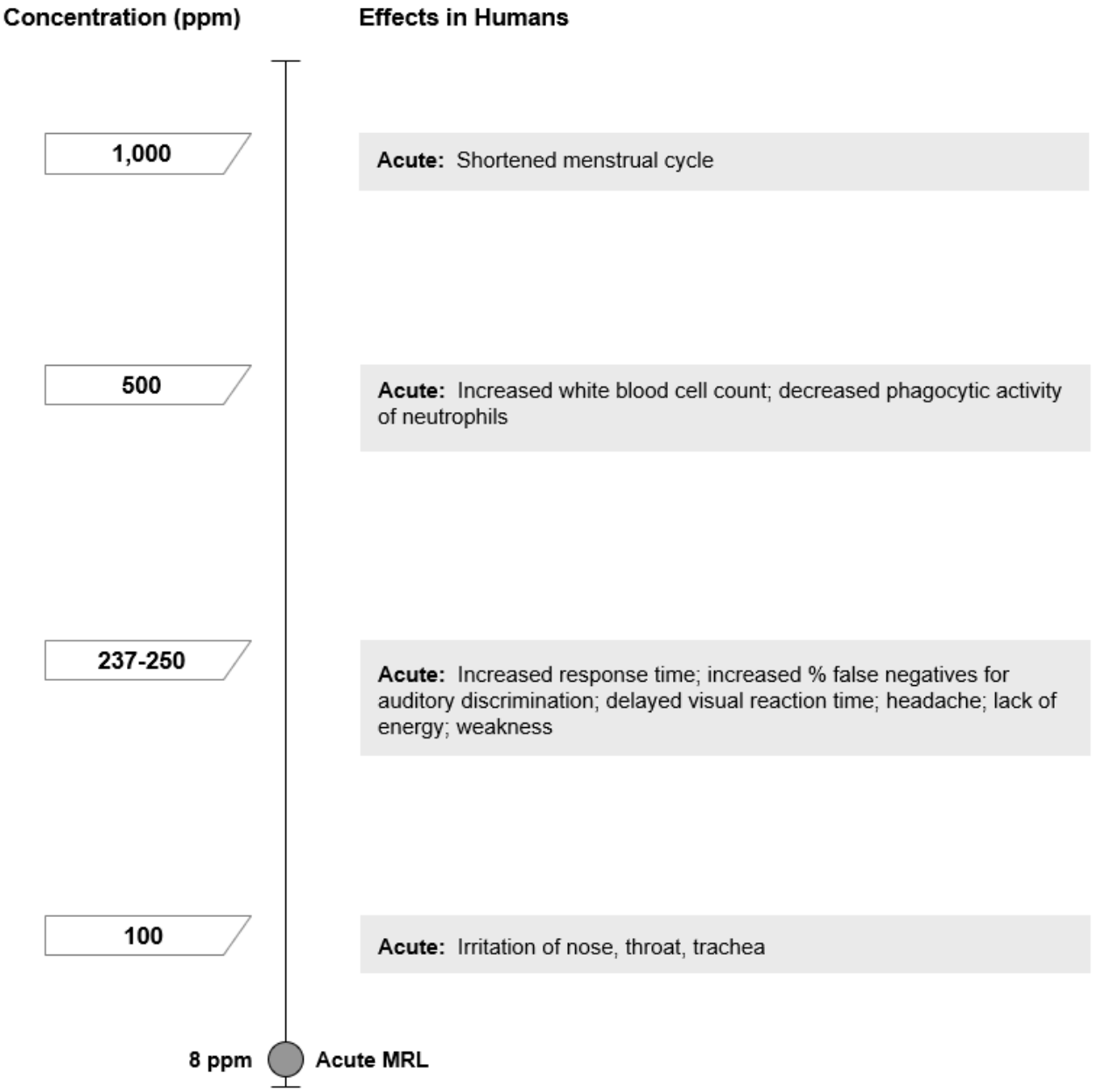
Neurological Effects. Neurological effects are the most common endpoint evaluated in the body of literature on acetone, occurring after oral or inhalation exposure. Neurological effects in humans exposed to acetone range from dizziness and headaches (Pomerantz 1950; Raleigh and McGee 1972) to dulling of reflexes (Chen et al. 2002; Haggard et al. 1944), unconsciousness (Ross 1973), and anger and hostility (Dick et al. 1989). Neurological effects, including narcosis, increases in anger and hostility, and loss of coordination have been observed in animals exposed to acetone (NTP 1988; Specht et al. 1939).

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



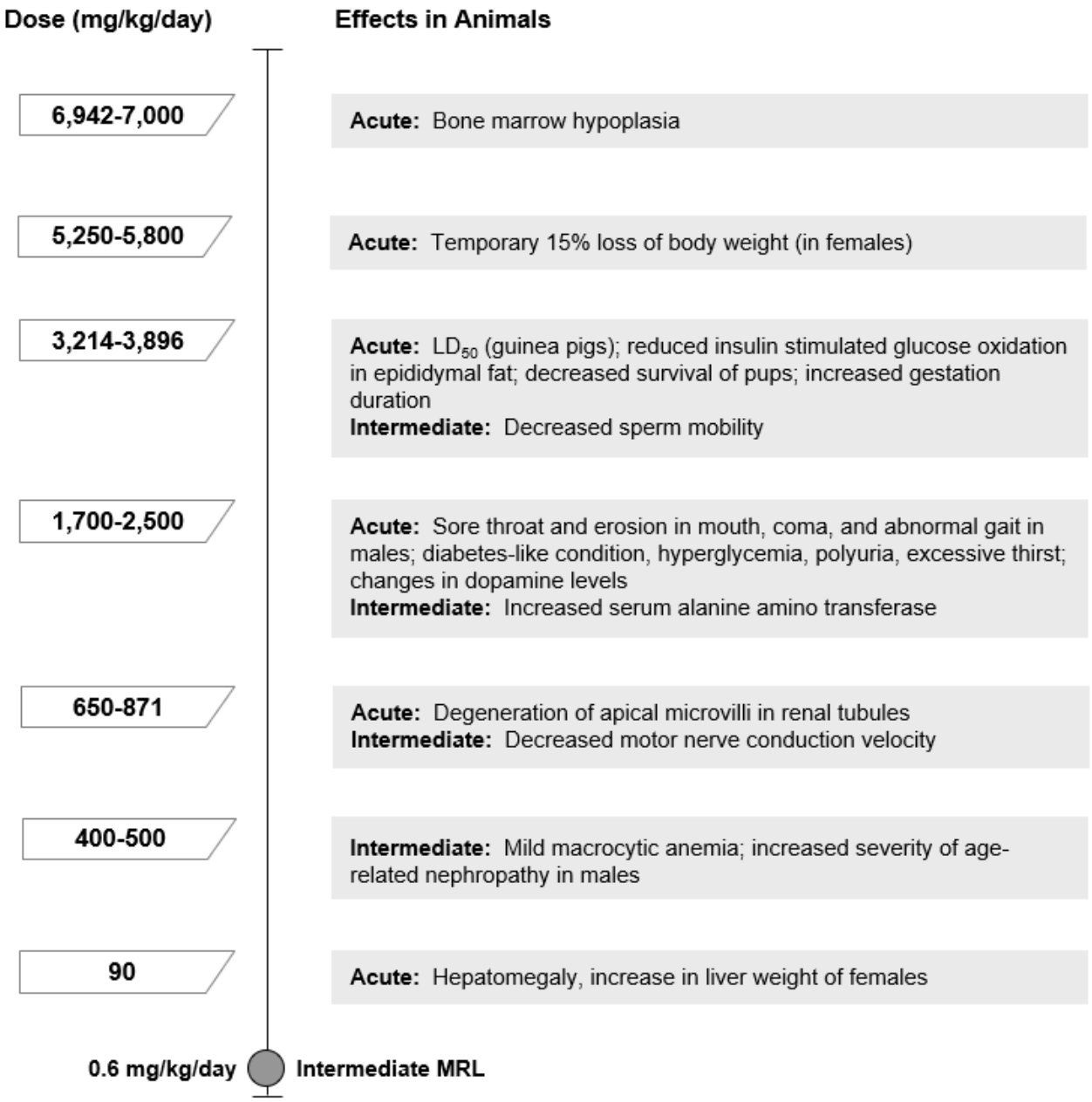
*Durations noted in Figure 1-1 refer to the duration of exposure that led to the specified health effect. See Chapter 2 for further discussion of the data presented in Figure 1-1.

Figure 1-2. Health Effects Found in Humans Following Inhalation Exposure to Acetone*



*Durations noted in Figure 1-2 refer to the duration of exposure that led to the specified health effect. See Chapter 2 for further discussion of the data presented in Figure 1-2.

Figure 1-3. Health Effects Found in Humans and Animals Following Oral Exposure to Acetone*



*Durations noted in Figure 1-3 refer to the duration of exposure that led to the specified health effect. See Chapter 2 for further discussion of the data presented in Figure 1-3.

Hematological Effects. Hematological effects due to acetone were found in human and animal studies following inhalation and oral exposure. Humans exposed to acetone showed increased white blood cell counts (Herman et al. 1997; Matsushita et al. 1969a, 1969b). Male rodents exposed to acetone in drinking water had bone marrow hypoplasia and signs of macrocytic anemia (Dietz et al. 1991; NTP 1991). Differences in hematological effects have been observed based on animal species and sex (American Biogenics Corp. 1986), which may signify males' higher susceptibility to acetone.

Renal Effects. Most renal effects associated with acetone exposure are based on oral exposure studies in animals. Increased kidney weight was found in rats and mice after oral acetone exposure (Dietz et al. 1991; NTP 1991), and male rats showed degeneration of the apical microvilli of renal tubules (Brown and Hewitt 1984). The renal lesions present in some studies were thought to be a sign of acetone-compounded nephropathy normally found in aging rodents (American Biogenics Corp. 1986; NTP 1991). Severe renal effects including moderate tubulointerstitial nephritis (Chen et al. 2002) and renal failure (Piatkowski et al. 2007) were reported in human case studies following inhalation exposure to acetone, but no epidemiologic studies verifying these effects were located.

Respiratory Effects. Human studies evaluating the respiratory effects of inhaled acetone exposure primarily found irritation of the nose, throat, trachea, and lungs. The irritating properties of acetone in humans have been noted both in workers who were exposed to acetone occupationally (Kiesswetter and Seeber 1995; Raleigh and McGee 1972; Ross 1973) and in volunteers under controlled laboratory conditions (Matsushita et al. 1969a, 1969b; Nelson et al. 1943). Animals exposed to higher concentrations of acetone had more severe respiratory effects including pulmonary congestion and hemorrhage (Specht et al. 1939). However, some animal studies did not observe respiratory effects on histopathological examination despite using high levels of acetone (Bruckner and Peterson 1981b; Schaper and Brost 1991).

Ocular Effects. Eye irritation has been associated with occupational (Mitran et al. 1997; Raleigh and McGee 1972) and voluntary (Matsushita et al. 1969a, 1969b; Nelson et al. 1943; Ross 1973) exposure to acetone. Unlike the other endpoints evaluated in this section, the ocular effects found in human and animal studies have primarily been observed following dermal exposure or direct eye-to-vapor contact.

Reproductive Effects. At high doses, acetone exposure has been associated with changes in testicular function such as decreases in sperm motility and increases in the numbers of abnormal sperm in rats but not mice (Dietz et al. 1991; NTP 1991). However, no changes in testicular morphology were observed,

and another study in rats by Larsen et al. (1991) found no significant decreases in male fertility. One study in male workers exposed to acetone and styrene found evidence of changes in sperm parameters (Jelnes et al. 1988).

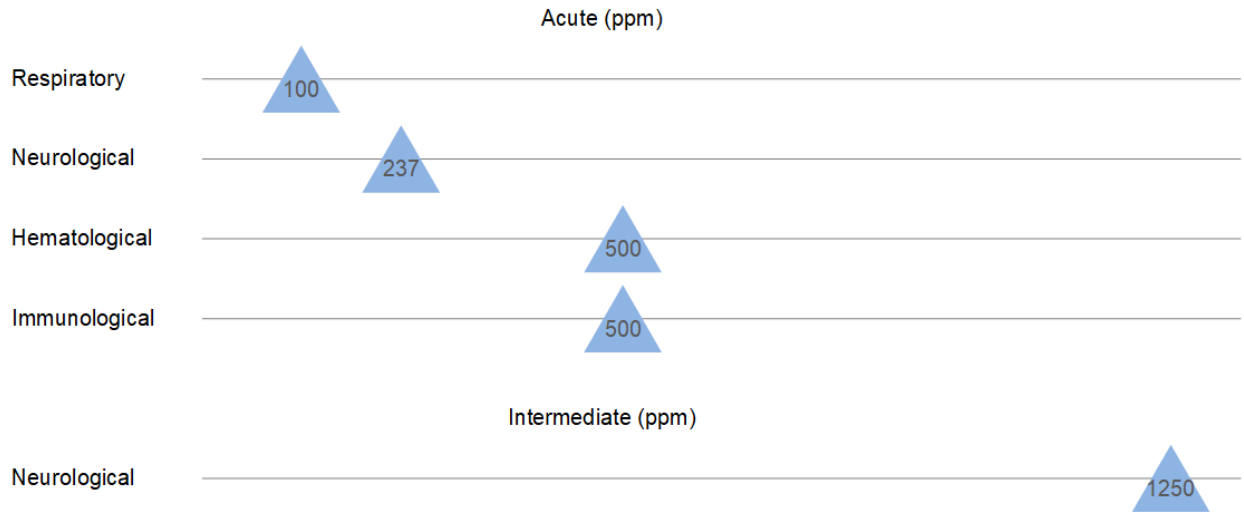
Acetone has not been evaluated by the Department of Health and Human Services or the International Agency for Research on Cancer (IARC) with regard to its carcinogenicity (IARC 2021; NTP 2021). The U.S. Environmental Protection Agency (EPA) determined that data are inadequate for an assessment of the human carcinogenic potential of acetone (EPA 2003).

1.3 MINIMAL RISK LEVELS (MRLs)

Minimal risk levels (MRLs) for inhalation and oral exposures to acetone were derived. Figures 1-4 and 1-5 summarize sensitive targets of acetone for inhalation and dermal exposures, respectively. As shown in Table 1-1 and discussed in greater detail in Appendix A, the inhalation database was only considered adequate for derivation of an acute-duration inhalation MRL for acetone. The oral database was only considered adequate for derivation of an intermediate-duration oral MRL.

Figure 1-4. Summary of Sensitive Targets of Acetone – Inhalation

The respiratory endpoint is the most sensitive target of acetone following inhalation exposure.
Numbers in triangles are the lowest LOAELs among health effects in humans.

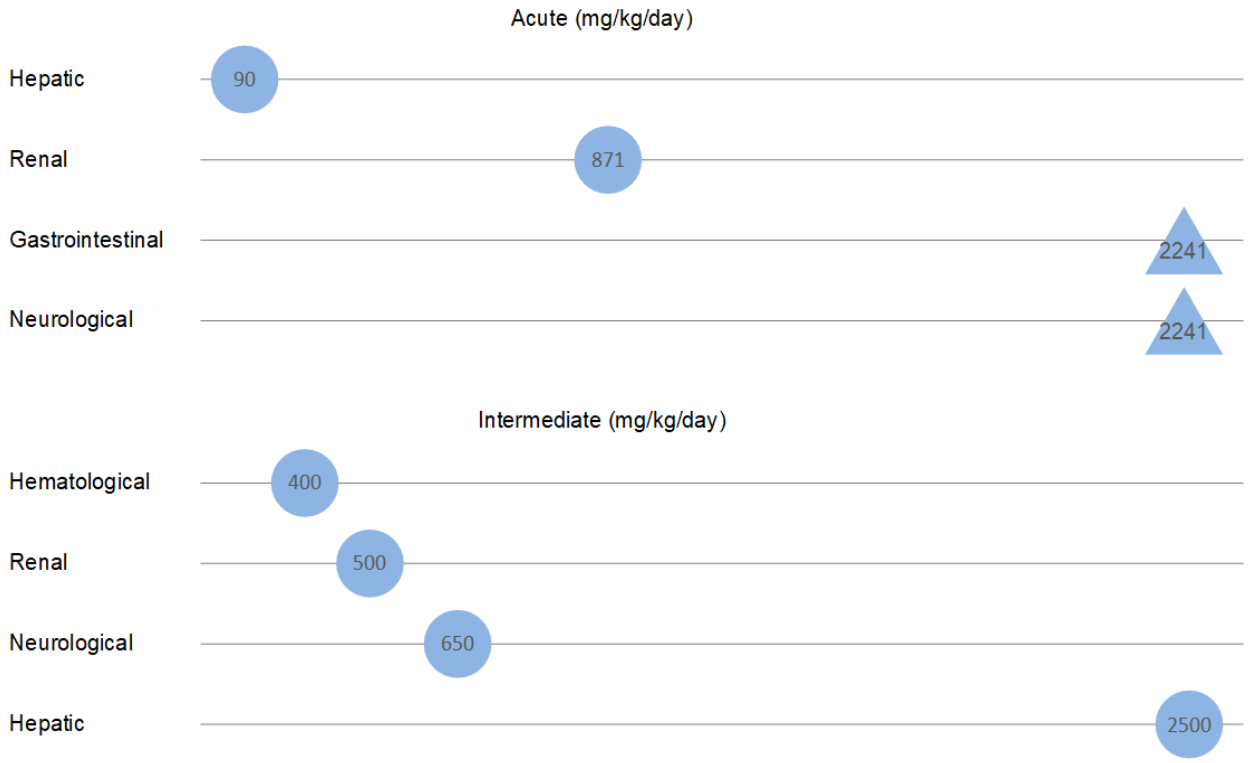


See Chapter 2 for further discussion of the data presented in Figure 1-4.

Figure 1-5. Summary of Sensitive Targets of Acetone – Oral

The hepatic and hematological endpoints are the most sensitive targets of acetone following oral exposure.

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



See Chapter 2 for further discussion of the data presented in Figure 1-5.

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

Exposure duration	MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty and modifying factor	Reference
Inhalation exposure (ppm)					
Acute	**8**	Neurobehavioral effects in humans	LOAEL: 237	UF: 30	Dick et al. 1989
Intermediate	Insufficient data for derivation of an MRL				
Chronic	Insufficient data for derivation of an MRL				
Oral exposure (mg acetone/kg/day)					
Acute	Insufficient data for derivation of an MRL				
Intermediate	**0.6**	Anemia with decreased reticulocyte count	$BMDL_{1SD}$: 57.0	UF: 100	Dietz et al. 1991; NTP 1991
Chronic	Insufficient data for derivation of an MRL				

[a]See Appendix A for additional information.

$BMDL_{1SD}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 1SD = dose associated with 1 standard deviation from the mean); LOAEL = lowest-observed-adverse-effect level; UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of acetone. 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 acetone, but may not be inclusive of the entire body of literature.

Summaries of the human observational studies are presented in Table 2-1. Other human and animal studies are presented in Table 2-2 and Figure 2-2, and oral studies are presented in Table 2-3 and Figure 2-3; dermal data are presented in Table 2-4.

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 (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR

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

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

The health effects of acetone have been evaluated in epidemiologic investigations, controlled human trials, and experimental animal studies. As shown in Figure 2-1, the majority of studies identified on acetone were of acute inhalation exposures. With the exception of body weight and endocrine effects, both human and animal studies were located for each health endpoint. Information on body weight effects were available from animal studies only, and no studies were located on the endocrine effects of acetone. The most commonly studied endpoint associated with acetone exposure was neurological effects.

Research on the health effects of acetone suggests several sensitive targets of toxicity:

- **Neurological endpoints.** Based on evidence from human and animal studies, acetone is associated with neurological effects ranging from mild neurobehavioral effects to severe narcosis. These effects have been observed following inhalation and oral exposures to acetone.

- **Hematological endpoints.** Studies of hematological effects in humans have been mixed, though significant changes in hematological parameters were observed in a controlled human exposure study and a case report. Several studies of oral exposures in rats and mice have observed hematological effects.

- **Renal endpoints.** Most evidence on the renal effects of acetone comes from animal studies of oral exposures to acetone. These studies indicate that there are species differences in the observed effects, with differences in susceptibility in males and females that vary by the specific renal parameter in question. There is also evidence of adverse renal effects from several human case studies.

- **Respiratory endpoints.** Human studies of inhalation exposures to acetone have shown irritation of the nose, throat, trachea, and lungs. Irritation has also been observed in animal studies, though at higher doses than in humans. The respiratory effects of oral exposures to acetone have not been extensively studied.

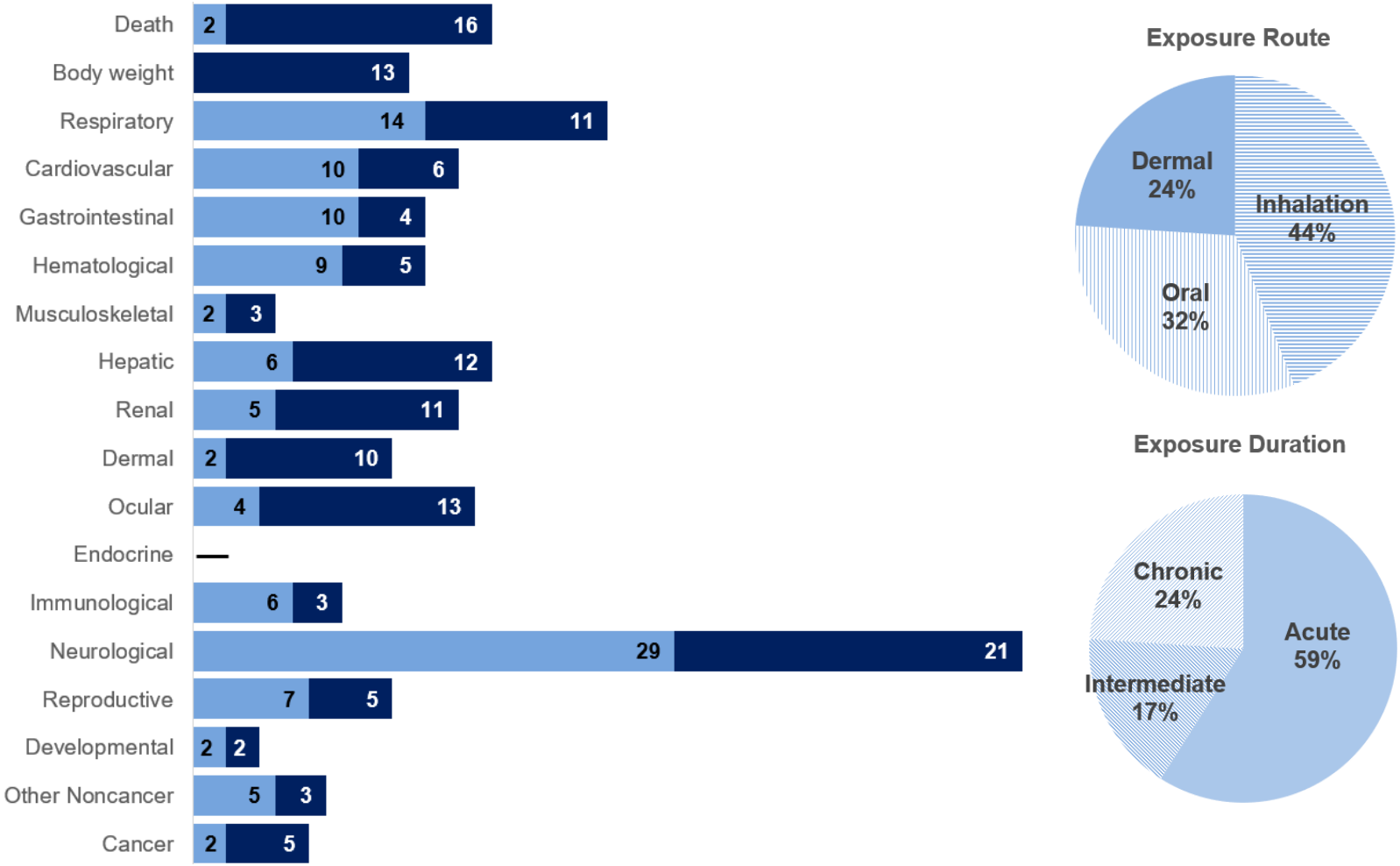
- **Ocular endpoints.** Acetone is also a known eye irritant, based on occupational studies in humans and animal studies of direct dermal/ocular application.

- **Reproductive effects.** Several animal studies have found that exposure to acetone is associated with reproductive effects in males, such as increases in the number of abnormal sperm. One study in humans found similar effects.

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

Most studies examined the potential neurological, respiratory, and hepatic effects of acetone

The relative number of studies conducted in **humans** and **animals** varied by endpoint (counts represent studies examining endpoint).



*Includes studies discussed in Chapter 2. A total of 131 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Health Effects in Humans Exposed to Acetone

Reference and study population	Exposure	Outcomes
Mitran et al. 1997 Acetone-exposed workers (n=71) and matched controls (n=86) at a coin printing and medal factory	**Exposure:** TWA concentrations of acetone of 416–890 ppm; mean exposure length of 14 years	Higher prevalence of upper respiratory tract irritation, dermal irritation, rheumatic symptoms (joint, bone, and muscular pain), eye irritation, gastrointestinal symptoms, and neurotoxicity (effects on mood, sleep, memory; headaches) in exposed workers as compared to controls, although no tests of significance were conducted. Exposed workers showed significantly delayed reaction time for visual tests ($p<0.001$) and significantly increased latencies (e.g., distal median nerve latency of 5.35 versus 2.70 milliseconds, $p<0.01$) and decreased amplitudes (e.g., distal median nerve amplitude of 2.63 vs. 7.08 mV, $p<0.01$) on several tests of motor nerve conduction velocity relative to controls.
Sinamora et al. 2018 Shoe factory workers exposed to acetone alone (n=67), with ≥5 years of exposure	**Exposure:** air monitoring (number of measurements not reported) acetone concentration of 57.90 ppm; cumulative exposure stratified by <7.7 and ≥7.7 ppm work year	No association between acetone exposure and restrictive pulmonary effects as assessed by FEV_1/FVC and FVC; OR (95% CI) 0.697 (0.170–2.861). Increased odds of chronic bronchitis; OR (95% CI) 3.563 (1.259–10.084).
Satoh et al. 1996 Male workers at an acetate fiber manufacturing plant: 110 exposed to acetone and 67 unexposed controls	**Exposure:** TWA concentrations of acetone of 19.6–1,018 ppm; mean concentration of 364 ppm and mean exposure length of 14.9 years	Exposed participants were more likely to self-report symptoms such as nausea, palpitations, weight loss, and eye irritation than controls. No significant differences in hematological parameters, neutrophil phagocytic activity, or serum biomarkers of liver function were observed between groups. Exposed workers had significantly lower scores on tests of simple reaction time (e.g., 246.7 versus 220.6 milliseconds in 30–44-year-olds on the first day post-work, $p<0.01$) and higher scores on digit span (e.g., 5.1 versus 6.7 in 30–44-year-olds on the first day post-work, $p<0.01$) than controls.

Table 2-1. Health Effects in Humans Exposed to Acetone

Reference and study population	Exposure	Outcomes
Tomei et al. 1999 33 male workers at a shoe repair factory and 61 age- and sex-matched controls	**Exposure:** mean acetone concentration of 560 ppm; co-exposure to other solvents: n-hexane (mean 62 mg/m^3), ethyl acetate (mean 8 mg/m^3), isomers of hexane (mean 38 mg/m^3), methylethylketone (mean 20 mg/m^3), and toluene (mean 9 mg/m^3)	Compared to controls, exposed workers had elevated mean alanine aminotransferase (31.1 versus 21.8, p<0.0001), AST (28.9 versus 21.0, p<0.0001), conjugated bilirubin (0.18 versus 0.03, p<0.0001), and alkaline phosphatase (163.5 versus 128.2, p<0.0001).
Nizyaeva 1982 Female factory workers and controls (sample sizes and further details not reported)	**Exposure:** mean acetone concentrations in different parts of the factory ranged from approximately 14 to 126 ppm **Adjustments:** no information on statistical methods or adjustments provided in study	Significant increases in incidences of pregnancy complications, including miscarriage (p<0.001), toxicosis (not otherwise described) (p<0.02), decreased hemoglobin levels (p<0.001), hypotension (p<0.001), and “weakness of labor activity” (p<0.01), as compared to controls.
Agnesi et al. 1997 Case-control study of spontaneous abortion in an Italian village with high proportion of shoe factory workers (108 cases and 108 matched controls)	**Exposure:** average acetone concentration in shoe factories of approximately 30 mg/m^3; co-exposure to several other solvents: n-hexane, cyclohexane, methylethylketone, heptane, methylcyclohexane, methylcyclopentane, 2-methylhexane, 3-methylhexane, 2-methylpentane, and 3-methylpentane **Logistic regression adjustments:** gravidity, previous abortions, level of education, smoking tobacco, consumption of alcohol, coffee and medicines, and marital status	Increased relative risk of spontaneous abortion in women exposed to high levels of solvents, as assessed by a job history questionnaire versus those with no occupational history of exposure to acetone. OR (95% CI): 3.85 (1.24–11.9), p<0.05

ALT = alanine aminotransferase; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; OR = odds ratio; TWA = time-weighted average

Table 2-2. Levels of Significant Exposure to Acetone – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
ACUTE EXPOSURE									
Dick et al. 1989									
1	Human 11 M, 11 F	1 day 4 hours/day	237	CS	Neuro		237[b]		Increases in response times and 3–8% increase in false negatives compared to pre-exposure auditory discrimination test results; increased anger, hostility (POMS psychological test)
DiVincenzo et al. 1973									
2	Human 4 M	1 day 2 hours/day	100, 500	BC CS HE	Hemato	500			
					Hepatic	500			
					Renal	500			
Haggard et al. 1944									
3	Human NS M	1–8 hours	21,049, 42,097, 63,146, 84,194	CS	Neuro			21,049	Signs of narcosis in 3–6 hours, loss of righting reflex in 8 hours
Matsushita et al. 1969a									
4	Human 5 M	1 day 6 hours/day	0, 100, 250, 500, 1,000	CS UR HE	Resp		100		Irritation of nose, throat, trachea
					Hemato	250	500		Increased white blood cell count; decreased phagocytic activity of neutrophils
					Immuno	250	500		Increased white blood cell count; decreased phagocytic activity of neutrophils
					Neuro		250		Lack of energy, general weakness

Table 2-2. Levels of Significant Exposure to Acetone – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
Matsushita et al. 1969b									
5	Human 6 M	6 days 6 hours/day	0, 250, 500	CS HE	Resp		250		Irritation of nose and throat
					Hemato	250	500		Increased white blood cell count; decreased phagocytic activity of neutrophils
					Immuno	250	500		Increased white blood cell count; decreased phagocytic activity of neutrophils
					Neuro		250		Delayed visual reaction time, headache, lack of energy, weakness
Muttray et al. 2005									
6	Human 12	4.5 hours, 1 time	247		Neuro	247			
Nelson et al. 1943									
7	Human 10 B	1 day 3–5 minutes/day	NS		Resp	200	500		Nose and throat irritation
Raleigh and McGee 1972									
8	Human 4 M	2–3 days 8 hours/day	901	CS NX	Resp		901		Throat and nose irritation
					Neuro	901			
Raleigh and McGee 1972									
9	Human 9 M	7 days 8 hours/day	1,006	CS NX	Resp		1,006		Irritation of nose and throat
					Neuro		1,006		Headache, light-headedness
Ross 1973									
10	Human 8 M	1 day 2 minutes 4 hours/day	12,000	CS	Resp		12,000		Throat and lung irritation
					Neuro			12,000	Unconsciousness, dizziness, unsteadiness, confusion, headache

Table 2-2. Levels of Significant Exposure to Acetone – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
Seeber et al. 1992									
11	Human 16 NS	4–8 hours	0, 1,000	CS	Neuro		1,000		Subjective symptoms of tension, tiredness, complaints and annoyance, not otherwise specified
Stewart et al. 1975									
12	Human 4 F	1 day 7.5 hours/day	1,000	CS UR NX HE	Repro		1,000		Shortened menstrual cycle
Bruckner and Peterson 1981a									
13	Rat 5 M	1 day 3 hours/day	12,600, 19,000, 25,300, 50,600	CS	Death			50,600	5/5 died
					Neuro			12,600	CNS depression measured by unconditioned performance and reflex tests
Frantik et al. 1996									
14	Rat (Wistar) 4 M	4 hours	1,680, 4,210		Neuro		1,680		10% decrease in seizure inhibition
Goldberg et al. 1964									
15	Rat 8–10 F	2 weeks 5 days/week 4 hours/day	0, 3,000, 6,000, 12,000, 16,000	CS BW	Bd wt	16,000			
					Neuro	3,000		6,000	Inhibition of avoidance behavior in 38% of the rats
Haggard et al. 1944									
16	Rat NS	5 minutes–8 hours	2,105, 4,201, 10,524	CS	Neuro	4,210		10,524	Signs of narcosis, loss of coordination in 100–250 minutes
Lee et al. 2008									
17	Rat (Sprague-Dawley) 40	6 days 1 hour/day	5,000, 10,000, 20,000	CS	Neuro	20,000	5,000		Decreased locomotor activity

Table 2-2. Levels of Significant Exposure to Acetone – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
NTP 1988									
18	Rat 10–31 F	14 days 7 days/week 6 hours/day GDs 6–19	0, 440, 2,200, 11,000	BC BI RX DX	Bd wt	2,200			
					Repro	11,000			
					Develop	2,200	11,000		Decreased fetal weight (8%)
					Other noncancer		11,000		Significantly reduced body weight (7%), uterine weight (19%), and extra-gestational weight gain (36%) of dams
Pozzani et al. 1959									
19	Rat 6 F	4 or 8 hours	NS	LE	Death			21,091	SLOAEL: LC_{50} 8 hours SLOAEL: LC_{50} 4 hours
Smyth et al. 1962									
20	Rat 6 F	1 day 4 hours/day	16,000	CS	Death			16,000	1/6 died
De Ceaurriz et al. 1984									
21	Mouse 10 M	4 hours	0, 2,032, 2,580, 2,858, 3,021	BH	Neuro	2,032		2,580	39% decrease in duration of immobility in behavioral despair swimming (Porsolt force swimming) test ($p<0.05$)
Glowa and Dews 1987									
22	Mouse 12 M	1 day	100–56,000	CS	Neuro	1,000	3,000		10% decreased response to food presentation in a fixed interval operant behavioral test
Kane et al. 1980									
23	Mouse 4 M	1 day 10 minutes/day	800–150,000		Resp		77,516		RC_{50} for sensory irritation

Table 2-2. Levels of Significant Exposure to Acetone – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
Mashbitz et al. 1936									
24	Mouse NS	4 hours	16,839, 25,258, 33,678, 42,097, 50,517, 55,989, 84,194	CS	Neuro			16,839	Drowsiness, staggering, prostration, clonic movements of hind legs, and deep narcosis
NTP 1988									
25	Mouse 10–33 F	1 day 6 hours/day	11,000	CS	Neuro			11,000	Severe narcosis
NTP 1988									
26	Mouse 10–33 F	12 days 7 days/week 6 hours/day GDs 6–17	0, 440, 2,200, 6,600	CS RX DX	Hepatic	2,200	6,600		Significantly increased absolute and relative liver weight of dams ($p<0.05$)
					Repro	6,600			
					Develop	2,200		6,600	Significantly increased incidence of late resorption, decreased fetal weight [8%], reduced sternebral ossification ($p\leq0.05$)
					Other noncancer	6,600			
Schaper and Brost 1991									
27	Mouse 4 M	1 or 5 days 0.5 hours/day	0, 6,000	HP CS	Resp	6,000			

Table 2-2. Levels of Significant Exposure to Acetone – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
Specht et al. 1939									
28	Guinea pig 5 NR	2 days 24 hours/day	10,000	GN CS	Death			10,000	5/5 died
					Resp		10,000		Lung congestion in guinea pigs that died
					Hepatic		10,000		Fatty liver in guinea pigs that died
					Renal		10,000		Renal tubular distention
					Other noncancer		10,000		Congestion of spleen
Specht et al. 1939									
29	Guinea pig 10 F	1 day 25 minutes–-23.4 hours/day	21,800	GN CS	Death			21,800	2/10 died
					Neuro			21,800	Narcosis, coma, paralysis
Specht et al. 1939									
30	Guinea pig 9 NR	1 day 22–26 hours/day	20,000	GN CS	Death			20,000	8/9 died
					Resp			20,000	Marked congestion and hemorrhage of lungs
					Hepatic		20,000		Fatty liver in guinea pigs that died
					Renal		20,000		Distention of glomerular capsule
					Other noncancer		20,000		Marked congestion and hemorrhage of spleen
Specht et al. 1939									
31	Guinea pig 18 NR	1 day 3–8.75 hours/day	50,000	GN CS	Death			50,000	8/8 died at 3–4 hours exposure
					Resp			50,000	Pulmonary congestion and hemorrhage
					Hepatic		50,000		Mild fatty deposition
					Renal			50,000	Congestion and distention of glomeruli
					Other noncancer			50,000	Congestion and hemorrhage of spleen

Table 2-2. Levels of Significant Exposure to Acetone – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
INTERMEDIATE EXPOSURE									
Stewart et al. 1975									
32	Human 10 M, 10 F	6 weeks 2–5 days/week 1–7.5 hours/day	0, 200, 1,000, 1,250	CS UR HE NX	Resp	1,250			
					Cardio	1,250			
					Hemato	1,250			
					Hepatic	1,250			
					Renal	1,250			
					Neuro		1,250		Increased visual evoked response
Bruckner and Peterson 1981b									
33	Rat 36 M	2–8 weeks 5 days/week 3 hours/day	0, 19,000	BW OW HP BC BI	Resp	19,000			
					Cardio	19,000			
					Hepatic	19,000			
					Renal	19,000			
					Neuro			19,000	Decreased brain weight relative to controls
Christoph et al. 2003									
34	Rat (Crl:CD BR) 10 M	13 weeks 5 days/week 6 hours/day	1,000, 2,000, 4,000		Neuro	4,000			

Table 2-2. Levels of Significant Exposure to Acetone – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
CHRONIC EXPOSURE									
Ott et al. 1983a, 1983c									
35	Human 168 M, 77 F	3 months–23 years 5 days/week 8 hours/day (occupational)	380, 770, 1,070	CS HE	Hemato Hepatic	1,070 1,070			

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 8 ppm. The LOAEL of 237 ppm was divided by an uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability). Highlighted rows indicate an MRL principal study.

B = both male and females; BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CNS = central nervous system; CS = clinical signs; Develop = developmental; DX = developmental toxicity; F = female(s); GD = gestation day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; LC_{50} = concentration producing 50% death; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NR = not reported; NS = not specified; NX = neurological function; OW = organ weight; POMS = Profile of Mood States; RC_{50} = concentration of an airborne chemical that produces a 50% decrease in respiratory rate; Repro = reproductive; Resp = respiratory; SLOAEL = serious LOAEL; UR = urinalysis

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

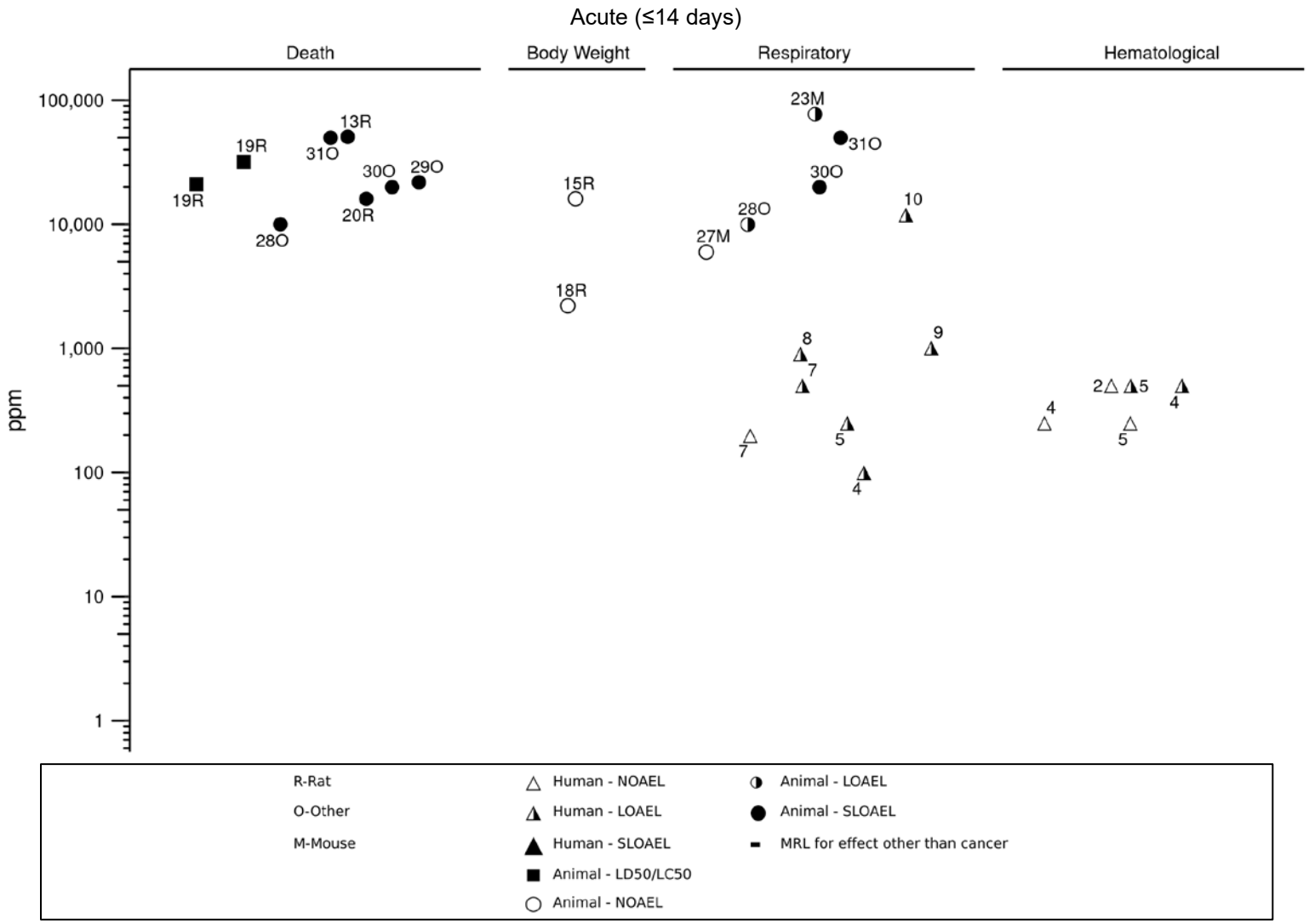


Figure 2-2. Levels of Significant Exposure to Acetone – Inhalation

Acute (≤14 days)

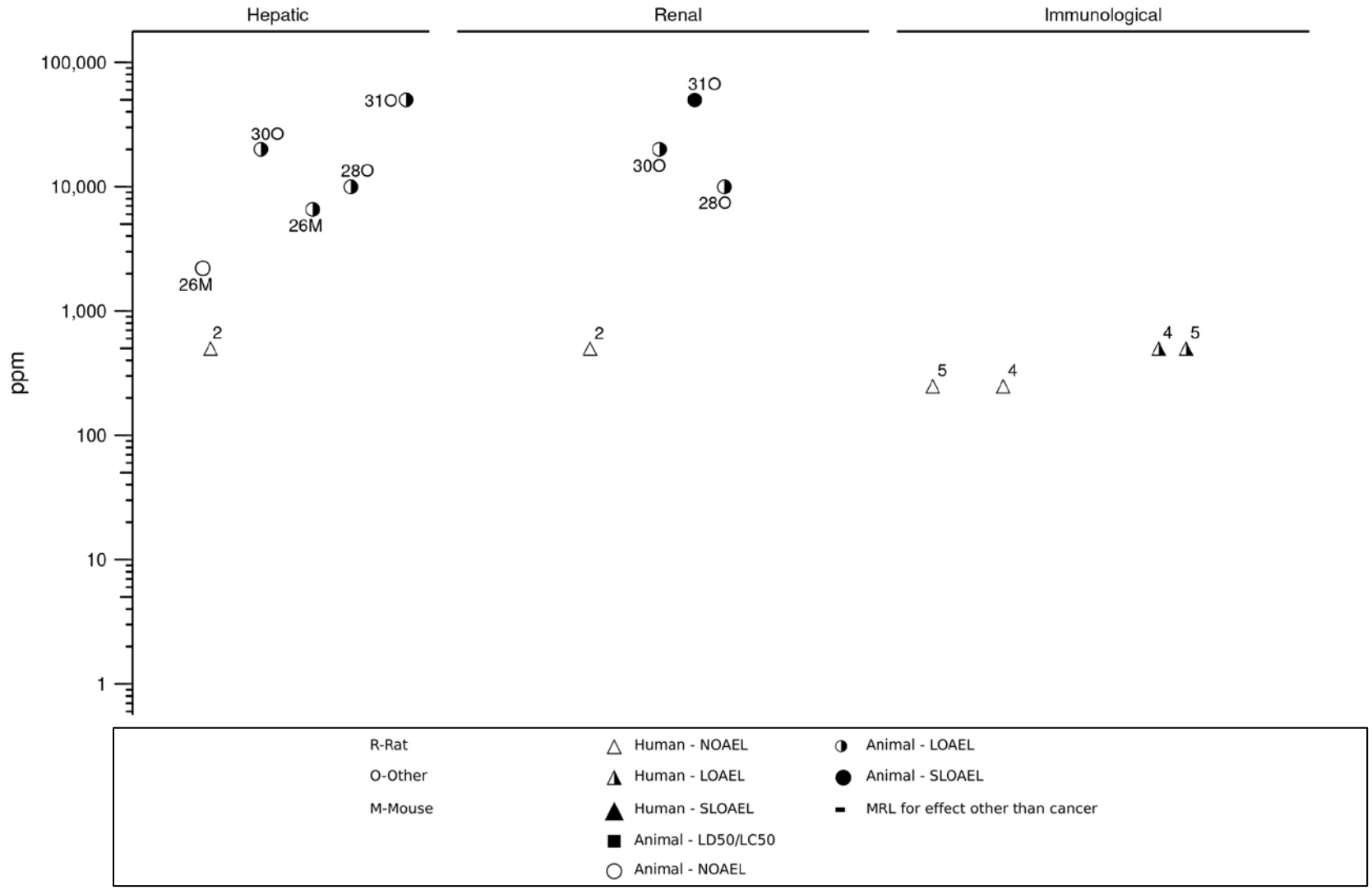


Figure 2-2. Levels of Significant Exposure to Acetone – Inhalation

Acute (≤14 days)

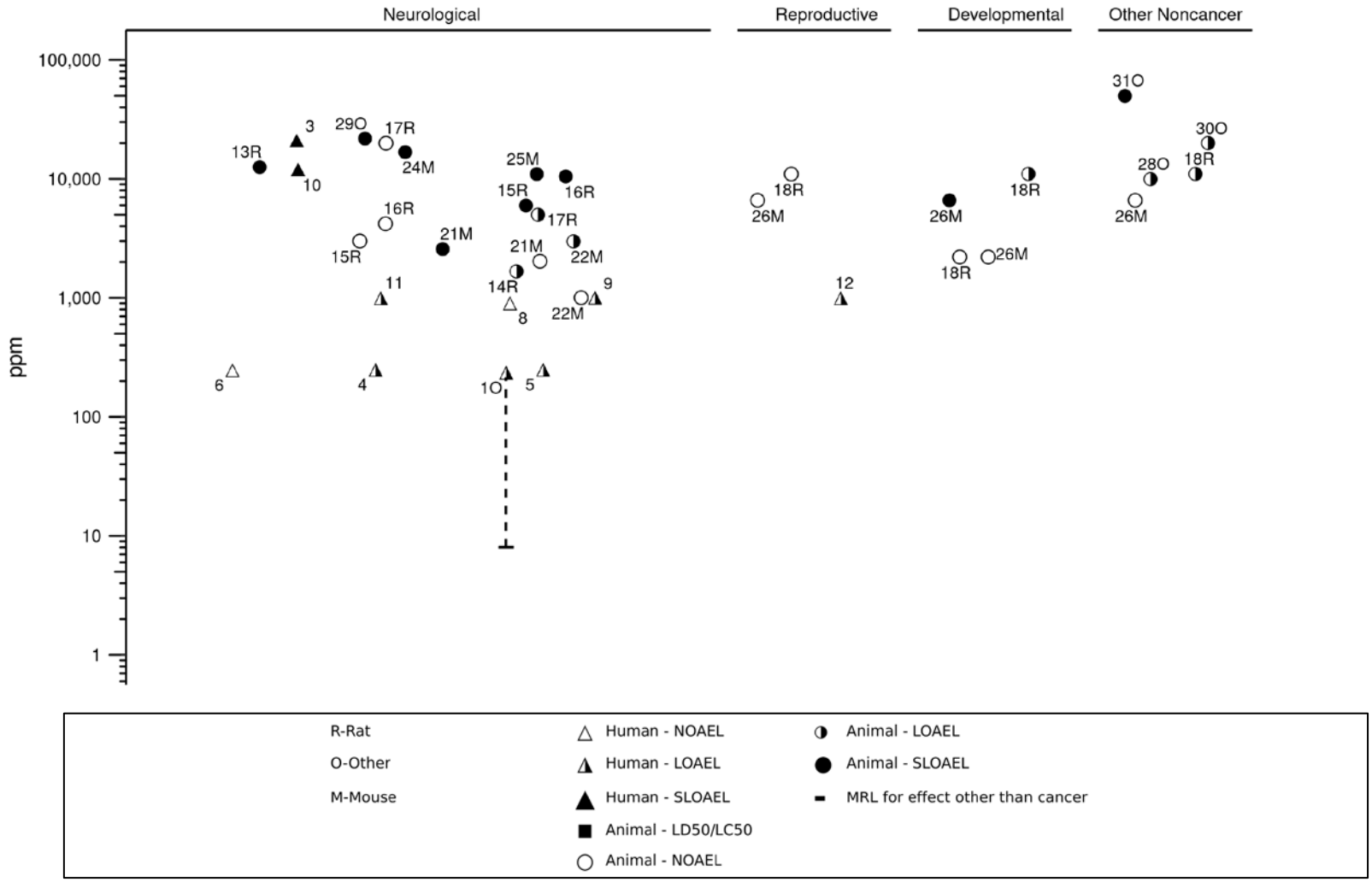


Figure 2-2. Levels of Significant Exposure to Acetone – Inhalation

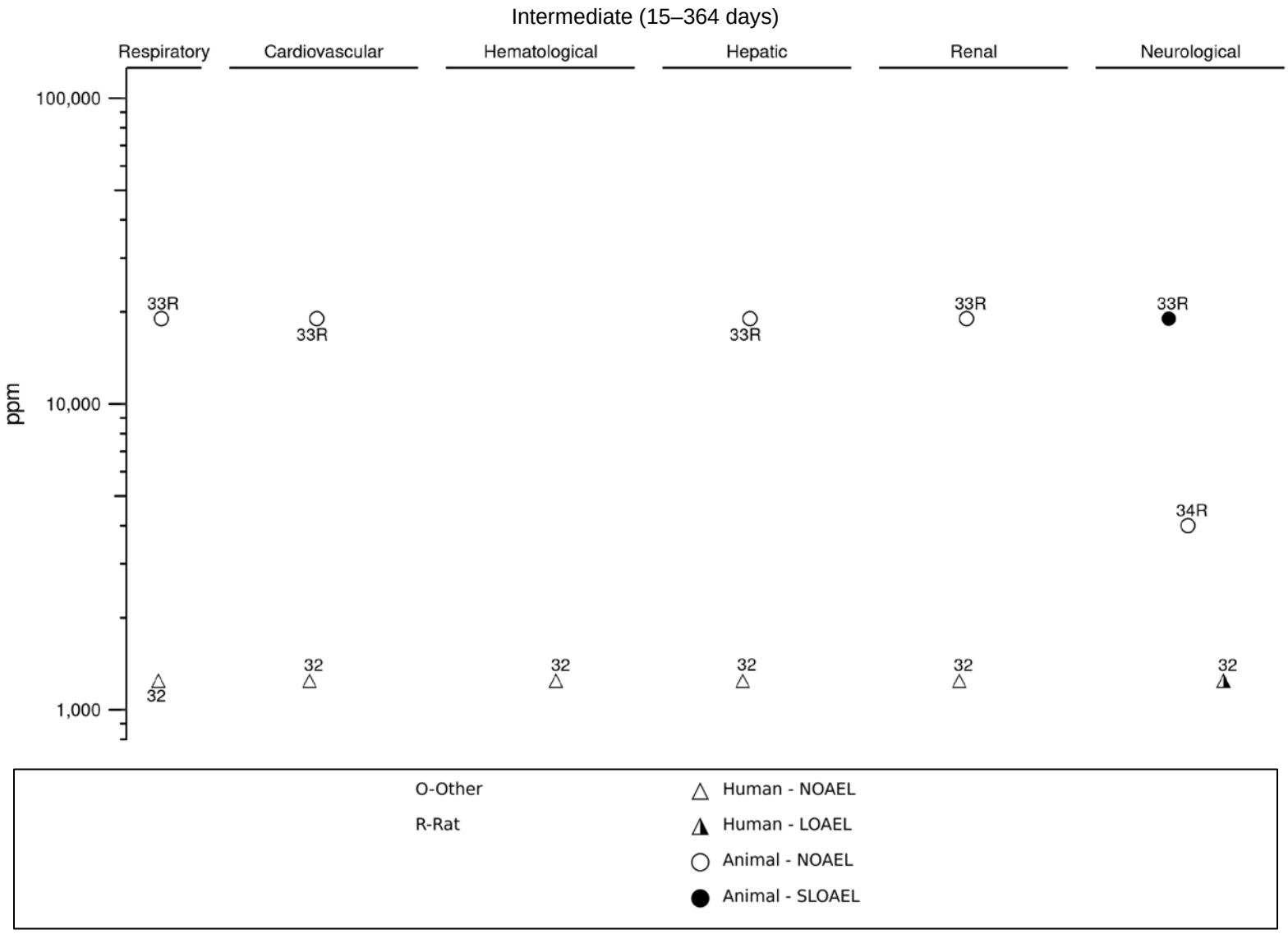


Figure 2-2. Levels of Significant Exposure to Acetone – Inhalation

Chronic (≥365 days)

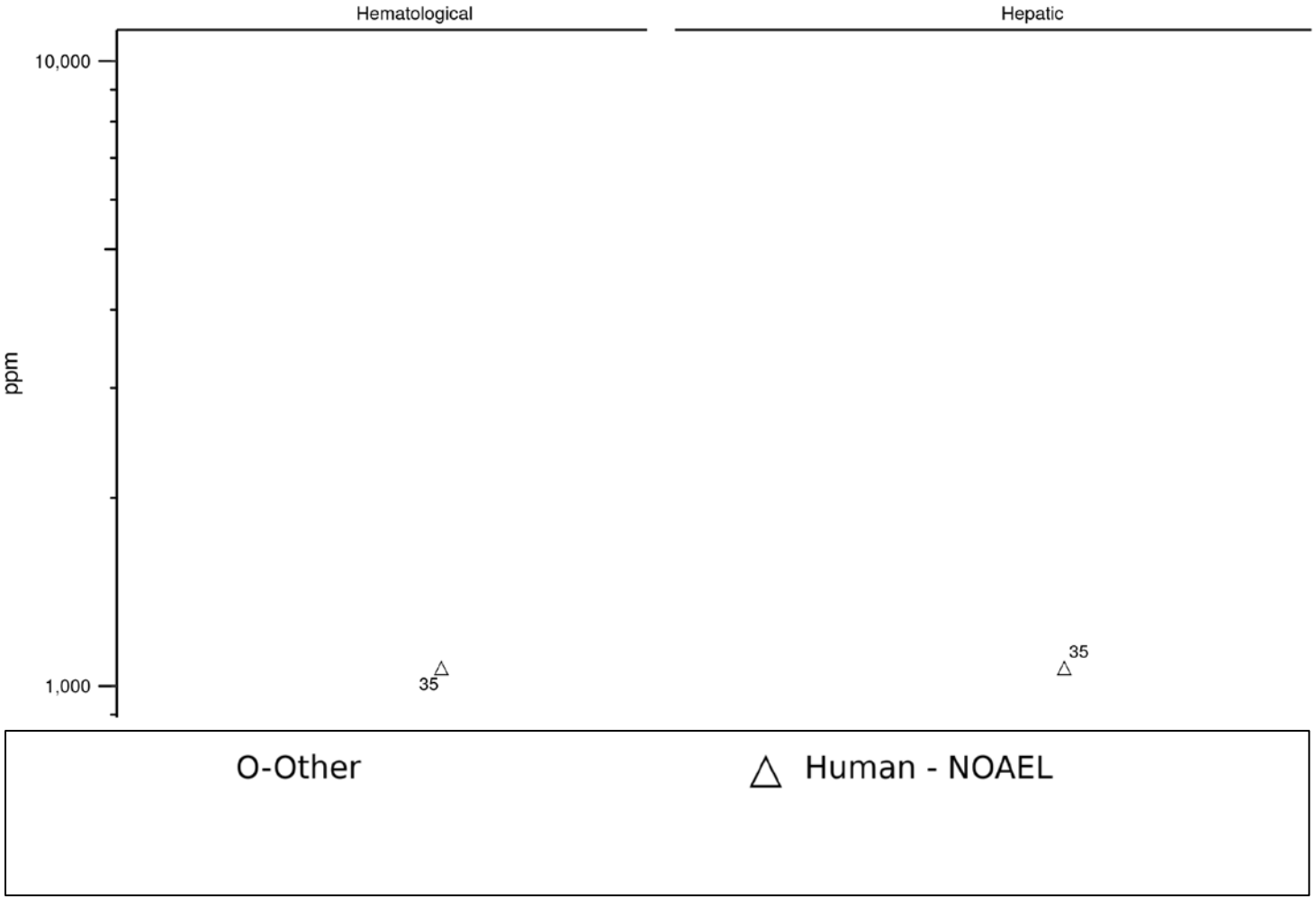


Table 2-3. Levels of Significant Exposure to Acetone – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
Brown and Hewitt 1984									
1	Rat 6 M	1 day 1 time/day (GO)	0, 871	HP BC OR	Hepatic	871			
					Renal		871		Degeneration of apical microvilli in renal tubules
Charbonneau et al. 1986b									
2	Rat 6 M	1 day 1 time/day (GO)	0, 196, 588, 1,177	BC	Hepatic	1,177			
Freeman and Hayes 1985									
3	Rat 5 F	1 day 1 time/day (G)	5,370–6,980	BW GN CS	Death			5,800	LD_{50}
					Bd wt		5,800		Temporary 15% loss of body weight
					Neuro			5,800	Prostration
Kanada et al. 1994									
4	Rat (Sprague-Dawley) 4–5 M	1 time (G)	2,438	HP	Neuro		2,438		~20% increase in a dopamine metabolite in hypothalamus
Mathias et al. 2010									
5	Rat (Wistar) 16 M	1 time (G)	7,000	BC, HP	Hepatic		7,000		77% reduction of hepatic GSH levels and 53% decrease in liver vitamin E at 24 hours
NTP 1991; Dietz et al. 1991									
6	Rat 5 M, 5 F	14 days (W)	M: 0, 714, 1,616, 2,559, 4,312, 6,942 F: 0, 751, 1,485, 2,328, 4,350, 8,560	BW OW WI GN HP CS	Hemato	4,312		6,942	Bone marrow hypoplasia
					Hepatic	8,560			
					Renal	8,560			
					Other noncancer	8,560			

Table 2-3. Levels of Significant Exposure to Acetone – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Plaa et al. 1982									
7	Rat 6–7 M	1 day 1 time/day (GW)	0, 1,961	BC BI	Hepatic	1,961			
Plaa et al. 1982									
8	Rat 9–10 M	3 days 2 times/day (GW)	0, 157, 392	BC BI	Hepatic	392			
Ross et al. 1995									
9	Rat (Wistar) 6–8 F	14 days (W)	0, 90.8	BI HP	Hepatic		90		Hepatomegaly, 14% increase in liver weight
Skutches et al. 1990									
10	Rat 5–10 M	3–7 days (W)	0, 3,214	BW FI WI BI	Other noncancer		3,214		Reduced insulin stimulated glucose oxidation in epididymal fat
Valentovic et al. 1992									
11	Rat 4 M	2 days 3 times in 2 days (GW)	0, 1,766	FI WI OR UR	Renal	1,766			
					Other noncancer	1,766			
EHRT 1987									
12	Mouse 50 F	10 days GDs 6–15 1 time/day (GW)	0, 3,500	BW CS RX DX	Bd wt	3,500			
					Repro			3,500	Reduced reproduction index, increased gestation duration
					Develop			3,500	Decreased survival of pups
Jeffery et al. 1991									
13	Mouse 4 F	10 days *ad libitum* (W)	0, 1,900	HP BI	Hepatic	1,900			

Table 2-3. Levels of Significant Exposure to Acetone – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
NTP 1991; Dietz et al. 1991									
14	Mouse 5 M, 5 F	14 days (W)	M: 0, 965, 1,579, 3,896, 6,348, 10,314 F: 0, 1,569, 3,023, 5,481, 8,804, 12,725	BW OW WI GN HP CS	Hepatic	1,579	3,896		Minimal to mild hepatocellular hypertrophy
					Renal	12,725			
					Other noncancer	12,725			
Tanii et al. 1986									
15	Mouse 4 M	Once (G)	NS	LE	Death			5,250	LD_{50}
Striegel and Carpenter 1961									
16	Guinea pig NS M	Once (G)	NS	LE	Death			3,687	LD_{50}
INTERMEDIATE EXPOSURE									
American Biogenics Corp. 1986									
17	Rat 10 M, 10 F	46–47 days 1 time/day (GW)	0, 100, 500, 2,500	BW FI GN BC CS UR HE	Hemato	500	2,500		Increased hemoglobin, hematocrit, mean cell volume
					Hepatic	500	2,500		Increased serum alanine aminotransferase
					Neuro	500	2,500		Excessive salivation
					Other noncancer	2,500			
American Biogenics Corp. 1986									
18	Rat 20 M, 20 F	93–95 days 1 time/day (GW)	0, 100, 500, 2,500	BW OW FI GN HP CS UR HE	Resp	2,500			
					Cardio	2,500			
					Gastro	2,500			

Table 2-3. Levels of Significant Exposure to Acetone – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hemato	500	2,500		Increased hemoglobin, hematocrit, mean cell hemoglobin, mean cell volume, decreased platelets
					Musc/skel	2,500			
					Hepatic	500	2,500		Increased serum alanine aminotransferase
					Renal	100	500		Increased severity of age-related nephropathy in males
					Dermal	2,500			
					Neuro	500	2,500		Decreased brain weight, salivation
					Other noncancer	2,500			
Ladefoged et al. 1989									
19	Rat 11 M	6 weeks (W)	0, 650	BW GI WI OR NX	Neuro		650		Decreased motor nerve conduction velocity
					Other noncancer	650			
Larsen et al. 1991									
20	Rat 10 M	6 weeks (W)	0, 1,071	HP CS RX	Repro	1,071			
NTP 1991; Dietz et al. 1991									
21	Rat 10 M, 10 F	13 weeks (W)	M: 0, 200, 900, 3,400 F: 0, 300, 1,200, 3,100	BW OW WI GN HP CS HE	Repro	3,100 F			
						200 M		3,400 M	11.7% decreased sperm motility

Table 2-3. Levels of Significant Exposure to Acetone – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
NTP 1991; Dietz et al. 1991									
22	Rat 10 M, 10 F	13 weeks (W)	M: 0, 200, 400, 900, 1,700, 3,400 F: 0, 300, 600, 1,200, 1,600, 3,100	BW OW WI GN HP CS HE	Resp	3,400			
					Cardio	3,400			
					Gastro	3,400			
					Hemato	200[b]	400		Mild macrocytic anemia
					Musc/skel	3,400			
					Hepatic	3,400			
					Renal	900	1,700		Increased incidence and severity of nephropathy in males
					Dermal	3,400			
					Neuro	3,400			
					Other noncancer	3,400			
Spencer et al. 1978									
23	Rat 3 NS	12 weeks *ad libitum* (W)	0, 732	BW WI HP CS	Neuro	732			
					Other noncancer	732			
NTP 1991; Dietz et al. 1991									
24	Mouse 10 M, 10 F	13 weeks (W)	M: 0, 380, 1,353, 4,858 F: 0, 892, 4,156, 11,298	BW OW WI GN HP CS HE	Repro	11,298 F 4,858 M			

Table 2-3. Levels of Significant Exposure to Acetone – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
NTP 1991; Dietz et al. 1991									
25	Mouse 10 M, 10 F	13 weeks (W)	M: 0, 380, 611, 1,353, 2,258, 4,858 F: 0, 892, 2,007, 4,156, 5,954, 11,298	BW OW WI GN HP CS HE	Resp	11,298			
					Cardio	11,298			
					Gastro	11,298			
					Hemato	11,298			
					Musc/skel	11,298			
					Hepatic	11,298			
					Renal	11,298			
					Dermal	11,298			
					Neuro	11,298			
					Other noncancer	11,298			
Woolhiser et al. 2006									
26	Mouse (CD-1) 8 M	28 days (W)	121, 621, 1,144	BC	Immuno	1,144			

[a]The number corresponds to entries in Figure 2-3.
[b]Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.6 mg/kg/day calculated using benchmark dose analysis. The $BMDL_{1SD}$ of 57 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). Highlighted rows indicate an MRL principal study. See Appendix A for details.

BC = 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; (G) = gavage-not specified; (GO) = gavage-oil; (GW) = gavage-water; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathological; Immuno = immunological; LD_{50} = lethal dose, 50% death; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurotoxicity; OW = organ weight; Repro = reproductive; Resp = respiratory; RX= reproductive toxicity; UR = urinalysis; (W) = water; WI = water intake

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

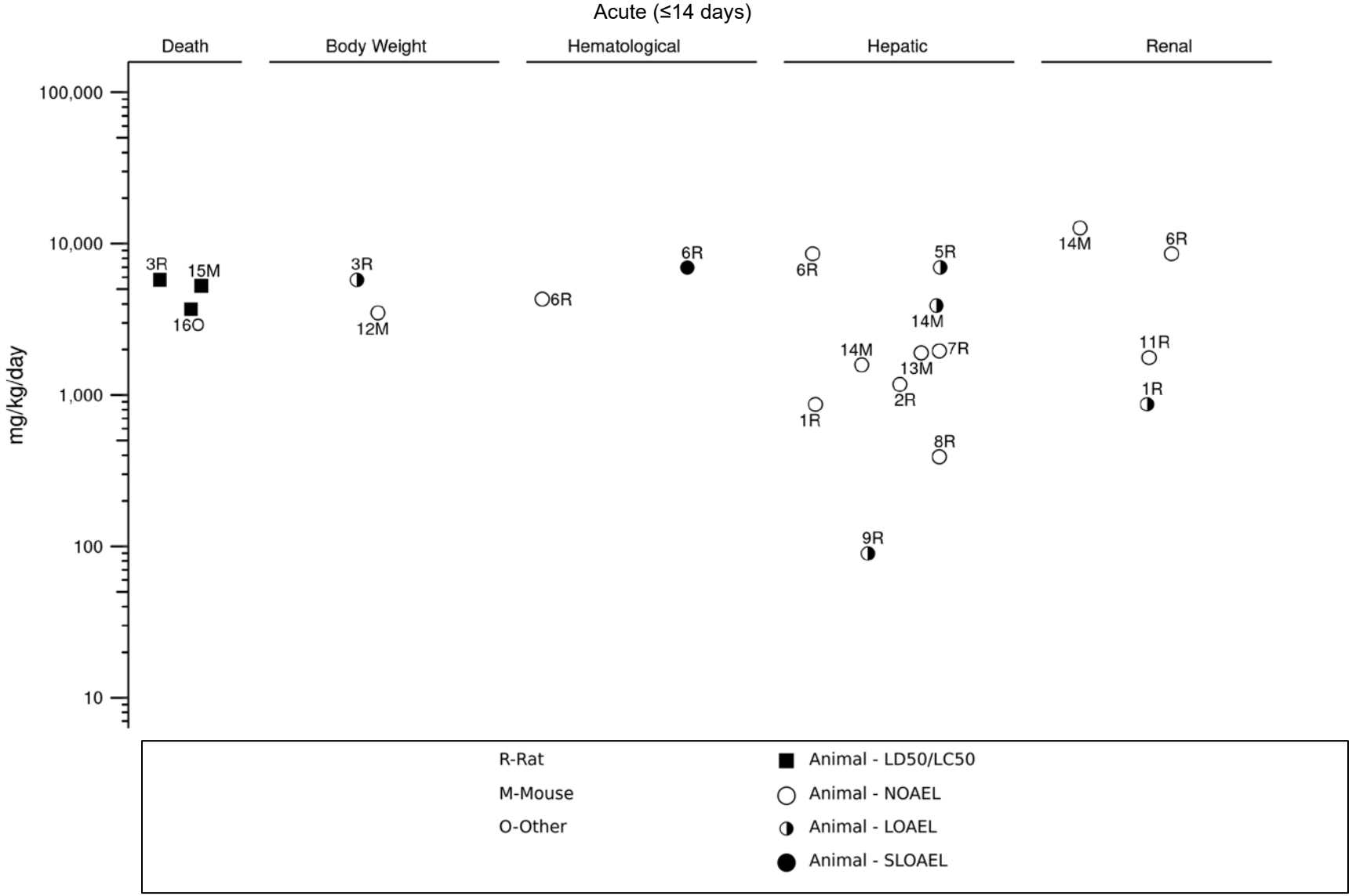


Figure 2-3. Levels of Significant Exposure to Acetone – Oral

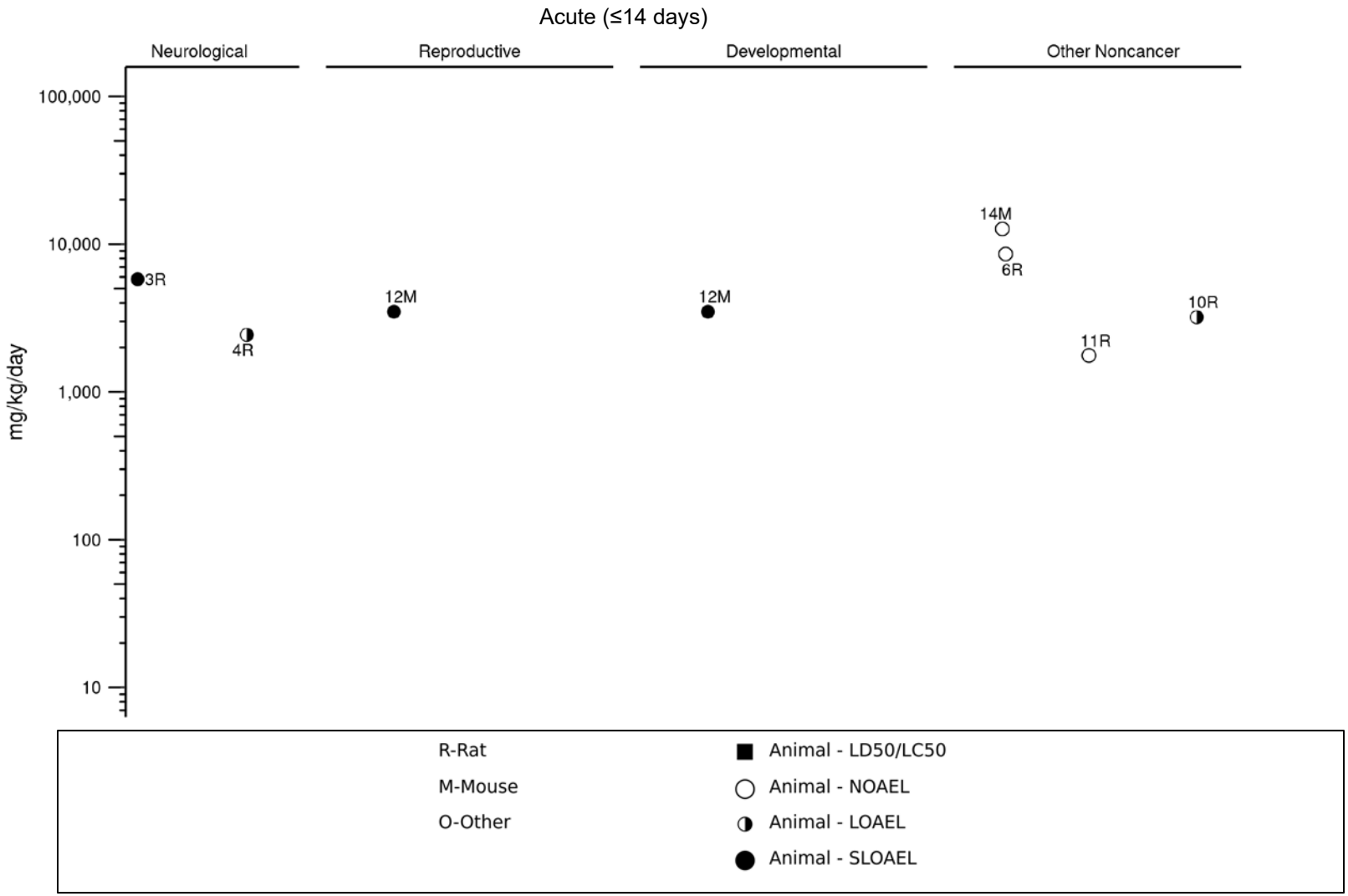


Figure 2-3. Levels of Significant Exposure to Acetone – Oral

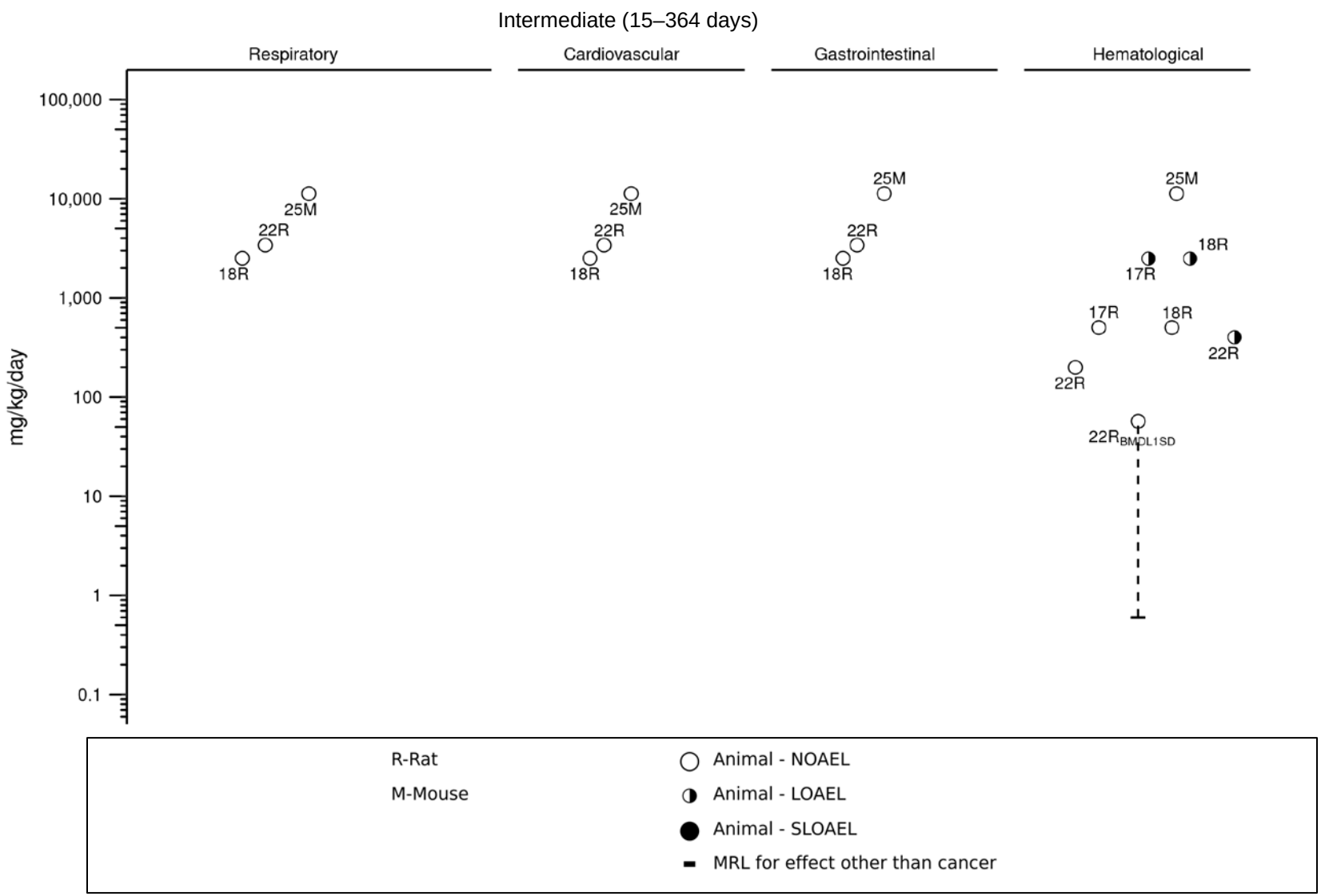


Figure 2-3. Levels of Significant Exposure to Acetone – Oral

Intermediate (15–364 days)

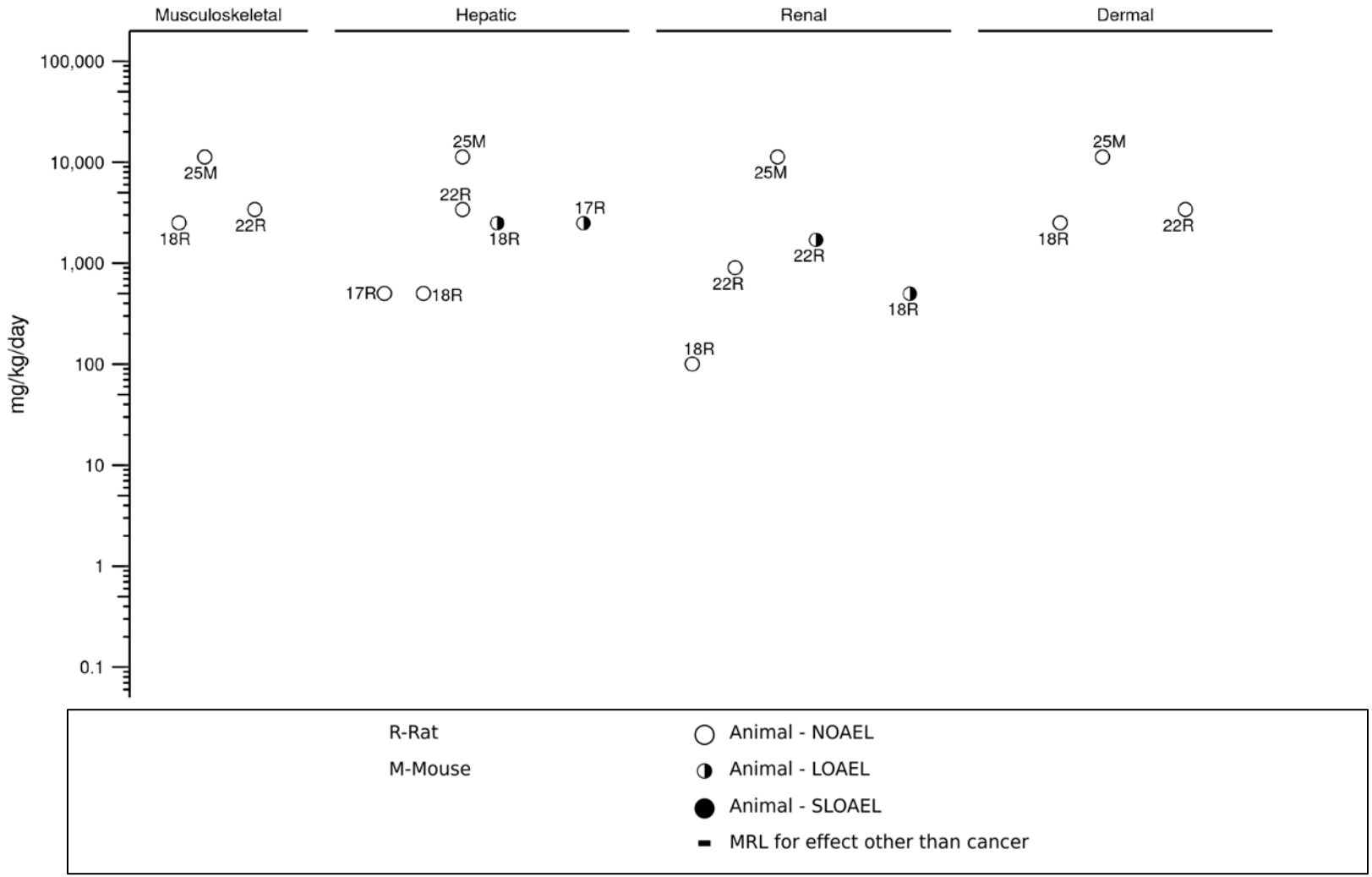


Figure 2-3. Levels of Significant Exposure to Acetone – Oral

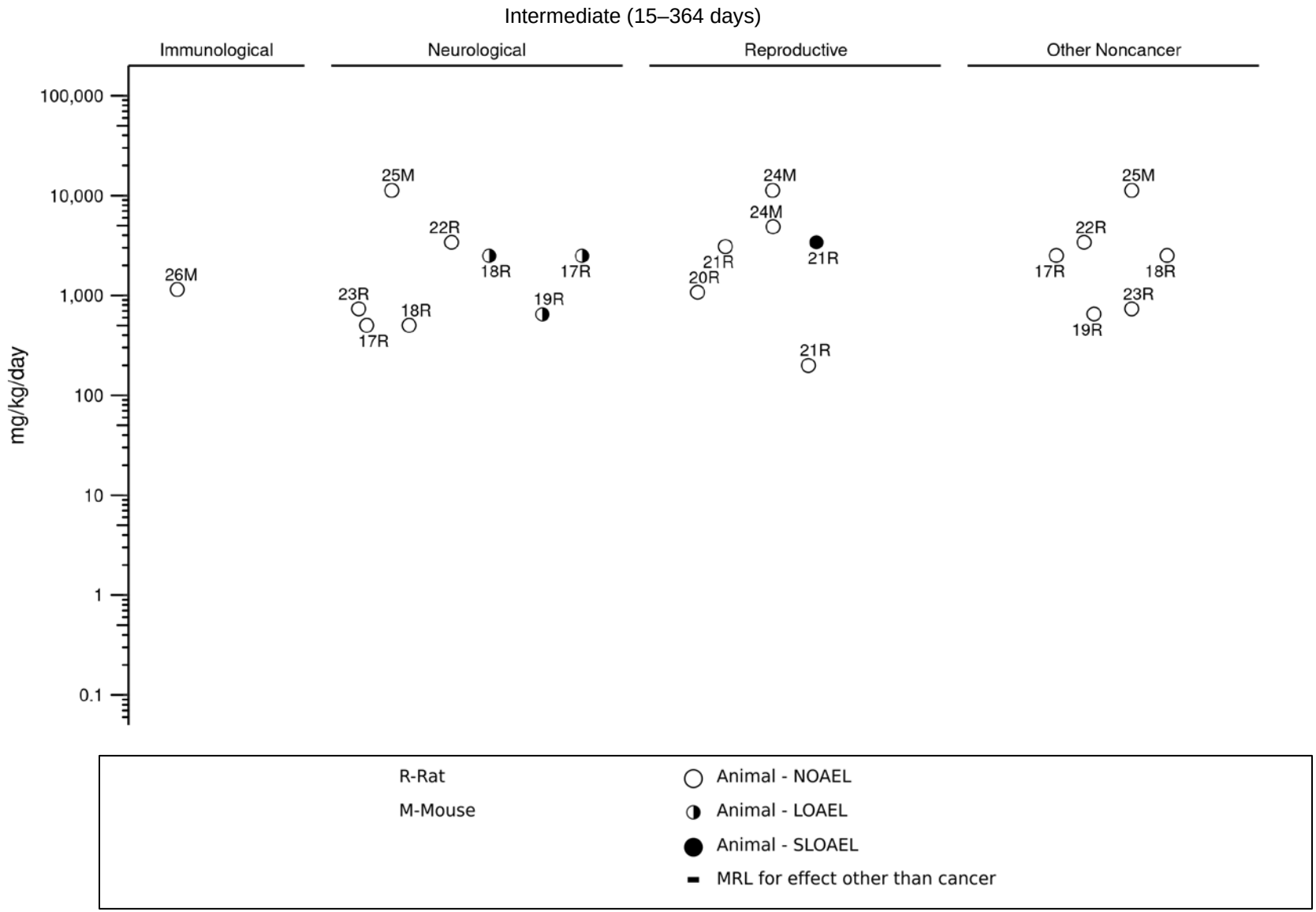


Table 2-4. Levels of Significant Exposure to Acetone – Dermal

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Lupulescu and Birmingham 1975									
1	Human 6 NR	1 day 90 minutes/day	1 mL	BI	Dermal		1		Decreased protein synthesis
Lupulescu et al. 1972, 1973									
2	Human 6 M	1 day 30 or 90 minutes/day	1 mL	HP CS	Dermal		1		Histological and ultrastructural degenerative changes in epidermis
Matsushita et al. 1969a									
3	Human 5 M	1 day 6 hours/day	0, 100, 250, 500, 1,000 ppm	CS UR HE	Dermal		100		Eye irritation
Nelson et al. 1943									
4	Human 10 B	1 day 3– 5 minutes/day	NS		Ocular	200	500		Eye irritation
Ross 1973									
5	Human 8 M	1 day 2 minutes– 4 hours/day	12,000 ppm	CS	Dermal		12,000		Eye irritation
Sallee and Sappington 1949									
6	Human NS	4–8 hours/day (occupational)	300– 3,000 ppm	CS	Dermal		2,000		Mild eye irritation
Iversen et al. 1988									
7	Mouse NR F	Once	0, 0.2 mL	BI	Dermal		0.2		Slight increase in DNA synthesis in skin
Specht et al. 1939									
8	Guinea pig 10 F	1 day 25 minutes– 23.4 hours/day	21,800 ppm	GN CS	Dermal		21,800		Lacrimation

Table 2-4. Levels of Significant Exposure to Acetone – Dermal

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Bolkova and Cejkova 1983									
9	Rabbit NR	1 day 1 minute/day	20 drops 96% acetone	BI	Dermal			20	Reversible corneal burns
Carpenter and Smyth 1946									
10	Rabbit NR	Once	0.005–0.02 mL	HP	Ocular			0.01	Severe eye necrosis
Larson et al. 1956									
11	Rabbit 5 M	1 day 3 minutes/day	4 ppm	OW	Dermal		4		Edema of eye mucous membrane
Smyth et al. 1962									
12	Rabbit NR	Once	0.005 mL	CS	Ocular			0.01	Severe corneal burn
Smyth et al. 1962									
13	Rabbit 5 NR	Once	0.01 mL	CS	Ocular	0.01			
INTERMEDIATE EXPOSURE									
Iversen et al. 1981									
14	Mouse 25 M, 25 F	18 weeks 2 times/week	0.1 mL	HP BI	Dermal		0.1		Moderate hyperplasia of epidermis
Rengstorff et al. 1972									
15	Guinea pig 12 B	3 weeks 3 days/week	0.5 mL	OP	Dermal			0.5	Cataracts
Taylor et al. 1993									
16	Guinea pig 15 NS	6 months 5 days/week 1 time/day	0.5 mL	BW CS OP	Dermal		0.5		Mild erythema
					Other noncancer		0.5		Transient weight loss of 60 g
Pe'er et al. 1992									
17	Rabbit 17 NS	12–16 weeks 1 time/week	10 µL/week	HP CS	Dermal		10		Uveal melanocytic hyperplasia

Table 2-4. Levels of Significant Exposure to Acetone – Dermal

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Rengstorff et al. 1976									
18	Rabbit 5 M, 5 F	3 weeks 3 days/week	0, 1.0 mL	OP	Dermal	1			
CHRONIC EXPOSURE									
DePass et al. 1989									
19	Mouse 40 M	502 days 3 times/week	667 mg/kg	GN HP	Dermal		667		Dermatitis in 2/40, hyperplasia in 1/40, and hyperkeratosis in 1/40

B = both sexes; BI = biochemical changes; Cardio = cardiovascular; CS = clinical signs; DNA = deoxyribonucleic acid; F = female(s); Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathological; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NR = not reported; NS = not specified; OP = ophthalmology; OW = organ weight; Repro = reproductive; Resp = respiratory; UR = urinalysis

2.2 DEATH

There are very few reports of deaths in humans attributable to acetone. Between 1994 and 1996, there were over 10,000 incidents of acetone exposure reported to the American Association of Poison Control Centers (AAPCC); only 3 of these cases resulted in death (Johanson 2012). In a review of 1,352 incidents of human exposure to acetone from the 2017 Annual Report of the American Association of Poison Control Centers National Data Collection System, no fatalities were reported (Gummin et al. 2018). Moreover, only seven cases involving exposure to acetone were associated with a major medical problem, which was defined as an issue that was life-threatening or resulted in significant residual disability or disfigurement (Gummin et al. 2018). However, co-exposures to other chemicals may have occurred, and details on exposure and outcomes beyond those noted here were not documented within the report. In a retrospective mortality study of 948 employees (697 men, 251 women) of a cellulose fiber plant where acetone was used as the only solvent, no significant excess risk of death from any cause (all causes, malignant neoplasm, circulatory system disease, ischemic heart disease) compared with rates for the U.S. general population was found (Ott et al. 1983a, 1983b). The workers had been employed at the plant for at least 3 months to 23 years. Industrial hygiene surveys found that median time-weighted average (TWA) acetone concentrations were 380 (low exposure jobs including low production and some jobs in preparation), 770 (moderate exposure jobs including inspectors and service jobs in filament), and 1,070 (high exposure jobs including operator jobs in filament extrusion) ppm.

Studies of acute inhalation exposures to acetone in animals indicate that high concentrations are required to result in death. Signs of narcosis usually precede death in animals from high exposure levels (see Section 2.15). An 8-hour lethal dose (LD_{50}) value of 21,091 ppm and a 4-hour LD_{50} value of 31,994 ppm were found for female rats (Pozzani et al. 1959). Inhalation exposure to acetone for a few hours has resulted in death in rats at concentrations ranging from 16,000 to 50,600 ppm (Bruckner and Peterson 1981a; Smyth et al. 1962) and in guinea pigs at concentrations ranging from 10,000 to 50,000 ppm (Specht et al. 1939). In general, concentrations of acetone at the upper end of these ranges resulted in death sooner than concentrations at the lower end. That very high concentrations of acetone are required to cause death of animals is reinforced by the fact that no deaths were reported for rats exposed to acetone at 4,220 ppm for 8 hours (Haggard et al. 1944) or mice exposed to <84,194 ppm for 8 hours (Mashbitz et al. 1936).

High LD_{50} values have also been observed following acute oral exposure to acetone in several species. An oral LD_{50} value of 5,250 mg/kg was found for male ddY mice (a strain of mice often used as a

spontaneous animal model for IgA nephropathy [Imai et al. 1985]) (Tanii et al. 1986), and an oral LD_{50} value of 3,687 mg/kg was found for male guinea pigs (Strieger and Carpenter 1961). In a study to determine which doses to use in a developmental study, oral dosing of pregnant mice (four per dose group) with acetone during gestation resulted in the death of one mouse at 2,400 mg/kg/day and one mouse at 4,800 mg/kg/day (EHRT 1987). All mice exposed to 7,908 mg/kg/day of acetone died. No controls were used in the range-finding study. One of two rabbits given 7,844 mg/kg acetone by gavage died within 19 hours of dosing, and two rabbits given 5,491 mg/kg survived, while one rabbit given 3,922 mg/kg died in 96 hours (Walton et al. 1928). Oral doses of 7,500 or 8,000 mg/kg acetone were fatal to two immature dogs (Albertoni 1884). However, no controls were included in these studies, and the small numbers of animals used limits the reliability of the findings. In general, the lethality of acetone in rats appears to vary by age and specific strain examined. A higher LD_{50} value was found for young adult rats than for older adult rats, but the difference was not statistically significant (Kimura et al. 1971). Higher LD_{50} values were found for Wistar rats (Smyth et al. 1962) and Nelson rats (Pozzani et al. 1959) than for Sprague-Dawley rats (Kimura et al. 1971). The LD_{50} value determined by Freeman and Hayes (1985), who also used Sprague-Dawley rats, is in line with values for 14-day-old and young adult Sprague-Dawley rats.

No fatalities were observed after dermal exposure to acetone in animals. In studies to determine the dermal LD_{50} values for acetone in rabbits (Roudabush et al. 1965; Smyth et al. 1962) and guinea pigs (Roudabush et al. 1965), the highest doses tested did not result in death. Therefore, LD_{50} values are >20 mL/kg (>15,688 mg/kg) for rabbits (Smyth et al. 1962) and >9.4 mL/kg (>7,373 mg/kg) for guinea pigs (Roudabush et al. 1965).

No studies were located regarding death of animals after intermediate- or chronic-duration exposure to acetone.

2.3 BODY WEIGHT

No human studies have evaluated the effect of acetone exposure on body weight. Studies on acute-duration acetone exposure in animals have shown mixed results with regard to changes in body weight. For example, rats treated by gavage with a lethal dose of acetone (LD_{50} of 5,800 mg/kg) lost 15% of their body weight at 48 hours after dosing (Freeman and Hayes 1985). However, treatment of rats by gavage with 1,766 mg/kg/day for 2 days (Valentovic et al. 1992) or with drinking water that provided lower doses (<1,200 mg/kg/day) for up to 2 weeks (Furner et al. 1972; Hetu and Joly 1988) did not affect body

weight gain. Rats maintained on drinking water for 14 days at higher doses displayed >10% decreased body weight gain compared to controls, but the decrease was associated with reduced water consumption probably due to unpalatability (Dietz et al. 1991; NTP 1991). In contrast, mice similarly treated had decreased water consumption at doses ≥6,348 mg/kg/day, but no effects on body weight gain occurred at doses <12,725 mg/kg/day.

There is some evidence to suggest that pregnancy may make animals more susceptible to body weight reduction. In a developmental study, rats exposed to acetone at 11,000 ppm, but not mice exposed to 6,600 ppm, intermittently during gestation had significantly ($p<0.05$) reduced body weight gain from gestation day (GD) 14 onward and reduced extragestational body weight on GD 20 (NTP 1988). However, in a behavioral study, no effect on body weight gain was observed in female rats exposed to 16,000 ppm intermittently for 2 weeks (Goldberg et al. 1964). Maternal body weight was slightly (5%) but significantly ($p=0.02$) reduced on day 3 postpartum in mice treated with 3,500 mg/kg/day acetone by gavage during gestation (EHRT 1987).

Studies of longer durations of exposure to acetone in animals have also shown mixed results. In intermediate-duration studies, gavage or drinking water treatment of rats or mice with acetone did not result in reductions in body weight except in cases where fluid consumption was reduced (American Biogenics Corp. 1986; Ladefoged et al. 1989; NTP 1991; Spencer et al. 1978). A transient weight loss of 60 g over a 2-week period was noted in hairless guinea pigs to which acetone was applied to the skin for 6 months (Taylor et al. 1993). In a 2-week study of exposures in drinking water, rats administered acetone at concentrations of approximately 90 mg/kg/day showed the same body weight gain as controls (Ross et al. 1995).

2.4 RESPIRATORY

Human studies evaluating the respiratory effects of inhaled acetone exposure primarily found irritation of the nose, throat, trachea, and lungs. The irritating properties of acetone in humans have been noted both in workers who were exposed to acetone occupationally (Kiesswetter and Seeber 1995; Raleigh and McGee 1972; Ross 1973) and in volunteers under controlled laboratory conditions (Matsushita et al. 1969a, 1969b; Nelson et al. 1943). Raleigh and McGee (1972) examined two sites involving occupational exposure to acetone. At the first site, nine workers were exposed to a TWA acetone concentration of 1,006 ppm. Four workers reported throat irritation and two reported nasal irritation. Of the four employees at the second site exposed to similar acetone concentrations in air, one reported throat

irritation and three reported nasal irritation. Out of eight male workers who had been exposed to an unknown quantity of acetone from a leaking storage tank, one worker reported respiratory irritation and one reported chest tightness (Ross 1973). Workers (n=16) exposed to a mean acetone concentration of approximately 1,000 ppm self-reported symptoms of respiratory irritation and difficulty breathing (Kiesswetter and Seeber 1995). In a controlled exposure study, volunteers were asked to give their subjective complaints, and some reported irritation of the nose, eyes, and throat following exposure to 100 ppm for 6 hours, with more subjects reporting nose, eye, and throat irritation at increasing exposure levels (Matsushita et al. 1969b). Self-reported symptoms also included the loss of the ability to smell acetone as exposure proceeded. In another controlled experiment, the majority of approximately 10 subjects, although exposed for only 3–5 minutes, estimated that they could tolerate an exposure level of 200 ppm for an 8-hour work shift (Nelson et al. 1943). Pulmonary function testing of 18 volunteers exposed <1,250 ppm acetone intermittently for various durations in a complex protocol revealed no abnormalities caused by the exposure, but 3 volunteers reported sporadic throat irritation (Stewart et al. 1975). Jones and Brautbar (1997) concluded that the type of pulmonary function test used in a medical examination determines which endpoints can be effectively evaluated. The study authors performed spirometry and methacholine stimulation tests on 42 patients with a history of occupational solvent exposure, and found that while only 10–15% of patients who reported respiratory systems had abnormal screening spirometry, 42% had abnormal methacholine stimulation results. They attributed this difference in test results to volatile organic compound-associated bronchial hyperreactivity, which would not be detected by spirometry (Jones and Brautbar 1997). In a study of 1,091 male gun-factory workers, 411 occupationally exposed to solvents and 680 unexposed to solvents at work, solvent exposure was identified as a risk factor for self-reported asthma-related symptoms in smokers (odds ratio [OR] 1.4, 95% confidence interval [CI] 1.0–1.9, p=0.003) and nonsmokers (OR 2.4, 95% CI 1.4–4.4, p=0.002). The study authors attributed this effect to the sensitizing effects of solvents; however, the study did not quantify exposure to solvents used in the factory, which included toluene, butanol, xylene, benzene, and trichloroethylene in addition to acetone (Cakmak et al. 2004). A cross-sectional study of 67 shoe factory workers exposed to acetone alone for ≥5 years found increased odds of chronic bronchitis (OR 3.563; 95% CI 1.259–10.084) (Sinamora et al. 2018). However, no association was observed between acetone and restrictive pulmonary “disturbance” as assessed by spirometry (OR 0.697; (5% CI 0.170–2.861). Measured exposure was reported as 57.90 ppm, although little information on this measurement, such as number of measurements and duration of measurement, was reported.

Some degree of sensory adaptation to inhaled acetone in humans is apparent. For example, workers who had been occupationally exposed to acetone displayed reduced sensitivity to both its odor and irritancy in acute-duration exposure tests. People without prior occupational exposure to acetone who served as controls in the experiment did not have such sensory adaptation. In the experiment, 27 workers and age- and sex-matched controls had been exposed to 800 ppm acetone for 20 minutes. The results of the experiment suggest that the general population may be more sensitive to the acute irritant effects of inhaled acetone than workers with repeated exposure (Dalton et al. 1997; Wysocki et al. 1997). Additionally, any sensory adaptation to chemical irritants is thought to be reversible if enough time passes between exposures (Dalton et al. 2006).

Despite evidence of some sensory adaptation, high and/or chronic exposures to acetone may still lead to respiratory injury. A 49-year-old male who had been accidentally sprayed with acetone during roadwork application developed edema within the bronchial tree (Piatkowski et al. 2007). Increased prevalence of upper respiratory tract irritation was reported among acetone-exposed workers (n=71) compared with matched controls (n=86) at a coin-printing factory (Mitran et al. 1997). Eight-hour acetone exposure levels in the workplace air of the exposed workers ranged from 988 to 2,114 mg/m^3 (416–890 ppm). The mean length of exposure was 14 years.

Exposure of animals to much higher concentrations of acetone than those reported in humans has resulted in respiratory effects. Pulmonary congestion, edema, and hemorrhage of the lungs were observed in guinea pigs that died after exposure to 10,000 ppm continuously for 1 or 2 days, to 20,000 ppm continuously for 1 day, or to 50,000 ppm for a few hours (Specht et al. 1939). The pulmonary congestion and edema were attributed to the irritating effects of acetone on the mucosa. The hemorrhage may have been a consequence of death. Respiratory rates also decreased in the guinea pigs during exposures, but the decrease was probably a consequence of the narcotic effects of acetone (see Section 2.15). In mice exposed to acetone for 10 minutes, the calculated concentration of acetone that decreased the respiratory rate 50% (RD_{50}) was 77,516 ppm. The decrease in respiratory rates occurred within the first few seconds of exposure, but respiratory rates started to increase again after a few minutes of exposure and returned to baseline levels within 10 minutes of exposure. Therefore, the study authors concluded that the decrease in respiratory rate was due to sensory irritation, but the mice adapted to the irritant properties. The RD_{50} for acetone was higher than the values calculated for other solvents, indicating that acetone is a weak irritant (Kane et al. 1980). Also demonstrating the role of acetone as an irritant, 20 male and female rhesus macaque monkeys exposed to acetone vapors via artificial ventilation for 10 breaths (25 seconds) showed significant stimulation of the rapidly adapting receptors (RARs) in their airways without changes

in peak intratracheal pressure (Ravi et al. 1995). 40–50-day-old male mice exposed to a mixture of solvents from five home remodeling products did not show signs of sensory irritation at ambient temperatures. However, when the materials were heated to 70°C, the products released higher levels of solvents and respiratory depression was observed. The study authors only reported concentrations for the top five volatile organic chemicals (VOCs) emitted by each product. At ambient temperature, acetone was measured in oak veneer at a concentration of 82 µg/m^3. Acetone was one of the most commonly emitted VOCs at 70ºC, being measured in concentrations of 50 µg/m^3 in ceiling tile, 102 µg/m^3 in Spanished wallcovering, and 2,591 µg/m^3 in oak veneer. However, this study included extensive co-exposures with other VOCs, making it difficult to determine whether acetone was the sole cause of the respiratory changes (Muller and Black 1995). In 16 mice exposed to 6,000 ppm acetone for 0.5 hours/day for 1 or 5 days, no effects on the time of inspiration, time of expiration, time between breaths, or tidal volume were found. In addition, acetone exposure caused no changes in lung weight, lung volume displacement, or histological evidence of pulmonary pathology (Schaper and Brost 1991). Histological examination of the lungs of 4–14-week-old male rats exposed intermittently to a high concentration of acetone (19,000 ppm) for 2–8 weeks revealed no evidence of treatment-related lesions (Bruckner and Peterson 1981b).

Oral exposure of humans to acetone has not been studied extensively. One case report found that a 47-year-old woman with a history of acetone ingestion arrived in the emergency room in respiratory distress, but did not need artificial ventilation. Respiratory failure in cases of acetone poisoning is likely due to acetone-induced central nervous system (CNS) depression (Kumarvel and Da Fonseca 2007).

Oral exposure of animals to acetone has been associated with changes in respiration rate and difficulty breathing, which may be attributable to the role of the lungs in acetone excretion or to the depressive effect of acetone on the CNS. However, lung microsomes of three hamsters exposed to 8% acetone in drinking water for 7 days had a 500% increase of aniline hydroxylase activity, an activity associated with CYP2E1 (CYP2E1) (Ueng et al. 1991). Furthermore, the level of CYP2E1 and the activity of butanol oxidase increased 6-fold in microsomes from the nasal mucosa of rabbits exposed to 1% acetone in drinking water for 1 week (Ding and Coon 1990). Changes in respiratory rates (either increases or decreases), along with signs of narcosis, were observed in rabbits dosed with >3,922 mg/kg acetone (Walton et al. 1928), and irregular respiration, along with signs of narcosis, was observed in dogs dosed with 4,000 mg/kg (Albertoni 1884). In a range-finding study to determine which doses to use in a developmental toxicity study, mice that died at doses >4,800 mg/kg/day for 10 days displayed wheezing and/or rapid and labored breathing, accompanied by signs of severe narcosis, prior to death (EHRT 1987).

However, the apparent respiratory effects probably reflect the severely compromised condition of these animals, rather than a toxic effect of acetone on the lungs. Gross necropsy of a dog dosed with 8,000 mg/kg acetone revealed no effects on the lungs, but the lungs were not examined histologically (Albertoni 1884). Histological examination of the lungs of rats and mice (10 of each sex per dose group) exposed to acetone in drinking water at concentrations up to 50,000 ppm for 13 weeks (Dietz et al. 1991; NTP 1991) or of rats given acetone in water by gavage once daily at doses up to 2500 mg/kg/day for 13 weeks (American Biogenics Corp. 1986) revealed no treatment-related lesions. Thus, acetone by itself does not appear to be toxic to the lungs of animals when administered by the oral route, but it may cause changes in lung function indirectly due to suppression of the CNS. Additionally, the induction of lung microsomal enzymes suggests that acetone may potentiate the respiratory effects induced by other chemicals (see Section 3.4).

2.5 CARDIOVASCULAR

Information regarding cardiovascular effects in humans following inhalation exposure to acetone is inconsistent. High pulse rates (120–160/minute) were commonly found in patients exposed to acetone by inhalation and/or dermally after application of casts for which acetone was used in the setting solution (Chatterton and Elliott 1946; Hift and Patel 1961). In a controlled laboratory study, electrocardiography of volunteers (8 males and 10 females ranging in age from 18 to 27 years old) exposed to <1,250 ppm acetone intermittently for various durations revealed no alterations, compared with their preexposure electrocardiograms (Stewart et al. 1975). A cross-sectional study of 471 car manufacturing plant workers found that co-exposure to noise and solvents was associated with elevated OR of hypertension (OR 4.22, 95% CI 3.21–40.84, $p<0.001$). The effects of this co-exposure appear to be additive, as the ORs of hypertension in noise-exposed workers and solvent-exposed workers were 9.43 (95% CI 2.81–23.46, $p=0.001$) and 4.38 (95% CI 1.27–10.53, $p=0.028$), respectively. However, acetone was found only at one of the two work sites at levels (42 ppm) well below the Threshold Limit Value (TLV) for 8-hour exposures to acetone (250 ppm), and the effects of solvents in this study may be attributable to the other organic solvents found at the manufacturing plant (Attarchi et al. 2013). A retrospective mortality study of 948 workers (697 men, 251 women) employed for at least 3 months to 23 years at a cellulose fiber plant where acetone was used as the only solvent found no significant excess risk of death from circulatory system disease or ischemic heart disease compared with rates for the U.S. general population (Ott et al. 1983a, 1983b). Industrial hygiene surveys found that median TWA acetone concentrations were 380, 770, and 1,070 ppm based on job categories.

Acetone inhalation studies in animals have found little evidence of cardiovascular effects. Reduced heart rates were observed in guinea pigs exposed to various high concentrations (1, 2, or 5% acetone in air) for acute durations varying from 3 to 48 hours (Specht et al. 1939), but were probably a consequence of the narcotic effects of acetone (Section 2.15). Necropsy of the guinea pigs revealed no effects on the heart, but histological examination was not performed. Histological examination of the hearts of rats exposed intermittently to a high concentration of acetone (19,000 ppm) for 2–8 weeks revealed no evidence of treatment-related lesions (Bruckner and Peterson 1981b).

Human case studies following oral acetone exposure or acetone ingestion have shown tachycardia, acidosis, and changes in blood pressure (Herman et al. 1997; Kumarvel and Da Fonseca 2007; Slutzman et al. 2015). In a 1997 case report from the LeBonheur Children's Medical Center in Memphis, a mother was found to have been injecting fingernail polish remover into her 17-month-old daughter's gastrostomy tube, resulting in gastric fluid with an acetone concentration of 1:1024. The child received a blood cell transfusion to treat a low red blood cell count and also had tachycardia, an elevated pulse (131 beats/minute), and low blood pressure (87/55 mmHg) (Herman et al. 1997). Two case studies on adult women who ingested nail polish remover during alcohol withdrawal found sinus tachycardia (Kumarvel and Da Fonseca 2007; Slutzman et al. 2015). The 34-year-old woman with a toxicology screen showing an acetone level >300 mg/L had relative hypotension (105/70 mm Hg despite a history of hypertension), while the 47-year-old woman with a history of acetone ingestion but no measured exposure level had hypertension (180/120 mm Hg). However, the association between these endpoints and acetone ingestion is difficult to establish, given the pre-existing conditions (e.g., alcohol use disorder) and co-exposures found in these case reports.

Animal studies on oral acetone exposure have not found significant adverse effects on the heart. Histological examination of the hearts of rats and mice exposed to high levels of acetone (5,000–100,000 pm) in drinking water for 13 weeks (Dietz et al. 1991; NTP 1991) or of rats given acetone in water by gavage once daily up to 2,500 mg/kg/day for 13 weeks (American Biogenics Corp. 1986) did not reveal treatment-related lesions. However, the heart-to-brain weight ratio was significantly increased ($p<0.01$) in the female rats treated by gavage with 2,500 mg/kg/day. In the absence of histologically observable lesions, the toxicological significance of the increased heart weight is questionable.

No studies on the cardiovascular effects of direct dermal exposure to acetone were found. However, case reports of four children and one adult exposed to acetone dermally and via inhalation during the application of casts described high pulse rates (120–160/minute) (Chatterton and Elliott 1946; Harris and

Jackson 1952; Hift and Patel 1961; Pomerantz 1950; Renshaw and Mitchell 1956). One case report stated that 2 L of setting fluid consisting of 90% acetone was used (Harris and Jackson 1952); details on the amounts of acetone used in the remaining cases were not provided.

One animal study evaluating the cardiovascular effects of dermal acetone exposure found evidence of damage to the heart. In this chronic exposure study, amyloidosis was observed in the organs of approximately 50% of mice (12 out of 23) with lumbo-sacral regions that were painted twice weekly with an unspecified quantity of acetone for 12 months (Barr-Nea and Wolman 1977). Although the study authors stated that the heart was the second most common site of amyloidosis, the number of mice with amyloidosis in the heart was not reported. Additionally, the study authors noted that mice painted with oil dissolved in acetone did not show increases in the incidence of amyloidosis; the effects of acetone on amyloidosis were not conclusive.

2.6 GASTROINTESTINAL

Case reports have described vomiting of blood and gastrointestinal hemorrhage in patients who had hip casts applied with acetone present in the setting fluid (Chatterton and Elliott 1946; Fitzpatrick and Claire 1947; Harris and Jackson 1952; Hift and Patel 1961; Pomerantz 1950; Renshaw and Mitchell 1956; Strong 1944). In the only case report that provided the amount of acetone applied, 2 L of a setting fluid containing 90% acetone was used (Harris and Jackson 1952). As the vomitus contained blood several hours after vomiting first commenced, the gastrointestinal hemorrhage may have been due to the trauma of repeated vomiting. These patients had a strong odor of acetone in their breath. One patient had a blood acetone level of 15 mg/100 mL 26 hours after application of the cast (Harris and Jackson 1952). These patients were exposed to acetone by inhalation during and after cast application (evaporation). In addition, there may have been dermal exposure. In several cases, exposure occurred in well-ventilated areas and was thus considered to be mainly via direct dermal absorption (Hift and Patel 1961).

Acetone-exposed workers (n=71) had increased prevalence of gastrointestinal symptoms including nausea (13% acetone-exposed, 6% controls), loss of appetite (9% acetone-exposed, 1% controls), hyperacidity (15% acetone-exposed, 1% controls), bad taste (23% acetone-exposed, 1% controls), and abdominal pains (13% acetone-exposed, 1% controls) compared to matched controls (n=86) at a coin-printing factory (Mitran et al. 1997). Eight-hour acetone exposure levels in the workplace air of the exposed workers ranged from 988 to 2,114 mg/m^3 (416 to 890 ppm); the mean length of exposure was 14 years.

No studies were located regarding gastrointestinal effects per se in humans after oral exposure to acetone, but a man who intentionally drank ≈200 mL of pure acetone had a red and swollen throat and erosions in the soft palate and entrance to the esophagus (Gitelson et al. 1966). In addition, a 17-month old infant was intentionally and repeatedly poisoned by a caregiver injecting nail polish remover into the infant's gastronomy tube (Herman et al. 1997). The product was made up of acetone and a small amount of isopropyl alcohol. The infant was exposed to an estimated minimum dose of 4.88 mL/kg and experienced bloody diarrhea, persistent portal venous gas, and abdominal distension.

Necropsy of guinea pigs that died after exposure to high concentrations of acetone (1, 2, or 5% in air) for acute durations ranging from 3 to 48 hours revealed no effects on the stomach (Specht et al. 1939), but histological examination was not performed.

Significantly increased levels of cytochrome P-450IA1 (CYP1A1) in duodenal microsomes and cytochrome P-450IIB2 (CYP2B2) in duodenal and jejunal microsomes from four rats exposed to acetone intragastrically (1 mL at 50% volume/volume, or v/v, dissolved in water) for 3 days were found (Carriere et al. 1992). No increase in CYP2E1 was found in these microsomal preparations. Oral exposure of animals to acetone has not resulted in adverse effects on the gastrointestinal tract in intermediate-duration studies. Histological examination of the gastrointestinal tract of rats and mice (10 of each sex per dose group) exposed to acetone in drinking water at concentrations up to 50,000 ppm for 13 weeks (Dietz et al. 1991; NTP 1991) or of rats given acetone in water by gavage once daily up to 2,500 mg/kg/day for 13 weeks (American Biogenics Corp. 1986) did not reveal treatment-related lesions.

2.7 HEMATOLOGICAL

Human studies evaluating the hematological effects of inhaled acetone have reported varying results. In a health evaluation survey of 168 men and 77 women employed at a cellulose fiber production plant where acetone was used as the only solvent, all hematological parameters were within normal limits. The workers had been employed at the plant for at least 3 months to 23 years. Industrial hygiene surveys found median TWA acetone concentrations of 380, 770, and 1,070 ppm, based on job categories (Ott et al. 1983a, 1983c). A cross-sectional study of 110 male acetate fiber plant workers found no hematological effects in workers exposed to acetone at TWAs ranging from 19.6 to 1,018 ppm when compared to 67 unexposed male coworkers (Satoh et al. 1996).

Hematological effects have been observed in humans after inhalation exposure to acetone in controlled laboratory studies of volunteers. Statistically significant increased white blood cell counts and decreased phagocytic activity of neutrophils, compared with controls, were observed in volunteers (five or six per dose group) after a 6-hour exposure or repeated 6-hour exposures for 6 days to 500 ppm (Matsushita et al. 1969a, 1969b). No significant difference was seen in hematological parameters in the volunteers exposed to 250 ppm compared with controls. In contrast, hematological findings were within normal limits in 4 volunteers exposed to 500 ppm for 2 hours (DiVincenzo et al. 1973) and 18 volunteers exposed to up to 1,250 ppm acetone repeatedly for 1–7.5 hours/day for as long as 6 weeks (Stewart et al. 1975).

In animals, no studies were located regarding hematological effects after inhalation exposure to acetone.

No epidemiological studies directly examined hematological endpoints in humans after oral exposure to acetone. However, a 1997 case study reporting hematological parameters for a 17-month-old girl whose mother repeatedly injected nail polish remover into her gastronomy tube (acetone concentration in gastric contents of 1:1024) found hematological effects attributable to acetone poisoning. After admission to the hospital, the child received a red blood cell transfusion to combat her low volume percentage of red blood cells. Following the poisoning events, the child's white blood cell count was elevated (22,900/mm^3 after the second poisoning event and 27,100/mm after the third). The nail polish remover used in this case was mostly acetone combined with a small amount of isopropyl alcohol, so it is likely that the observed effects are attributable to acetone (Herman et al. 1997). A case study of a 47-year-old female patient with suspected ingestion of an unknown quantity of acetone reported an elevated (26x109/L) white blood cell count (Kumarvel and Da Fonseca 2007).

Exposure of three rabbits to 863 mg/kg/day acetone in drinking water for 7 days resulted in a 12.9-fold increase in the levels of CYP2E1 in bone marrow microsomes (Schnier et al. 1989). Hematological effects of oral exposure to acetone have been observed in rats but not in mice. Bone marrow hypoplasia was observed in five of five male rats exposed to acetone in drinking water for 14 days at 6,942 mg/kg/day, but not at 4,312 mg/kg/day (Dietz et al. 1991; NTP 1991). None of the female rats had bone marrow hypoplasia. Although mice were similarly treated for 14 days in this study, the study authors did not specify whether bone marrow was examined; however, in 13-week studies by the same authors, no hematological effects or histologically observable lesions in hematopoietic tissues were found in mice (Dietz et al. 1991; NTP 1991). Another mouse study found that CD-1 mice exposed continuously for 28 days to acetone in drinking water at doses of approximately 121, 621, and 1,144 mg/kg/day did not have significantly different hematological parameters than controls. Based on their evaluation of

hemoglobin, hematocrit, corpuscular volume, platelets, red, and white blood cells, along with non-hematological endpoints, the study authors established a NOAEL of 1,144 mg/kg/day (Woolhiser et al. 2006).

In contrast to the mouse data, Dietz et al. (1991) and NTP (1991) found evidence of macrocytic anemia in male rats exposed to acetone in drinking water for 13 weeks. This evidence consisted of significantly ($p<0.05$ or $p<0.01$) decreased hemoglobin concentration, increased mean corpuscular hemoglobin and mean corpuscular volume, decreased erythrocyte counts, decreased reticulocyte counts and platelets, and splenic hemosiderosis. The LOAEL for these effects was 400 mg/kg/day, and the NOAEL was 200 mg/kg/day. The number of affected parameters increased as the dose increased; the highest dose tested in male rats was 3,400 mg/kg/day.

In female rats, hematological effects consisted of statistically significant increased lymphocyte counts, increased mean corpuscular hemoglobin and mean corpuscular volume at the highest dose (3,100 mg/kg/day), and decreased platelets at the highest and next-to-highest dose levels (3,100 and 1,600 mg/kg/day, respectively) (Dietz et al. 1991; NTP 1991). The biological significance of the hematological effects in female rats was not clear, but the effects were not consistent with anemia. Sex differences in the hematological effects of acetone exposure were also found in rats treated by gavage (American Biogenics Corp. 1986). Gavage treatment for 46–47 days significantly ($p<0.01$) increased hemoglobin, hematocrit, and mean cell volume in high-dose males (2,500 mg/kg/day), but not in females. With longer duration treatment (13 weeks), both high-dose males ($p<0.01$) and females ($p<0.05$) had increased hemoglobin and hematocrit, and high-dose males ($p<0.01$) also had increased mean cell hemoglobin and mean cell volume and decreased platelets. Thus, it appears that species and sex differences exist for hematological effects of oral exposure to acetone.

No human or animal studies evaluating hematological effects after dermal exposure to acetone were located.

2.8 MUSCULOSKELETAL

Several studies in humans were located regarding musculoskeletal effects after exposure to acetone. Increased prevalence of rheumatic symptoms such as bone pain (21% acetone-exposed, 5% controls), joint pain (21% acetone-exposed, 4% controls), vertebral column pain (15% acetone-exposed, 8% controls), and muscular pain (13% acetone-exposed, 2% controls) were reported among acetone-exposed

workers (n=71) compared to matched controls (n=86) at a coin-printing and medal factory (Mitran et al. 1997). Eight-hour acetone exposure levels in the workplace air of the exposed workers ranged from 988 to 2,114 mg/m^3 (416–890 ppm); the mean length of exposure was 14 years. A man who was accidentally sprayed with acetone during roadwork application later developed rhabdomyolysis and subsequent acute renal failure (Piatkowski et al. 2007). The investigator attributed the development of these effects to acute-duration inhalation exposure to acetone.

Studies on acetone exposure in animals have failed to find significant associations with musculoskeletal effects. Histological examination of femurs of rats and mice exposed to acetone in drinking water at concentrations up to 50,000 ppm for 13 weeks (Dietz et al. 1991; NTP 1991), or of rats given acetone in water by gavage once daily at doses up to 2,500 mg/kg/day for 13 weeks (American Biogenics Corp. 1986) did not reveal treatment-related lesions. Skeletal muscle was not examined histologically in the 13-week drinking water study (Dietz et al. 1991; NTP 1991), but histological examination of the skeletal muscle in rats in the 13-week gavage study did not reveal treatment-related lesions (American Biogenics Corp. 1986).

2.9 HEPATIC

Epidemiological and controlled human studies indicate that acetone is not associated with adverse hepatic effects in humans. Clinical chemistry parameters indicative of liver injury (e.g., serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactic acid dehydrogenase, alkaline phosphatase, ornithine carbamoyl transferase, cholesterol, triglycerides, bilirubin, lipids, etc.) were within normal limits in four volunteers after a single 2-hour exposure to 500 ppm acetone (DiVincenzo et al. 1973) or 1,250 ppm intermittently for up to 7.5 hours/day, several days per week over the course of 6 weeks (Stewart et al. 1975). In a health evaluation survey of 168 men and 77 women employed for at least 3 months to 23 years at a cellulose fiber production plant where acetone was used as the only solvent, all clinical blood chemistry parameters in exposed workers (AST, ALT, lactic acid dehydrogenase, alkaline phosphatase, total bilirubin, and albumin) were within normal limits (Ott et al. 1983a, 1983c). Industrial hygiene surveys found median TWA acetone concentrations of 380, 770, and 1,070 ppm, based on job categories. Workers (n=110) exposed to acetone at a mean concentration of 364 ppm (range of 19.6–1,018 ppm) for a mean of 14.9 years (range of 0.5–34.3 years) displayed no significant differences in serum markers of liver function relative to controls (Satoh et al. 1996). In a study of a shoe repair factory, 33 workers exposed to a mixture of solvents including acetone at approximately 560 ppm for a mean of 8.7 years had elevated mean ALT, AST, conjugated bilirubin, and

alkaline phosphatase as compared to controls (Tomei et al. 1999). However, acetone comprised only 10% of the solvent mixture used, which also contained 30% n-hexane, 27% C6 isomers of hexane, 11% ethyl acetate, 20% methyl ethyl ketone, and 3% toluene.

Fatty deposits were found in the livers upon autopsy of guinea pigs that died after inhalation exposure to high concentrations of acetone (1, 2, or 5% in air) for acute durations ranging from 3 to 48 hours (Specht et al. 1939). In contrast, intermittent exposure of rats to a high concentration of acetone (19,000 ppm) for 2–8 weeks did not produce signs of liver toxicity, assessed by the measurement of serum aspartate aminotransferase, lactic acid dehydrogenase, liver weights, and histological examination of the liver (Bruckner and Peterson 1981b).

Inhalation exposure to acetone at lower concentrations does not appear to be toxic to the liver of animals; however, acetone potentiates the hepatotoxicity induced by some other chemicals (see Section 3.4). The mechanism by which acetone exerts the potentiation is through the induction or increased activity of liver microsomal monooxygenases, particularly enzymes associated with CYP2E1 (see Sections 2.21 and 3.4). Most of the studies showing enzyme induction have been conducted by the oral route (see Section 2.21). In acute inhalation studies in rats, acetone exposure resulted in statistically significant increases in the liver concentration of cytochrome P450 (CYP), the activity of ethoxycoumarin O-deethylase (associated with CYP2B1), and the activity of glutathione-S-transferase, and decreased liver free glutathione content (Brondeau et al. 1989; Vainio and Zitting 1978). Induction of microsomal enzymes is considered an adaptive physiological response to xenobiotics, rather than an adverse effect by itself; however, in some scenarios, it potentiates the toxicity of other chemicals (Brady et al. 1989).

In a developmental study, mice exposed intermittently to 6,600 ppm acetone on GDs 6–19 had significantly increased absolute and relative liver weights compared with controls ($p<0.05$) (NTP 1988). Increased liver weight is considered a sign of maternal toxicity in developmental studies. The increased liver weight could have been associated with enzyme induction.

Acetone by itself is moderately toxic to the liver of animals, but acetone potentiates the hepatotoxicity of some other chemicals by inducing microsomal enzymes that metabolize other chemicals to reactive intermediates (see Sections 2.21 and 3.4). Numerous studies have investigated these mechanisms to identify the specific CYP isoenzymes involved (Barnett et al. 1992; Carriere et al. 1992; Chen et al. 1994; Puccini et al. 1992). In these studies in general, rats, mice, rabbits, or hamsters were given acetone by gavage in water or in drinking water for 1 day to 2 weeks. Microsome preparations from the livers were

then analyzed for CYP content, enzyme activities associated with specific CYP isoenzymes (particularly CYP2E1), and identification of the specific isoenzymes. Acetone has also been shown to increase the activity of glutathione S-transferase (Sippel et al. 1991). In rats exposed to acetone in drinking water, increases in CYP content, microsomal biotransformation activity, and peroxisomal fatty acid oxidation were observed (Orellana et al. 2001). These topics are discussed more fully in Sections 2.21 and 3.4. Induction of microsomal enzymes is considered a normal physiological response to xenobiotics rather than an adverse effect, unless it is accompanied by increased liver weight and other hepatic effects. Mice exposed to acetone in drinking water for 14 days had dose-related increased liver weights at ≥965 mg/kg/day, probably associated with microsomal enzyme induction (Dietz et al. 1991; NTP 1991). The increased liver weight was accompanied by hepatocellular hypertrophy at 3,896 mg/kg/day. In rats treated for 14 days, increased liver weight was stated to occur at the same or lower doses as in the 13-week study (see below), but more definitive information regarding the doses was not provided. Histological examination revealed no treatment-related hepatic effects in rats.

As stated above, acetone by itself is only moderately toxic to the liver in animals. In mice exposed to 1,900 mg/kg/day acetone in the drinking water for 10 days, histological examination of the liver revealed no hepatic lesions (Jeffery et al. 1991). Acetone did not increase the level of serum ALT in rats at 871 mg/kg (Brown and Hewitt 1984); the levels of serum ALT or bilirubin at 1,177 mg/kg (Charbonneau et al. 1986b); or the activities of hepatic glucose-6-phosphatase, serum ALT, and serum ornithine carbamoyltransferase in rats given 1,961 mg/kg for 1 day or 392 mg/kg/day for 3 days (Plaa et al. 1982). However, in an intermediate-duration study, male rats, but not female rats, treated by gavage with 2,500 mg/kg/day, but not 500 mg/kg/day, for 46–47 days and for 13 weeks had statistically significant increased levels of serum alanine amino transferase (American Biogenics Corp. 1986). Liver weights were statistically significantly increased in female rats at ≥500 mg/kg/day, but not at 100 mg/kg/day, and in male rats at 2,500 mg/kg/day after 13 weeks, but organ weights were not measured in the rats treated for 46–47 days. In the 13-week drinking water study, liver weights were also significantly ($p<0.01$) increased in both sexes of rats at the same concentration (20,000 ppm, which was equivalent to 1,600 mg/kg/day for females, 1,700 mg/kg/day for males) and in female mice, but not male mice, at 11,298 mg/kg/day (Dietz et al. 1991; NTP 1991). However, in the mice, the increased liver weight was not associated with hepatocellular hypertrophy seen in the 14-day study, suggesting a development of tolerance. Rats administered acetone in drinking water at concentrations of approximately 90 mg/kg/day for 14 days displayed significantly increased liver weights relative to controls (Ross et al. 1995).

Acetone has been associated with markers of oxidative stress in livers of exposed animals. Rats were assessed for liver oxidative balance and lipid content after treatments with acetone in water (5% mass/volume, or m/v) for 28 days (de Almeida et al. 2010). Compared with controls, acetone treated rats had decreased hepatic GSH and increased hepatic vitamin E, glycemia, cholesterolemia, and hepatic fat, which is similar to the features of non-alcoholic steatohepatitis (NASH). A single administration of 7.0 g acetone/kg body weight at 35% (m/v) in rats resulted in an increase in markers of lipid peroxidation in the liver (Mathias et al. 2010).

Obesity may make animals more susceptible to the hepatic effects of acetone. Groups of obese and lean mice maintained on high-fat diets were given acetone in drinking water (2%) for 2 weeks to induce CYP2E1 (Dey and Cedebaum 2007). This study used homozygous obese C57BL/6J ob/ob mice in the obese groups, which are leptin-deficient mice that are bred to exhibit obesity (Drel et al. 2006). Controls consisted of obese and lean mice maintained on the same diet as the experimental mice but not given acetone. Acetone induced more extensive fatty changes and mild necrosis in the livers of the obese mice compared with the livers of both control lean and control obese mice. The acetone-treated obese mice also had higher caspase-3 activity, numerous apoptotic hepatocytes, increased protein carbonyls, malondialdehyde, 4-hydroxynonenal-, and 3-nitrotyrosine-protein adducts, and elevated levels of inducible nitric oxide synthase.

In the one dermal study of hepatic effects located, amyloidosis was observed in the livers of mice with lumbo-sacral regions that were painted twice weekly with an unspecified quantity of acetone for 12 months (Barr-Nea and Wolman 1977).

Taken together, the data indicate that acetone induces liver microsomal enzymes, increases liver weights, and may cause liver injury, as evidenced by increased serum levels of liver enzymes associated with liver injury and hepatocellular hypertrophy. Species and sex differences exist in susceptibility to acetone-induced liver effects.

2.10 RENAL

Several case studies indicate that exposure to acetone may be associated with renal effects in humans. Minimal glomerulopathy and moderate tubulointerstitial nephritis were diagnosed in a 55-year-old woman following occupational exposure to a cleansing solution consisting principally of acetone (70% acetone; composition of the remainder of the solution is unknown) (Chen et al. 2002). The woman had

been using the solution periodically for approximately 2 years and had no prior history of renal disease. Acute renal failure was diagnosed in a 49-year-old male who had been accidentally sprayed with acetone during roadwork application. Because the man had significant injury to the respiratory tract, inhalation was the suspected major route of exposure (Piatkowski et al. 2007). Mild functional renal insufficiency was diagnosed in a 56-year-old woman with a serum acetone concentration of 3,900 mg/L at hospital admission, who was suspected of having ingested a large quantity of acetone (Kostusiak et al. 2003). However, the woman had a known history of alcohol use disorder.

No indication that acetone caused renal effects in humans was found in controlled studies of volunteers. Clinical blood chemistry parameters indicative of kidney injury (e.g., blood urea nitrogen, uric acid) and urinalysis parameters were within normal limits in volunteers exposed to acetone at concentrations of 500 ppm for 2 hours (DiVincenzo et al. 1973) or ≤1,250 ppm intermittently for up to 7.5 hours/day, several days per week over the course of 6 weeks (Stewart et al. 1975).

The only indication that inhalation exposure to acetone causes renal effects in animals was a finding of congestion or distention of renal tubules or glomeruli in guinea pigs that died after exposure to high concentrations of acetone (1, 2, or 5% in air) for acute durations ranging from 3 to 48 hours (Specht et al. 1939). Rats exposed intermittently to 19,000 ppm of acetone via inhalation (n=36) for <8 weeks had significantly decreased kidney weights ($p<0.01$) after 4 weeks of exposure compared with controls, but not after 2 or 8 weeks of exposure, or at 2 weeks postexposure (Bruckner and Peterson 1981b). Blood urea nitrogen levels were not affected by acetone exposure, and no evidence of histological changes in the kidneys were found. In the absence of other evidence of renal toxicity, the sporadically reduced kidney weight cannot be considered an adverse effect.

Acetone can also induce enzymes in microsomes prepared from kidneys. In hamsters given drinking water containing 8% acetone for 7 days (Ueng et al. 1991), or 3% acetone for 10 days (Menicagli et al. 1990), the microsomes prepared from kidneys had increased levels of CYP and cytochrome b5 and/or statistically significantly increased activities of p-nitrophenol hydroxylase, aniline hydroxylase, and aminopyrine-N-demethylase. Microsomes prepared from kidneys of rats treated with a single dose of acetone at 4 mL/kg body weight had increased levels of CYP2E1 and increased activity of N-nitrosodimethylamine demethylase (Hong et al. 1987).

Oral exposure of rats and mice to acetone has resulted in effects on the kidney. Degeneration of the apical microvilli of renal tubules was reported in male rats after a single oral dose of acetone in corn oil,

but not in corn oil treated controls (Brown and Hewitt 1984). The incidence of this lesion was not reported. However, in rats treated with 1,766 mg/kg/day acetone for 2 days, no significant difference was found for kidney weight, blood urea nitrogen (BUN) levels, or organic ion accumulation compared with controls (Valentovic et al. 1992). In 14-day drinking water studies, mice had dose-related increased kidney weights at >6,348 mg/kg/day (Dietz et al. 1991; NTP 1991). In rats treated for 16 days, increased kidney weight occurred at the same or lower doses as in the 13-week study (see below), but more definitive information regarding the doses was not provided. Histological examination of the kidneys revealed no treatment-related lesions in rats or mice.

In the 13-week drinking water study, significantly ($p<0.01$) increased kidney weights were seen in female rats at 1,600 and 3,100 mg/kg/day and in male rats only at 3,400 mg/kg/day (Dietz et al. 1991; NTP 1991). Male rats were given doses of 200, 400, 900, 1,700, and 3,400 mg/kg/day and female rats given doses of 300, 600, 1,200, 1,600, and 3,100 mg/kg/day. Conversely, compared to controls, male rats given acetone in the drinking water at doses of ≥1,700 mg/kg/day had increased incidence and severity of nephropathy that was not accompanied by hyaline droplet accumulation, whereas females given doses of ≥1,700 mg/kg/day did not (Dietz et al. 1991; NTP 1991). Male and female rats were approximately 6–7 weeks old when the study started. In the 13-week gavage study, kidney weights were significantly ($p<0.05$ or $p<0.01$) increased in female rats at >500 mg/kg/day and in male rats at 2,500 mg/kg/day (American Biogenics Corp. 1986). In addition, renal proximal tubule degeneration and intracytoplasmic droplets of granules (hyaline droplets) in the proximal tubular epithelium were seen in both control and treated rats at similar incidence, but the severity of these lesions showed a dose-related increase in males at >500 mg/kg/day and in females at 2,500 mg/kg/day. The renal lesions seen in both the gavage study and the drinking water study may represent an enhancement by acetone of the nephropathy commonly seen in aging rats (American Biogenics Corp. 1986; NTP 1991). In addition, male rats possess a protein, alpha 2u-globulin, which humans do not have. The presence of this protein in male rat kidneys can initiate a sequence of events that can result in accumulation of hyaline droplets which can in turn result in nephropathy. No renal effects were observed in mice given acetone in the drinking water for 13 weeks (Dietz et al. 1991; NTP 1991). Thus, sex differences exist in susceptibility to acetone-induced renal effects, with kidney weight increases occurring in female rats at lower doses than in male rats, but histopathological lesions occurring in male rats at lower doses than in females.

One study of dermal exposure to acetone in animals was located. Amyloidosis was observed in the kidneys of mice with lumbo-sacral regions that were painted twice weekly with an unspecified quantity of

acetone for 12 months (Barr-Nea and Wolman 1977). Amyloidosis occurred in approximately 50% of mice (12 of 23), but the exact proportion occurring in the kidney was not specified.

2.11 DERMAL

No studies were located regarding dermal effects in humans after oral or inhalation exposure to acetone. Liquid acetone has caused dermal effects in humans exposed by direct skin contact. A laboratory technician being treated with squaric acid dibutyl ester in acetone for patchy alopecia areata on her scalp developed acute contact dermatitis after handling acetone for 2 years (Tosti et al. 1988). Patch testing with 10% acetone in olive oil showed a strong positive reaction (see Section 2.14). Superficial burns to the skin were observed in a 49-year-old male who had been accidentally sprayed with acetone during roadwork application (Piatkowski et al. 2007). Application of 1.0 mL directly to the skin of the forearms of six or seven volunteers for 30 or 90 minutes resulted in histological and ultrastructural degenerative changes in the epidermis (Lupulescu and Birmingham 1976; Lupulescu et al. 1972, 1973) and decreased protein synthesis (Lupulescu and Birmingham 1975) compared with untreated skin. The degenerative changes included a reduction and disorganization of the horny layers, intercellular edema, and vacuolization of the stratum spinosum. Application of 1.0 mL acetone/ether (1:1) mixture to the skin of 11 Caucasian volunteers for 1 minute did not result in detectable erythema (Berardesca et al. 1992). In a study of self-reported skin problems in workers in the plastics industry, occupational exposures to acetone were associated with a nonsignificant increase in risk of unspecified skin conditions (Socie et al. 1996). However, the sample size of workers exposed to acetone was small (n=28) and co-exposure to additional potential irritants occurred.

Histological examination of skin of rats and mice after exposure to drinking water containing acetone for 13 weeks at doses <3,400 mg/kg/day (rats) and 11,298 mg/kg/day (mice) revealed no treatment-related effects (Dietz et al. 1991; NTP 1991).

Dermal effects have also been studied in animals after direct application of acetone to the skin, though evidence is mixed. Application of 0.2 mL acetone to the shaved skin of mice increased deoxyribonucleic acid (DNA) synthesis in the skin, compared to untreated shaved controls (Iversen et al. 1988). The increased DNA synthesis was considered a reaction to slight irritation. Application of 1.0 mL to the uncovered shaved skin of rabbits did not result in irritation within 24 hours (Smyth et al. 1962). No effects on microvascular leakage were observed when 20 µL acetone was unocclusively applied to the skin of rat abdomens (Futamura et al. 2009). Moderate hyperplasia of the epidermis was observed in

hairless mice treated twice weekly with 0.1 mL acetone for 18 weeks (Iversen et al. 1981). The hyperplasia persisted for 10 weeks after the end of treatment. Hyperplasia was also observed in the ears and flank of hairless mice after treatment with acetone-soaked cotton balls twice daily for 7 days (Denda et al. 1996). Rabbits exposed to a paint stripper mixture containing acetone, xylene, and methanol for 4 hours under semi-occluded conditions showed severe erythema and slight to moderate edema (Hazelton Laboratories 1994). In addition, serious dermal effects such as possible necrosis and scar tissue were observed, indicating the mixture was corrosive. Application of 0.5 mL/day for 6 months to the dorsal thorax of hairless guinea pigs resulted in only mild erythema at the site of application (Taylor et al. 1993). Amyloidosis was observed in the skin of mice whose lumbo-sacral regions were painted twice weekly with an unspecified quantity of acetone for 12 months (Barr-Nea and Wolman 1977). Amyloidosis was observed in the organs of 12 of 23 exposed mice, but the prevalence of amyloidosis specifically in the skin was not reported. In a study in which acetone-treated mice were used as negative controls for a skin painting study of organosilanes, treatment with acetone alone 3 times/week for 502 days resulted in cases of hyperplasia (1 of 40), dermatitis (2 of 40), and hyperkeratosis (1 of 40) at the site of application (De Pass et al. 1989).

2.12 OCULAR

Eye irritation is a common complaint of workers exposed to acetone vapors occupationally (Mitran et al. 1997; Raleigh and McGee 1972) and in volunteers exposed under controlled conditions (Cometto-Muniz and Cain 1995; Matsushita et al. 1969a, 1969b; Nelson et al. 1943; Ross 1973). Cometto-Muniz and Cain (1995) reported an eye irritation threshold of 100,000 ppm based on the ability of 10 volunteers to detect acetone in eyes. However, other studies indicate irritation at lower concentrations. For example, eye irritation was reported by seven of nine workers exposed to TWA acetone concentrations of approximately 1,000 ppm (Raleigh and McGee 1972). Mitran et al. (1997) found an increased prevalence of ocular irritation among workers exposed to TWA acetone concentrations of 988–2,114 mg/m^3 for a mean of 14 years (n=71) compared to matched controls (n=86) at a coin-printing factory. Ocular irritation was self-reported by 33% of exposed workers and only 2% of matched controls, although the study authors did not report tests of significance.

Several human controlled exposure studies have found that a majority of participants report eye irritation at acetone concentrations of 500 ppm or above. These studies examined exposures to participants for 3–5 minutes (n=10) (Nelson et al. 1943), 5.25 hours (n=5) (Matsushita et al. 1969a), or 6 hours for 6 days (n=6) (Matsushita et al. 1969b). In a report of the experience at the Tennessee Eastman Corporation on

acetone concentrations not associated with injury, it was noted that acetone is mildly irritating to the eyes at 2,000–3,000 ppm, with no irritation persisting after exposure ceases (Sallee and Sappington 1949). Lacrimation has also been observed in guinea pigs exposed to acetone vapors (Specht et al. 1939).

No studies were located regarding ocular effects in humans after oral exposure to acetone. Histological examination of eyes and skin of rats and mice after exposure to drinking water containing acetone for 13 weeks at doses <3,400 mg/kg/day (rats) and 11,298 mg/kg/day (mice) revealed no treatment-related effects (Dietz et al. 1991; NTP 1991). Similarly, ophthalmoscopic examination of the eyes of rats treated by gavage with acetone at doses <2,500 mg/kg/day revealed no ocular lesions (American Biogenics Corp. 1986).

Ocular effects have been observed in animals after direct instillation of acetone into the eyes and after application of acetone to the skin. In rabbits, direct instillation of acetone into the eye has resulted in reversible cornea1 burns (Bolkova and Cejkova 1983), edema of mucous membranes (Larson et al. 1956), severe eye necrosis, corneal burns (Carpenter and Smyth 1946; Smyth et al. 1962), and uveal melanocytic hyperplasia (Pe'er et al. 1992). Application of 0.5 mL acetone directly to shaved skin of 9–18-week-old male and female guinea pigs 3 times/week for 3 weeks or 5 times/week for 6 weeks resulted in cataract development (Rengstorff and Khafagy 1985; Rengstorff et al. 1972). In contrast, rabbits did not develop cataracts after application of 1.0 mL to the shaved skin intermittently for 3 weeks (Rengstorff et al. 1976). The difference in response between the guinea pigs and rabbits reflect species differences in susceptibility to the cataractogenic effects of acetone. Although the rabbits received twice as much acetone as the guinea pigs, the possibility that rabbits would have developed cataracts if an even larger quantity of acetone had been applied was not ruled out. However, no cataracts or lens opacities were found in hairless guinea pigs to which acetone (0.5 mL/day, 5 days/week) was applied to the skin for 6 months (Taylor et al. 1993). Genetic differences in susceptibility between the hairless guinea pigs (Taylor et al. 1993) and the normal guinea pigs (Rengstorff and Khafagy 1985; Rengstorff et al. 1972) was considered possible but unlikely (Taylor et al. 1993). Lacrimation was observed in guinea pigs exposed to acetone vapor in air at a concentration of 21,800 ppm for 25 minutes (Specht et al. 1939). The degree of lacrimation increased with longer exposure.

Mild irritation was observed in the eyes of rabbits that received 10 µL acetone applied directly to the cornea of the right eye (Maurer et al. 2001). The mean normalized depth of injury was <10% in the corneal and was limited to the epithelium and superficial stroma. The majority of the regions showed no

stromal injury. The injury was first seen after 3 hours, and it persisted for up to 3 days, with complete recovery at the 35-day determination.

2.13 ENDOCRINE

No studies were located regarding endocrine effects in humans or animals after exposure to acetone.

2.14 IMMUNOLOGICAL

Evidence on the immunological effects in humans after inhalation exposure to acetone is mixed. Statistically significant increased white blood cell counts, increased eosinophil counts, and decreased phagocytic activity of neutrophils were found in male volunteers exposed to 500 ppm for a single 6-hour exposure or intermittently for 6 days (Matsushita et al. 1969a, 1969b). The NOAEL value of 250 ppm and LOAEL value of 500 ppm are recorded and plotted in Figure 2-2. No significant difference in these parameters was seen in the volunteers exposed to 250 ppm compared with controls. In a study of occupational exposure, no significant differences in total white blood cell count, differential white blood cell count, or neutrophil phagocytic activity were found between workers exposed to acetone concentrations in air ranging from 20–1,018 ppm and controls (Satoh et al. 1996). Hematological parameters, including total white cell counts and differential white cell counts, were within normal limits in other volunteers exposed to 500 ppm for 2 hours (DiVincenzo et al. 1973), or <1,250 ppm acetone intermittently for durations in a study with a complex protocol (Stewart et al. 1975); however, these investigators did not examine the phagocytic activity of neutrophils.

No studies were located regarding immunological effects in animals after inhalation exposure to acetone. Effects on the spleen are discussed in Section 2.18 (Other Noncancer Effects).

No studies were located regarding immunological effects in humans after oral exposure to acetone. Exposure of CD-1 male mice to acetone in the drinking water at average doses as high as 1,144 mg/kg/day for 28 days resulted in no evidence of immunotoxicity, as assessed by the antibody plaque-forming cell assay performed to measure the T cell-dependent anti-sheep red blood cell immunoglobulin M response (Woolhiser et al. 2006). Furthermore, there were no treatment-related effects on thymus weights. See Section 2.18 for discussion of effects on the spleen.

The only information regarding immunological effects in humans after dermal exposure to acetone is a case report in which a laboratory technician who was treating patchy alopecia areata on her scalp with squaric acid dibutyl in acetone developed acute contact dermatitis after handling the acetone-based product for 2 years (Tosti et al. 1988). Patch testing with 10% acetone in olive oil showed a strong positive reaction. This acetone sensitization is considered a rare complication of sensitizing therapies for alopecia areata.

There is some evidence that dermal exposure to acetone in animals may be associated with immunological effects. Female mic e(5–6 weeks old) were administered acetone on dorsal or flank skin over four treatments with concentrations ranging from 50 to 300 µL (Singh et al. 1996). One hour after the last treatment, mice were immunized. Compared to controls, mice treated with acetone had delayed and shortened IgM secretion in response to immunization, indicating that acetone can modulate humoral immunity. Repeated application of acetone to skin of hairless mice increased cytokine production in the epidermis and dermis, as indicated by tumor necrosis factor (TNF) and interleukin (IL)-1α staining (Denda et al. 1996). Effects on the spleen are discussed in Section 2.18 (Other Noncancer Effects).

2.15 NEUROLOGICAL

Case reports have described patients who became comatose or collapsed after hip casts were applied with acetone present in the setting fluid (Chatterton and Elliott 1946; Fitzpatrick and Claire 1947; Harris and Jackson 1952; Renshaw and Mitchell 1956; Strong 1944). In addition, a woman experienced headache, dizziness, weakness, difficulty speaking, and depression after a cast containing acetone had been applied (Pomerantz 1950). These patients had a strong odor of acetone in their breath, and acetone was detected in the urine and blood. These patients were exposed to acetone by inhalation during cast application and from evaporation from the casts after the applications. In addition, dermal exposure could not be ruled out. In another case of neurological effects (drowsiness, fretfulness, irritability, restlessness, uncoordinated hand movement, nystagmus) developing after application of a cast, exposure was considered to be mainly dermal because an airblower was used continuously during the application to dissipate the fumes (Hift and Patel 1961). However, because the patient had kept his head under a blanket, some inhalation of acetone evaporating from the cast may have occurred.

Workers exposed to acetone in the past commonly experienced neurological effects. In an on-site medical appraisal of nine workers, in which the TWA exposure concentration was 1,006 ppm, three of the workers mentioned headache and lightheadedness as subjective symptoms (Raleigh and McGee 1972). In

another on-site medical appraisal of four workers, in which the TWA exposure concentration was 901 ppm, none of the workers complained of neurological effects (Raleigh and McGee 1972). The medical examinations included the Romberg test, finger-to-nose test, and observations for nystagmus (involuntary rapid repetitive movement of the eyes). These tests revealed no neurobehavioral effects in either study. Symptoms such as unconsciousness, dizziness, unsteadiness, confusion, and headache were experienced by seven workers exposed to >12,000 ppm acetone while cleaning out a pit containing acetone that had escaped from nearby tanks (Ross 1973). The degree of the symptoms varied depending on the length of time that the workers had spent in the pit (2 minutes to 4 hours). Mitran et al. (1997) reported increased signs of neurotoxicity (mood disorders, irritability, memory difficulty, sleep disturbances, and headache) among acetone-exposed workers (n=71) compared to matched controls (n=86) at a coin-printing factory. In addition, acetone-exposed workers showed significant decreases in measures of attention and delays in tests of nerve conduction velocity and visual reaction time relative to controls. Eight-hour acetone exposure levels in the workplace air of the exposed workers ranged from 988 to 2,114 mg/m^3 (416–890 ppm); the mean length of exposure was 14 years. Kiesswetter et al. (1994) reported a correlation of acetone urine concentrations with symptoms of annoyance, tension, tiredness, and discomfort in a group of eight acetone-exposed workers compared to eight unexposed controls. A correlation of these symptoms was not found with exposure concentrations (1,138 ppm in the first half of the work shift, 717 ppm in the second half of the work shift). Eight workers exposed to approximately 1,000 ppm of acetone self-reported significant increases in tension, tiredness, annoyance, and complaints relative to matched controls (Kiesswetter and Seeber 1995). However, exposed workers did not show significant differences in performance on simple reaction time or vigilance tests. Length of exposure of the workers was not reported. Satoh et al. (1996) reported symptoms of heavy, vague, or faint feelings in the head, along with impaired neurobehavioral responses, in a group of 110 male workers at an acetate fiber manufacturing plant where acetone was used in the production of cellulose-containing dope. Controls consisted of 67 unexposed workers at the same facility. Acetone levels at the end of the work shift measured 5–1,212 ppm in the breathing zone (mean of 361.4 ppm). In a case study of occupational exposure, a neurological examination of a woman who had been using a cleaner consisting of 70% acetone for approximately two years revealed symptoms of flaccid quadriplegia and loss of tendon reflexes (Chen et al. 2002).

Neurological and behavioral effects have also been documented in volunteers tested under controlled laboratory conditions. The relationship between concentration and duration of exposure on the development of narcosis was demonstrated in volunteers exposed to acetone at 21,049–84,194 ppm for 1–8 hours (Haggard et al. 1944). As the concentration increased, the time to observations of signs of

narcosis (not otherwise described), loss of righting reflex, and loss of corneal reflex decreased. It should be noted that these concentrations of acetone are extremely high, and exposure to lower concentrations of acetone for shorter durations has resulted in unconsciousness in some workers, as discussed above. Additional neurological effects included general lack of energy and weakness, headache, and delayed visual reaction time (Matsushita et al. 1969a, 1969b); subjective symptoms of tension, tiredness, complaints (not otherwise specified), and annoyance (Seeber and Kiesswetter 1991; Seeber et al. 1992); increases in response and the percent false negatives in auditory discrimination tests and increases in anger and hostility (Dick et al. 1989); and increased visual evoked response (Stewart et al. 1975). Other neurological and neurobehavioral tests (e.g., electroencephalography, choice reaction time, visual vigilance, dual task, memory scanning, postural sway, Romberg test, or heel-to-toe test) were also conducted on these volunteers, but acetone exposure had no effect on these parameters. A study of exposure to a mixture of 250 ppm acetone and 25 ppm toluene for 4.5 hours in 12 healthy males similarly found no significant effects on tests of reaction time or vigilance, although the study authors noted that nonsignificant changes in the electroencephalograph results may be indicative of subclinical neurological effects (Muttray et al. 2005).

Narcotic effects have been observed in animals exposed acutely to acetone vapors. The narcotic effects observed in animals after inhalation exposure to acetone depend upon the duration and the magnitude of exposure. The narcotic effects appear to proceed through several stages (i.e., drowsiness, incoordination, loss of autonomic reflexes, unconsciousness, respiratory failure, and death) as concentrations and durations increase. The acute data suggest that concentrations >8,000 ppm generally are required to elicit overt signs of narcosis, although neurobehavioral effects, when assessed by specific behavioral tests, have been observed at lower concentrations. The relationship between concentration and duration of exposure on the development of narcosis was demonstrated in rats exposed to acetone at 2,105–126,291 ppm for 5 minutes to 8 hours (Haggard et al. 1944). While exposure to 2,105 or 4,210 ppm for 8 hours resulted in no signs of narcosis or effects on righting reflex or cornea1 reflex, these effects were observed at higher concentrations. At increasing concentrations >10,524 ppm, the time to observations of signs of narcosis, loss of righting reflex, and loss of cornea1 reflex decreased. The responses correlated with blood acetone levels. Similar concentration- and duration-response relationships were found in mice exposed to 16,839–84,194 ppm acetone for up to 4 hours (Mashbitz et al. 1936). Neurological responses included drowsiness, staggering, prostration, clonic movements of hind legs, and deep narcosis. Narcosis, evidenced by decreased respiratory and heart rates, paralysis, and coma were observed in guinea pigs exposed to 21,800 ppm continuously for periods ranging from 25 minutes to 24 hours (Specht et al. 1939). The degree of narcosis increased as the exposure duration increased. In a developmental study,

virgin and pregnant mice experienced severe narcosis after a single 6-hour exposure to 11,000 ppm on the first day, but narcosis was no longer observed when the exposure was lowered to 6,600 ppm 6 hours/day for the rest of the study (NTP 1988).

Neurobehavioral effects, indicative of narcosis, have been observed in rats, mice, and baboons acutely exposed to acetone vapors. Baboons exposed to acetone in air at 500 ppm continuously for 7 days showed increases in the amount of time before response on a delayed match-to-sample discrimination task (Geller et al. 1979a). In another study by the same research group, rats (n=3) were exposed via inhalation to 150 ppm acetone for durations of 0.5, 2, 1, or 4 hours to investigate effects on a multiple fixed ratio-fixed interval schedule of food reinforcement (Geller et al. 1979b). The 1-hour duration tests increased response rates, but exposures to acetone of ≥2 hours caused a decrease in response rates; the study authors noted that this pattern is similar to that observed following exposure to known depressants. In another study of schedule-controlled responses to food, Glowa and Dews (1987) found that 30-minute exposures to acetone in 12 mice did not result in significant changes in responses at concentrations of 1,000 ppm or lower, but exposures to 3,000 to 10,000 ppm were associated with slight decreases in responses, 30,000 ppm with no responses in most mice, and 56,000 ppm with no responses in all mice. The study authors estimated that a concentration of 10,694 ppm would be associated with a 50% decrease in responses. Goldberg et al. (1964) examined inhibition of avoidance behavior and escape response in mice (8–10 per dose group) exposed to acetone in air at concentrations of 3,000, 6,000, 12,000, or 16,000 ppm for 4 hours/day, 5 days/week for a total of 10 days. Mice exposed to concentrations of ≥6,000 ppm displayed significantly increased inhibition of avoidance behavior and escape response. Ataxia was observed during the first day of exposure to 12,000 or 16,000 ppm, but these effects were not observed on subsequent days, indicating that some tolerance to acetone developed.

Decreased duration of immobility was observed in a behavioral despair swimming test in male mice (six per dose group) exposed to concentrations of acetone ranging from 2,032 to 3,021 ppm for 4 hours (De Ceaurriz et al. 1984). In a series of studies, Frantík and colleagues observed associations between acetone exposure and inhibition of electrically-evoked seizures (Frantík et al. 1994, 1996; Vodičková et al. 1995). The estimated concentration of acetone associated with a 30% decrease in seizure response after a 4-hour inhalation exposure in male rats was 3,500 ppm and after a 2-hour inhalation exposure in female mice was 5,000 ppm (Frantík et al. 1994). A 4-hour exposure to acetone in rats at 1,680 or 4,210 ppm was associated with a 10 and 50% inhibition of seizure response, respectively (Frantík et al. 1996).

Similar neurological effects have been observed following intermediate-duration exposures in animals. In rats exposed to 19,000 ppm acetone via inhalation for 3 hours/day, 5 days/week over 8 weeks, CNS depression was observed, as measured by five tests of unconditioned performance and reflex (Bruckner and Peterson 1981a). Acetone exposure also resulted in a statistically significant decrease ($p<0.02$) in absolute brain weight, but no exposure-related histological lesions (Bruckner and Peterson 1981b). Exposure of male rats (10 per dose group) to acetone vapor concentrations of 1,000, 2,000 or 4,000 ppm for 6 hours/day, 5 days/week for 13 weeks did not cause effects on schedule-controlled operant performance at 2 weeks post-exposure as compared to unexposed controls. Operant sessions were run prior to daily exposures to avoid confounding with transient acute effects (Christoph et al. 2003). In a study of conditioned place preference, mice exposed to acetone ranging from 5,000–20,000 ppm showed decreases in locomotor activity but did not display a preference for chambers associated with acetone exposure (Lee et al. 2008). Female mice were exposed by inhalation to acetone (4 mL placed on cotton in a glass in the inhalation chamber) for 5 hours/day, 5 days/week for 4 weeks and assessed for effects on the nasal olfactory neuroepithelium; a 4-week recovery period followed the exposure period (Buron et al. 2009). The acetone concentration during each exposure rose during the first 1.5 hours to a constant level of about 8,000 ppm for the remaining 3.5 hours. Olfactory sensitivity, assessed by how the mice avoided acetone in a maze, was increased (less time spent in the acetone compartment of maze) during weeks 2 and 4 of exposure and during weeks 6 and 8 (post-exposure). Histological examination of the olfactory neuroepithelium of similarly exposed mice revealed a significant decrease in the number of cells at week 2, an increase at week 4 that remained at week 6, and a recovery by week 8. During the exposure period, thickness of the olfactory epithelium remained stable at week 0 and week 2, and decreased at week 4. During the post-exposure period, thickness of the olfactory epithelium increased at week 6, and recovered by week 8. Immunohistological evaluations for olfactory marker protein (OMP) and proliferating cell nuclear antigen (PCNA) showed no change in OMP, indicating no damage to olfactory neuroreceptors. However, the number of PCNA-positive cells was decreased in the basal layer during week 2 and returned to baseline levels by the end of the experiment, indicating an increase in mitotic activity. Results of this study suggest that acetone exposure impacts nasal function and causes selective cell damage.

The narcotic effects of acetone occur after oral exposure as well as inhalation exposure. Several case reports describe patients in minimally responsive, lethargic, or comatose conditions after ingesting acetone. A man who intentionally ingested about 200 mL of pure acetone (about 2,241 mg/kg) subsequently became deeply comatose, but responded to treatment with intravenous saline, glucose, and sodium lactate (Gitelson et al. 1966). Six days later, he was ambulatory, but a marked disturbance of gait was observed. This condition had improved upon follow-up examination 2 months later. In a case study

of intentional acetone poisoning through a feeding tube, Herman et al. (1997) reported narcotic symptoms and tonic-clonic activity in a 30-month-old child. Additional case reports identified are confounded by coexposure to other possible narcotic agents; however, the lethargic and comatose condition of the patients in these case reports were attributed to acetone poisoning. For example, a 30-month-old male child ingested most of a 6-ounce (178 mL) bottle of nail polish remover containing 65% acetone and 10% isopropyl alcohol and was deemed unresponsive with Glasgow Coma Score of 3 (Gamis and Wasserman 1988). His blood acetone level was 4.45 mg/mL. Three women with documented histories of alcohol use disorder intentionally ingested acetone and experienced narcotic effects, with blood acetone levels ranging from >0.3 to 2.5 mg/mL (Kallenberg et al. 2008; Ramu et al. 1978; Slutzman et al. 2015). Acetone poisoning was additionally associated with vasogenic brain edema in one of these women, which was revealed by magnetic resonance imaging conducted upon hospital admission (Kallenberg et al. 2008). Her clinical symptoms improved within days, and a 1-year follow-up exam showed normal neurological status and magnetic resonance images. One case study described a man who became comatose after intentionally ingesting 720 mL of sake (alcoholic beverage) followed by an unknown quantity of liquid cement containing a mixture of polyvinyl chloride, acetone, 2-butanone, and cyclohexanone; however, the coma was attributed primarily to cyclohexanol, the metabolite of cyclohexanone in the liquid cement (Sakata et al. 1989).

In acute experiments with animals in which high oral doses of acetone resulted in death, severe neurological signs of toxicity preceded death. In a study to determine the LD_{50} value for acetone in rats (5,800 mg/kg), a state of prostration, usually without convulsions, preceded death (Freeman and Hayes 1985). In a study to determine which doses to use in a developmental study, oral dosing of pregnant mice with acetone during gestation resulted in languid behavior with subsequent death in one of four mice at 2,400 mg/kg/day and at 4,800 mg/kg/day (EHRT 1987). At 7,908 mg/kg/day, all exposed mice died, and they displayed a hunched appearance and became prostrate before death. No controls were used in this range-finding study. Rabbits dosed orally with 3,922, 5,491, or 7,844 acetone displayed signs of narcosis, the degree and the time to onset being dependent on dose (Walton et al. 1928). Signs of narcosis included weakness, depression, and unconsciousness. Doses of 7,500 and 8,000 mg/kg were administered to immature dogs (one per dose) and resulted in incoordination, staggering, falling, tremors, delirium, prostration, coma, and eventual death (Albertoni 1884). No controls were used in this experiment. The NOAEL in dogs was identified as 1000 mg/kg/day, and higher doses resulted in neurological symptoms. In a study of oral exposure to a dose of 2,438 mg/kg acetone in rats (approximately one-quarter of the estimated LD_{50}), examination of brains after sacrifice found significant increases in the presence of a

dopamine metabolite in the hypothalamus, indicating that acetone exposure may alter dopamine metabolism (Kanada et al. 1994).

Neurological effects have also been observed following intermediate oral exposures to acetone. A significant ($p<0.05$) reduction in nerve conduction velocity, but no effect on balance time in the rotorod test, was observed in rats treated for 6 weeks with acetone in drinking water at a dose of 650 mg/kg/day. However, no reduction in nerve conduction velocity was found when tested at 3, 4, or 5 weeks of dosing (Ladefoged et al. 1989). No histopathological lesions were found in tissues sampled from the cervico-medullary junction of the spinal cord; posterior tibial nerve proximal to the calf muscle branches; cerebellar vermis; thoracic, lumbar, and sacral spinal cord; L5 and L6 dorsal and ventral roots and spinal ganglia; and three levels of the sciatic nerve and the plantar nerves in the hindfeet of rats administered 732 mg/kg/day acetone in the drinking water for 12 weeks (Spencer et al. 1978). In another intermediate duration study, rats given 2,500 mg/kg/day acetone by gavage salivated excessively beginning on the 27th day of treatment (American Biogenics Corp. 1986). At the terminal sacrifice after 13 weeks of treatment, absolute brain weight was decreased in the male rats, but histological examination of the brain revealed no lesions. No clinical or histological evidence of neurotoxicity was observed in the rats or mice treated with higher doses for 13 weeks in the drinking water study (Dietz et al. 1991; NTP 1991). The fact that clinical signs of neurotoxicity were seen in the rats treated by gavage (American Biogenics Corp. 1986), but not in the rats or mice given higher doses in drinking water (NTP 1991), may reflect the intermittent nature of ad libitum dosing via drinking water, compared with the bolus nature of a gavage dose.

No studies were located regarding neurological effects in animals after dermal exposure to acetone.

Two animal studies were located regarding the neurological effects of intraperitoneal exposures to acetone. In a study of male mice, the estimated dose required to produce anesthesia in 50% of animals tested was 59.6 mmol/kg (Tanii 1996). No significant effects on social behaviors were observed in mice injected with acetone at a dose of 16 mM/kg for 3 days (Kasprowska-Liśkiewicz et al. 2017).

2.16 REPRODUCTIVE

Information regarding reproductive effects in humans after inhalation exposure to acetone is limited. Shortened menstrual cycles were reported by three of four women exposed to 1,000 ppm acetone for 7.5 hours in a laboratory study of volunteers (Stewart et al. 1975). In these women, menstrual periods

were 1 week or more early, and occurred after 4 days of exposure. This finding has not been corroborated in other studies. Women workers in a Russian factory where workroom levels of acetone ranged from 14 to 126 ppm were reported to have statistically significantly increased incidences of pregnancy complications, including miscarriage, toxicosis (not otherwise described), decreased hemoglobin levels and hypotension, and "weakness of labor activity," compared with controls (Nizyaeva 1982). However, the number of women studied, further consideration of confounding factors (such as age, history of smoking tobacco, use of alcohol), description of workroom monitoring methods, and statistical methods were not reported. Therefore, no conclusions can be made from this report.

In an epidemiological study of pregnancy outcomes in 556 female laboratory workers, no statistically significant difference in the incidence of miscarriage was found between those exposed to a variety of solvents including acetone and those not exposed to solvents (Axelsson et al. 1984). Exposure levels were not quantified in this study. Additional epidemiological studies on occupational exposure to solvents found an elevated risk of miscarriage in women exposed to solvents, but were unable to specifically attribute these findings to acetone (Agnesi et al. 1997; Beaumont et al. 1995; Swan et al. 1995). Beaumont et al. (1995) examined female employees of a semiconductor factory and found a higher risk of spontaneous abortion in women directly involved in fabrication. However, exposures to acetone and other solvents were not quantified. In a follow up study to Beaumont et al. (1995), job categories were used to estimate exposure rankings for specific chemicals from none to high (0–3), but no environmental monitoring was conducted. There was an elevated relative risk (RR) of miscarriage for women occupationally exposed to acetone (RR 1.86, 95% CI 1.26–2.64), but this association was not significant after the model was adjusted for exposure to other solvents and fluoride (RR 1.06, 95% CI 0.50–2.10) (Swan et al. 1995). Agnesi et al. (1997) found that women characterized as having high occupational exposure to a mixture of solvents during pregnancy had an increased risk of miscarriage (RR 3.85, 95% CI 1.24–11.9), but acetone levels in this study were approximately 30 ppm, well below the TLV and below the levels of other solvents to which the women had been exposed. An epidemiological study examining the effects of occupational exposure in female laboratory personnel in Sweden demonstrated significantly decreased fertility rates in women who reported working with acetone (0.72, 95% CI 0.53–0.97). However, exposures in this study were self-reported via questionnaire, and therefore, despite the authors' assurance that any bias in reporting was nondifferential, the association between acetone exposure and fertility rate may not be accurate.

One epidemiological study of 25 male workers at a reinforced plastic production plant found evidence of increased sperm mortality and immotility as compared to 46 age-matched controls recruited from a

fertility clinic. Breathing zone measurements of acetone in the production plant ranged from 164 to 224 mg/m^3 (69–94 ppm) and styrene ranged from 294 to 552 mg/m^3 (69–130 ppm). Male production plant workers had significantly increased percentages of abnormal sperm (53 versus 40%, $p<0.021$), and defects in sperm morphology occurred primarily in sperm heads. However, the male workers had greater percentages of live sperm (80 versus 60%, $p<0.000$) and lower percentages of immotile sperm (30 versus 40%, $p<0.001$) than controls (Jelnes et al. 1988). This study has several limitations. It is difficult to parse out the effects of acetone exposure because workers were co-exposed to high concentrations of styrene. In addition, the control group was recruited from a fertility clinic and thus may not be representative of the general population.

Only one study was located on the reproductive effects of inhalation exposures to acetone in animals. No reproductive effects, as measured by number of implants, percent live pups, and mean percent resorptions per litter, were observed in rats exposed to up to 11,000 ppm acetone or mice exposed to up to 6,600 ppm (NTP 1988).

No studies were located regarding reproductive effects in humans after oral exposure to acetone. Reproductive effects were assessed in pregnant mice exposed by gavage to 3,500 mg/kg acetone once per day during GDs 6 to 15 (EHRT 1987). The reproductive index was significantly reduced ($p=0.05$) (number of females producing viable litters/number of surviving females that were ever pregnant; 24/31 treated compared with 34/36 controls). In addition, acetone treatment significantly ($p<0.01$) increased the duration of gestation from 18.1 days in controls to 18.5 days in treated mice.

No effects were observed on the fertility of male Wistar rats treated with drinking water containing acetone at 1,071 mg/kg/day for 6 weeks (Larsen et al. 1991). The indices of fertility examined were successful matings with untreated females, number of pregnancies, number of fetuses, testicular weight, seminiferous tubule diameter, and testicular lesions. However, male Sprague-Dawley rats treated with 3,400 mg/kg/day acetone in drinking water for 13 weeks had significantly increased ($p<0.01$) relative testes weight, which may have been attributable to the observed reduction in body weight, and significantly ($p<0.05$) decreased sperm motility, caudal weight, and epididymal weight, as well as increased incidences of abnormal sperm (Dietz et al. 1991; NTP 1991). No testicular lesions were observed upon histological examination. Vaginal cytology examinations of the female rats revealed no effects. No effects on sperm morphology and vaginal cytology were observed in mice similarly treated with drinking water containing acetone for 13 weeks at doses <4,858 mg/kg/day in males and <11,298 mg/kg/day in females.

The highest NOAEL values and all LOAEL values in each species and duration category from all reliable studies are recorded and plotted in Figure 2-2.

No studies were located regarding reproductive effects in humans after dermal exposure to acetone.

2.17 DEVELOPMENTAL

Information regarding developmental effects in humans after inhalation exposure to acetone is limited. Statistically significant increased incidences of developmental effects, such as intrauterine asphyxia of fetuses and decreased weight and length of neonates, were reported for women workers in a Russian factory, where workroom levels of acetone ranged from 14 to 126 ppm (Nizyaeva 1982). However, the number of women studied, further description of the exposed and control groups (such as age, history of smoking tobacco, use of alcohol), description of workroom monitoring methods, and statistical methods were not reported. Therefore, no conclusions can be made from this report. In an epidemiological study of pregnancy outcomes among 556 female laboratory workers, no statistically significant differences in the incidences of miscarriage, perinatal death rate, or malformations were found between those exposed to a variety of solvents, including acetone, and those not exposed to solvents (Axelsson et al. 1984). Exposure levels were not quantified in this study.

In a developmental study in rats exposed intermittently to acetone during gestation, the only effect was a slight, but significant ($p<0.05$), decreased mean male and female fetal body weight at 11,000 ppm (NTP 1988). It should be noted that the dams exposed at this level had significantly ($p<0.05$) reduced body weight during gestation, reduced uterine weight, and reduced extragestational weight on GD 20. No effects were seen on sex ratio, incidence of fetal variations, reduced ossification sites, or mean fetal variations. The percentage of litters with at least one fetal malformation was higher in the 11,000 ppm group than in the control group, but no statistically significant increased incidences of fetal malformations were observed. In mice similarly exposed during gestation, however, there was a slight, but significant ($p<0.05$) increase in percent late resorptions, decrease in mean male and female fetal weights, and increase in the incidence of reduced sternebral ossification in the 6,600 ppm group. The only evidence of maternal toxicity at this exposure level was statistically significant increased absolute and relative liver weight. No effects were found on the number of implantations per litter, percent live fetuses/litter, sex ratio, incidence of malformations or skeletal variations combined. The NOAEL values and LOAEL

values for developmental effects in rats and mice after inhalation exposure are recorded in Table 2-2 and plotted in Figure 2-2.

No studies were located regarding developmental effects in humans after oral exposure to acetone. In a reproduction study, treatment of pregnant mice during GDs 6–10 with 3,500 mg/kg/day acetone significantly ($p<0.01$) reduced postnatal pup survival (EHRT 1987). The average weight of each live pup/litter was significantly reduced ($p=0.01$) on postpartum day 0, but pups from the acetone treated groups gained significantly ($p<0.01$) more weight than controls from postpartum day 0 to 3. As this study was not designed as a teratology study, fetuses or pups were not examined for internal malformations or skeletal anomalies.

The LOAEL value of 3,500 mg/kg/day for developmental effects in mice is recorded in Table 2-3 and plotted in Figure 2-3.

No studies were located regarding developmental effects in humans or animals after dermal exposure to acetone.

2.18 OTHER NONCANCER

One case-control study found an association between occupational exposure to acetone-containing organic solvent mixtures and hearing loss (Unlu et al. 2014). In a case-control study of 469 workers from a bus and truck plant, workers were divided into three exposure groups: (1) noise only, (2) noise and mixture solvents at a permissible level, and (3) mixture solvents at a permissible level only. A control group contained 119 individuals randomly selected who were not exposed to noise or solvents (Unlu et al. 2014). Compared to controls, workers combined across all groups had significant hearing impairment at the lowest frequency examined (250 Hz) and the highest three frequencies examined (4,000, 6,000, and 8,000 Hz). The investigators of this study also found that combined exposure to mixed solvents and noise can exacerbate hearing loss at high frequencies.

In a study involving 27 workers (23 females, 14 smokers) in a cellulose fiber production plant, in which acetone was the primary solvent used, occupational exposure to acetone was found to significantly reduce perceived odor intensity of acetone in a 20-minute exposure to 800 ppm, relative to the perception of 32 individually age- and sex-matched control subjects with no prior history of exposure to acetone (Dalton et al. 1997).

Mitran et al. (1997) examined neurotoxicity associated with occupational exposure to acetone and other chemicals and found increased rheumatic syndromes among 71 workers exposed to acetone at TWA concentrations ranging from 988 to 2,114 mg/m^3, compared to 86 controls. Specifically, the ratios of exposed/controls were as follows: bone pain 21/5%; joint pain 21/4%; vertebral column pain 15/8%; and muscular pain 13/2%. The study authors did not report significance, and only reported frequencies and percentages.

Oral exposure to acetone in both humans and animals can result in diabetes-like symptoms (e.g., hyperglycemia and glycosuria) (Barnett et al. 1993; Gitelson et al. 1966). For example, a man who intentionally drank about 200 mL (about 2,241 mg/kg) of pure acetone had been treated at a hospital for acetone poisoning, but 4 weeks after the ingestion, he noticed excessive thirst and polyuria, and 2.5 months after ingestion, he was hyperglycemic (Gitelson et al. 1966). In a controlled animal experiment, five male Wistar albino rats were exposed daily for 3 days by gavage to 15 mmol/kg acetone (Barnett et al. 1993). Immunoblot analysis of hepatic microsomal proteins revealed that treatment with acetone increased the apoprotein levels of cytochromes P-450IA2 (CYP1A2), P-450B1/2 (CYPB1/2), and CYP2E1, compared to controls.

Patsner (1993) found that topical application of an acetone-soaked pack successfully treated life-threatening vaginal bleeding for two patients with recurrent gynecologic cancer. There were no immediate side effects other than pain, and no long-term adverse effects were noted.

Amyloidosis was observed in the adrenals and pancreas of mice whose lumbo-sacral regions were painted twice weekly with an unspecified quantity of acetone for 12 months (Barr-Nea and Wolman 1977). In addition, marked congestion and hemorrhage of the spleen were observed upon autopsy of guinea pigs that died after exposure to various high concentrations of acetone (1, 2, or 5% in air) for acute durations ranging from 3 to 48 hours (Specht et al. 1939). However, these effects could have been corollaries of death.

2.19 CANCER

Two identified studies examined the association between cancer and acetone in humans. In a retrospective mortality study of 948 employees (697 men, 251 women) of a cellulose fiber plant where acetone was used as the only solvent, no significant excess risk of death from any cause, including

malignant neoplasm, was found when compared with rates for the U.S. general population (Ott et al. 1983a, 1983b). The workers had been employed at the plant for at least 3 months to 23 years. Industrial hygiene surveys found that median TWA acetone concentrations were 380, 770, and 1,070 ppm, based on job categories. In a case-control study, Kerr et al. (2000) examined the associations between parental occupational exposures to a variety of chemicals and risk of neuroblastoma in children up to 14 years old. The study authors found an elevated risk of neuroblastoma in the children of mothers exposed to acetone (OR 3.1; 95% CI 1.7–5.6). However, the analysis only controlled for a few confounders, such as age at diagnosis and socioeconomic status. Additionally, the study authors noted the potential for recall bias and over-reporting.

No studies were located regarding cancer in animals after inhalation or oral exposure to acetone. In skin painting studies in which acetone-treated mice were used as a negative vehicle control for organosilanes (De Pass et al. 1989) or flame retardants (Van Duuren et al. 1978), no evidence was found to suggest that acetone alone was a skin carcinogen. Acetone was also negative as a tumor initiator (Roe et al. 1972) and as a tumor promoter for 7,12-dimethylbenz[a]anthracene (Roe et al. 1972; Van Duuren et al. 1971; Weiss et al. 1986).

Acetone has not been evaluated by IARC or the HHS with regard to its carcinogenicity (IARC 2021; NTP 2021). The EPA determined that data are inadequate for an assessment of the human carcinogenic potential of acetone (EPA 2003).

2.20 GENOTOXICITY

Two studies were located regarding genotoxicity associated with occupational exposures to acetone. In a study of male footwear-industry workers in Brazil, cytogenetic assay results showed that the mean damage index for workers using solvent-based adhesives was significantly greater than workers using water-based adhesives and control groups (Heuser et al. 2005). No significant differences between groups were found in micronucleus tests of binucleated lymphocytes and exfoliated buccal cells. However, the solvent-based adhesives used by the workers consisted primarily of toluene, rather than acetone. Female footwear-industry workers in Bulgaria exposed to a mixture of solvents including acetone at concentrations of approximately 160–390 ppm did not show excess DNA damage relative to controls (Pitarque et al. 1999).

No studies were located regarding genotoxic effects in humans after oral exposure to acetone. No studies were located regarding genotoxicity in animals after inhalation, oral, or dermal exposure.

Numerous studies were conducted *in vitro*; results are summarized in Table 2-5. Mostly negative results were obtained in bacterial (De Flora 1981; De Flora et al. 1984; De Marini et al. 1991; Ishidate et al. 1984; Kawachi et al. 1980; Kubinski et al. 1981; McCann et al. 1975; Reifferscheid and Heil 1996; Rossman et al. 1991; Yamaguchi 1985; Zieger et al. 1992) and yeast (Abbandandolo et al. 1980; Albertini 1991) assays and in plant seeds (Gichner and Veleminsky 1987) with or without metabolic activation, but some results were positive in *Escherichia coli* when acetone was in the triplet state (Menck et al. 1986; Rahn et al. 1974) and in yeast for aneuploidy (Zimmermann 1983; Zimmermann et al. 1984, 1985) and for mitotic chromosome malsegregation (Albertini 1991) without metabolic activation. Mostly negative results were obtained in assays for cell transformation, chromosomal aberrations, sister chromatid exchange, colony formation inhibition, and gene mutation in cultured animal cells (Amacher et al. 1980; Chen et al. 1984; DiPaolo et al. 1969; Freeman et al. 1973; Kawachi et al. 1980; Mishra et al. 1978; Pienta 1980; Rhim et al. 1974; Tates and Kriek 1981), and for sister chromatid exchange and unscheduled DNA synthesis in cultured human fibroblasts and skin epithelial cells (Abe and Sasaki 1982; Kawachi et al. 1980; Lake et al. 1978). Acetone did not increase the number of micronuclei in binucleated human lymphocytes *in vitro* (Zarani et al. 1999). However, some positive results were obtained for chromosomal aberrations in Chinese hamster fibroblasts (Ishidate et al. 1984) and hamster lung fibroblasts (Kawachi et al. 1980), inhibition of metabolic cooperation in Chinese hamster cells (Chen et al. 1984), chromosome malsegregation in porcine brain tubulin (Albertini et al. 1988), and DNA fragmentation of human epithelial cells (Costa et al. 2006). In one study, acetone produced a false positive result in a biotransformation assay of BALB/c-3T3 cells; the study authors concluded that the result was a false positive because significant transforming activity only occurred at treatment doses above the upper dose limit of the assay (Matthews et al. 1993). Acetone did not promote the transforming activity initiated by nine known genotoxic and carcinogenic chemicals, including N-methyl-N'-nitro-N-nitrosoguanidine, benzo[a]pyrene, 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole, 3-amino-1-methyl-5H-pyrido[4,3-b]indole, butylated hydroxyanisole, butylated hydroxytoluene, sodium nitrite, sodium saccharin, and 3-methylcholanthrene (Sakai and Sato 1989). The mostly negative results in bacteria and cultured animal cells and the negative results in human fibroblasts and skin epithelial cells indicate that acetone poses little threat for genotoxicity in humans. However, peripheral lymphocytes, fibroblasts, and skin epithelial cells from workers exposed to acetone could be examined for chromosomal aberrations to confirm this hypothesis.

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

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
Prokaryotic organisms				
Salmonella typhimurium (TA100, TA98)	Reverse mutation	–	–	Yamaguchi 1985
S. typhimurium (TA92, TA94, TA98, TA100, TA1535, TA1537)	Reverse mutation	–	ND	Ishidate et al. 1984
S. typhimurium (TA98, TA100, TA1535, TA1537)	Reverse mutation	–	ND	McCann et al. 1975
S. typhimurium (TA100, TA98)	Reverse mutation	–	–	Kawachi et al. 1980
S. typhimurium (TA98, TA100, TA1535, TA1537)	Reverse mutation	–	–	Zeiger et al. 1992
Escherichia coli ($WP_S(\lambda)$)	Prophage λ induction	–	–	DeMarini et al. 1991; Rossman et al. 1991
E. coli (λ phage)	DNA damage	+[a]	ND	Menck et al. 1986
E. coli CR63 colitis bacteriophage	Transfection (induction of phase)	–	–	Vasavada and Padayatty 1981
E. coli B(3)T	DNA chain breaks thymidine dimers	+[a]	ND	Rahn et al. 1974
E. coli	DNA binding	–	–	Kubinski et al. 1981
Bacillus subtilis	Rec assay	–	–	Kawachi et al. 1980
Fungi				
Saccharomyces cerevisiae D61.M	Aneuploidy	ND	+	Zimmermann 1983; Zimmermann et al. 1984, 1985
S. cerevisiae D61.M	Mitotic chromosome malsegregation	ND	+	Albertini 1991
S. cerevisiae D61.M	Increased frequency of resistant colonies	ND	–	Albertini 1991
Saccharomyces pombe	Forward mutation	–	–	Abbandandolo et al. 1980
Plants				
Arabidopsis thaliana seeds	Gene mutation	ND	–	Gichner and Veleminsky 1987
Mammalian cells				
Syrian hamster embryo cells	Cell transformation	ND	–	Di Paolo et al. 1969
Syrian hamster embryo cells	Cell transformation	ND	–	Pienta 1980
CHO cells	Chromosomal aberrations	–	–	Tates and Kriek 1981
Chinese hamster fibroblasts	Chromosomal aberrations	ND	+	Ishidate et al. 1984
Hamster lung fibroblasts	Chromosomal aberrations	ND	+	Kawachi et al. 1980

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

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference
CHO cells	Sister chromatid exchange	–	–	Tates and Kriek 1981
Chinese hamster cells	Sister chromatid exchange	ND	–	Abe and Sasaki 1982
Hamster lung fibroblasts	Sister chromatid exchange	ND	–	Kawachi et al. 1980
Chinese hamster V79 cells	Inhibition of metabolic cooperation (intracellular communication)	ND	+	Chen et al. 1984
Chinese hamster V79 cells	Inhibition of colony formation	ND	–	Chen et al. 1984
AKR leukemia virus-infected mouse embryo cells	Cell transformation	ND	–	Rhim et al. 1974
Mouse lymphoma TK cells	Gene mutation	ND	–	Amacher et al. 1980
Mouse BALB/c-3T3 cells	Cell transformation	+	+	Matthews et al. 1993
Rat embryo culture	Cell transformation	ND	–	Freeman et al. 1973
Rat embryo cells infected with Rauscher leukemia virus	Cell transformation; ouabain resistance	–	–	Mishra et al. 1978
Porcine brain tubulin	Chromosome malsegregation	ND	+	Albertini et al. 1988
Human fibroblasts	Sister chromatid exchange	ND	–	Kawachi et al. 1980
Human fibroblasts	Sister chromatid exchange	ND	–	Abe and Sasaki 1982
Human skin epithelial cells	Unscheduled DNA synthesis	ND	–	Lake et al. 1978
Human epithelial cells	DNA fragmentation	ND	–	Costa et al. 2006
Human lymphocytes	Number of micronuclei	–	–	Zarani et al. 1999

– = negative result; + = positive result; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; ND = not determined

In vivo genotoxicity studies were conducted by the intraperitoneal route for micronuclei formation in Chinese hamsters (Basler 1986) and for cell transformation in fetal cells from pregnant hamsters (Quarles et al. 1979a, 1979b) with negative results. In addition, tests for gene mutation in silk worms by an unspecified route were negative (Kawachi et al. 1980). Results from *in vivo* genotoxicity studies are shown in Table 2-6.

Table 2-6. Genotoxicity of Acetone *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Chinese hamsters (injected interperitoneally)	Micronuclei in erythrocytes	–	Basler 1986
Pregnant hamsters (injected interperitoneally)	Cell transformation in fetal cells	–	Quarles et al. 1979a, 1979b
Silk worms	Gene mutation	–	Kawachi et al. 1980

– = negative result

2.21 MECHANISM OF ACTION

Most of the toxic effects of acetone do not appear to be due to any of its metabolites. As is typical of solvents, acetone is irritating to the mucous membranes. Acetone is also narcotic, and although the mechanism by which acetone exerts its effects on the CNS is unknown, as a solvent, it may interfere with the composition of membranes, altering their permeability to ions. The mechanisms by which acetone produces hematological, hepatic, renal, reproductive, and developmental effects is unknown, but acetone has been found to distribute to all of these target organs, including the brain, and can undergo transplacental transfer. Renal toxicity may be due to the formation of formate and may involve α2u-globulin, which has been observed in rats. As shown in numerous studies, one of the main effects of acetone is the induction of microsomal enzymes, particularly CYP2E1 (see Section 2.9). Enzyme induction is probably responsible for the increased liver and kidney weights observed in animals by virtue of the increase in protein content. Acetone also potentiates the toxicity of numerous other chemicals primarily by increasing their metabolism to toxic intermediates by the induction of CYP2E1, or otherwise interfering with their metabolism and elimination.

Results of Orellana et al. (2001) support a hypothesis that ketone bodies such as acetone may be common inducers of microsomal and peroxisomal fatty acid oxidation. In this study, parameters of oxidative stress, microsomal CYP activity, and peroxisomal fatty acid oxidation were assessed in the liver of rats that had received acetone (1% v/v) in the drinking water for 7 days. Compared to the livers of controls, livers of acetone-exposed rats showed increases in CYP content, microsomal biotransformation activity, peroxisomal fatty acid oxidation, and catalase activity and decreases in hepatic activity of superoxide dismutase and glutathione peroxidase without altering glutathione and malondialdehyde content. These results suggest that ketone bodies such as acetone could be common inducers of microsomal and peroxisomal fatty acid oxidation. However, the results also suggest that acetone-induced increases in

CYP and peroxisomal fatty acid oxidation are not related to significant changes in hepatic oxidative stress.

Stadler et al. (2008) provide evidence of inducible nitric oxide synthetase (iNOS) mediated free radical production and protein oxidation in acetone-induced ketosis by using male iNOS and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase knockout mice receiving acetone in a single intragastric dose or in drinking water for 5 days or 3 weeks. In the acute intragastric experiment, free radical production was unchanged in NADPH oxidase knockout mice. However, free radical production was greatly decreased in iNOS knockout mice, indicating that iNOS may play a role in acetone-induced free radical production. Longer-term exposure to acetone via drinking water resulted in iNOS over-expression and protein radical formation in the liver. Other results included enhanced lipid peroxidation and protein oxidation after 21 days of acetone treatment in control and NADPH oxidase knockout mice, but not in iNOS knockout mice. These results together indicate that acetone administration can result in iNOS over-expression that leads to protein oxidation and lipid peroxidation via a free radical-dependent mechanism. The authors discuss the implication of high levels of ketosis with the development of complications in diabetes.

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

3.1 TOXICOKINETICS

Information on the toxicokinetics of acetone are available from studies of humans and animals.

- Following exposure from exogenous sources, acetone is rapidly and passively absorbed from the lungs and gastrointestinal tract. Acetone can also be absorbed through the skin.

- Acetone is highly water soluble and is widely distributed to tissues and organs throughout the body, especially to tissues with high water content. It is not likely to accumulate with repeated exposure. Acetone can also undergo transplacental transfer to the fetus. In addition, acetone is distributed to mother's milk, and represents a source of excretion from the mother and exposure for infants.

- Metabolism of acetone is independent of route of exposure and similar in humans and animals. It involves three separate gluconeogenic pathways, with ultimate incorporation of carbon atoms into glucose and other products of intermediary metabolism, with generation of carbon dioxide. Metabolism takes place primarily in the liver. Physiological status, such as diabetes and fasting, and genetic predisposition for obesity can alter the pattern of metabolism.

- The main route of excretion is via the lungs regardless of the route of exposure with very little excreted in the urine. Acetone is excreted both unchanged and, following metabolism, mainly as carbon dioxide. Elimination is generally complete in 48–72 hours after the last exposure, depending on the exposure concentration, duration, and factors such as biological sex and level of physical activity.

Although the focus of this profile is on the effects of exposure to acetone from exogenous sources, a full understanding of the toxicokinetics requires consideration of the metabolic fate of endogenous acetone. Acetone is one of three ketone bodies that occurs naturally throughout the body (Le Baron 1982; Vance 1984). Under normal conditions, the production of ketone bodies occurs almost entirely within the liver and to a smaller extent in the lung and kidney (Gavino et al. 1987; Le Baron 1982; Vance 1984). The process is continuous, and the three products are excreted into the blood and transported to all tissues and organs of the body where they can be used as a source of energy. Two of these ketone bodies, acetoacetate and β-hydroxybutyrate, are organic acids that can cause metabolic acidosis when produced in large amounts. Acetone, in contrast, is nonionic and is derived endogenously from the spontaneous and enzymatic breakdown of acetoacetate (Dabek et al. 2020; Kimura et al. 1986; Koorevaar and Van Stekelenburg 1976; Lopez-Soriano and Argiles 1985; Lopez-Soriano et al. 1985; Reichard et al. 1979; Van Stekelenburg and Koorevaar 1972). Endogenous acetone is eliminated from the body either by excretion into urine and exhaled air or by enzymatic metabolism (Charbonneau et al. 1986c; Haggard et al. 1944; Owen et al. 1982; Reichard et al. 1986; Wigaeus et al. 1981). Under normal circumstances,

metabolism is the predominant route of elimination for endogenous acetone and handles 70–80% of the total body burden.

Levels of endogenous acetone can fluctuate greatly due to normal diurnal variations (Wildenhoff 1972). In addition, circulating levels of endogenous acetone can fluctuate greatly depending on a person's age (Paterson et al. 1967; Peden 1964), nutritional status and fasting (Jones 1987; Kundu et al. 1993; Levy et al. 1973; Lewis et al. 1977; Neiman et al. 1987; Reichard et al. 1979; Rooth and Carlstrom 1970; Williamson and Whitelaw 1978), and degree of physical activity (Koeslag et al. 1980). These physiological states all place high energy demands upon the body, which result in increased fatty acid utilization and higher-than-normal blood levels of acetone. Infants and young children typically have higher acetone blood levels than adults due to their higher energy expenditure (Peden 1964). Pregnancy and lactation can also lead to higher-than-average blood levels of acetone (Bruss 1989; Paterson et al. 1967). In addition to these normal physiological conditions, a number of clinical states can result in acetonemia and/or acetonuria in humans. In each of these conditions, the ketosis can be traced to the increased mobilization and utilization of free fatty acids by the liver. The conditions include diabetes (Kobayashi et al. 1983; Levey et al. 1964; Reichard et al. 1986; Rooth 1967; Rooth and Ostenson 1966), trauma (Smith et al. 1975), and alcohol use disorder (Phillips et al. 1989; Tsukamoto et al. 1991).

3.1.1 Absorption

Studies of inhalation exposures in humans indicate that, due to its high blood-air partition coefficient (167–330), acetone is rapidly and passively taken up by the respiratory tract and absorbed into the bloodstream (Fiserova-Bergerova and Diaz 1986; Haggard et al. 1944; Paterson and Mackay 1989; Sato and Nakajima 1979). Experiments in humans exposed to 23–4,607 ppm for up to 4 hours have measured pulmonary uptakes ranging from ≈30 to 80% (DiVincenzo et al. 1973; Landahl and Herrmann 1950; Nomiyama and Nomiyama 1974a; Pezzagno et al. 1986; Wigaeus et al. 1981). The reason for the wide range in reported values involves the unique aqueous wash-in/wash-out effect when acetone is inhaled, which can lead to spurious results (Schrikker et al. 1985, 1989). During this phenomenon, acetone, which is highly water soluble, will dissolve in epithelial cells during inspiration (wash-in) and evaporate during expiration (wash-out). This could account for the lower than expected pulmonary absorption based on the high blood/air partition coefficient (Johanson 1991; Wigaeus et al. 1981). Exhaled breath levels of acetone in humans rose during exposure and reached steady-state within ≈2 hours during exposure to concentrations between 125 and 250 ppm (Brown et al. 1987; Nomiyama and Nomiyama 1974a).

Uptake and absorption of acetone in humans following inhalation exposures depends on factors such as concentration, duration, and level of physical activity. Uptake was directly proportional to exposure concentration and duration (DiVincenzo et al. 1973; Wigaeus et al. 1981). Uptake also increased as the level of physical activity increased, due to increased pulmonary ventilation (DiVincenzo et al. 1973; Haggard et al. 1944; Jakubowski and Wieczorek 1988; Wigaeus et al. 1981). Lungs (including the mouth and trachea) retained a greater percentage of inspired acetone (55%) than the nasal cavity (18%) in humans, indicating that the nasal cavity absorbs acetone less readily than the rest of the respiratory system (Landahl and Herrmann 1950). Blood levels of acetone rose rapidly during exposure for up to 4 hours with no indication that steady-state was reached (Brown et al. 1987; Dick et al. 1989; DiVincenzo et al. 1973), suggesting that during exposure, the rate of absorption exceeded the rate of distribution and elimination. In humans exposed to 100 or 500 ppm acetone for 2 or 4 hours, 75–80% of the amount of acetone inspired was absorbed by blood after 15 minutes of exposure, and 20–25% remained in the dead space volume (DiVincenzo et al. 1973). Higher inspired amounts resulted in higher blood levels (DiVincenzo et al. 1973; Haggard et al. 1944; Matsushita et al. 1969a; Pezzagno et al. 1986). A correlation between blood level at the end of exposure and exposure concentration was found in humans exposed to 23–208 ppm for 2–4 hours (Pezzagno et al. 1986). No significant difference in uptake or retention was found between men and women (Brown et al. 1987). External temperature appears to alter absorption of inhaled acetone. An experimental study in five human subjects showed that for a constant air concentration of acetone (495 ppm), blood levels of acetone increased as the external temperature increased from 21 to 30°C (Marchand et al. 2021). After a 4-hour exposure at 21°C, the mean venous blood acetone concentration was 22.14 mg/L, compared to 27.65 ppm at 30°C, an increase of approximately 25%. The study authors suggested that the increased venous blood concentrations at higher temperatures was due to physiological changes associated with thermoregulation.

Studies on absorption of acetone following oral exposure in humans are limited but likewise indicate high levels of absorption, as with inhalation exposure. In a series of experiments conducted in male volunteers given acetone orally at 40–80 mg/kg, an estimated 65–93% of the administered dose was eliminated via metabolism, with the remainder excreted in the urine and expired air in about 2 hours, indicating rapid and extensive gastrointestinal absorption (Haggard et al. 1944). In a human who ingested 137 mg/kg acetone on an empty stomach, the blood level of acetone rose sharply to a peak 10 minutes after dosing (Widmark 1919). In other experiments, the subject ingested the same dose 10 or 12 minutes after eating porridge. The blood acetone level rose slowly over 48–59 minutes to levels of about one-half to two-thirds of that achieved after taking acetone on an empty stomach. Thus, the presence of food in the gastrointestinal tract may lead to a slower rate of absorption.

Measurement of acetone in blood and urine of patients who accidentally or intentionally ingested acetone indicated that acetone was absorbed, but the percentage absorbed cannot be determined from the data. In one case, a man ingested liquid cement that provided an approximate dose of acetone of 231 mg/kg (Sakata et al. 1989). His plasma acetone level was about 110 µg/mL and his urinary level was 123 µg/mL 5 hours after ingestion, but he had been subjected to gastric lavage. In another case, a woman who had ingested nail polish remover had a blood acetone level of 0.25 g/100 mL (2.5 mg/mL) upon admission to the hospital (Ramu et al. 1978). The authors estimated that her body burden was 150 g acetone at the time of admission. The serum acetone level of a 30-month-old child was 445 mg/100 mL (4.45 mg/mL) 1 hour after ingestion of a 6-ounce bottle of nail polish remover (65% acetone) (Gamis and Wasserman 1988).

Dermal absorption of acetone has also been demonstrated in humans. Application of cotton soaked in acetone to a 12.5 cm^2 uncovered area of skin of volunteers for 2 hours/day for 4 days resulted in blood levels of acetone of 5–12 µg/mL, alveolar air levels of 5–12 ppm, and urinary concentrations of 8–14 µg/mL on each day (Fukabori et al. 1979). Higher blood, alveolar air, and urinary levels were obtained when the daily exposure increased to 4 hour/day: 26–44 µg/mL in blood, 25–34 ppm in alveolar air, and 29–41 µg/mL in urine. The absorption was fairly rapid, with peak blood levels appearing at the end of each daily application. Although precautions were taken to limit inhalation of acetone vapors, the study authors noted that it was not possible to completely prevent inhalation, and the acetone concentration in the breathing zone of one subject was found to be 0.4–0.6 ppm. From the alveolar air and urine concentrations, it was estimated that a 2-hour dermal exposure over 12.5 cm^2 of skin was equivalent to a 2-hour inhalation exposure to 50–150 ppm, and a 4-hour dermal exposure was equivalent to a 2-hour inhalation exposure to 250–500 ppm acetone.

Similar to humans, animals also absorb acetone rapidly during inhalation exposure. Measurement of blood acetone levels in 13-week-old male and female rats after 4–6 hours of exposure to various concentrations shows that blood levels correlate well with exposure concentrations (Charbonneau et al. 1986a, 1991; NTP 1988) and are highest immediately after exposure (NTP 1988). In male rats exposed to 1.50 ppm for 0.5–4 hours, measurement of blood acetone concentrations during exposure revealed that blood levels increased steadily for 2 hours and then remained constant for the next 2 hours of exposure (Geller et al. 1979b). Blood acetone levels also correlated well with exposure concentration in dogs exposed for 2 hours (DiVincenzo et al. 1973). Blood levels were 4, 12, and 25 mg/L after exposures to 100, 500, and 1,000 ppm, respectively. Comparison of uptakes in dogs and humans revealed that humans

absorbed a greater absolute quantity under comparable exposure conditions, but when expressed in terms of kg body weight, male and female dogs absorbed 5 times more than humans. In anesthetized dogs allowed to inhale concentrated vapors of acetone spontaneously from a respirator at various ventilation rates, uptake by the respiratory tract was 52% at flow rates of 5–18 L/minute and 42% at ventilation rates of 21–44 L/minute (Egle 1973). Retention in the lower respiratory tract was 48% at 4–18 L/minute and 37.5% at 21–50 L/minute. Retention by the upper respiratory tract was 57% at 4–18 L/minute. The effect of exposure concentration on total uptake was studied at a range of ventilation rates equated with exposure concentrations. Percent uptakes were 52.1% at a mean concentration of 212 ppm, 52.9% at 283 ppm, and 58.7% at 654 ppm. These results indicate the respiratory uptake of acetone by dogs is similar to human uptake values reported by Landahl and Herrmann (1950). The retention in the upper respiratory tract was higher than in the lower respiratory tract of dogs (Egle 1973). Exposure concentration had little effect on retention. The absorption of acetone by the nasal walls of anesthetized dogs, in which the nasal passage was isolated, increased when the airflow rate was increased (Aharonson et al. 1974). This suggests that increased airflow decreases the proportion of acetone that reaches the lungs.

In rats exposed continuously to 2,210 ppm for 9 days, peak acetone blood levels of approximately 1,020–1,050 mg/L were reached in 3–4 days and remained at this level for the duration of exposure (Haggard et al. 1944). In rats exposed to 4,294 ppm for 12 days, acetone blood levels plateaued at 2,420–2,500 mg/L in 4 days. Blood levels in rats exposed to these concentrations for 8 hours/day were about half of those reached during continuous exposure. The amount of acetone absorbed in the first 8 hours exceeded the amount eliminated in the next 16 hours of exposure to fresh air, leading to a small accumulation. However, the accumulation during intermittent exposure did not reach the levels achieved during continuous exposure. In other experiments of rats exposed to 2,105–126,291 ppm, the time to peak blood level decreased as the exposure concentration increased (Haggard et al. 1944).

As was found in humans (Landahl and Herrmann 1950) and dogs (Egle 1973), disposition of acetone in the upper respiratory tract of rats, mice, guinea pigs, and hamsters indicates that relatively little acetone is absorbed from the upper respiratory tract (Morris 1991; Morris and Cavanagh 1986, 1987; Morris et al. 1986, 1991). The deposition efficiency was greater in Sprague-Dawley rats than in Fischer-344 rats. Deposition was similar in B6C3Fl mice and Fischer-344 rats, and greater than in Hartley guinea pigs and Syrian golden hamster. No difference was found between male and female Sprague-Dawley rats (Morris et al. 1991). The differences among strains and species could not be attributed to differences in metabolism because acetone is not significantly metabolized in the upper respiratory tract of these species

(Morris 1991). Rather, the difference was attributed to differences in upper respiratory tract perfusion rates (Morris 1991; Morris and Cavanagh 1987).

Experiments in rats indicated that acetone is rapidly and almost completely absorbed from the gastrointestinal tract after oral exposure. No studies were located regarding absorption of acetone in other animal species after oral exposure to acetone. A rat given ^{14}C-acetone at a dose of 1.16 mg/kg expired 47.4% of the dose as ^{14}C-carbon dioxide over the 13.5-hour collection period (Price and Rittenberg 1950). Another rat given about 7.11 mg/kg ^{14}C-acetone by gavage once a day for 7 days expired 67–76% of the administered radioactivity as ^{14}C-carbon dioxide and 7% as ^{14}C-acetone over a 24-hour period after the last dose. From these data, absorption of least 74–83% of the administered dose can be inferred. A rat dosed with 6.19 mg/kg ^{14}C-acetone expired 4.24% of the radiolabel as unchanged ^{14}C-acetone over 5.5 hours, indicating rapid absorption. In rats given a single gavage dose of 1,177 mg/kg acetone, the maximum blood level of 850 µg/mL was reached in 1 hour and declined gradually to about 10 µg/mL over 30 hours (Plaa et al. 1982). In another experiment, peak blood levels and the time to peak blood levels were compared after various gavage doses to rats. After a dose of 78.44 mg/kg, the maximum blood level of acetone of about 200 µg/mL was reached in 3 hours and declined to 10 µg/mL at 12 hours, where it remained for the next 12 hours. After a dose of 196.1 mg/kg, the peak blood level was 400 µg/mL at 6 hours and declined biphasically to 50 µg/mL at 12 hours and to 30 µg/mL at 18 hours where it remained for the next 6 hours. After a dose of 784.4 mg/kg, the peak level was 900 µg/mL at 1 hour and declined to 300 µg/mL at 12 hours, 110 µg/mL at 18 hours, and 50 µg/mL at 24 hours. After a dose of 1,961 mg/kg, the peak level was 1,900 µg/mL at 3 hours and declined slowly to 400 µg/mL at 24 hours. In other studies where rats were given similar or higher doses of acetone, plasma acetone levels rose proportionately with dose in rats given acetone as single doses by gavage (Charbonneau et al. 1986a; Lewis et al. 1984) or in the drinking water for 7 days (Skutches et al. 1990).

In a study comparing blood levels of acetone in fasting male rats to those in male rats that received oral doses of acetone, peak blood levels of acetone of about 35 and 110 µg /mL were reached within about 3 hours after dosing of rats with 78 and 196 mg/kg acetone, respectively (Miller and Yang 1984). The levels returned to background levels within the next 16 hours. At an acetone dose of 20 mg/kg, the blood level increased to about 5 µg/mL over 19 hours, when the rats were sacrificed. In rats fasted for 48 hours, blood acetone levels increased continuously to about 13 µg/mL. While the maximal blood concentrations of the treated rats differed considerably from that of the fasting group, the areas under the curve for the 78 and 196 mg/kg groups were comparable to the fasting groups.

Conflicting data were located regarding the effect of vehicle on the gastrointestinal absorption of acetone. In one study, maximum blood levels were higher and achieved earlier in male rats given acetone by gavage in water than in rats given acetone by gavage in corn oil (Charbonneau et al. 1986a). The slower absorption of acetone in corn oil may have resulted from a delayed gastric emptying due to the presence of corn oil (fat) in the stomach. In a later study, however, very little difference in blood and liver levels of acetone were found in male rats given the same dose of acetone in water or in corn oil (Charbonneau et al. 1991).

There are little data regarding the absorption of acetone in animals after dermal exposure. One study reported a permeability coefficient (K_p) for acetone of 0.00249 cm-hour^{-1} when administered to the skin of newly deceased piglets (Schenk et al. 2018). The findings of cataract formation in guinea pigs exposed dermally (Rengstorff and Khafagy 1985; Rengstorff et al. 1972) (see Section 2.12) indicated that acetone was absorbed from the skin of the guinea pigs.

3.1.2 Distribution

There are limited data regarding distribution of acetone or its metabolites in humans. Biomonitoring conducted in workers at a plastics factory found similar regression slopes between air concentrations or acetone and its levels in serum, whole blood, and urine, indicating that acetone is evenly distributed throughout the body (Mizunuma et al. 1993). Acetone was detected in cerebrospinal fluid in a 55-year-old man who ingested 1 L of acetone (Gregoire et al. 2018). In addition, acetone is well absorbed into the blood from the respiratory and gastrointestinal tract of humans (see Section 3.1.1) and is highly water soluble. Therefore, widespread distribution, especially to tissues with high water content, is expected.

Biomonitoring studies in humans indicate that maternal-fetal transfer and maternal-infant transfer of acetone occur. Acetone was identified in maternal and cord blood collected at the time of delivery, indicating transplacental transfer (Dowty et al. 1976). Of eight samples of breast milk from lactating women from four urban areas, all were found to contain acetone (Pellizzari et al. 1982). Whether the source of acetone was endogenous or exogenous could not be determined. Nevertheless, the data indicate that acetone is distributed to mother's milk, and represents a source of excretion from the mother and exposure for infants.

The distribution of acetone has been studied in mice exposed to acetone by inhalation (Wigaeus et al. 1982). Mice were exposed to 500 ppm ^{14}C-acetone for 1, 3, 6, 12, and 24 hours or for 6 hours/day for 1,

3, or 5 consecutive days, after which they were immediately killed. Radioactive unmetabolized acetone and total radioactivity were found in blood, pancreas, spleen, thymus, heart, testes, vas deferens, lungs, kidneys, brain, liver, muscle, brown adipose tissue, subcutaneous adipose tissue, and intraperitoneal adipose tissue. A common feature was an increase in tissue concentration of acetone and total radioactivity during the first 6 hours after exposure, with no further accumulation observed after 6 hours except in the liver and brown adipose tissue. The continued accumulation of radioactivity in these tissues could be the result of high metabolic turnover. Only about 10% of the radioactivity in the liver at 24 hours was unmetabolized acetone. When the mice were exposed intermittently on 3 or 5 consecutive days, most tissues showed no or only a small additional increase in radioactivity after more than 1 day of exposure; however, the concentration in adipose tissue increased significantly with increasing exposure duration up to 5 days. Elimination of acetone was fastest in blood, kidneys, lungs, brain, and muscles with half-lives of about 2–3 hours during the first 6 hours after exposure. The slowest elimination was in subcutaneous adipose tissue with a half-time of >5 hours. Elimination of acetone was complete in all tissues by 24 hours after exposure, but total radioactivity, indicative of metabolites, was still present in all tissues except blood and muscle. These data indicate that acetone is not selectively distributed to any tissues but is more evenly distributed in body water. In addition, acetone is not likely to accumulate with repeated exposure.

In another study of inhalation exposure, rats (n=4) were exposed to 1,000 ppm of acetone for 8 hours/day for 3 consecutive days (Scholl and Iba 1997). Plasma concentrations of acetone were 122, 107, and 125 µg/mL at 30 minutes after exposure on days 1, 2, and 3, respectively. Plasma elimination followed first-order kinetics in rats that were terminated after exposure to 1,000 ppm for 3 hours/day for 3 days. The half-life for elimination was 4.5 hours, and the area under the curve (AUC) was 950 µg-hour/mL. Inhalation exposure of the rats to 1,000 ppm of acetone for 3 hours/day for 10 days resulted in concentrations of 35.3 µg/g of acetone in plasma, 13.2 µg/g in liver, 11.4 µg/g in the lung, and 21.8 µg/g in the kidney (Scholl and Iba 1997).

Acetone has also been detected in the plasma of rats following oral exposures. In rats receiving acetone in drinking water (7.5% v/v) for 11 consecutive days, plasma concentrations of acetone on day 1 were in the range of 315–800 µg/mL. The plasma concentration appeared to plateau at about 1,200 µg/mL by day 4 (Scholl and Iba 1997). Acetone was additionally found in the liver of rats after oral exposure (Charbonneau et al. 1986a, 1991). No other studies were located regarding the distribution of acetone or its metabolites in animals. However, acetone is well absorbed from the gastrointestinal tract (see

Section 3.1.1) and is highly water soluble. Therefore, widespread distribution, especially to tissues with high water content, is expected.

No studies were located regarding distribution of acetone or its metabolites in animals after dermal exposure. However, the findings of cataract formation in guinea pigs exposed dermally (Rengstorff and Khafagy 1985; Rengstorff et al. 1972) (see Section 2.12) indicated that acetone was absorbed from the skin of the guinea pigs and distributed to the eyes.

Similar to humans, there is evidence of transplacental transfer of acetone in animals. Acetone and its metabolites were found in fetuses from rats injected intravenously with 100 mg/kg acetone on GD 19 (Peinado et al. 1986).

One study investigated the pharmacokinetics of intravenously injected radiolabeled acetone in baboons (Gerasimov et al. 2005). Acetone uptake in the brain was rapid in both the cerebellum and white matter, reaching peaks of approximately 0.02% of the injected dose within 1–2 minutes after injection. Acetone had a half-time of clearance from peak uptake of 31 and 38 minutes in the cerebellum and white matter, respectively. The brain/blood uptake ratio for acetone reached a peak of 1.0 and plateaued around 4–5 minutes after injection.

3.1.3 Metabolism

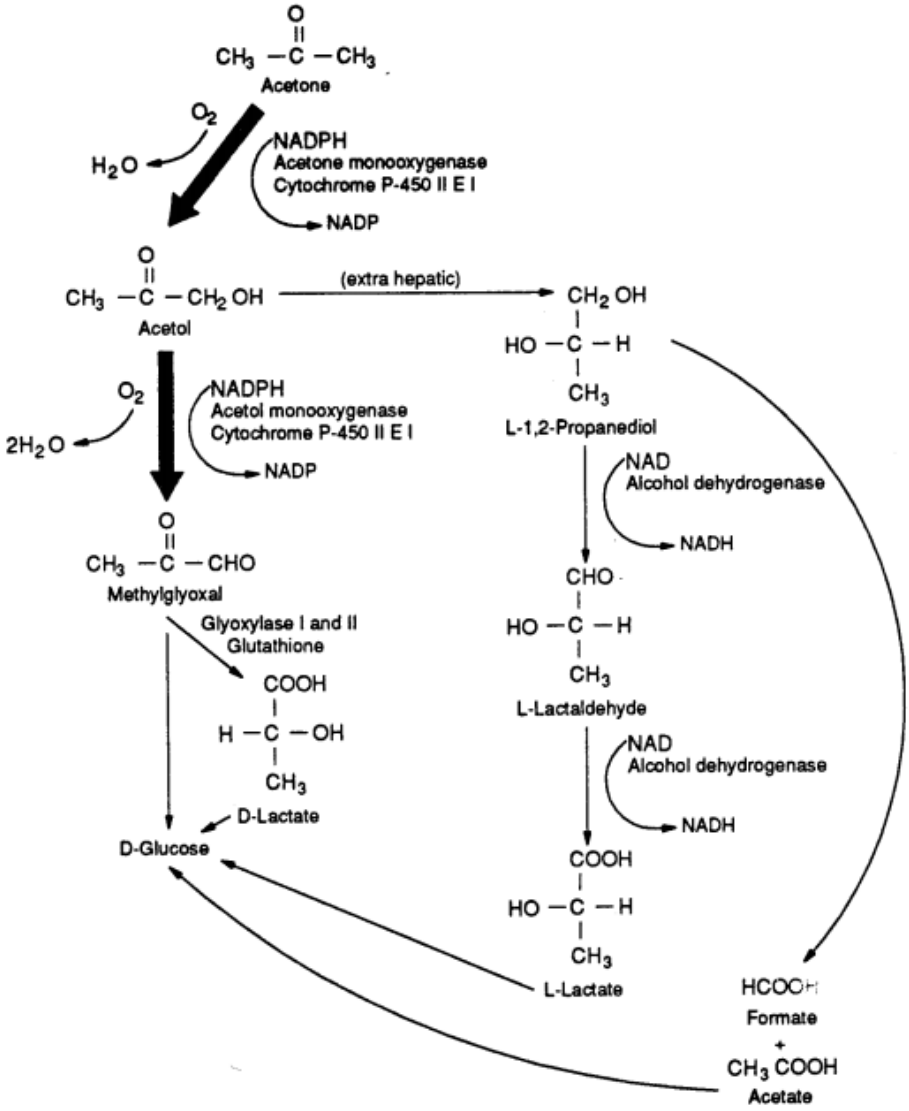
The metabolic fate of acetone is independent of route of administration and involves three separate gluconeogenic pathways, with ultimate incorporation of carbon atoms into glucose and other products and substrates of intermediary metabolism with generation of carbon dioxide. The metabolic pathways appear to be similar in humans and animals. The primary (major) pathway involves hepatic metabolism of acetone to acetol and hepatic metabolism of acetol to methylglyoxal, while two secondary (minor) pathways are partially extrahepatic, involving the extrahepatic reduction of acetol to L-1,2-propanediol. Some of exogenous acetone is unmetabolized and is excreted primarily in the expired air with little acetone excreted in urine (see Section 3.1.4).

The only studies located regarding the metabolism of acetone in humans were conducted in non-obese fasted, obese fasted, and male and female diabetic patients (Reichard et al. 1979, 1986). The involvement of gluconeogenesis was demonstrated in non-obese patients fasted for 3 days (n=6), obese patients fasted for 3 days (n=6), and obese patients fasted for 21 days (n=3) before intravenous injection of

2-[^{14}C]-acetone (Reichard et al. 1979). The percentages of ^{14}C-glucose in plasma derived from ^{14}C-acetone were 4.2, 3.1, and 11.0% in the three respective groups, suggesting the involvement of gluconeogenesis. Cumulative ^{14}C-carbon dioxide excretion by the lungs during the 6-hour collection period accounted for 17.4, 21.5, and 4.9% in the three respective groups. Radioactivity was also incorporated into plasma lipids and plasma proteins. Unmetabolized acetone in the expired air accounted for 14.7, 5.3, and 25.2%; urinary excretion of acetone accounted for 1.4, 0.6, and 1.3%, respectively; and *in vivo* metabolism accounted for 83.9, 94.1, and 73.5%, respectively, of the radioactivity. Intravenous infusion of 2-[^{14}C]-acetone into patients with diabetic ketoacidosis resulted in a mean plasma acetone turnover rate of 6.45 µmol/kg/minute (Reichard et al. 1986). Analysis of glucose in urine revealed a labeling pattern in five of the six patients consistent with the involvement of pyruvate in the gluconeogenic pathway. A different pathway may have operated in the other patient. Acetol and 1,2-propanediol were also detected in the plasma, and the concentrations of these metabolites were directly related to the plasma level of acetone. The results demonstrated high plasma acetone levels in decompensated diabetic patients. The suggested pathway of acetone metabolism in these patients was acetone to acetol to 1,2-propanediol to pyruvate and ultimately to glucose, but other pathways may exist between subclasses of diabetic patients.

The metabolism of acetone has been studied extensively in animals, primarily in rats, and three separate pathways of gluconeogenesis have been elucidated (Figure 3-1). These pathways are consistent with the metabolic fate of acetone in humans, discussed above. The elucidation of these pathways has been performed in experiments in which rats, mice, or rabbits were exposed by inhalation, by gavage, via drinking water, or by intravenous, subcutaneous, or intraperitoneal injection of nonradiolabeled acetone or to acetone labeled with ^{14}C in the methyl groups, number 2 carbon atom, or all three carbon atoms (Casazza et al. 1984; Hallier et al. 1981; Hetenyi and Ferrarotto 1985; Johansson et al. 1986; Koop and Casazza 1985; Kosugi et al. 1986a, 1986b; Mourkides et al. 1959; Price and Rittenberg 1950; Puccini et al. 1990; Rudney 1954; Sakami 1950; Sakami and LaFaye 1951; Skutches et al. 1990). In these experiments, identification of metabolites in liver, plasma, or urine, the labeling patterns of ^{14}C incorporation into metabolites from ^{14}C-acetone in plasma or in liver, or the results of enzyme reactions using microsomes from acetone treated animals have led to the pathways illustrated in Figure 3-1.

Figure 3-1. Proposed Metabolic Pathway for Acetone in Humans



Sources: Casazza et al. 1984; Dietz et al. 1991; Kosugi et al. 1986a

In the first step, acetone is oxidized (hydroxylation of a methyl group) to acetol by acetone monooxygenase (also called acetone hydroxylase), an activity that is associated with CYP2E1 and requires oxygen and NADPH (Casazza et al. 1984; Johansson et al. 1986; Koop and Casazza 1985; Puccini et al. 1990). CYP2E1 can be induced by fasting, experimental diabetes, or exposure to ethanol or acetone (Johansson et al. 1988; Patten et al. 1986; Puccini et al. 1990). When the rate of acetone oxidation was evaluated in microsomes with acetone added to the incubation system, microsomes from rats (Johansson et al. 1986) and mice (Puccini et al. 1990) pretreated with acetone had a 7–8 times greater acetone oxidation rate than microsomes from control rats or mice. Thus, acetone induces its own metabolism.

The formation of acetol is common to all three pathways. Subsequent conversion of acetol to methylglyoxal in microsomes is catalyzed by acetol monooxygenase (also called acetol hydroxylase), an activity that is also associated with CYP2E1 and requires oxygen and NADPH (Casazza et al. 1984; Johansson et al. 1986; Koop and Casazza 1985). Methylglyoxal can then be converted to D-glucose by an unidentified pathway, and/or possibly by catalysis by glyoxalase I and II and glutathione to D-lactate, which is converted to D-glucose (Casazza et al. 1984). The conversion of methylglyoxal to D-lactate by the actions of glyoxalase I and II is well established (Racker 1951), but may represent a minor pathway in the metabolism of acetone (Casazza et al. 1984; Kosugi et al. 1986a, 1986b; Thornalley 1990). The unidentified pathway by which methylglyoxal is converted to D-glucose may involve conversion of methylglyoxal to pyruvate by 2-oxoaldehyde dehydrogenase, an activity identified using aqueous extracts of sheep liver acetone powders (Monder 1967).

Investigations that included CYP2E1-null mice have confirmed the importance of CYP2E1 in acetone catabolism *in vivo* (Bondoc et al. 1999; Chen et al. 1994). In the study of Bondoc et al. (1999), acetone levels were measured in non-fasted and 48-hour-fasted wild type and CYP2E1-null mice. Fasting is known to result in the elevation of acetone levels in the blood. Blood acetone levels in non-fasted wild type and CYP2E1-null mice were not significantly different from one another. However, fasted CYP2E1-null mice exhibited 24-fold increased blood acetone levels compared to their non-fasted controls. The wild-type fasted mice, on the other hand, exhibited only a 2- to 4-fold increase in blood acetone levels compared to their non-fasted controls. Chen et al. (1994) assessed the role of CYP2E1 in acetone catabolism by measuring acetone levels at different time points in rats that had been treated with diallyl sulfide (DAS, a CYP2E1 inhibitor) at a variety of dose levels. The study authors noted DAS dose-dependent increases in the time to peak blood acetone level and in the time to return to pre-dose levels, suggesting an important role of CYP2E1 in acetone catabolism.

In the second and third pathways, acetol is converted to L-1,2-propanediol by an extrahepatic mechanism that has not been characterized (Casazza et al. 1984; Kosugi et al. 1986a, 1986b; Rudney 1954; Skutches et al. 1990). The two pathways then diverge from the point of production of 1,2-propanediol. In the second pathway, 1,2-propanediol formed extra-hepatically returns to the liver where it is converted to L-lactaldehyde via nicotinamide adenine dinucleotide (NADH)-dependent alcohol dehydrogenase (Casazza et al. 1984; Kosugi et al. 1986a, 1986b), and L-lactaldehyde, in turn, is converted to L-lactate (Casazza et al. 1984; Ruddick 1972; Rudney 1954) via NADH-dependent aldehyde dehydrogenase (Casazza et al. 1984). L-lactate can then be converted to D-glucose (Casazza et al. 1984). In the third

pathway, the L-1,2-propanediol formed extra-hepatically returns to the liver where it is degraded by an uncharacterized mechanism to acetate and formate (Casazza et al. 1984; Ruddick 1972).

Several studies have traced the labeling patterns of ^{14}C from 2-[^{14}C]-acetone or 1,3-[^{14}C]-acetone to gluconeogenic precursors and formate to incorporation of ^{14}C into glycogen, glycogenic amino acids, fatty acids, heme, cholesterol, choline, and urea (Mourkides et al. 1959; Price and Rittenberg 1950; Sakami 1950). The pattern of labeling suggested the involvement of the "acetate and formate" pathway. The ultimate fate of glucose is entry into glycolysis or into the tricarboxylic acid cycle, via pyruvate and acetyl coenzyme A (CoA) with the liberation of carbon dioxide, and subsequent electron transport and oxidative phosphorylation with the production of ATP (Lehninger 1970). Fatty acids, amino acids, and glycogen may also enter stages of intermediary metabolism.

The relative importance of the three pathways in the metabolism of acetone may depend upon the amount of acetone administered. When a trace amount of 2-[^{14}C]-acetone was administered intravenously to rats, the pattern of incorporation of ^{14}C into glucose was consistent with the production of glucose via the methylglyoxal/lactate pathway (Kosugi et al. 1986a). When a higher dose of 2-[^{14}C]-acetone (325 mg/kg) was injected, the pattern of incorporation was more consistent with the 1,2-propanediol pathway. These results suggest that at low doses of acetone or endogenous acetone, the methylglyoxal and lactate pathways predominate, but at higher doses, these pathways become saturated and metabolism is shunted to the formate-acetate branch of the 1,2-propanediol pathway.

In addition to the pathways illustrated in Figure 3-1, 2,3-butanediol (Casazza et al. 1984) and isopropyl alcohol (Lewis et al. 1984) were detected in the blood of rats after oral dosing with acetone and were deemed to be unrelated to the ingestion of these chemicals. The positions of 2,3-butanediol and isopropyl alcohol in the metabolic scheme are not clear.

That acetone is extensively metabolized has been demonstrated by the finding of high percentages of ^{14}C-carbon dioxide in the expired air of animals exposed to ^{14}C-acetone (Mourkides et al. 1959; Price and Rittenberg 1950; Sakami 1950; Sakami and LaFaye 1951; Wigaeus et al. 1982) (see Section 3.1.4).

Although the liver is the primary site of acetone metabolism, radioactive unmetabolized acetone and total radioactivity were found in blood, pancreas, spleen, thymus, heart, testes, vas deferens, lungs, kidneys, brain, liver, muscle, brown adipose tissue, subcutaneous adipose tissue, and intraperitoneal adipose tissue of mice after inhalation exposure to ^{14}C-acetone (Wigaeus et al. 1982) (see Section 3.1.2). The fraction of

total radioactivity that was not still acetone represented metabolites. Elimination of acetone was complete in all tissues by 24 hours after exposure, but total radioactivity, indicative of metabolites, was still present in all tissues except blood and muscle. Whether these tissues (other than the liver) were capable of metabolizing acetone or whether the metabolites themselves were distributed to the tissues was not clear. However, microsomes from the lungs of hamsters exposed to acetone in drinking water for 7 days had a 500% increased activity of aniline hydroxylase, an enzyme associated with CYP2E1 (Ueng et al. 1991). Furthermore, the level of CYP2E1 increased 6-fold in microsomes from the nasal mucosa of rabbits exposed to acetone in drinking water for 1 week (Ding and Coon 1990). In hamsters given drinking water containing acetone for 7 days (Ueng et al. 1991) or 10 days (Menicagli et al. 1990), microsomes prepared from kidneys had increased levels of CYP and cytochrome b. These results suggest that acetone metabolism, which involves CYP2E1, may occur in the lungs and kidneys of hamsters and the nasal mucosa of rabbits. Incubation of acetone with homogenates of nasal mucosa from mice indicated that acetone was metabolized via a NADPH-dependent pathway *in vitro*, but no evidence of *in vivo* metabolism of acetone by the upper respiratory tract was found in mice, rats, guinea pigs, or hamsters (Morris 1991). Injection of pregnant rats with acetone on GD 19 resulted in high levels of 1,2-propanediol and acetol in the fetuses (Peinado et al. 1986). Whether these findings reflect transfer of the metabolites from the dams or metabolism of transferred acetone by the fetuses was not resolved.

Very few differences have been found among species in the metabolism of acetone. The pathways illustrated in Figure 3-1 appear to operate in rats, mice, and rabbits. In microsomes from rabbits exposed to acetone via drinking water, it was found that the oxidation of acetol could be catalyzed by cytochromes P-4503b (IIC3), 2 (IIB6), and 4(IA2), as well as by cytochrome P-4503a (P-450IIE1) (Koop and Casazza 1985). Only CYP2E1 could catalyze the oxidation of acetone to acetol. No studies were located regarding the ability of other isoenzymes of CYP to catalyze these reactions in other species.

Physiological or genetic status may alter the metabolism of acetone. When nondiabetic and diabetic 6-week-old male rats were treated by gavage with 99.5% pure acetone (containing <0.01% isopropyl alcohol) at doses of 1,000, 2,000, or 4,000 mg/kg, isopropyl alcohol deemed unrelated to the ingestion of the chemical was detected in the blood (Lewis et al. 1984). The levels of isopropyl alcohol and acetone increased with increasing dose in the diabetic rats, although with plateaus for both acetone and isopropyl alcohol at 1,000 and 2,000 mg/kg doses, but leveled off in the nondiabetic rats, indicating either saturation of the metabolic pathway from acetone to isopropyl alcohol or a reversibility of the conversion at high doses. It was suggested that in the diabetic rats, acetone and NADH, both needed for isopropyl alcohol production from acetone, presumably via alcohol dehydrogenase, may be diverted to gluconeogenic

pathways to meet the diabetic rat's need for glucose, resulting in the short plateau. The subsequent rise of both compounds at the high dose of acetone in the diabetic rats could be accounted for by greater generation of NADH from fatty acid oxidation in the diabetic rat, which reduces acetone to isopropyl alcohol, accounting for the rising level of isopropyl alcohol. Liver homogenates from mice heterozygous for the obesity gene treated with acetone were more effective in converting acetone to lactate than liver homogenates from non-obese homozygous mice treated with acetone (Coleman 1980). The more effective conversion by heterozygous mice may account for their prolonged survival on the starvation regimen, compared with non-obese mice. In pregnant and virgin rats (either fed or fasted) injected intravenously with acetone, plasma acetol levels were not significantly different between fasted and nonfasted rats, but pregnant rats had significantly lower levels than virgin rats (Peinado et al. 1986). Liver levels of acetol were also significantly lower in pregnant rats than in nonpregnant rats. Methylglyoxal levels were very high in the livers and plasma of nonfasted rats (pregnant or nonpregnant), but fasting resulted in much lower levels. No major differences were found in the expiration of carbon dioxide between fasted and diabetic rats injected intraperitoneally with acetone (Mourkides et al. 1959) or in the labeling pattern of ^{14}C derived from ^{14}C-acetone into glucose among nonfasted diabetic, fasted diabetic, nondiabetic nonfasted, and fasted nondiabetic rats injected intravenously with ^{14}C-acetone (Kosugi et al. 1986a, 1986b).

3.1.4 Excretion

The main route of excretion of acetone is via the lungs, regardless of the route of exposure. Acetone is excreted both unchanged and, following metabolism, mainly as carbon dioxide. Studies have been conducted in humans exposed by inhalation, but these studies have followed the elimination only of unchanged acetone from blood and the excretion of unchanged acetone in the expired air and urine.

A case report of a 55-year-old man who ingested 1 L of acetone estimated a terminal half-life of 17 hours (Gregoire et al. 2018). In humans exposed to acetone up to 1,250 ppm for up to 7.5 hours/day in a complex protocol for 16 weeks, the concentration of acetone in venous blood was directly related to the vapor concentration and duration of exposure, and inversely related to the time elapsed following exposure (Stewart et al. 1975). The rate of elimination of acetone from blood was constant regardless of blood acetone concentration (DiVincenzo et al. 1973). Half-times for blood elimination of 3–3.9 hours have been estimated in humans exposed to 100–500 ppm for 2–4 hours (Brown et al. 1987; DiVincenzo et al. 1973; Wigaeus et al. 1981). A study of workers exposed to 0.34 ppm during an 8-hour shift found an estimated half-life of 5.8 hours for acetone in blood (Wang et al. 1994). Elimination half-times of 3.9

and 6.2 hours have been estimated for arterial and venous blood, respectively, in volunteers (n=8) exposed to acetone concentrations ranging from 712 to 1,309 ppm (Wigaeus et al. 1981). No differences in elimination half-times were found between men and women (Brown et al. 1987). The elimination from blood was found to be complete in 24 hours after a 6-hour exposure in subjects exposed to 250 ppm, in 32 hours in subjects exposed to 500 ppm, and in 48 hours in subjects exposed to 1,000 ppm (Matsushita et al. 1969a). When 22 year-old men were exposed to 250 ppm for 6 hours/day for 6 days, the blood levels of acetone rose each day and returned to baseline levels in the morning after each daily exposure (Matsushita et al. 1969b). At an exposure concentration of 500 ppm, however, the blood levels declined each day, but not to baseline levels. At the end of the 6-day exposure, blood acetone levels declined to baseline within 2 days for the 250 ppm group and within 3 days for the 500 ppm group. Another study measured urinary acetone on the morning after occupational exposure to acetone concentrations above 300 ppm and found elevated concentrations relative to baseline (Satoh et al. 1995). However, by the end of the second day of exposure, there was no evidence of significant acetone accumulation; urinary acetone concentrations were similar to those at the end of the first day. From the half-time and the data on time to return to baseline levels, it appears that at higher concentrations, acetone may accumulate slightly in the blood during daily intermittent exposure, such as would be experienced by workers.

The rate and pattern of respiratory excretion of acetone is influenced by exposure concentration, duration, the level of physical activity during exposure, and biological sex. In humans exposed to acetone up to 1,250 ppm for up to 7.5 hours/day in a complex protocol for up to 6 weeks, the rate of respiratory excretion was a function of the duration, and the concentration of acetone in breath after exposure was directly related to the time-average concentration during exposure, with constant duration (Stewart et al. 1975). The length of time after exposure in which acetone could be detected in the expired air was related to the magnitude of exposure, with acetone still readily detectable 16 hours after exposure to 1,000 or 1,250 ppm for 7.5 hours. Excretion of acetone by the lungs was complete within 20 hours postexposure in humans exposed to 237 ppm for 4 hours (Dick et al. 1989). During exposure for 2 hours, the acetone concentration in expired air rose to 20 ppm in humans exposed to 100 ppm and to 90–100 ppm in those exposed to 500 ppm (DiVincenzo et al. 1973). After exposure to 100 ppm, the expired air concentration of acetone declined biphasically over the next 7 hours to 5 ppm. However, after exposure to 500 ppm, the expired air concentration dropped sharply to 2 ppm and declined to 1 ppm over the next 7 hours. DiVincenzo et al. (1973) observed prolonging the exposure duration to 4 hours resulted in a <2-fold increase in acetone levels in postexposure expired air, which may reflect a greater loss of acetone through metabolism and urinary excretion. Exercise during the exposure period increased the elimination almost 2-fold. In humans exposed to acetone at rest, during exercise at a constant workload, or during exercise

with step-wise increments in workload, expiration of acetone via the lungs amounted to 63, 74, and 138 mg, respectively, at approximately 0.25–4 hours postexposure and to 48, 77, and 197 mg, respectively, over the next 4–20 hours (Wigaeus et al. 1981). Excretion of acetone from the lungs and kidneys (combined) amounted to 16, 20, and 27% of the amount absorbed in the three respective groups of subjects. Urinary excretion amounted to only 1% of the total uptake. Women expired acetone more slowly than men after a 4-hour exposure to 127–131 ppm, but the percentages excreted by the lungs were not statistically significantly different between men and women (17.6% for men, 15.0% for women) (Nomiyama and Nomiyama 1974b).

Very little unchanged acetone is excreted in the urine (DiVincenzo et al. 1973; Kawai et al. 1992; Vangala et al. 1991; Wigaeus et al. 1981). Urinary excretion is biphasic (Pezzagno et al. 1986). Peak urinary excretion occurred between 1 and 3.5 hours after exposure (Matsushita et al. 1969b; Wigaeus et al. 1981). In male volunteers exposed to 497 or 990 ppm acetone for 4 hours, cumulative acetone excretion in urine at 18 hours after cessation of exposure was 89.5 mg, suggesting slow excretion of acetone in the urine (Vangala et al. 1991). The amount of acetone excreted in the urine is influenced by the exposure concentration, duration of exposure, and level of physical activity during exposure. The acetone concentration in the urine ranged from 0 to 17.5 mg/L at the end of the 8-hour workshift in 45 workers exposed to 0–70 ppm acetone (baseline urinary concentration in 343 nonexposed subjects averaged 1.5 mg/L) (Kawai et al. 1992). Acetone levels in the preshift urine samples were significantly higher than baseline levels when acetone exposure on the previous day was >15 ppm. There was no significant difference between baseline urine levels and preshift urine levels when the previous day's exposure was <15 ppm. In humans exposed for 6 hours, peak urinary levels were found within the first hour after exposure and were 5.2 mg/dL in subjects exposed to 1,000 ppm, 2.9 mg/dL in subjects exposed to 500 ppm, and 1.8 mg/dL in subjects exposed to 250 ppm (Matsushita et al. 1969b). The returned to baseline levels occurred within 48 hours for the 1,000 ppm group, within 32 hours for the 500 ppm group, and within 24 hours in the 250 ppm group. When human subjects were exposed for 6 hours/day for 6 days, urinary levels of acetone rose each day and declined to baseline levels by the following morning each day when the exposure concentration was 250 ppm (Matsushita et al. 1969a). At an exposure level of 500 ppm, however, urinary levels declined each day, but not to baseline levels. At the end of the 6-day exposure period, urinary acetone levels returned to baseline within 2 days for the 250 ppm group and within 3 days for the 500 ppm group. Therefore, excretion was more complete after exposure to lower concentrations, and at higher concentrations, acetone may accumulate somewhat during daily intermittent exposure, such as would be experienced occupationally. Total 24-hour urine content of acetone was 1.25 mg in subjects exposed to 100 ppm for 2 hours and 3.51 mg in subjects exposed to 500 ppm for

2 hours (DiVincenzo et al. 1973). Prolonging the duration to 4 hours in the 100-ppm group resulted in a total of 1.99 mg acetone in the urine. A slight increase in the urinary content of acetone (1.39 mg) was found when humans exposed to 100 ppm for 2 hours exercised during the exposure. The nature of physical activity during exposure also influenced the urinary excretion. At 3–3.5 hours after exposure, 8.5, 8.5, and 13.4 mg were excreted by the kidneys in subjects exposed at rest, during exercise at a constant workload, and during exercise with stepwise increments in workload, respectively (Wigaeus et al. 1981).

One human controlled exposure study on excretion was identified, in which volunteers ingested 60–80 mg/kg acetone (Haggard et al. 1944). The elimination of acetone in expired air and urine was determined; acetone concentration in expired air was measured 1 hour after administration and 30 minutes thereafter and in urine, acetone concentrations were determined 2 hours later. Over an observation period of 4 hours, the authors estimated that 64–93% of the administered dose was metabolized and 7–36% was eliminated via urine and expired air.

The only other information regarding excretion of acetone in humans after oral exposure is from case reports of accidental or intentional ingestion of materials containing acetone plus other components that may have influenced the elimination of acetone. In a man who ingested liquid cement containing 18% acetone (231 mg/kg), 28% 2-butanone, and 29% cyclohexanone and 720 mL sake (alcoholic beverage), the plasma level of acetone was ≈1,120 µg/mL 5 hours after ingestion and declined to 65 µg/mL at 18 hours, 60 µg/mL at 24 hours, and <5 µg/mL at 48 hours (Sakata et al. 1989). A first-order plasma elimination rate constant of 0.038/hour and a half-time of 18.2 hours were calculated. The urinary level of acetone decreased gradually from about 123 µg/mL at 5 hours after ingestion to about 61 µg/mL at 19 hours. In a case of an individual known to have alcohol use disorder who had ingested nail polish remover and whose blood acetone level was 0.25 g/dL (2.5 mg/mL) upon admission to the hospital, the blood level of acetone declined in a log-linear manner to about 0.06 g/dL (0.6 mg/mL) about 86 hours after admission, with a half-life of 31 hours (Ramu et al. 1978). The calculated clearance of acetone from the lungs was 29 mL/minute or 0.39 mL/minute/kg. A half-time of 25 hours for lung clearance was calculated, which is in agreement with the observed plasma elimination half-time of 31 hours. The serum acetone level of a 30-month-old male child was 445 mg/100 mL (4.45 mg/mL) 1 hour after ingestion of a 6-ounce bottle of nail polish remover (65% acetone) and declined to 2.65 mg/mL at 117 hours, to 0.42 mg/mL at 48 hours, and to 0.04 mg/mL at 72 hours (Gamis and Wasserman 1988). The half-time of acetone in this patient was 19 hours in the severe early stage and 13 hours in later stages of intoxication, which suggested to the authors greater metabolism and/or excretion in children, compared with adults.

Information regarding excretion of acetone after dermal exposure of humans is limited, but the main route of excretion is via the lungs, with little excreted in the urine. Application of an unspecified quantity of acetone to a 12.5 cm^2 area of skin of volunteers for 2 hours/day for 4 days resulted alveolar air levels of 5–12 ppm and urinary concentrations of 8–14 µg/mL on each day (Fukabori et al. 1979). These levels returned to baseline levels by the next day after each exposure. Higher alveolar air and urinary levels were obtained when the daily exposure increased to 4 hours/day: 25–34 ppm in alveolar air, and 29–41 µg/mL in urine, but these levels also returned to baseline each day.

Physiological status may influence the disposition of endogenous and exogenous acetone in humans. In groups of nonobese patients fasted for 3 days, obese patients fasted for 3 days, and obese patients fasted for 21 days and injected intravenously with ^{14}C-acetone, 8–29% of the urinary acetone was ^{14}C-labeled (Reichard et al. 1979). The concentrations of urinary acetone were 1.2, 0.4, and 2.6 µmol/mL in 3-day-fasted nonobese, 3-day-fasted obese, and 21-day-fasted obese patients, respectively. The rates of urinary acetone excretion were 1.2, 0.4, and 1.7 µmol/minute, respectively, suggesting marked renal reabsorption or back-diffusion. The percentages of measured acetone production that could be accounted for by excretion via the lungs were 14.7, 5.3, and 25.2%, respectively. The percentages that could be accounted for by urinary excretion were 1.4, 0.6, and 1.3%, respectively. Cumulative excretion of ^{14}C-carbon dioxide during the 6-hour turnover study periods accounted for 17.4, 21.5, and 4.9%, respectively. Thus, nonobese subjects fasted for 3 days excreted more acetone at higher rates than did obese subjects fasted for 3 days. However, excretion by the obese patients fasted for 21 days exceeded that by both 3-day-fasted groups. These differences are probably related to the effect that the degree of starvation ketosis has on the metabolism and overall disposition of acetone.

As in humans, acetone is excreted mainly by the lungs of animals. Studies in animals have followed the elimination of acetone from blood and tissues, excretion of acetone and carbon dioxide in expired air, and the urinary excretion of formic acid.

Blood levels of acetone were highest immediately after a 4-hour exposure of rats to acetone (Charbonneau et al. 1986b). In rats exposed to 10,000 ppm, the blood level dropped from 2,114 to 5 µg/mL in 25 hours. In rats exposed to 15,000 ppm, the blood level dropped from 3,263 to 50 µg/mL after 25 hours. Elimination from blood was biphasic in rats exposed to 10,000 and 15,000 ppm, perhaps indicating saturation. Elimination from blood was triphasic in rats exposed to 1,000, 2,500, or 5,000 ppm and was complete within 17–25 hours. In dogs exposed to 100, 500, or 1,000 ppm acetone for 2 hours,

blood levels declined in a log-linear manner with a half-time of 3 hours, similar to that observed in humans (DiVincenzo et al. 1973). Blood levels declined from 25 mg/L immediately after exposure to 10 mg/L at 5 hours postexposure for the 1,000 ppm group, from 12 to 3 mg/L for the 500 ppm group, and from 4 to 1.5 mg/L for the 100 ppm group. Elimination of radioactivity and ^{14}C-acetone was fastest from blood, kidney, lung, brain, and muscle tissues of mice exposed to 500 ppm ^{14}C-acetone for 6 hours, with half-times of 2–3 hours during 6 hours postexposure (Wigaeus et al. 1982). Elimination of acetone was complete in 24 hours in all tissues, but radioactivity (indicative of metabolites) was still present in all tissues except blood and muscle. When rats were exposed for 5 days, acetone tended to accumulate in adipose tissue.

Excretion of acetone in air followed pseudo-first-order kinetics in rats exposed to <20 ppm acetone for 1–7 days, while at higher concentrations, saturation kinetics were observed (Hallier et al. 1981). In male rats exposed to 500 ppm ^{14}C-acetone for 6 hours, 42 µmol of radioactive acetone and 37 µmol ^{14}C-carbon dioxide were excreted in the expired air during a 12-hour postexposure period, with 95 and 85%, respectively, recovered in the first 6 hours postexposure (Wigaeus et al. 1982). Radioactive acetone accounted for 52% and radioactive carbon dioxide accounted for 48% of the expired radioactivity. The concentration of acetone in the expired breath of dogs exposed to 100, 500, or 1,000 ppm acetone for 2 hours declined in a log-linear manner (DiVincenzo et al. 1973). The breath levels were directly related to the magnitude of exposure. Breath levels declined from 1.6 ppm at 30 minutes after exposure to 0.3 ppm at 300 minutes in the 100-ppm group, from 6.8 to 1.5 ppm in the 500 ppm group, and from 15 to 4 ppm in the 1,000 ppm group.

Urinary excretion of formic acid was followed for 7 days in rats exposed to 62,000 ppm acetone for 2 days. The rate of formic acid excretion was 344 µg/hour compared with 144 µg /hour in controls (Hallier et al. 1981).

Information regarding the excretion of acetone after oral exposure in animals is available only for rats. As is the case after inhalation exposure, acetone, mainly as carbon dioxide, is excreted primarily by the lungs. In a rat given 1.16 mg/kg ^{14}C-acetone by gavage in water, expiration of ^{14}C-carbon dioxide totaled 47.4% of the administered radioactivity over the 13.5-hour collection period (Price and Rittenberg 1950). In another experiment, a rat was given 7.11 mg/kg radioactive acetone. A small amount of radioactive acetone (10%) was found in the expired air. Radioactive carbon dioxide and acetate were also detected. In a rat made diabetic by alloxan and given 6.15 mg/kg ^{14}C-acetone, a total of 7.29% of the administered radioactivity was expired as acetone and 51.78% as carbon dioxide. Radioactive acetate was detected in

the urine. These data indicate that very little acetone (<10%) was excreted by the lungs after small doses of acetone. A major fraction was oxidized to carbon dioxide and some of the derived carbon was used for acetylation. The diabetic rat was also able to oxidize acetone, but only to ≈70% of that in the non-diabetic rat.

The dose of acetone influences the elimination of acetone from blood (Plaa et al. 1982). At a dose of 78.44 mg/kg, the maximum blood level of 200 µg/mL at 3 hours declined to 10 µg/mL at 12 hours, where it remained for the next 12 hours (data inadequate to calculate total body clearance). At a dose of 196.1 mg/kg, the maximum blood level of 400 µg/mL at 6 hours declined biphasically to 50 µg/mL at 12 hours and to 30 µg/mL at 18 hours where it remained at 24 hours (total body clearance of 64 mL/hour). At a dose of 784.4 mg/kg, the maximum blood level of 900 µg/mL at 1 hour declined to 300 µg/mL at 12 hours, to 110 µg/mL at 18 hours, and to 50 µg/mL at 24 hours (total body clearance of 86 mL/hour). At a dose of 1,961 mg/kg, the maximum blood level of 1,900 µg/mL at 3 hours declined slowly to 400 µg/mL at 24 hours (total body clearance of 75 mL/hour). Thus, total body clearance was independent of dose, but the half-time for elimination increased from 2.4 hours for 196.1 mg/kg, to 4.9 hours for 784.4 mg/kg, and 7.2 hours for 1,961 mg/kg.

The vehicle (corn oil or water) in which acetone is administered has little influence on the elimination of acetone from blood (Charbonneau et al. 1986a). After gavage treatment of rats with 78, 196, 392, 784, or 1,177 mg/kg acetone in corn oil or water, elimination was biphasic for the two higher doses and triphasic for the lower doses. Acetone elimination from blood declined to <5 to <10 µg/mL by 18–26 hours for all doses, but minor differences were found between water and corn oil as vehicle. The blood concentration curves from rats given acetone in water more closely resembled those from rats exposed by inhalation.

No studies were located regarding excretion of acetone by animals after dermal exposure.

Contrary to evidence from human studies, no major differences were observed among fed non-diabetic rats, fasted non-diabetic rats, and fed diabetic rats in the excretion of ^{14}C-carbon dioxide from the lungs after intraperitoneal injections of ^{14}C-acetone (Mourkides et al. 1959). However, the dose level influenced the pattern of metabolism and, hence, the excretion of carbon dioxide. Rats that received 9.3–22.7 mg/kg radioactive acetone rapidly metabolized acetone, as evidenced by exhalation of 24–43% of the administered radioactivity as ^{14}C-carbon dioxide within the first 3 hours after dosing. Rats that received 258–460 mg/kg radioactive acetone exhaled only 2.1–5.7% of the radiolabel as carbon dioxide in the first 3 hours, 2.8–7.8% in the next 3–6 hours, and 16–29% in the next 6–24 hours. Rats injected

subcutaneously with ^{14}C-acetone also excreted the derived radioactive carbon mainly as carbon dioxide. In rats fasted for 24 hours and given 170 mg/kg radioactive acetone, 27% of the radiolabel was excreted as carbon dioxide in 4 hours (Sakami and LaFaye 1951). Rats fasted for 48 hours before the subcutaneous dose of 174 mg/kg radioactive acetone excreted 53% of the radiolabel as carbon dioxide over a 14-hour collection period (Sakami 1950).

Fasted pregnant rats had an enhanced capacity for acetone elimination compared with fasted or fed virgin rats or fed pregnant rats, after intravenous dosing with 100 mg/kg (Peinado et al. 1986). While the elimination of acetone from plasma was biphasic in all groups, the fasted pregnant rats eliminated acetone at a faster rate than the other groups.

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

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

PBPK models have been developed to simulate the behavior of acetone in rats and humans exposed by various routes (Clewell et al. 2001; Gentry et al. 2002; Huizer et al. 2012; Kumagai and Matsunaga 1995; Mörk and Johanson 2006). Clewell and coworkers (Clewell et al. 2001; Gentry et al. 2002) developed a PBPK model intended to simulate the behavior of isopropanol and its major metabolite, acetone, in rats and humans for intravenous, intraperitoneal, oral, inhalation, and dermal exposure. The model was specifically intended to be used for human health risk assessment for isopropanol. The model is capable of simulating exposures to acetone as well (Gentry et al. 2003) and was expanded to simulate exposure to isopropanol during pregnancy (Gentry et al. 2002). Validation of acetone metabolism was performed by use of intravenous, oral, and inhalation exposure data from rats and by use of inhalation and oral exposure data from humans. Huizer et al. (2012) used a similar model to investigate uncertainty and variability in biological parameters after simulated occupational exposure to isopropanol. The PBPK model developed

by Mörk and Johanson (2006) accounts for variation in workload by separating working and resting muscle groups.

The PBPK model of Kumagai and Matsunaga (1995) was designed to account for uptake of acetone in the mucous layer of the respiratory tract. By adjusting the value for the volume of the mucous layer and the rate of respiration, the study authors found that the simulated acetone concentrations in arterial blood, end exhaled air, urine, and fatty tissues were well matched to experimental data.

Mörk and Johanson (2006) designed a PBPK model for acetone to account for differences in the behavior of acetone in blood and exhaled air at different levels of physical exercise. The model involves deeper parts of the mucous membrane in absorption and desorption of acetone than the ones used in previous modeling exercises and includes separate compartments for working and resting muscles. In a follow-up study, the authors used Bayesian population analysis to derive improved estimates of population variability and uncertainty in the PBPK model parameters (Mörk et al. 2009). Using the PBPK model, Mörk and Johanson (2010) derived chemical-specific adjustment factors (CSAFs) for acetone by Monte Carlo simulations. According to the simulations, CSAFs for occupational exposure were 1.6, 1.8, and 1.9 for 90^{th}, 95^{th}, and 97.5^{th} percentiles, respectively. The corresponding CSAFs for the general population were 2.1, 2.9, and 3.8. CSAFs for children from 3 months of age to 10 years of age were 4.2–4.8, 4.7–5.0, and 5.0–5.9 for the 90^{th}, 95^{th}, and 97.5^{th} percentiles, respectively.

3.1.6 Animal-to-Human Extrapolations

Acetone appears to have similar target organs in animal and humans, such as the hematological system and the CNS. Toxicokinetic studies have been conducted in both humans and animals, especially in humans exposed by inhalation. There appears to be very few differences between animal species, and the dog appears to be a good model for extrapolating absorption results to humans (DiVincenzo et al. 1973). Metabolic pathways have been elucidated primarily in rats, but mice and rabbits have also been studied. Metabolism involves three different pathways of gluconeogenesis (Casazza et al. 1984; Kosugi et al. 1986a, 1986b). The first step in the metabolism of acetone is dependent on CYP2E1 (Casazza et al. 1984), which acetone induces, and this induction has been demonstrated in rats (Johansson et al. 1988), mice (Bánhegyi et al. 1988), hamsters (Ueng et al. 1991), and rabbits (Ding and Coon 1990). It appears that the metabolic pathways operate in all tested species. The distribution of acetone has been studied only in mice exposed by inhalation (Wigaeus et al. 1982). Acetone was widely distributed to organs and

tissues throughout the body. This is expected to be true for all species by virtue of its high water solubility, facilitating distribution through the water compartments of the body.

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

Several lines of evidence from studies in animals indicate that sex differences exist in the susceptibility to effects caused by acetone. Male rats were more susceptible than female rats to acetone's hematological, hepatic, and renal effects, and effects on reproductive organs (American Biogenics Corp. 1986; NTP 1991). In a study of humans exposed to acetone in air during light exercise for 2 hours, women had higher levels of acetone in blood, saliva, and exhaled air than men (Ernstgard et al. 2003). While results in animals cannot always be extrapolated to humans, it is possible that men may be more susceptible than women to the hematological, hepatic, renal, and reproductive effects of acetone. Furthermore, acetone may exacerbate preexisting hematological, liver, kidney, or reproductive disorders in humans.

In a lethality study among male and female newborn rats, male and female 14-day-old rats, and male adult rats, susceptibility to the lethal effects of acetone generally decreased with increasing maturity (Kimura et al. 1971).

Pregnant rats exposed to acetone by inhalation during gestation had reduced body weights (NTP 1991), while nonpregnant rats exposed to a higher concentration for a longer duration did not show any effects on body weight (Goldberg et al. 1964). Pregnant rats also had lower plasma and liver levels of acetol, the first intermediate in the overall metabolism of acetone, than virgin rats (Peinado et al. 1986), suggesting differences in the rate of acetone metabolism. It is possible that the condition of pregnancy made these rats more susceptible to body weight changes, and this susceptibility might apply to humans. Exposure to acetone and increased endogenous ketone levels through gestational diabetes are known to increase hepatic CYP2E1 in pregnant mothers; however, gestational diabetes does not appear to increase placental CPY2E1 in humans (Pasanen 1988).

The role of acetone in fasting and diabetes is complicated and not well understood (Reichard et al. 1979, 1986). Acetone is produced endogenously and, as demonstrated in humans, more acetone is produced endogenously by fasting, which can result in ketosis (Reichard et al. 1979). In one human study, subjects on various ketogenic diets with lower body mass index produced more acetone (Prabhakar et al. 2015). In diabetics, ketoacidosis has been identified as the main pathological response to malabsorption of glucose (Dabek et al. 2020). Ketogenic diets, which induce a mild ketonemia, have been shown to promote endogenous ketone body production (Dabek et al. 2020). Acetone exposure of rats resulted in a reduced insulin-stimulated glucose oxidation rate, and the reduction was greater in fasted rats than in fed rats, indicating that the insulin resistance indigenous to fasting may be attributed in part to metabolic influences of acetone (Skutches et al. 1990).

Diabetics may also be more susceptible to the effects of acetone. Acetone-induced insulin resistance (Skutches et al. 1990) might also result in greater hyperglycemia in diabetics. Patients with diabetic ketoacidosis have higher plasma levels of endogenous acetone (Reichard et al. 1986), and exposure to exogenous acetone may increase the levels further. Similar results were found in rats. Diabetic rats had higher plasma acetone levels than nondiabetic rats after treatment with the same doses of acetone, due to the higher endogenous level of acetone in the diabetic rats and differences in the metabolism of acetone to isopropyl alcohol (Lewis et al. 1984). Diabetic rats were also less able to oxidize acetone than nondiabetic rats (Price and Rittenberg 1950). While research suggests that the metabolic pathway for acetone is similar in rats and humans, studies of acetone exposure in diabetic and obese animals have been conducted at higher doses than expected background human environmental exposures. That said, a human study showed decreasing breath acetone levels along with decreasing insulin levels in type 1 diabetic patients during a hypoglycemic clamp, a technique involving infusion of insulin and glucose to

produce a stepwise reduction in blood glucose (Turner et al. 2009). Results of this study indicate that variation in metabolic status and/or changes in glycaemia in type 1 diabetics may affect acetone levels.

Groups of obese and lean mice maintained on high-fat diets were given acetone in drinking water (2%) for 2 weeks to induce CYP2E1 (Dey and Cedebaum 2007). This study used homozygous obese C57BL/6J ob/ob mice in the obese groups, which are leptin-deficient mice that are bred to exhibit obesity (Drel et al. 2006). Controls consisted of obese and lean mice maintained on the same diet as the experimental mice but not given acetone. Acetone induced more extensive fatty changes, and mild necrosis in the livers of the obese mice compared with the livers of both control lean and control obese mice. The acetone-treated obese mice also had higher caspase-3 activity; numerous apoptotic hepatocytes; increased protein carbonyls, malondialdehyde, 4-hydroxynonenal-, and 3-nitrotyrosine-protein adducts; and elevated levels of inducible nitric oxide synthase. These results suggest that obesity contributes to liver toxicity and that the damage is enhanced by exposure to acetone through its induction of CYP2E1.

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 acetone 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 acetone 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 acetone 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

Acetone concentrations in expired air, blood, and urine have been monitored in a number of studies of humans exposed to acetone in the workplace as well as in controlled laboratory situations, and studies show that acetone levels in the body are an accurate indicator of acetone exposure (Leung and Paustenbach 1988). A study of 659 factory workers exposed to acetone occupationally reported a strong positive correlation between acetone levels in workplace air and acetone levels in workers' urine after their shift (Ghittori et al. 1987). However, acetone is cleared from breath, urine, and blood within 1–3 days, so these methods are useful for monitoring only for recent exposure to acetone. In addition, these methods can be used to detect or confirm relatively high exposure to acetone, such as what might occur in the workplace or from accidental ingestion; but they cannot be used to detect lower environmental exposures in the general population at levels that are expected to be lower than those observed in occupational settings. The detection of acetone odor in the breath can alert a physician that a nondiabetic patient has been exposed to acetone (Harris and Jackson 1952; Strong 1944). It should be noted that exposure to other chemicals that are metabolized to acetone, such as isopropyl alcohol, could also lead to elevated blood, expired air, or urinary levels of acetone.

Levels of endogenous acetone can fluctuate greatly due to normal diurnal variations (Wildenhoff 1972). In addition, physical exercise (Koeslag et al. 1980), nutritional status and fasting (Jones 1987; Kundu et al. 1993; Levy et al. 1973; Lewis et al. 1977; Neiman et al. 1987; Reichard et al. 1979; Rooth and Carlstrom 1970; Williamson and Whitelaw 1978), trauma (Smith et al. 1975), and pregnancy and lactation (Bruss 1989; Paterson et al. 1967) place high energy demands upon the body, resulting in

increased fatty acid utilization and higher than average blood levels of acetone. Diabetes (Kobayashi et al. 1983; Levey et al. 1964; Reichard et al. 1986; Rooth 1967; Rooth and Ostenson 1966) and alcohol use (Phillips et al. 1989; Tsukamoto et al. 1991) may result in higher levels of endogenous acetone. Infants and young children typically have higher acetone in their blood than adults due to their higher energy expenditure (Peden 1964). These factors and physiological states can complicate measuring acetone levels in blood, breath, and urine for biomonitoring purposes.

In a group of 115 workers, alveolar air samples obtained during the workshift were collected at the same time as breathing zone acetone concentrations (Brugnone et al. 1980). The mean ratio of alveolar air acetone and breathing zone acetone was 0.288. Correlations were high between alveolar air concentrations and breathing zone concentrations. Because the alveolar air samples and breathing zone concentrations were collected at the same time, and because the equilibration of alveolar air with environmental air requires some time, the alveolar samples might not necessarily reflect the environmental concentration. Similar results were obtained in a group of 20 workers in a shoe factory in which the mean environmental air concentrations ranged from 10 to 12 ppm at four sampling times (Brugnone et al. 1978). The mean alveolar concentrations ranged from 2.75 to 3.75 ppm at three sampling times during the workshift. The correlation was good between workroom air concentration and alveolar air concentration, indicating that alveolar air concentrations of acetone are useful for monitoring concurrent occupational exposure to acetone. In a group of 110 male workers exposed to acetone for an average of 14.9 years, alveolar air samples were collected before work and at the end of work on 2 consecutive days (Fujino et al. 1992). The breathing zone concentrations of acetone were measured for each individual with personal monitors and ranged from 0 to about 1,200 ppm, with most concentrations between 100 and 500 ppm. The average concentration of acetone in alveolar air before exposure on the first day was 2.95 ppm. Alveolar air concentrations at the end of the workday (range of about 20–300 ppm, average not reported) correlated strongly with exposure concentrations (r=0.65). It was estimated that the alveolar air concentrations corresponding to 750 ppm (the current American Conference of Governmental Industrial Hygienists [ACGIH] TLV for short-term exposure to acetone) and to the Japan Association of Industrial Health acceptable concentration of 200 ppm were 177 and 56.2 ppm, respectively.

Expired air concentrations of acetone have also been studied in volunteers exposed to acetone in controlled laboratory situations. In 11 men and 11 women exposed to 237 ppm acetone for 2 or 4 hours, alveolar breath samples collected immediately after exposure contained mean levels of acetone of 21.5 ppm in those exposed for 2 hours and 25.8 ppm in those exposed for 4 hours (Dick et al. 1989). The

alveolar air concentrations of acetone dropped to 12.8 ppm by 90 minutes after the 4-hour exposure and to baseline levels of 0.6 ppm by 20 hours postexposure. In humans exposed to acetone at up to 1,250 ppm for up to 7.5 hours/day in a complex protocol for up to 6 weeks, the rate of respiratory excretion was a function of the duration, and the concentration of acetone in breath after exposure was directly related to the time-average concentration during exposure, with constant duration (Stewart et al. 1975). The length of time after exposure in which acetone could be detected in breath was related to the magnitude of exposure; acetone was still readily detectable 16 hours after exposure to 1,000 or 1,250 ppm for 7.5 hours. Breath analysis can be used as a rapid method to estimate the magnitude of recent acetone exposure, but should only be used to assess recent exposures because the elimination of acetone in expired air is generally complete within 1 day.

As discussed in Section 3.1.4, the level and nature of physical activity, the exposure concentration, the duration of exposure, and biological sex can influence the rate and amount of acetone elimination in the breath (DiVincenzo et al. 1973; Nomiyama and Nomiyama 1974a, 1974b; Pezzagno et al. 1986; Wigaeus et al. 1981). In general, more acetone is expired faster following exposure to high concentrations than to low concentrations (DiVincenzo et al. 1973). Doubling the duration of exposure almost doubles the total amount of acetone expired. Exercise during exposure eliminates nearly twice the amount in expired air compared with exposure to the same concentration at rest, due to increased uptake from increased pulmonary ventilation. Furthermore, exercising at stepwise increments in workload during exposure results in greater respiratory elimination than exercising at a constant workload (Wigaeus et al. 1981). Women appeared to expire acetone more slowly than men, but the total expired by women was not statistically significantly different than the total expired by men (Nomiyama and Nomiyama 1974a, 1974b).

Acetone is mainly excreted in the expired air after oral exposure as well as after inhalation exposure (see Section 3.1.4). Because urinary clearance of acetone is minimal, the calculated clearance of acetone from the lungs was 29 mL/minute or 0.39 mL/minute/kg for a patient who ingested nail polish remover using an average minute ventilation of 9.65 L/minute based on the patient's age, weight, and sex (Ramu et al. 1978). With a volume of distribution of 0.82 L/kg, the calculated half-life was 25 hours.

Monitoring of expired air for acetone exposure should take into consideration baseline levels of acetone, because acetone is produced endogenously in the body, especially during fasting and in diabetics. In addition, the ingestion of ethanol can influence the breath levels of acetone. Endogenous levels of acetone in normal humans averaged 0.56 ppm (Phillips and Greenberg 1987). Endogenous levels of

acetone in alveolar air in a group of volunteers in an experimental study averaged 0.108 ppm (Wigaeus et al. 1981). Breath sampling of volunteers under normal conditions found a mean alveolar gradient (difference between concentrations in exhaled air and inhaled ambient air) of 27.91 for acetone, indicating that the rate of *in vivo* synthesis is greater than the rate of clearance (Phillips et al. 1999). In healthy men who had fasted for 12 hours, the breath acetone levels ranged from 0.96 to 1.7 ppm (Jones 1987). Fasting for 36 hours resulted in average acetone breath levels of 14–66 ppm. However, in fasting men who ingested 0.25 g/kg of ethanol, the breath acetone levels decreased by 40% after a 12-hour fast and by 18% after a 36-hour fast (Jones 1988).

Acetone is metabolized to carbon dioxide (see Section 3.1.3), which is eliminated in expired air (see Section 3.1.4). However, because carbon dioxide is the main constituent of normal expired air, expired carbon dioxide has not been monitored to determine acetone exposure.

Although unchanged acetone is excreted mainly by the lungs, urinary levels are sufficiently high for monitoring purposes. In a group of 104 workers employed at factories in which breathing zone levels of acetone ranged from <242 to <1,452 ppm, urine was collected before the workshift and 4 hours after the shift started (Pezzagno et al. 1986). A close correlation was found between the TWA workroom concentration and the urinary concentration of acetone. The equation obtained was: urinary concentration (µmol/L) = 0.033 x TWA environmental concentration (µmol/m^3) - 0.005 ($r=0.94$, $n=104$). In another study of 28 workers, personal breathing zone monitoring revealed wide variation depending on the type of job and ranged from <1 to 30 ppm (Kawai et al. 1990a). Results of stationary monitoring revealed workroom concentrations ranging from 1.4 to 16.2 ppm. Urine was collected at the end of the workshift, and acetone was detected in the urine of all the workers. The concentration of acetone in urine was linearly correlated with the breathing zone concentration as follows: acetone in urine (mg/L) = 0.10 + 0.40 x breathing zone concentration (ppm) ($r=0.90$, $p<0.01$). Therefore, urinary levels of acetone are useful for monitoring occupational exposure. In another study, postshift urinary levels of acetone in 45 workers exposed to 0–70 ppm acetone ranged from 0 to 17.5 mg/L (Kawai et al. 1992). The baseline urinary level of acetone in nonexposed subjects was 1.5 mg/L. Acetone levels in preshift urine samples were significantly higher than baseline levels when acetone exposure on the previous day was >15 ppm, but there was no significant difference between baseline urine levels and preshift urine levels when acetone exposure on the previous day was <15 ppm. In a group of 110 male workers exposed to acetone for an average of 14.9 years, urine samples were collected before work and at the end of work for 2 consecutive days (Fujino et al. 1992). The breathing zone concentrations of acetone were measured for each individual with personal monitors and ranged from 0 to about 1,200 ppm, with most concentrations

between 100 and 500 ppm. The average urinary concentration before exposure on the first day was 2.44 mg/L. Urinary levels at the end of the workshift (range of about 5–150 ppm, average not reported) correlated with exposure concentration (r=0.71). It was estimated that the urinary concentrations corresponding to 750 ppm (the current ACGIH TLV for short-term exposure to acetone) and to the Japan Association of Industrial Health acceptable concentration of 200 ppm were 76.6 and 21.6 mg/L, respectively.

Acetone has also been detected in the urine of 15 men and women exposed to acetone under controlled laboratory conditions. In volunteers exposed to 23–208 ppm for 2–4 hours, the urinary concentrations of acetone immediately after exposure ranged from 18.8 to 155.2 µmol/L and displayed statistically significant linear relationships with the exposure concentrations (Pezzagno et al. 1986). The regression equation for subjects exposed for 2 hours at rest was: acetone in urine (µmol/L) = 0.0125 x environmental concentration (µmol/m^3) + 5.87 (r=0.98, n=5). For subjects exposed for 4 hours at rest the equation was: acetone in urine (µmol/L) = environmental concentration (µmol/m^3) + 6.97 (r=0.96, n=5). For the subjects exposed for 2 hours with exercise, the equation was: acetone in urine (pmol/L) = environmental concentration (µmol/m^3) - 4.52 (r=0.99, n=5). At 4 hours after the cessation of exposure, the urine concentration increased to 120% of that measured immediately after exposure, then fell to 65% at 7 hours, 45% at 9 hours, 35% at 12 hours, and 15% at 20 hours post-exposure. Urinary acetone was completely cleared within 20 hours from subjects exposed to 242 or 542 ppm for 2 hours, regardless of whether or not they had exercised during exposure (Wigaeus et al. 1981). In a group of subjects exposed to acetone vapors for about 6 hours, urinary levels of acetone peaked within the first hour after exposure to 1.8 mg/dL at 250 ppm, 2.9 mg/dL at 500 ppm, and 5.3 mg/dL at 1,000 ppm and declined rapidly post-exposure to control levels within 24, 32, and 48 hours, respectively (Matsushita et al. 1969b). In subjects exposed to 250 ppm for 6 hours/day for 6 days either at rest or during exercise, the urinary levels returned to pre-exposure levels by the next morning each day and within 48 hours after the last exposure day, regardless of whether or not they had exercised (Matsushita et al. 1969a). However, in subjects exposed to 500 ppm 6 hours/day for 6 days, the level of acetone in the urine fell each day, but not to pre-exposure baseline levels. After the last day of exposure, urinary levels returned to baseline levels within 3 days. Baseline urinary levels of acetone in these subjects were about 0.1 mg/dL. Therefore, the rate of urinary clearance is dependent on the magnitude of exposure.

Acetone can also be detected in urine after oral exposure. In a male patient who was admitted to the hospital in a comatose condition after ingesting sake (alcoholic beverage) and liquid cement containing 18% acetone (231 mg/kg), urinary clearance of acetone was followed, but after he had been subjected to

gastric lavage (Sakata et al. 1989). Urine levels of acetone decreased gradually from 123 µg/mL at 5 hours after ingestion to about 61 µg/mL at 19 hours. Acetone then disappeared more rapidly from the urine.

Formic acid was detected in the urine of rats collected for 7 days after exposure to 62,000 ppm acetone in air, and was excreted at a rate of 344 µg formic acid/hour, compared with controls that excreted formic acid at a rate of 144 µg/hour (Hallier et al. 1981). The authors concluded that the low rate of formic acid excretion by rats suggests that 24 hours is an insufficient period of time for following formic acid excretion in order to biomonitor acetone exposure in humans.

Blood levels of acetone can also be useful for exposure monitoring, but blood sampling is less desirable because it is more invasive. In a group of 110 male workers exposed to acetone for an average of 14.9 years, blood samples were collected before work on the first day and at the end of work on the second day (Fujino et al. 1992). The breathing zone concentrations of acetone were measured for each individual with personal monitors and ranged from 0 to about 1,200 ppm, with most concentrations between 100 and 500 ppm. The average blood concentration before exposure on the first day was 3.80 mg/L. Blood levels at the end of the workshift (range of about 2 to 225 mg/L, average not reported) correlated strongly with exposure concentration (r=0.65). It was estimated that the blood concentrations corresponding to the current ACGIH TLV for short-term exposure to acetone of 750 ppm and to the Japan Association of Industrial Health acceptable concentration of 200 ppm were 118 and 41.4 mg/L, respectively. Subjects exposed to 100 or 500 ppm for 2 or 4 hours had a blood acetone clearance half-life of 3 hours (DiVincenzo et al. 1973). The rate of blood elimination was constant regardless of blood acetone concentration. In volunteers exposed to 237 ppm acetone, blood levels of acetone averaged 2.0 µg/mL preexposure, 9.0 µg/mL after 2 hours of exposure, 15.3 µg/mL after 4 hours of exposure, 11.9 µg/mL at 90 minutes postexposure, and 1.5 µg/mL at 20 hours postexposure (Dick et al. 1989). Therefore, elimination of acetone from blood was complete 20 hours after exposure. Results were similar for subjects exposed to acetone vapors for 6 hours (Matsushita et al. 1969b). Maximum blood levels of acetone achieved and blood clearance of acetone were exposure concentration related, but not in direct proportion. At an exposure level of 250 ppm, the maximum blood level was 2 mg/dL and returned to baseline levels within 24 hours. At an exposure level of 500 ppm, the maximum blood level was 4.7 mg/dL and returned to baseline levels within 32 hours. At an exposure level of 1,000 ppm, the maximum blood level of 6.0 mg/dL returned to baseline levels within 48 hours. In subjects exposed 6 hours/day for 6 days, maximum blood levels on each day were similar to those seen in the subject exposed only 1 day (Matsushita et al. 1969a). Blood levels returned to baseline levels on the morning

after exposure on each day when the exposure concentration was 250 ppm. With an exposure concentration of 500 ppm, however, blood levels declined each day, but not to baseline levels. As with urinary clearance, blood clearance of acetone at the end of the 6-day exposure period returned to baseline within 2 days at 250 ppm and within 3 days at 500 ppm. Baseline blood levels of acetone in these subjects were about 0.1 mg/dL. In subjects exposed to 242 or 542 ppm for 2 hours, the arterial blood concentration 1 hour post-exposure plotted as a function of total uptake gave a linear relationship, indicating that an arterialized capillary sample during or after exposure may be useful for exposure monitoring (Wigaeus et al. 1981). In humans exposed to acetone up to 1,250 ppm for up to 7.5 hours/day in a complex protocol for up to 6 weeks, the concentration of acetone in venous blood was directly related to the vapor concentration and duration of exposure and inversely related to the time elapsed following exposure (Stewart et al. 1975). Using a physiologically-based pharmacokinetic model, Leung and Paustenbach (1988) calculated a biological exposure index of 35 mg acetone/L blood for occupational exposure. The authors reported a baseline acetone blood level of 2 mg/L. This value is in agreement with baseline levels determined in other studies: 0.016 mM (0.93 mg/L) (Gavino et al. 1986), 0.03 mmol/L (1.74 mg/L) (Trotter et al. 1971), and 2,100 ppb (2.1 mg/L) (Ashley et al. 1992).

Similar rates of blood acetone clearance occur after oral exposure. In a patient admitted to the hospital in a comatose condition after ingesting liquid cement containing 18% acetone (231 mg/kg), the plasma level of acetone was 110 µg/mL at 5 hours after ingestion and declined to 65 µg/mL at 18 hours, to 60 µg/mL at 20 hours, and to <5 µg/mL at 48 hours (Sakata et al. 1989). The gastric contents of a patient were analyzed using infrared spectrophotometry and found to contain 1 mL acetone/100 mL (Fastlich 1976). This analytical method was developed to detect volatile solvents in gastric contents due to accidental ingestion of these solvents.

Acetone has been identified in breast milk of lactating women (Pellizzari et al. 1982).

3.3.2 Biomarkers of Effect

The most consistently observed effect of acetone exposure in animals is the induction of microsomal enzymes, particularly of CYP2E1 (see Sections 2.21, 3.1.3, and 3.4). The enzyme induction has been associated with increased liver weights and hepatocellular hypertrophy due to the increased protein content (NTP 1991). Acetone itself is only moderately toxic to the liver of animals, as most studies have found no clinical or histological evidence of liver damage. However, increased levels of serum alanine aminotransferase beyond the expected range, which constitutes clinical evidence of liver damage, have

been found in rats in one study (American Biogenics Corp. 1986). CYP2E1 is associated with the metabolism of acetone itself, but acetone is not metabolized to toxic intermediates (see Section 2.3). However, the induction of this enzyme by acetone is the mechanism by which acetone potentiates the hepatotoxicity, nephrotoxicity, genotoxicity, and perhaps the reproductive and hematological toxicity of other chemicals (see Section 2.6). CYP2E1 can be induced by a variety of other factors, such as exposure to ethanol, fasting, and experimental diabetes (Johansson et al. 1986; Puccini et al. 1990); therefore, the induction is not specific to acetone. Moreover, the detection of enzyme induction might require invasive methods, such as liver biopsy.

Exposure of animals to acetone has resulted in degeneration of apical microvilli in renal tubules (Brown and Hewitt 1984) and enhancement of nephropathy commonly seen in aging rats (NTP 1991), but these effects have not been associated with increased levels of blood urea nitrogen.

As is typical of many organic solvents, acetone is irritating to respiratory mucosa, the skin, and eyes. Acetone exposure can also result in such nonspecific narcotic effects such as headache, dizziness, lightheadedness, confusion, unconsciousness (DiVincenzo et al. 1973; Matsushita et al. 1969a, 1969b; Nelson et al. 1943; Raleigh and McGee 1972; Ross 1973), some neurobehavioral and hematological effects (Dick et al. 1989; Matsushita et al. 1969a; Stewart et al. 1975), and perhaps menstrual disorders (Stewart et al. 1975). In addition, patients who had hip casts applied with acetone as the setting fluid became nauseous, vomited blood, and had a strong odor of acetone in the breath. These symptoms were associated with the subsequent development of unconsciousness (Harris and Jackson 1952; Strong 1944). The detection of a strong acetone odor on the breath and nausea could alert physicians to the development of more serious sequelae, such as gastrointestinal hemorrhage and narcosis.

Because acetone is a ketone, acetone exposure can lead to ketosis and other diabetes-like symptoms in humans (Gitelson et al. 1966) and to reduced insulin-stimulated glucose oxidation in animals (Skutches et al. 1990). Again, the detection of a strong odor of acetone on the breath, or high levels of acetone in blood or urine can alert physicians to these effects.

In male rats, acetone exposure resulted in anemia as detected by hematological parameters (American Biogenics Corp. 1986; NTP 1991), and in increased testes weight, decreased sperm motility, caudal and epididymal weight, and increased incidences of abnormal sperm (NTP 1991). Hematological tests and tests for sperm motility and abnormalities could be used to screen humans for possible hematological and fertility effects.

Dermal exposure of humans to acetone irritated the skin, which when examined by light and electron microscopy, showed signs of degenerative changes in the epidermis (Lupulescu and Birmingham 1976; Lupulescu et al. 1972, 1973). Decreased protein synthesis was also found (Lupulescu and Birmingham 1975). Overt signs of skin irritation could alert physicians to possible degenerative changes. Allergic reactions to acetone can be detected by patch testing (Tosti et al. 1988).

As most of the effects from acetone exposure are not specific to acetone, there is no reliable biomarker of effect that can be used to detect or screen for possible effects from exposure to acetone at levels reasonably likely to occur outside the workplace or from accidental ingestion.

3.4 INTERACTIONS WITH OTHER CHEMICALS

While acetone by itself is only moderately toxic, it potentiates the toxicity of a variety of chemicals, including halogenated alkanes and alkenes, benzene, dichlorobenzene, ethanol, 2,5-hexanedione, nitrosamines, acetonitrile, and acetaminophen. The most extensively studied interactions are those with carbon tetrachloride and chloroform. In most of the interactions discussed below, acetone exerts its potentiating effect by inducing microsomal mixed function oxidases, in particular CYP2E1 and CYP2E1-dependent enzyme activities, that bioactivate the other chemicals to reactive metabolites.

Halogenated Alkanes and Alkenes. No studies were located regarding the effects of coexposure of humans to acetone and carbon tetrachloride. However, acetone, a metabolite of isopropyl alcohol, was implicated in a study of workers in an isopropyl alcohol packaging plant who became ill after accidental exposure to carbon tetrachloride (Folland et al. 1976). Fourteen workers became ill (nausea, vomiting, headache, and weakness or abdominal pain, dizziness, diarrhea, and blurred vision). Workers in closer proximity to isopropyl alcohol were especially affected. Renal failure and hepatitis developed in four of the workers with closer proximity to isopropyl alcohol. Expired air samples subsequently taken from workers during isopropyl alcohol bottling revealed strikingly elevated levels of acetone (means of 19 ppm in workers on the bottling line and 7.5 ppm in more remote workers). Their blood acetone levels were 3–30 times higher than the normal range. Thus, it appeared that isopropyl alcohol, by way of acetone, predisposed the workers to the hepatotoxicity and renal toxicity induced by carbon tetrachloride.

The potentiation of carbon tetrachloride-induced hepatotoxicity and renal toxicity by acetone has been well documented in rats. Pretreatment of rats by gavage with acetone enhanced the hepatotoxicity of

carbon tetrachloride, as evidenced by the statistically significantly increased relative liver weights, increased severity of histopathological lesions (necrosis, hepatocellular swelling, lipid droplets), activities of serum alanine aminotransferase and ornithine carbamoyltransferase, the serum concentration of bilirubin, and/or the liver concentration of triglycerides compared with the liver toxicity induced by carbon tetrachloride alone in several studies (Charbonneau et al. 1985, 1986a, 1986c, 1988, 1991; Plaa and Traiger 1972; Plaa et al. 1973, 1982; Traiger and Plaa 1973, 1974). Acetone treatment alone had no effect on these parameters. The potentiation increased in a dose-related manner at single doses of acetone >0.25 mL/kg (>196 mg/kg); doses of <0.10 mL/kg (<78 mg/kg) are ineffective (Charbonneau et al. 1986a; Plaa et al. 1982; Traiger and Plaa 1973). In rats given the minimal effective dose of acetone (196 mg/kg) twice daily for 3 days (total dose 1,177 mg/kg), carbon tetrachloride-induced liver toxicity was further enhanced over that of a single dose of 196 mg/kg acetone (Plaa et al. 1982). However, repetitive dosing of acetone (6x196 mg/kg = 1,177 mg/kg; 12 hours between doses) potentiated the liver toxicity of carbon tetrachloride to a lesser extent than a single dose of 1,177 mg/kg. Administration of the noneffective dose (78 mg/kg) twice a day for 3 days (total dose 468 mg/kg) did not affect the liver toxicity of carbon tetrachloride, even though the cumulative dose of 468 mg/kg, if given as a single dose, would have been high enough to cause significant potentiation. When a dose of acetone of 1.5 mL/kg (1,177 mg/kg) was given once, divided into 6 doses of 0.25 mL/kg (196 mg/kg) over 3 days (cumulative dose 1,177 mg/kg), or into 12 doses of 0.125 mL/kg (98 mg/kg) over 3 days (cumulative dose 1,177 mg/kg), or infused intravenously over 3 days, before challenge with carbon tetrachloride, the most severe potentiation occurred with the single dose, followed by 6 divided doses, and then by 12 divided doses. The intravenous infusion did not enhance the toxicity of carbon tetrachloride. The maximum blood levels calculated from pharmacokinetic parameters for the different acetone treatment regimens showed a direct relationship with the degree of potentiation. The results indicate that threshold blood, and hence liver, concentrations must be exceeded before potentiation occurs. Acetone pretreatment also prolonged the time required for complete recovery induced by carbon tetrachloride exposure (Charbonneau et al. 1985). With carbon tetrachloride alone, the severity of liver toxicity increased temporally in rats sacrificed 24 and 48 hours after dosing, but liver toxicity was no longer observed at 96 hours. Following pretreatment with acetone, the liver toxicity induced by carbon tetrachloride was enhanced and increased in severity at all sacrifice times, even at 96 hours. Gavage pretreatment of rats with 1,452 mg/kg/day acetone in corn oil twice weekly for <12 weeks, followed by carbon tetrachloride challenge, resulted in decreased body weight gain and 35% mortality, compared with no effect on body weight gain and 5% mortality in rats given corn oil and challenged with carbon tetrachloride (Charbonneau et al. 1986c). Rats treated with acetone plus carbon tetrachloride also had statistically significantly decreased relative liver weights and statistically significant increased kidney weights at all

four sacrifice times, compared with corn oil plus carbon tetrachloride rats. Bilirubin concentrations and collagen content were also enhanced. Histological examination revealed fully developed cirrhosis in the acetone plus carbon tetrachloride rats, compared to less severe cirrhosis with corn oil plus carbon tetrachloride. Renal toxicity was also enhanced, as evidenced by statistically significantly elevated blood urea nitrogen levels in the acetone pretreated rats, compared with corn oil pretreated rats. It should be noted that acetone displays a greater degree of potentiation when it is administered in corn oil than in water (Charbonneau et al. 1986a, 1991), and it appears that corn oil alone can be toxic to the liver (Charbonneau et al. 1991).

Inhalation exposure of rats to acetone vapors also displays a threshold effect (Charbonneau et al. 1986a). In rats exposed to 1,000, 2,500, 5,000, 10,000, or 15,000 ppm acetone for four hours, and challenged 18 hours later with carbon tetrachloride, the liver toxicity of carbon tetrachloride was enhanced in a concentration-related manner at ≥2,500 ppm acetone. The noneffective concentration was 1,000 ppm. No cumulative effect of repetitive inhalation exposure to acetone on the carbon tetrachloride-induced liver toxicity was found, but maximum blood levels of acetone correlated with the degree of potentiation.

When rats were challenged with a mixture of trichloroethylene and carbon tetrachloride, the minimal effective dose of acetone required to enhance the liver toxicity of carbon tetrachloride decreased at least five-fold, indicating that mixtures of haloalkanes can cause severe liver injury, and prior exposure to acetone can markedly affect the response produced by the mixtures (Charbonneau et al. 1988).

The mechanism of acetone potentiation of carbon tetrachloride-induced liver toxicity involves the induction of mixed function oxidase microsomal enzymes. In microsomes prepared from rats treated by gavage with acetone at 2.5 mL/kg (1,961 mg/kg) and incubated with ^{14}C-carbon tetrachloride, covalent binding of radioactivity to microsomal protein increased 3–4 times that of control microsomes (Sipes et al. 1973). The time course followed the increased activity of N-nitrosodimethylamine N-demethylase, indicating enzyme induction. Furthermore, aminothiazole, an inhibitor of CYP and mixed function oxidase induction, reduced the potentiation by acetone of carbon tetrachloride-induced liver toxicity (Traiger and Plaa 1973). Studies have indicated that the effects of acetone on the toxicity of carbon tetrachloride are caused by induction of CYP forms belonging to at least two gene subfamilies, CYP2B and CYP2E (Johansson et al. 1988; Kobusch et al. 1989). Complementary DNA and protein sequencing analyses have shown that these CYP gene subfamilies are similar in rats and humans (Song et al. 1986). Acetone treatment caused a nine-fold increase in CYP2E1 accompanied by a similar increase in the rate of NADPH-dependent metabolism of carbon tetrachloride (Johansson et al. 1988). Acetone treatment

also increased the amount of messenger ribonucleic acid (mRNA) and apoprotein of CYP2B1 10- to 30-fold, suggesting regulation of CYP2B1 at the transcriptional level. mRNA coding for CYP2E1 was increased by a combination of fasting and acetone treatment, but not by treatment with acetone alone. The results suggested an enhanced rate of CYP2E1 gene transcription, CYP2E1 mRNA stabilization, or other posttranscriptional mechanisms. The exact mechanism by which acetone increases the CYP subfamilies is a subject of recent and on-going investigations. The findings that pretreatment of rats or rabbits with acetone results in increases in CYP2E1 and associated enzyme activities, but has no effect on the level of CYP2E1 mRNA, suggests that regulation of acetone-induced CYP2E1 occurs at the posttranscriptional level (Hong et al. 1987; Johansson et al. 1988; Porter et al. 1989; Ronis and Ingelman-Sundberg 1989; Ronis et al. 1991; Song et al. 1986, 1989). In microsomal and ribosomal preparations from rats administered acetone intraperitoneally, the polyribosomal distribution of CYP2E1 mRNA shifted, compared with controls, suggesting that the induction of CYP2E1 by acetone involved enhanced translation efficiency through increased loading of ribosomes of CYP2E1 mRNA (Kim et al. 1990). However, in another study, incorporation of 3H-leucine into CYP2E1 in microsomes from rats treated with acetone was lower than that in control microsomes, but the rate of translation of the CYP2E1 mRNA was about the same in both sets of microsomes, indicating that CYP2E1 is not induced by an increase in the rate of translation of its mRNA (Song et al. 1989). Furthermore, incorporation of $NaH^{14}CO^3$ was three-fold less in acetone induced CYP2E1 protein than in controls. The rate of disappearance of radiolabel from CYP2E1 in controls was biphasic, with half-lives of 7 and 37 hours for the fast and slow phase, respectively. However, in acetone-treated rats, the fast phase was absent, with a monophasic half-life of 37 hours. These results demonstrated that the induction of CYP2E1 by acetone is due primarily to protein stabilization. In microsomes and lysosomes from rats treated with acetone, CYP2E1 and CYP2B1 increased, but the increase was greater in microsomes (Ronis and Ingelman-Sundberg 1989; Ronis et al. 1991). Quantification of the proteins in lysosomes indicated that CYP2E1 and CYP2B1 are degraded via an autophagosomal/autolysosomal pathway. The study authors speculated that CYP2E1 is catalytically inactivated in microsomes prior to degradation in lysosomes and that acetone may interfere with the inactivation. Thus, the induction CYP2B1 appears to occur at the transcriptional level, while the induction of CYP2E1 by acetone appears to occur through stabilization of the apoprotein.

One study located suggests that induction of CYP may not be the only mechanism responsible for the interaction between acetone and carbon tetrachloride (Raymond and Plaa 1996). In an investigation of rats, examination of the liver membranes showed that acetone altered the effects of carbon tetrachloride on plasma membrane enzymes and membrane fluidity. Thus, the mechanism may involve the effects of co-exposure to acetone on membrane integrity.

Pretreatment of mice with carbon tetrachloride has been found to enhance the toxicity of acetone. In mice intraperitoneally pretreated with olive oil, the oral LD_{50} of acetone was 5,250 mg/kg, but in mice pretreated with a 20% solution of carbon tetrachloride in olive oil, the LD_{50} of acetone was 4,260 mg/kg (Tanii et al. 1986). The dose of carbon tetrachloride alone did not result in any death. The authors suggested that carbon tetrachloride inactivated the microsomal monooxygenase system, thereby inhibiting the inactivation of acetone.

Acetone also potentiates the hepato- and nephrotoxicity of chloroform. Pretreating rats with 15 mmol/kg (871 mg/kg) acetone in corn oil by gavage 18 hours prior to a challenge dose of 0.5 mL/kg chloroform in corn oil statistically significantly increased the relative kidney weight, inhibited lactate stimulated accumulation of p-aminohippurate and the accumulation of tetraethylammonium ion in kidney slices, and resulted in vacuolar degeneration in the tubular epithelium, but not necrosis, compared with corn oil controls (Hewitt et al. 1980). No effects on these parameters were observed with acetone alone or in rats pretreated with corn oil and challenged with chloroform. Acetone pretreatment also statistically significantly increased the plasma activities of alanine aminotransferase (32-fold) and ornithine carbamoyltransferase (134-fold), compared with corn oil pretreated controls challenged with chloroform, and caused balloon cells with pyknotic nuclei in the centrilobular region of the liver. Acetone alone and chloroform alone did not cause liver lesions. In rats treated by gavage with acetone in corn oil at 58, 290, 436, 581, 726, or 871 mg/kg and challenged with 0.5 mL/kg chloroform in corn oil, acetone showed a dose-dependent decrease in p-aminohippurate uptake and an increase in plasma creatinine levels, with maximum effects seen at doses between 290 and 581 mg/kg acetone (Brown and Hewitt 1984). Renal necrosis, hyaline bodies, and/or tubular casts were seen in 3/6 rats at 58 mg/kg acetone and in 4/6–5/6 rats at higher doses. Acetone pretreatment also statistically significantly increased plasma activities of alanine aminotransferase at ≥290 mg/kg. Balloon cells and necrosis were observed in 2/6 rats pretreated with 58 mg/kg and in most of the rats pretreated with ≥290 mg/kg. The effects of acetone pretreatment and chloroform challenge were greater than the effects of corn oil pretreatment and chloroform challenge. Pretreating rats by gavage with 0.5 mL/kg acetone (871 mg/kg) in corn oil prior to a challenge dose of chloroform (0.5 mL/kg) in corn oil statistically significantly increased the plasma activities of ALT and ornithine carbamoyltransferase above that seen in rats pretreated with corn oil and challenged with chloroform, and the potentiation was maximal at 18 hours (Hewitt et al. 1987). Microsomes from the acetone treated rats showed increased activities of ethoxycoumarin O-deethylase and NADPH-dependent cytochrome c reductase and statistically significantly increased rates of covalent binding of radioactivity from ^{14}C-chloroform in the reaction medium, compared with control microsomes. Results were similar

with microsomes prepared from rats treated by gavage with 2.5 mL/kg (1,961 mg/kg) acetone in corn oil. Acetone enhanced the covalent binding of radioactivity of ^{14}C-chloroform two-fold compared with control microsomes and increased the activity of N-nitrosodimethylamine N-demethylase (Sipes et al. 1973), an activity associated with CYP2E1. Thus, acetone increased the biotransformation of chloroform.

The involvement of CYP2E1 was confirmed with microsomes from rats given a gavage dose of acetone (871 mg/kg) in corn oil (Brady et al. 1989). Acetone statistically significantly increased the CYP content, the activity of N-nitrosodimethylamine N-demethylase, and the content of CYP2E1, but not CYP2B1, compared with control microsomes. Furthermore, no effect was seen on the activity of benzphetamine demethylase, an activity associated with CYP2B1. The acetone-induced microsomes also showed a three-fold enhancement of CYP2E1-dependent chloroform metabolism, but the activity required the presence of cytochrome b5. No increased CYP2B1-dependent metabolism was seen. The involvement of CYP2E1 was further demonstrated by inhibition of the reaction with a monoclonal antibody to CYP2E1 and by alternate substrates for CYP2E1 such as pyrazole, benzene, nitrosodimethylamine, and diallyl sulfate.

Acetone also potentiates the toxicity of other halogenated alkanes. In rats injected intraperitoneally with acetone in saline at doses of 581, 1,162, 1,742, or 2,323 mg/kg 48 hours prior to a gavage dose of dichloromethane (0.4 mL/kg), statistically significant increased blood levels of carboxyhemoglobin were observed at 21,742 mg/kg acetone, compared with controls challenged with dichloromethane (Pankow and Hoffmann 1989). The results indicated that acetone increased the metabolism of dichloromethane to carbon monoxide. Results obtained with fasting rats or rats pretreated with isoniazid, which also induces CYP2E1, produced similar potentiation of dichloromethane-induced carboxyhemoglobinemia, thus implicating induction of CYP2E1 as the mechanism whereby acetone increased the metabolism of dichloromethane to carbon monoxide.

While neither bromodichloromethane or dibromochloromethane were hepatotoxic (assessed by relative liver weight and plasma activities of alanine aminotransferase and ornithine carbamoyltransferase) in rats at the sublethal doses used, acetone pretreatment at 871 mg/kg by gavage in water resulted in liver toxicity at lower challenge doses of these compounds (Hewitt et al. 1983). Neither bromodichloromethane nor dibromochloromethane alone displayed appreciable toxicity to the kidney (assessed by relative kidney weight, accumulation of p-aminohippurate and tetraethylammonium ion in kidney slices, and blood urea nitrogen). However, pretreatment with acetone resulted in statistically significant increased kidney weight, inhibition of p-aminohippurate uptake, and increased levels of blood

urea nitrogen after challenge with bromodichloromethane. With a challenge dose of dibromochloromethane, only blood urea nitrogen was significantly increased by acetone pretreatment. Acetone pretreatment of rats by gavage at doses of 196 and 392 mg/kg, prior to challenge with 1,1,2-trichloroethane, potentiated 1,1,2-trichloroethane-induced increased activity of plasma alanine aminotransferase (MacDonald et al. 1982a). However, higher pretreatment doses of acetone did not potentiate the toxicity and may have decreased the severity. Pretreatment of rats with acetone (392 mg/kg) followed by a challenge dose of ^{14}C-1,1,2-trichloroethane did not increase covalent binding of radioactivity to microsomal proteins but resulted in a greater decline in the content of reduced glutathione. When ^{14}C-trichloroethane was added *in vitro*, covalent binding of the radiolabel statistically significantly increased in microsomes from rats treated with acetone, compared with control microsomes (MacDonald et al. 1982b). The *in vitro* covalent binding was inhibited 80% by the addition of reduced glutathione. It was suggested that acetone alters the bioactivation and the detoxification of 1,1,2-trichloroethane, but the exact mechanism is unclear.

Acetone also potentiated the hepatotoxicity of chlorinated alkenes. Inhalation exposure of adult male rats to 10,000 ppm acetone vapor for 2 hours prior to or during concomitant inhalation exposure to 2,000 ppm 1,1-dichloroethene resulted in statistically significant increased activity of serum alpha-ketoglutarate transaminase, compared with that induced by 1,1-dichloroethene alone (Jaeger et al. 1975). A biphasic pattern of potentiation of the liver toxicity induced by 1,1-dichloroethene was observed in rats pretreated orally with acetone at several dose levels (Hewitt and Plaa 1983). At doses of 290 and 581 mg/kg acetone prior to challenge with 1,1-dichloroethene, statistically significant increased activities of plasma alanine aminotransferase and ornithine carbamoyltransferase were observed, compared with water pretreated rats challenged with 1,1-dichloroethene. At higher pretreatment doses of acetone (≥871 mg/kg), the effect on these parameters diminished and acetone appeared to have a protective effect. Treatment of rats with 1,1-dichloroethene did not result in any evidence of nephrotoxicity, but acetone pretreatment statistically significantly reduced the accumulation of tetraethylammonium ion in kidney slices. The biphasic pattern of potentiation/protection may be related to alterations in the rate and/or pattern of 1,1-dichloroethene bioactivation, such as, bioactivation to reactive intermediates or decreased detoxification by decreasing hepatic glutathione levels at the potentiating doses of acetone.

Benzene. Although potentiation of benzene toxicity by acetone has not been specifically tested, microsomes from rats treated with acetone (3,922 mg/kg) for 1 or 2 days produced an 8-fold increase in the rate of NADPH-dependent oxidation of benzene and induced CYP, in particular CYP2E1 (Johansson et al. 1988; Johansson and Ingelman-Sundberg 1988). Addition of inhibitors of CYP2E1 inhibited the

oxidation of benzene in microsomes from acetone treated rats, providing further evidence that this form of CYP is involved. In addition, antibodies to rabbit CYP2E2 and rat CYP2E1 inhibited the oxidation of benzene by 80–100% in microsomes prepared from rabbits and rats treated with acetone. In hepatocytes from rabbits given acetone (863 mg/kg/day) in drinking water for 7 days, immunoblot analysis identified three distinct cytochromes: CYP2E1, CYP2A1, and CYP2A2 (Schnier et al. 1989). In bone marrow cells from the treated rabbits, CYP2E1 and CYP1A1 were identified. Quantitative analysis revealed that acetone treatment resulted in a 7.3-fold induction of CYP2E1 in liver and a 12.9-fold induction of CYP2E1 in bone marrow cells. Acetone slightly decreased the concentration of CYP reductase in bone marrow, and increased the ratio of CYP2E1 to reductase by 16.4 times and the ratio of CYP1A1 to reductase by 2 times. Hepatic microsomes from acetone-treated rabbits were 4.8 times more active than control microsomes in benzene hydroxylation, an activity of CYP2E1. Acetone-induced marrow microsomes were 9.4 times more active in benzene hydroxylation. In a study of mice, acetone pretreatment via drinking water was associated with significant increases in the percent and mass of hydroxylated benzene metabolites after exposure to benzene at 600 ppm (Kenyon et al. 1998). Thus, the stimulation of benzene metabolism by acetone occurs by a mechanism similar to that of the stimulation of carbon tetrachloride metabolism by acetone. The results suggest that acetone may potentiate the toxicity of benzene, because bioactivation is required for the expression of hematotoxicity of benzene (Sammett et al. 1979; Snyder et al. 1975). It should be noted that commercial acetone may contain low levels of benzene (Pubchem 2021).

Dichlorobenzene. Inhalation exposure of rats to acetone vapors at 4,785, 10,670, or 14,790 ppm for 4 hours increased the CYP contents and the activity of glutathione-S-transferase, with the greatest increases occurring at the 4,785 ppm level (Brondeau et al. 1989). When the rats were challenged 18 hours later by inhalation exposure to 1,2-dichlorobenzene, the level of CYP and the activity of glutathione-S-transferase were no different from that seen with acetone alone. However, acetone preexposure potentiated the liver toxicity of 1,2-dichlorobenzene at the lowest exposure, reduced it at 10,670 ppm, and suppressed it at 14,790 ppm. In mice exposed to 6,747, 8,910, or 14,345 ppm acetone for 4 hours, followed by a challenge by 1,2-dichlorobenzene, acetone preexposure caused an interactive glucose-6-phosphatase response in the mediolobular area of the liver. It was suggested that, at low concentrations, acetone induces the microsomal enzymes that convert 1,2-dichlorobenzene to toxic intermediates. However, because the glutathione-S-transferase activity did not increase in rats preexposed to acetone and challenged with 1,2-dichlorobenzene, the diminished liver toxicity induced by 1,2-dichlorobenzene after preexposure to the higher concentrations cannot be explained by detoxification via enhanced glutathione conjugation. Instead, two microsomal enzymes may be involved, in which, at

low concentrations of acetone, one (activating) enzyme is induced, but at higher concentrations concomitant induction of the second enzyme system could result in protection.

Ethanol. Acetone potentiated the CNS toxicity of ethanol in mice (Cunningham et al. 1989). Mice were pretreated with an intraperitoneal injection of acetone in corn oil at 581, 1,162, or 2,323 mg/kg, and 30 minutes later injected with 4,000 mg/kg ethanol. At 1,162 and 2,323 mg/kg, acetone statistically significantly prolonged the duration of the loss of righting reflex induced by ethanol. In mice given 2,323 mg/kg acetone prior to 2,000 mg/kg ethanol, the blood level of ethanol was statistically significantly higher at all time intervals measured, and acetone pretreatment significantly decreased the mean elimination rate of ethanol.

In vitro, acetone inhibited the activity of liver alcohol dehydrogenase, a reaction responsible for 90% of ethanol elimination. It was suggested that acetone produced a prolongation of the CNS toxicity of ethanol by reducing its elimination.

Other Ketones. The neurological and reproductive effects of coexposure to acetone and 2,5-hexanedione has been studied in animals. In rats exposed to 0.5% 2,5-hexanedione, 0.5% acetone (650 mg/kg/day), or to a combination of 0.5% 2,5-hexanedione and 0.5% acetone in drinking water for 6 weeks, peripheral motor nerve conduction velocity was measured weekly from the third week of dosing (Ladefoged et al. 1989). Acetone alone reduced the nerve conduction velocity compared with controls only at 6 weeks, while 2,5-hexanedione alone significantly reduced it from the third week on. The combination treatment resulted in a statistically significant greater reduction than was seen with 2,5-hexanedione alone on the fourth and sixth week. Acetone alone had no effect on balance time in the rotorod test, but balance time was statistically significantly reduced from the second week with the combination treatment, and the reduction was greater than that with 2,5-hexanedione alone from the fourth week on. In a similar dosing regimen for 7 weeks, coexposure to 2,5-hexanedione and acetone statistically significantly inhibited acquisition, but not performance of spatial learning (assessed in the radial arm maze) above that seen with 2,5-hexanedione alone (Lam et al. 1991). Brain weights of rats exposed to 2,5-hexanedione alone or to the combination were significantly reduced, with greater reduction in the coexposed group. Both treatments reduced synaptosomal 5-hydroxytryptamine uptake rate, but the combination treatment did not reduce the uptake below that seen with 2,5-hexanedione alone. In a companion report of these treatment groups, there was no significant difference on the number and size of neurons in the cerebral cortex between rats treated with 2,5-hexanedione alone or rats coexposed to 2,5-hexanedione and acetone (Strange et al. 1991).

In follow-up experiments, Ladefoged et al. (1994) included histological examination of the sciatic and tibial nerves in rats immediately after a 6-week exposure period and in rats 10 weeks after cessation exposure (recovery period). As in previous experiments, acetone potentiated 2,5-hexanedione-induced effects in open field ambulation and rearing balance in the rotarod tests, and grip strength. The ambulation effects were reversible during the recovery period by all treatments, but the effects on rearing and balance were reversible in the 2,5-hexanedione group only. That is, the potentiation by acetone persisted. Histological examination revealed that after exposure, giant axon swelling was induced by 2,5-hexanedione and the combination of 2,5-hexanedione and acetone, and a change in the distribution of fiber area size occurred in rats exposed to 2,5-hexanedione alone. The lesions observed in the co-exposure group were statistically similar to the effects of 2,5-hexanedione alone, but appeared aggravated by co-exposure, as seen by conventional pathological evaluation. After the 10-week recovery period, the nerve tissues appeared normal. The investigators concluded that neurotoxicity of the combined exposure was not reversible and that the mechanism of acetone potentiation is probably an effect on the toxicokinetics of 2,5-hexanedione.

Acetone alone had no effect on indices of fertility in male rats but potentiated the reproductive toxicity of 2,5-hexanedione when coadministered, compared with that seen with 2,5-hexanedione alone (Larsen et al. 1991). The rats were exposed to drinking water containing 0.13, 0.25, or 0.5% 2,5-hexanedione or in combination with 0.5% acetone for 6 weeks. Fertility was assessed by mating the exposed males with nonexposed females. 2,5-Hexanedione alone or the combination had no effects on the number of matings. 2,5-Hexanedione alone at 0.5% statistically significantly decreased the number of pregnancies, the number of fetuses, and the testicular weight. The combination treatments further reduced all indices, and at 0.5% 2,5-hexanedione plus 0.5% acetone, complete infertility occurred. Morphological assessment of the testes revealed mild to moderate vacuolization, chromatin margination, epithelial disruption, multinucleated giant cells, and/or atrophy in rats exposed to 2,5-hexanedione alone after 6 weeks of treatment, and the combination increased the severity of these lesions. When assessed 10 weeks after the end of treatment, the lesions were still present.

The mechanism by which acetone potentiates or adds to the toxicity of 2,5-hexanedione in rats is not known, but coexposure of rabbits to 2,5-hexanedione and acetone altered the pharmacokinetic parameters of 2,5-hexanedione (Ladefoged and Perbellini 1986). The combined treatment decreased the body clearance of 2,5-hexanedione, compared to the clearance of 2,5-hexanedione alone.

In a neurobehavioral study in volunteers, 11 men and 11 women exposed to 237 ppm acetone, 12 men and 13 women exposed to 200 ppm 2-butanone (methyl ethyl ketone), and 8 men and 13 women exposed simultaneously to acetone (125 ppm) and 2-butanone (100 ppm) for 4 hours were subjected to psychomotor tests (choice reaction time, visual vigilance, dual task, memory scanning), sensorimotor tests (postural sway), and psychological tests (profile of mood states) (Dick et al. 1989). Acetone exposure alone produced small but statistically significant changes in performances from controls in two measures of auditory tone discrimination (increased response time and increased false alarm) and hostility in men only. Neither 2-butanone alone nor the combination of acetone and 2-butanone produced any statistically significant changes. Furthermore, no interactions between acetone and 2-butanone on the uptake or elimination of acetone or 2-butanone were found in the same human subjects (Brown et al. 1987). From this limited information, it appears that acetone and 2-butanone do not interact to produce neurological effects.

Styrene. Information regarding interactions between acetone and styrene in the expression of toxic effects in animals is limited. In rats exposed to 2.2 mmol/kg styrene by intraperitoneal injection, a co-injection of 2.2 mmol/kg acetone was ineffective at attenuating symptoms of toxicity (Ikeda and Hirayama 1978). Several studies in humans have reported that coexposure to acetone and styrene produce different changes in the content or activity of biotransformation enzymes in the liver and lungs, compared with the changes seen with styrene alone (Elovaara et al. 1990, 1991; Vainio and Zitting 1978). A study of 19 male workers exposed to styrene and acetone in air at work for 4 hour intervals reported an inverse correlation between acetone concentration in air and styrene metabolite levels in subjects' urine post-shift, suggesting that acetone may slow metabolism of styrene (Marhuenda et al. 1997). However, in 23–34 year-old men exposed for 2 hours to 293 mg/m^3 styrene alone or to a mixture of 301 mg/m^3 styrene and 1,240 mg/m^3 (517 ppm) acetone, there was no indication that acetone alters the uptake, distribution, metabolism, or elimination of styrene (Wigaeus et al. 1984).

Nitrosamines. Acetone potentiated the hepatotoxicity of N-nitrosodimethylamine in rats pretreated by gavage with 2.5 mL/kg (1,961 mg/kg) acetone in water 24 hours prior to a challenge intraperitoneal dose of 75 mg/kg N-nitrosodimethylamine (Lorr et al. 1984). The acetone pretreatment doubled the plasma activity of alanine aminotransferase ($p<0.005$) and increased the extent and severity of liver necrosis and hemorrhage, compared with that seen with N-nitrosodimethylamine alone. Microsomes prepared from rats treated with N-nitrosodimethylamine had diminished N-nitrosodimethylamine-N-demethylase activity, compared with microsomes from untreated mice. The results indicate that N-nitrosodimethylamine N-demethylase, an activity associated with CYP2E1, is responsible for the

activation of N-nitrosodimethylamine to a toxic intermediate, and that the induction of this enzyme by acetone potentiates the hepatotoxicity. Similar results were seen in Ko et al. (1987), where rat liver microsomes pre-treated with acetone inhibited nitrosodimethylamine demethylase activity up to 70%, and rat P450 pre-treated with acetone was inhibited up to 92%. Microsomes from mice given 2,614 mg/kg acetone increased the covalent binding of radioactivity from [^{14}C]-N-nitrosodimethylamine to microsomal DNA, RNA, and protein (Sipes et al. 1978). Microsomes from rats pretreated with acetone had a four-fold increased activity of N-nitrosodimethylamine demethylase and a six-fold increase in DNA methylation compared with control microsomes (Hong and Yang 1985). Several studies have shown that acetone given to rats or mice enhances the microsomal activity of N-nitrosodimethylamine N-demethylase in a dose-related manner (Miller and Yang 1984; Patten et al. 1986; Sipes et al. 1973, 1978; Tu et al. 1983; Yoo et al. 1990), and this activity is associated with CYP (Miller and Yang 1984; Tu et al. 1983; Yoo et al. 1990), in particular CYP2E1 (Patten et al. 1986; Yoo et al. 1990). Acetone pretreatment of rats also enhanced the denitrosation of N-nitroso-dimethylamine in microsomes, and antibodies against CYP2E1 inhibited this activity (Yoo et al. 1990). Similar results were obtained with N-nitrosodiethylamine deethylation and denitrosation. The rates of both types of reactions depended upon the concentration of the nitrosamine in the reaction mixture, leading to the conclusion that CYP2E1 has a role in the metabolism of low concentrations of these nitrosamines, and that this form of the enzyme is important in the carcinogen activation.

In Ames assays, addition of acetone to the S-9 mix inhibited the mutagenicities of N-nitrosodimethylamine, N-nitrosodiethylamine, and 6 oxidative derivatives of these two chemicals in *Salmonella typhimurium* TA100 at a concentration of <5.2 mg/0.1 mL (52,000 mg/L) nitrosamines (Mori et al. 1985). Acetone also inhibited the metabolism of N-nitrosodimethylamine, N-nitrosomethyl (2-hydroxypropyl) amine, and N-nitrosomethyl (2-oxopropyl) amine *in vitro*. In contrast, another study found that the S-9 mix prepared from mice treated with acetone strongly enhanced the mutagenicity of N-nitrosodimethylamine in the Ames assay in *S. typhimurium* TA92, which was more sensitive to N-nitrosodimethylamine than TA100 (Glatt et al. 1981). This assay used concentrations of the nitrosamine at <20 mM (1,491 mg/L). However, acetone did not enhance the mutagenicity in the host-mediated assay. The authors explained that *in vitro*, the activity of the dilute metabolizing system is limiting for the activity of N-nitrosodimethylamine, such that induction increases mutagenicity, whereas *in vivo*, N-nitrosodimethylamine is completely metabolized in both induced and noninduced animals. The reason for the different effects of acetone on the mutagenicity of nitrosamines in the studies by Mori et al. (1985) and Glatt et al. (1981) could be related to differences in the assay system (e.g., acetone added to medium versus acetone-induced S-9), to the difference in concentration of the nitrosamines, or to the different

strains of *S. typhimurium*. Microsomes from rats pretreated with acetone increased the activity of N-nitrosodimethylamine demethylase and increased the mutagenicity of N-nitrosodimethylamine in Chinese hamster lung V79 cell cultures at low substrate concentrations (0.1 and 4 mM or 5.8 and 232 mg/L) compared with untreated microsomes (Yoo and Yang 1985). However, a slight decrease in mutagenic activity was found at a N-nitrosodimethylamine concentration of 200 mM (11,616 mg/L). Acetone induced microsomes also enhanced the mutagenic activity of N-nitrosomethylethylamine, N-nitrosodiethylamine, and N-nitrosomethylbutylamine, but not N-nitrosomethylbenzylamine or N-nitrosomethylaniline. The findings that lower concentrations enhanced the mutagenicity of N-nitrosodimethylamine (Glatt et al. 1981; Yoo and Yang 1985) are consistent with the conclusions of Yoo et al. (1990) that CYP2E1 is important in the activation of the carcinogen at low concentrations.

Acetonitrile. Acetone also potentiates the toxicity of acetonitrile. When rats were given a 1:1 mixture of acetone plus acetonitrile by gavage, the acute LD_{50} was 3–4 times lower than the predicted LD_{50} for additive toxicity (Freeman and Hayes 1985). The LD_{50} values of these chemicals alone were 5,800 mg/kg for acetone and 4,050 mg/kg for acetonitrile, while the LD_{50} for the mixture was 1,160 mg/kg, compared with the predicted value of 4,770 mg/kg. However, deaths occurred later with the mixture than with either acetone or acetonitrile alone. Blood cyanide (a toxic metabolite of acetonitrile) levels were higher, but peaked at a later time, in the rats given the mixture than in those given acetonitrile alone. Administration of a second dose of acetone 30 hours after administration of the mixture protected the rats from lethality to a degree similar to that seen with a dose of sodium thiosulfate (an antidote used for cyanide poisoning). It was suggested that, initially, acetone competitively inhibits the metabolism of acetonitrile to cyanide but later induces an isoenzyme of CYP that catalyzes the metabolism of acetonitrile to cyanide, hence explaining the greater toxicity of the mixture seen at a later time. To test this hypothesis, the metabolism of acetonitrile by microsomes from rats treated with acetone at the same dose that potentiated the toxicity was compared with that by noninduced microsomes (Freeman and Hayes 1988). The metabolism of acetonitrile required oxygen and NADPH and was inhibited by known inhibitors of CYP. Microsomes from acetone pretreated rats increased the Vmax, while acetone added to the reaction mixture *in vitro* competitively inhibited the conversion of acetonitrile to cyanide. The *in vitro* metabolism of acetonitrile was competitively inhibited by ethanol (which also induces CYP2E1), by dimethyl sulfoxide (which inhibits CYP2E1-dependent metabolism of ethanol), and by aniline (a substrate for CYP2E1). Thus, the mechanism for the potentiation of the toxicity of acetonitrile by acetone also appears to involve CYP2E1.

A case report describes a woman who was asymptomatic for 24 hours after ingesting an overdose of acetonitrile and acetone, but subsequently developed cardiovascular collapse and profound acidosis, and eventually died (Boggild et al. 1990). It was suggested that acetone delayed the onset of symptoms by initially inhibiting the metabolism of acetonitrile to cyanide, which is consistent with the mechanism proposed by Freeman and Hayes (1988).

Acetaminophen. Acetone has been reported to increase the hepatotoxicity of acetaminophen *in vitro* (Moldeus and Gergely 1980) and *in vivo* (Jeffery et al. 1991). The addition of acetone to phenobarbital-induced rat liver hepatocytes caused a three-fold increase in acetaminophen-glutathione conjugation due to enhanced CYP-dependent activation of acetaminophen to a toxic metabolite (Moldeus and Gergely 1980). The addition of acetone to the reaction system also caused loss of hepatocyte viability, which was not seen when acetone or acetaminophen were excluded from the system. According to the suggested mechanism, acetone enhanced a CYP-dependent activation of acetaminophen to a metabolite that conjugates with glutathione, thereby depleting hepatic glutathione stores, leading to accumulation of the reactive metabolite. In contrast, pretreatment of rats with 813 or 1,975 mg/kg acetone 18 hours and 1 hour prior to administration of acetaminophen resulted in an increased blood half-life of acetaminophen, a decreased rate constant for acetaminophen mercapturate formation, decreased acetaminophen sulfate formation, and decreased renal elimination of acetaminophen (Price and Jollow 1983). Acetone also decreased the incidence and severity of liver necrosis induced by acetaminophen. The authors suggested that acetone decreased the formation of an acetaminophen reactive metabolite. However, in mice pretreated orally with acetone at 1,900 mg/kg/day for 10 days and then given 600 mg/kg acetaminophen intraperitoneally 6 hours before sacrifice, a greater portion of the liver lobules with necrosis and hemorrhage was observed than when acetaminophen was administered alone (Jeffery et al. 1991). Acetone pretreatment followed by saline injection resulted in no hepatic lesions. When dimethylsulfoxide (DMSO), an inhibitor of CYP2E1, was incubated with microsomes prepared from the acetone-pretreated, acetaminophen-treated mice, a 91% inhibition of acetaminophen-glutathione conjugation was found compared to when DMSO was excluded from the incubation mixture. Presumably, the inhibition of glutathione conjugation by DMSO was due to inhibition of CYP2E1 to form the active metabolite of acetaminophen. Activation of acetaminophen to a reactive metabolite, N-acetyl-P-benzoquinone imine, which can bind to tissue macromolecules leading to necrosis at high doses of acetaminophen, is known to be dependent on CYP2E1 (Morgan et al. 1983; Raucy et al. 1989). NAPQI can also be detoxified via conjugation with glutathione. The addition of acetone to the reaction system enhances the formation of the glutathione conjugate in rat liver microsomes (Liu et al. 1991). These results support a mechanism whereby acetone enhances the CYP2E1-dependent conversion of acetaminophen to NAPQI, which in

turn conjugates with glutathione to deactivate it. Thus, acetone could decrease the toxicity of acetaminophen. However, if the dose of acetaminophen is high (leading to more N-acetyl-p-benzoquinone imine than can be handled by glutathione detoxification), glutathione is depleted and NAPQI accumulates. Thus, the induction of CYP2E1 by acetone to produce enough NAPQI from acetaminophen to deplete glutathione would result in an enhancement of acetaminophen-induced toxicity.

Pyridine. Iba et al. (1993) prepared microsomes from lungs and livers of rats exposed to 20 ppm pyridine by inhalation for 5–6 hours/day for 10 days, to acetone (7.5%, v/v) in drinking water for 10 days or by inhalation to 50% aqueous acetone for 5–6 hours/day for 10 days, or to acetone in combination with pyridine administered separately as above. Controls received water for inhalation and oral exposures. In the liver microsomes, there was induction of ethoxyresorufin O-deethylase (EROD) activity for oral acetone by 2.5-fold, for pyridine by inhalation by 2.8-fold, and for the combination of acetone and pyridine by 7.6-fold, indicating greater-than-additive interaction. The levels of CYP1A1 were induced by acetone, pyridine, and the combination by 8.3-, 6.6-, and 32.7-fold, respectively. These results indicated even greater synergistic interaction. Similar greater-than-additive interaction results were also found for methoxyresorufin O-demethylase (MEROD) and CYP1A2 in the liver microsomes. Microsomal EROD was induced by all treatments in the lung, and a synergistic interaction was even greater in the lung, with an increase that was 4-fold for acetone, 21-fold for pyridine, and 115.5-fold for the combination. CYP1A1 was also induced synergistically by acetone and pyridine in the lung microsomes.

Miscellaneous Chemicals. 9,10-Dimethyl-1,2-benzanthracene (DMBA) in acetone was more effective as a carcinogen than DMBA in mineral oil when applied to the tongues of hamsters (Marefat and Shklar 1977). In a study of 10 male volunteers, ingestion of 500 mg chlorzoxazone prior to inhalation of 250 ppm acetone for 2 hours resulted in slight but significant increases in steady state blood level and area under the blood concentration-time curve for acetone (Ernstgard 1999). A dose of 581 mg/kg acetone prior to administration of N-(3,5-dichlorophenyl)succinimide (NDPS), a fungicide, enhanced the NDPS-induced increase in blood urea nitrogen and kidney weight, but had no effect on NDPS-induced changes in urine volume or content, organic ion uptake by kidney slices, or renal pathology (Lo et al. 1987). Lower doses of acetone were ineffective. Because NDPS requires bioactivation by CYP-dependent microsomal enzymes in the liver before renal toxicity occurs, it appears that acetone potentiated the renal toxicity of NDPS by inducing a CYP capable of the bioactivation. Pretreatment of rats with acetone prior to administration of thiobenzamide enhanced the degree of liver necrosis and serum activity of alanine aminotransferase, while coadministration of acetone and thiobenzamide reduced the extent of liver damage (Chieli et al. 1990). In addition, liver microsomes from acetone treated rats statistically

significantly increased the rate of thiobenzamide-S-oxidation, which was dependent on a CYP enzyme. Thiobenzamide competitively inhibited acetone monooxygenase activity, which is highly specific for CYP2E1. The results indicated that pretreatment of rats with acetone induces CYP2E1, leading to enhanced bioactivation of thiobenzamide to a reactive metabolite and enhanced thiobenzamide-induced liver damage. However, when acetone and thiobenzamide were administered together, competition for the enzyme may have led to less bioactivation of thiobenzamide, thereby affording the protective effect of acetone. Acetone appears to afford protection against other toxic effects of other chemicals. Pretreatment of rats with acetone produced complete protection against clonic tonic convulsions induced by isonicotinic acid and electroshock-induced convulsion (Kohli et al. 1967). Because the protective action of acetone was nonspecific, a biochemical mechanism did not seem likely.

Acetone also increased the toxicity of oxygen (Tindberg and Ingelman-Sundberg 1989) and chromate (Cr[VI]) (Mikalsen et al. 1991). Pretreatment of rats with acetone prior to oxygen exposure potentiated the NADPH-dependent microsomal lipid peroxidation in the liver and lung and decreased the survival of the rats (Tindberg and Ingelman-Sundberg 1989). Oxygen also induced CYP2E1, indicating a role for CYP2E1 in oxygen-mediated tissue toxicity.

Coexposure of rats to acetone and sodium chromate (Cr[VI]) resulted in some macroscopic alterations in the liver (not otherwise described), whereas no liver toxicity was noted with chromate or acetone alone (Mikalsen et al. 1991). Cytochrome CYP2E1 exhibited high chromate reductase activity, and biochemical studies indicated that acetone caused the induction of microsomal Cr(V1) metabolism. While the interactions discussed above involve the potentiation of the toxicity of other chemicals by acetone, acetone has been found to antagonize the toxicity of semicarbizide (Jenney and Pfeiffer 1958). In mice injected intraperitoneally with 168 mg/kg semicarbizide, 93% had convulsions and 91% died. Pretreatment with 4,000 mg/kg acetone orally reduced the percentage of the semicarbizide-induced convulsions and mortality to 0%. A dose of 1,800 mg/kg acetone reduced the percentage of mice convulsing to 31%, delayed the onset of convulsions by 286%, reduced the percentage that exhibited unmodified seizure from 98 to 40%, reduced the mortality to 12.5%, and delayed the time to death by 125%. The authors attributed the protective effect of acetone to the presence of the keto group.

A study of co-exposure to acetone and di(ethylhexyl)phthalate in drinking water of rats for 4 or 9 weeks found no significant interactions between the two chemicals with regard to reproductive toxicity (Dalgaard et al. 1999). However, the general toxicity of di(ethylhexyl)phthalate, as assessed by clinical

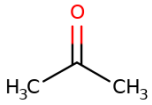
signs, decreases in body weight, and increases in mortality, was slightly increased by co-exposure to acetone.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

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

Table 4-1. Chemical Identity of Acetone

Characteristic	Information	Reference
Chemical name	Acetone	PubChem 2021
Synonym(s) and registered trade name(s)	Dimethyl ketone; 2-propanone; propan-2-one; beta-ketopropane	PubChem 2021
Chemical formula	C_3H_6O	Haynes et al. 2015
Chemical structure		Haynes et al. 2015
CAS Registry Number	67-64-1	Haynes et al. 2015

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Acetone is a colorless volatile liquid with a fruity odor and pungent, sweetish taste. It dissolves completely in water and is expected to volatilize from soil and water. Table 4-2 lists important physical and chemical properties of acetone.

Table 4-2. Physical and Chemical Properties of Acetone

Property	Information	Reference
Molecular weight	58.079	Haynes et al. 2015
Color	Colorless	PubChem 2021
Physical state	Liquid	Haynes et al. 2015
Melting point	-94.9°C	Haynes et al. 2015
Boiling point	56.08°C	Haynes et al. 2015
Critical temperature and pressure	508.1 K and 4.7 MPa	Haynes et al. 2015
Density at 20°C	0.7845 g/cm^3 at 25°C	Haynes et al. 2015
Taste	Pungent, sweetish	PubChem 2021
Odor	Fruity odor	PubChem 2021
Odor threshold:		PubChem 2021
Water	20 ppm, w/v	
Air	13 ppm, v/v	
Solubility:		
Water at 20°C	Miscible with water	Haynes et al. 2015
Organic solvents	Miscible with ethanol, diethyl ether, acetone, benzene, chloroform	
Partition coefficients:		
Log K_{ow}	-0.24	Haynes et al. 2015
Log K_{oc}	0.73 (estimated)[a]	Lyman 1982
Vapor pressure at 20°C		Haynes et al. 2015
Henry's law constant at 25°C		PubChem 2021
Degradation half-life in air via reaction with OH radicals	1.80x10^{-13} cm^3/molecule-second at 25°C	PubChem 2021
Dissociation constant	pKa 20	PubChem 2021
Heat of vaporization	30.99 kJ/mol at 25°C	Haynes et al. 2015
Autoignition temperature	465°C	Haynes et al. 2015
Flashpoint	-20°C	Haynes et al. 2015
Flammability limits in air (percent by volume)	2.5–12.8%	Haynes et al. 2015
Conversion factors	1 ppm = 2.38 mg/m^3 1 mg/m^3 = 0.42 ppm	
Incompatibilities and reactivity	Acetone and chloroform is a potentially explosive combination in the presences of a base; incompatible with nitric and sulfuric acid mixtures and hydrogen peroxide	Haynes et al. 2015

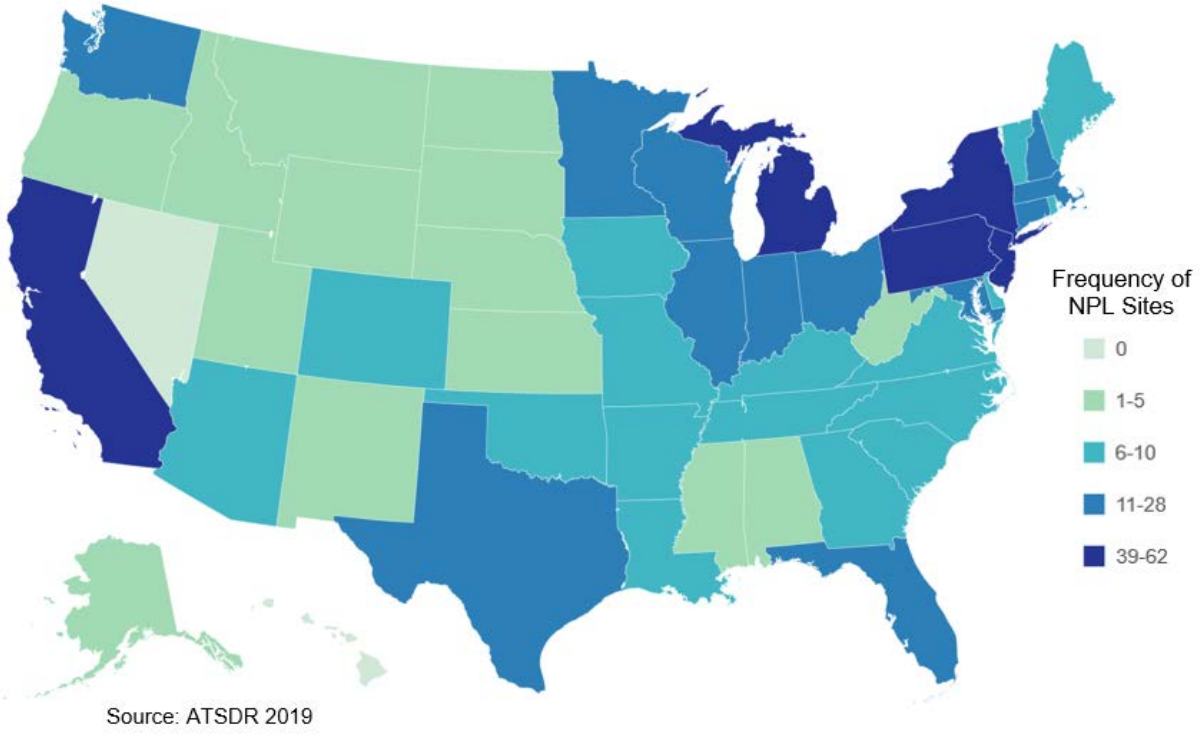
[a]Estimated by regression equation 4–13 in Lyman (1982).

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Acetone has been identified in at least 652 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which acetone has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 646 are located within the United States, 4 are located in Puerto Rico, 1 is located in Guam, and 1 is located in the Virgin Islands (not shown).

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



- Exposure to acetone primarily occurs by inhaling ambient air and by ingesting drinking water and food containing acetone, and can also be created as an endogenous metabolite. Acetone occurs naturally and from anthropogenic sources.

- Workers in certain industries, such as certain paint, plastic, artificial fiber, and shoe factories are likely exposed to much higher levels of acetone than the general population. Professional painters, commercial and household cleaners, smokers, frequent users of nail polish removers, and people who live near certain landfill sites (emitting higher than ambient levels of acetone) or other industrial sources of emission are also susceptible to higher exposure concentrations of acetone.

- Acetone is used primarily as an intermediate in chemical production and as a solvent.
- Reaction with hydroxyl radicals and photolysis are important fate processes in the atmosphere. Acetone has a reasonably long half-life in air and is transported long distances from its source of emission.
- The most important fate determining process for acetone in water, sediment, and soil is biodegradation. The important transport processes of acetone in soil are volatilization to the atmosphere and leaching into groundwater.

Acetone is emitted into the atmosphere both from natural and anthropogenic (human-made) sources. Natural sources of emission include plants and trees (Graedel et al. 1986; Isidorov et al. 1985; Khalil and Rasmussen 1992), volcanic eruptions (Isidorov et al. 1990), forest fires (Graedel et al. 1986), and insects and microbes (Graedel et al. 1986). Acetone is also produced endogenously and expired in human breath (Conkle et al. 1975). Some important anthropogenic sources of acetone in the air include vehicular exhaust (Graedel et al. 1986), chemical manufacturing (Graedel et al. 1986), tobacco smoke (Manning et al. 1983), wood burning and pulping (Graedel et al. 1986), refuse and polyethylene combustion (Graedel et al. 1986; Hodgkin et al. 1982; NAS 1976), petroleum production (Graedel et al. 1986), certain landfill sites (Hodgson et al. 1992; LaRegina et al. 1986), and solvent use (Graedel et al. 1986). The sensitized photoreaction of dissolved organic matter naturally produces acetone in seawater (Mopper and Stahovec 1986). Chemical manufacturing industries (EPA 1975), energy-related industries (Mohr and King 1985), and user industries (EPA 1975) release acetone to surface waters. Acetone is released into groundwater mainly as a result of leaching from municipal and industrial landfills (Brown and Donnelly 1988). The principal sources of acetone in soil are municipal and industrial discharge in landfills (EPA 1988b). Another source is atmospheric deposition (Grosjean and Wright 1983). Acetone is released in soil from natural sources, such as disposed agricultural and food wastes and animal wastes (Graedel et al. 1986).

The two processes that are important in determining the fate of acetone in the atmosphere are reaction with hydroxyl radicals and photolysis. The estimated half-life of acetone in the air due to combinations of these two reactions is 22 days (Meyrahn et al. 1986). Because of this reasonably long half-life, acetone is transported long distances from its source of emission. Wet deposition transports atmospheric acetone to surface water and the terrestrial surface (Grosjean and Wright 1983).

The most important fate determining process for acetone in water is biodegradation (Rathbun et al. 1982). Because of its high-water solubility, acetone does not adsorb significantly to sediment and suspended solids in water. The log K_{ow} value of -0.24 (see Table 4-2) suggests that bioconcentration of acetone in aquatic organisms is not significant. In addition, one study found that acetone does not appreciably

bioconcentrate in adult haddock (Rustung et al. 1931). Based on these data, acetone is not expected to biomagnify in aquatic or terrestrial food chains.

Biodegradation is the most important degradative process for acetone in sediment and soil (Rathbun et al. 1982). The important transport processes of acetone in soil are volatilization to the atmosphere and leaching into groundwater.

The levels of acetone in ambient air and water are generally low. The concentration of acetone in the atmosphere in remote areas is <1 ppb v/v (1 ppb=0.001 ppm) (Cavanagh et al. 1969; Arnold et al. 1986). Its mean concentration in the atmosphere of rural areas is <3 ppb (Shepson et al. 1991; Snider and Dawson 1985). The mean concentration of acetone in urban air in the United States is 6.9 ppb (Shah and Singh 1988; Li et al. 2018) but has been reported as low as 1.8 ppb (4.19 µg/m^3) (Liu et al. 2006).

Indoor air tends to have a higher concentration of acetone than outdoor air in the United States due to the use of household consumer products. A study of 100 homes in New Jersey reported a mean indoor air acetone concentration of 36.1 ppb (Weisel et al. 2008). In comparison, a study of 17 outdoor air samples across the United States reported a mean outdoor air acetone concentration of 6.9 ppb (Shah and Singh 1988). Homes with tobacco smokers also tend to have higher indoor air acetone concentrations than homes without tobacco smokers (20.8 versus 29.5 ppb) (Heavner et al. 1996).

The concentration of acetone in open ocean 200 m deep near the Bahamas was 0.35 ppb (Kieber and Mopper 1990). The concentration of acetone in the Potomac River in Virginia was below the detection limit of 40 ppb (Hall et al. 1987), and the level will be higher in water receiving industrial and municipal discharges containing acetone. An industrial landfill leachate in Michigan contained 62 ppm acetone (Brown and Donnelly 1988). A drinking water well in New Jersey that drew water from a contaminated aquifer had an acetone concentration of 3,000 ppb (Burmaster 1982). The concentration in drinking water from Seattle, Washington, was 1 ppb (Keith et al. 1976). A concentration of 6 ppb acetone was detected in the sediment of a creek adjacent to a landfill in Louisville, Kentucky (Stonebraker and Smith 1980). Acetone has been detected in the volatile components of several fruits and vegetables (Bartley and Schwede 1989; Lovegren et al. 1979).

The general population is exposed to acetone by inhaling ambient air, by ingesting drinking water and food containing acetone, and by using consumer products such as nail polish remover. No data for the total daily intake of acetone for the general population were located. However, there are data that

workers in certain industries, such as certain paint, plastic, artificial fiber, and shoe factories are exposed to high levels of acetone (Kawai et al. 1990a; Pezzagno et al. 1986). Professional painters, and commercial and household cleaners are also likely to be exposed to higher acetone concentrations than the general population. Among the general population, smokers, frequent users of nail polish removers (including beauty salon workers), and people who live near certain landfill sites (emitting higher than ambient levels of acetone) or other industrial sources of emission are susceptible to higher exposure concentrations of acetone.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Approximately 90% of acetone in the United States is manufactured by cumene peroxidation (ICIS 2017). In the peroxidation process, cumene is oxidized to a hydroperoxide, which is cleaved to yield acetone and phenol (Zakoshansky and Griaznov 1995). In the past, acetone was also commonly manufactured using isopropyl alcohol, which is catalytically dehydrogenated to yield acetone and hydrogen (ICIS 2017); however, this method has declined in use (ICIS 2017). Acetone may also be produced via the oxidation of propylene oxide (ICIS 2017).

No information is available in the TRI database on facilities that manufacture or process acetone 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). As of 2020, facilities that release 5,000 or more pounds of acetone into the atmosphere must report these releases (EPA 2020).

5.2.2 Import/Export

In the period from 2014 to 2018, general imports and imports for consumption of acetone were equal. General imports are total physical arrivals of acetone to the United States from other countries that either enter consumption channels immediately or enter into bonded warehouses or Foreign Trade Zones (FTZs) (US Census 2018). A bonded warehouse is an approved private warehouse used to store imports until duties or taxes are paid (US Census 2018). FTZs are specially licensed commercial and industrial areas in or near ports of entry where goods may be brought in without paying customs duties. Imports brought to FTZs can be manipulated (e.g., sold, stored, exhibited, repacked, cleaned, manufactured) prior to re-

export or entry (US Census 2018). U.S. imports of acetone fluctuated from 2014 to 2018, ranging from 93,639,132 kg in 2016 to 231,998,897 kg in 2018 (USITC 2019). Imports for consumption are the total amount of merchandise that has physically cleared through customs by either entering consumption channels immediately or leaving bonded warehouses or FTZs (US Census 2018). Both domestic exports and total exports of acetone fluctuated from 2014 to 2019 as well. U.S. domestic exports of acetone range from 159,620,412 kg in 2014 to 106,882,376 kg in 2018 (USITC 2019). Total exports range from 185,605,919 kg in 2015 to 118,081,807 kg in 2016 (USITC 2019). In 2018, there were 119,040,276 kg of total exports of acetone (USITC 2019).

5.2.3 Use

Acetone is used primarily as an intermediate in the chemical production of methyl methacrylate and bisphenol A (ICIS 2017). It is also commonly used as a solvent, particularly in the pharmaceutical industry (ICIS 2017). Additional uses of acetone include the manufacture of other chemicals such as methyl isobutyl ketone (ICIS 2017).

According to Chemical Data Reporting (CDR), acetone is used for personal care products; paints and coatings; adhesives and sealants; fabric, textile, and leather products; toys, playground, and sporting equipment; automotive care products; building/construction materials; as a chemical intermediate; in cleaning and furnishing care products; electrical and electronic products; lubricants and greases; metal products; plastic and rubber products; and water treatment products consumer and commercial product categories (CDR 2012, 2016). CDR data on industrial uses include acetone utilization as solvents which become part of the product formulation or mixture, intermediates, solvents for cleaning and degreasing, non-pesticidal agricultural chemicals, paper waterproofing, surface active agents, photosensitive chemicals, functional fluids (closed systems), laboratory chemicals, processing aids specific to petroleum production, a formulated mixture for automotive refinishing, paint additives and coating additives, ion exchange agents, fuels and fuel additives, viscosity adjustors, adhesives and sealant chemicals, and processing aids not otherwise listed (CDR 2012, 2016). Additionally, acetone may be used as a flavoring agent or solvent in food products (FDA 2019).

5.2.4 Disposal

A small amount of acetone is regenerated from solvent wastes produced during its use by reclaiming processes (Kupferschmid and Perkins 1986). Acetone can be removed from wastewater by air stripping

(PubChem 2021), but the vapor-phase acetone generated during stripping requires a suitable disposal method. The three methods commonly used for the disposal of waste containing acetone are underground injection, burial in sanitary landfills, and incineration. The underground injection of acetone-containing waste is allowed under the amended Section 148.10 of Code of Federal Regulations (EPA 1991). The land disposal of wastewaters containing spent acetone is allowed under Section 268.41 of the Code of Federal Regulations as long as the concentrations of acetone and other permissible spent cosolvents in the waste do not exceed 0.05 and 0.59 mg/L, respectively (EPA 1988a). Incineration under controlled conditions (to attain complete combustion) is one of the better methods of disposal for acetone, and incineration is easier when acetone is mixed with a more flammable solvent. The suitable methods for the destruction of acetone are fluidized bed incineration at a temperature of 450–980°C with residence times of seconds or rotary kiln incineration at 820–1,600ºC with residence times of seconds (PubChem 2021).

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

Acetone is emitted into the atmosphere both from natural and anthropogenic sources. Natural sources of emission include plants and trees. Acetone has been detected in a number of plant volatiles including onions, tomatoes, watermelon, nectarines, beans, and cannabis (Wang et al. 2019; Lewinsohn et al. 2005; Lovegren et al. 1979; Takeoka et al. 1988; Turner et al. 1980), and emissions have been detected from a

variety of trees including willow, aspen, birch, balsam poplar, oak, fir, pine, juniper, cedar, and cypress (Isidorov et al. 1985; Khalil and Rasmussen 1992). Acetone is produced endogenously and released as a component of human breath (Conkle et al. 1975; Krotoszynski 1977; Trotter et al. 1971). Volatiles from animal wastes, microbes, and insects are also examples of natural sources of acetone in the air (Graedel et al. 1986). In addition, forest fires and volcanic eruptions emit acetone into the atmosphere (Graedel et al. 1986; Isidorov et al. 1990). Approximately three-quarters of acetone emissions to air are expected to be a result of natural sources (Jacob et al. 2002). Prior to 2020, EPA (2005) did not require information on releases of acetone to the atmosphere from manufacturing and processing facilities. As of 2020, EPA requires that facilities must report atmospheric releases of acetone over 5,000 pounds (EPA 2020). However, no information of atmospheric releases of acetone have been reported to date. Still, acetone is one of the most common substances found at Superfund sites (EPA 1999).

Some important anthropogenic sources of acetone in the air are automobile and diesel exhaust (Inomata et al. 2013; Jacob et al. 2002; Song et al. 2010; Wang et al. 2020), biomass burning (Akagi et al. 2011; Jacob et al. 2002; Singh et al. 1994), chemical manufacture (Graedel et al. 1986), tobacco smoke (Manning et al. 1983), wood burning and pulping (Graedel et al. 1986; Kleindienst et al. 1986; Lipari et al. 1984), polyethylene burning (Hodgkin et al. 1982), refuse combustion (NAS 1976), petroleum production (Graedel 1978), certain landfill sites (Hodgson et al. 1992; LaRegina et al. 1986; Militana and Mauch 1989), and solvent uses (De Medinilla and Espigares 1988). Acetone is also formed in the atmosphere from the photochemical oxidation of propane, i-butane, and i-pentane (Arnold et al. 1986; Pozzer et al. 2010; Singh and Hanst 1981) and possibly from propylene oxide and epichlorohydrin (EPA 1985a). Atmospheric emissions are also likely from several consumer products including nail polish removers, particle board (Tichenor and Mason 1988), carpet backing (Hodgson et al. 1993), some paint removers (EPA 1986), and a number of liquid/paste waxes or polishes (Knoppel and Schauenburg 1989; Sack et al. 1992). Certain detergents/cleansers (Knoppel and Schauenburg 1989; Sack et al. 1992), adhesives, and carburetor and choke cleaners (EPA 1989) are also known to contain acetone.

Assessing levels of acetone requires strict quality assurance practices because environmental air samples can be inadvertently contaminated during laboratory preparation (EPA 2020).

5.3.2 Water

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

Acetone is released into surface water as wastewater from certain chemical manufacturing industries (Gordon and Gordon 1981; Hites and Lopez-Avila 1980; Jungclaus et al. 1978). It is also released in water from energy-related industries, such as coal-gasification (Mohr and King 1985; Pellizzari et al. 1979) and oil shale processing (Hawthorne and Sievers 1984; Pellizzari et al. 1979). Acetone was found in 27 of 63 effluent waters from a wide range of chemical industries in the United States (EPA 1979). A survey of industrial effluents indicates that acetone was detected in effluents from various industrial products such as paper, plastic, pharmaceutical, specialty cleaning and polishing products, paint and allied products, gum and wood chemicals, cyclic intermediates, industrial organic chemicals, gypsum products, and paper board products (EPA 1975).

Acetone is released to groundwater as a result of leaching from municipal and industrial landfills (Brown and Donnelly 1988; Connecticut Agricultural Experiment Station 1986; Gould et al. 1983; Steelman and Ecker 1984; Stonebraker and Smith 1980). Leaching from polyethylene distribution pipes may be a source of acetone in drinking water (Anselme et al. 1985). One of the sources of acetone in seawater is the sensitized photoreaction of dissolved organic matter (Mopper and Stahovec 1986).

5.3.3 Soil

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

Acetone leaches readily in soil (see Section 5.5.3). Therefore, the detection of acetone in leachate and groundwater from municipal and industrial landfills indicates the source of acetone in landfill soils is municipal and industrial waste. Zhang et al. (2012) showed that acetone is one of the top five ketones released from raw and aerobically treated municipal solid waste during anaerobic degradation during a simulated landfilling study. Other sources of acetone released into soil include disposal of agricultural and food waste, animal wastes (see Section 5.3.1), and atmospheric wet deposition. Household septic tank effluents are another source of acetone in soil because they can contain acetone and are discharged into the soil (EPA 1985b).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. Organic compounds with ambient vapor pressure >10^{-4} mmHg should exist almost entirely in the vapor phase (Eisenreich et al. 1981). Because the vapor pressure of acetone is 231 mmHg at 25°C (see Table 4-2), acetone should exist exclusively in the vapor phase in the atmosphere. Furthermore, the collection methods used for the quantification of acetone in the atmosphere (Jarke et al. 1981; Juttner 1986; LaRegina et al. 1986) indicate that atmospheric acetone exists as vapor. Due to the atmospheric half-life, which is on the order of days (see Section 5.4.2), acetone will be transported long distances in the air. Although not a large sink (Chatfield et al. 1987), small amounts of acetone will be removed from the atmosphere by wet deposition (Grosjean and Wright 1983), which will transport acetone from the atmosphere to surface water and soil. Due to its relatively low Henry's law constant, acetone should tend to diffuse from air to water, and studies have concluded that the atmosphere is a potential source of acetone to streams (Kenner et al. 2014; Pankow et al. 2006). While acetone may be released to the air from the ocean, Marandino et al. (2005) suggest that the ocean is more important as a sink for acetone, while Fischer et al. (2012) suggest that Northern Hemisphere oceans are sinks while tropical oceans are sources of acetone to the atmosphere. Other sinks include oxidation by OH, photolysis, and dry deposition, which may remove up to 95 Tg of acetone per year from the atmosphere (Jacob et al. 2002; Singh et al. 1994).

Water. The complete miscibility of acetone in water suggests that partitioning of acetone from the water column to sediments and suspended solids in water is not significant. The estimated low value of 0.73 for log K_{oc} (see Table 4-2) also suggests that adsorption of acetone to sediments and suspended solids is not significant. In the absence of water, acetone vapor adsorbs rather strongly to the clay component of soil by hydrogen bonding (Goss 1992; Steinberg and Kreamer 1993). The sorption is dependent on relative humidity, and increasing the humidity decreases sorption drastically. In water-saturated soil or sediment, only organic carbon, as indicated by K_{oc}, (and not hydrogen bonding) may control the sorption of acetone (Steinberg and Kreamer 1993). Experimental adsorption studies with kaolinite, montmorillonite, and stream sediments showed very little or no loss of acetone from water to the adsorbents (Rathbun et al. 1982). The transport of acetone from the water column to the atmosphere depends on the Henry's law constant. The Henry's law constant for acetone is 3.97×10^{-5} atm-m^3/mole (see Table 4-2). Therefore, volatilization of acetone from water, although not very fast, is significant (Thomas 1990). The volatilization rate of a chemical depends on the characteristics of the chemical and

the water and on other ambient conditions (e.g., water depth, suspended solid concentration, water current, wind speed, temperature). Based on an estimation method (Thomas 1990) and a Henry's law constant value of 4.26×10^{-5} atm-m^3/mole, the volatilization half-life of acetone from a model river 1 m deep, flowing at a current of 1 m/second with a wind velocity of 3 m/second is about 18 hours. The mean volatilization coefficient for acetone in a model outdoor stream ranged from 7.15×10^{-4} to 14.8×10^{-4}/minute (Rathbun et al. 1989, 1991). Therefore, the volatilization half-life of acetone from the model stream is in the range of 7.8–16.2 hours. It was concluded that volatilization dominates the fate of acetone in water (Rathbun et al. 1989, 1991). Results of a laboratory study (Rathbun et al. 1982) also concluded that volatilization is one of the important fate-determining processes for acetone in streams.

Sediment and Soil. The two significant transport properties for acetone in soil are volatilization and leaching. Leaching transports acetone from soil to groundwater. The rate of leaching from soil by rainwater depends on the conditions in the soil. Because acetone has a low K_{oc} value, sorption of acetone in water-saturated soil will be weak. The low retention ability will permit acetone to leach into groundwater. A sorption study with moist clay soils indicates that aqueous acetone causes swelling in these soils (Green et al. 1983), and this process may allow the retention of a small fraction of acetone. Groundwater monitoring studies (see Section 5.4.2) at landfill sites provided evidence of the importance of acetone leaching from soil. Volatilization transports acetone from soil to the atmosphere. The volatility rate of acetone from soil depends on the soil characteristics (moisture content, soil porosity, etc.). Because the acetone is weakly sorbed to soil, the volatility depends primarily on the moisture content of the soil. In dry soil, the volatilization rate from soil surfaces is high due to the high vapor pressure of acetone. In moist soil, the rate of volatilization tends toward that of acetone in water, which depends on the Henry's law constant. Acetone volatilizes moderately under these conditions. The detection of acetone at higher concentrations in downwind air of a landfill site, compared to upwind air (Militana and Mauch 1989), supports the importance of volatilization as a transport process in soil.

No data regarding the transport of acetone from soil to plants were located.

Other Media. The log K_{ow} value of -0.24 (see Table 4-2) suggests that bioconcentration of acetone in aquatic organisms is not significant. The measured bioconcentration factor for adult haddock exposed to acetone under static conditions at 7–9°C was <1 (Rustung et al. 1931). No data regarding the biomagnification potential of acetone in aquatic organisms were located; however, the low K_{ow} value suggests that biomagnification from animals of lower to higher trophic levels is unlikely.

5.4.2 Transformation and Degradation

Air. The reactions of acetone vapor with nitrogen oxides, hydroxyl radicals (OH), singlet molecular oxygen ($^1\Delta_g$, singlet atomic oxygen (O[^{3}P]), and nitrate radicals have been studied. Given the second order rate constants for the reactions of acetone with $^1\Delta_g$ (Datta and Rao 1979) and O(^{3}P) (Lee and Timmons 1977; Singh et al. 1994), and the concentrations of singlet molecular and atomic oxygen in the atmosphere (Graedel 1978), these reactions are insignificant in determining the fate of acetone in the atmosphere. The reaction of acetone with nitrate radicals in the atmosphere was also determined to be insignificant (Boyd et al. 1991). Smog chamber studies with acetone and nitrogen oxides conclude that acetone has low reactivity in terms of ozone and nitrogen dioxide formation and that the rate of disappearance of acetone by this process is low (Altshuller and Cohen 1963; Dimitriades and Joshi 1977; Yanagihara et al. 1977). The photochemical oxidation of acetone in the presence of nitrogen oxides produces small amounts of peroxyacetic acid and peroxyacetyl nitrate (Hanst and Gay 1983). In a self-made chamber, experiments with and without NaCl, $(NH_4)_2SO_4$, and $NaNO_2$ showed that acetone is not capable of forming secondary organic aerosols (Ge et al. 2017).

The two significant processes in determining the fate of acetone in the atmosphere are reaction with hydroxyl radicals and photolysis. The rate constant for the reaction of hydroxyl radicals with acetone at 25°C is in the range of 1.8–5.0x10^{-13} cm^3/molecule-second (Cox et al. 1980, 1981; PubChem 2021; Meyrahn et al. 1986). The estimated average lifetime of acetone due to reaction with hydroxyl radicals is 44.5 days (Meyrahn et al. 1986). The probable pathways for the reaction of acetone with hydroxyl radicals in the troposphere have been postulated, and methylglyoxal is the primary product of this reaction (Altshuller 1991). Acetone underwent significant photolysis with an artificial light of maximum emission at 300 nm (near-ultraviolet UVB) (Fujiki et al. 1978). Besides free radicals, the primary products of acetone photolysis in sunlight are carbon dioxide and acetylperoxynitrate (Altshuller 1991). The lifetimes of acetone due to photolysis under cloudless conditions at 40°N latitude and sea level during winter and summer are estimated to be 83 and 19 days, respectively (Martinez et al. 1992). The estimated average lifetime of acetone at 40°N due to combined hydroxyl radical reaction and photolysis is 32 days (Meyrahn et al. 1986), corresponding to a half-life of 22 days. Jacob et al. (2002) has estimated a mean tropospheric lifetime of 15 days. The lifetime of acetone in the upper troposphere increases with altitude and ranges from 10–20 days in the tropics to 75–250 days at mid-latitudes (Arnold et al. 2004). Due to the pressure dependence of the quantum yield, the rate of photodissociation will increase as altitude increases, whereas the reaction rate with hydroxyl radicals will decrease because temperature decreases at higher altitudes. Therefore, the lifetime of acetone in the atmosphere will remain approximately constant

with respect to altitude. However, the rate will show a pronounced dependence on latitude with greater losses of acetone occurring near the equator, compared to the poles (Meyrahn et al. 1986).

Water. Based on the rate constant for the reaction of acetone with hydroxyl radicals in water at pH 7 ($5.8–7.7x10^7$/M-second) (Anbar and Neta 1967) and the concentration of hydroxyl radicals in eutrophic waters ($3x10^{-17}$ M) (Mill and Mabey 1985), this reaction will not be significant in water. When distilled water or natural water containing acetone was exposed to sunlight for 2–3 days, no photodecomposition of acetone was observed (Rathbun et al. 1982). Therefore, photolysis of acetone in water is not an important process.

Many aerobic biodegradation screening studies with mixed microorganisms from waste-treatment plant effluents, activated sludge, or sewage have examined the biodegradability of acetone (Babeu and Vaishnav 1987; Bridie et al. 1979; EPA 1990; Ettinger 1956; Gaudy et al. 1963; Hatfield 1957; Heukelekian and Rand 1955; Lamb and Jenkins 1952; Price et al. 1974; Stafford and Northup 1955; Thom and Agg 1975; Urano and Kato 1986a, 1986b). These studies indicate that acetone is easily biodegradable with acclimatized microorganisms or after a suitable lag period (≈1 day) (Urano and Kato 1986a, 1986b), as long as the initial concentration of acetone is not at a toxic level. For example, acetone at a concentration of 500 mg/L was toxic to microorganisms when biooxidation of acetone by activated sludge was attempted (Gerhold and Malaney 1966). Biodegradation of acetone was much slower in seawater than in fresh water (Takemoto et al. 1981). After a suitable lag period (5 days), acetone biodegraded quantitatively under anaerobic conditions with anaerobic acetate enriched culture medium (Chou et al. 1978). A biodegradation study of acetone in natural water collected from Lago Lake near Athens, Georgia, determined that the biodegradation kinetics are multiphasic in nature and depend on the substrate concentration. The determined rate of degradation was faster at higher initial concentrations (the maximum concentration used was 0.5 mg/L) (Hwang et al. 1989).

In a laboratory experiment with natural stream water and sediment, no acetone was lost in 338 hours under sterile conditions in closed flasks. However, with nonsterile natural sediment, 100% of the acetone was lost in 500 hours following a lag period of 90 hours (Rathbun et al. 1982). The authors of this study concluded that biodegradation was one of the important processes for the loss of acetone in streams. Significant loss of acetone due to biodegradation was not observed in a later study where acetone was injected continuously in an outdoor model stream (Rathbun et al. 1988, 1989, 1991, 1993). Attempts to induce biodegradation by adding glucose and a nutrient solution containing bacteria acclimated to acetone were unsuccessful. The authors concluded that the residence time of acetone in the model stream

(6 hours) was too short for the bacteria to become acclimated in the water before initiation of biodegradation. However, this explanation may not be valid if attached bacteria, rather than free-floating bacteria, dominate the biodegradation process. As an alternative explanation, the study authors indicated that low levels of nitrate in the model stream may be responsible for the lack of acetone biodegradation.

Sediment and Soil. The biodegradation studies for water discussed above indicate that biodegradation of acetone in sediment and soil will be significant. No evidence was located to suggest that any degradation process other than biodegradation is important in sediment and soil. However, laboratory or field data examining the biodegradability of acetone in soil are lacking. One study of soil from a natural gas company isolated a gram-negative bacterium *(Paracoccus solventivorans)* capable of degrading acetone (Siller et al. 1996).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to acetone depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of acetone 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 acetone levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-1 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-2.

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

Media	Detection limit	Reference
Air (occupational)	0.006 ppm	NIOSH 2017
Air (occupational)	<0.01 ppm	Campbell and Moore 1979
Air (indoor and outdoor)	0.013 ppb	Zhu et al. 2005
Water	0.5 mg/L	Rahim and Basir 1981
Groundwater	0.01 mg/L	USGS 2001
Fresh and seawater	0.03 µg/L	Kieber and Mopper 1990

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

Media	Detection limit	Reference
Industrial runoff	100 µg/L	Line et al. 1997
Sediment and soil	100 µg/kg	EPA 1996

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

Table 5-2. Summary of Environmental Levels of Acetone in the United States

Media	Low	High	For more information
Outdoor air (ppbv)	80	4,700	Table 5-5
Indoor air (ppbv)	1.2	8,732	Table 5-6
Surface water (ppb)	14	53	Table 5-8
Ground water (ppb)	0	42,000	Section 5..5.2
Drinking water (ppb)	<6	68.36	Table 5-9
Food (ppb)	0.1	880	Section 5.5.4
Soil	1	5,300	Section 5.5.3

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

Table 5-3. Acetone 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 (µg/L)	280	528	28.2	174	119
Soil (mg/kg)	1.10	2.03	54.2	133	100
Air (ppb)	22.2	30.7	12.2	42	29

[a]Concentrations found in ATSDR sites measured at 1,867 NPL sites between 1981 and 2019 (ATSDR 2019). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Acetone is a volatile compound and is stable in air. Ambient air pollution data is collected by EPA as well as state, local, and tribal air pollution control agencies in the U.S. for the Air Quality System (AQS). Table 5-4 summarizes the calculated percentile distribution of arithmetic mean concentrations of acetone across the United States using data from AQS from 2016 to 2020.

Table 5-4. Percentile Distribution of Annual Mean Acetone Concentrations (ppb Carbon) Measured in Ambient Air at Locations Across the United States

Year	Number of U.S. locations	Percentile				
		25th	50th	75th	95th	Maximum
2016	170	3.41	7.62	12.3	21.3	44.7
2017	165	3.45	8.33	12.4	19.8	156
2018	166	3.94	8.14	12.4	19.4	116
2019	124	3.29	8.38	12.4	18.6	57.9
2020[a]	87	3.15	7.12	11.9	18.5	52.0

[a]Data current as of November 2020.

Source: EPA 2020

Levels of acetone in urban, rural, and remote areas in the United States and the level in the troposphere are shown in Table 5-5. Table 5-5 indicates that concentrations of acetone in air are variable and tend to be higher in urban rather than rural settings. Besides these data, air monitoring data from an urban area (Tulsa, Oklahoma), a rural area (Rio Blanco County, Colorado), and a remote area (Smoky Mountain, Tennessee) are also available (Arnts and Meeks 1981). These data are not presented in Table 5-5 because the samples were collected in Tedlar bags that are known to contaminate air samples with acetone. Tables 5-5 and 5-6 also indicate that the indoor concentration of acetone is generally higher than the outdoor concentration. Other investigators reported similar results (Jarke et al. 1981). The reason for the higher indoor air concentration is the use of acetone-containing consumer products inside homes. Herberger et al. (2010) reports that the average indoor air concentration of acetone is 570 $\mu g/m^3$, with possible sources including expired air.

Acetone in water volatilizes fairly rapidly; thus, there is potential for inhalation exposure during showering and bathing. ATSDR's three-compartment Shower and Household Water-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day by estimating the contribution from showering or bathing and the contribution from other water sources in the house, such as the dishwasher, clothes washer, and faucets. This information along with human activity patterns are used to calculate a daily TWA exposure concentration via inhalation exposure and from dermal uptake from skin contact. For example, using a tapwater concentration of 0.5 ppm, the SHOWER model v2.0 predicts a daily continuous-exposure concentration of 0.05 ppm for a four-person household. This concentration is well below ATSDR's acute, inhalation MRL of 8 ppm. ATSDR's

Table 5-5. Outdoor Air Monitoring Data for Acetone

Location(s)	Geographic type	Date(s)	Range (ppb)	Mean concentration (ppb)	Notes	Reference
United States		5/18/2004–7/14/2004	80–4,700	814.8	25 samples; 10 detections.	WQP 2021
Canada	All	2000–2009	0.003–14.8	No data	Measured 3,688 samples over 24-hour sampling periods; median of 1.2 ppb and 95th percentile of 2.8 ppb.	Environment Canada 2014
Canada	Rural	2000–2009	0.03–9.4	No data	Measured 285 samples over 24-hour sampling periods; median of 1.2 ppb and 95th percentile of 2.8 ppb.	Environment Canada 2014
Canada	Commercial	2000–2009	0.01–5.8	No data	Measured 460 samples over 24-hour sampling periods; median of 1.3 ppb and 95th percentile of 2.5 ppb.	Environment Canada 2014
Canada	Industrial	2000–2009	0.02–6.0	No data	Measured 3688 samples over 24-hour sampling periods; median of 1.2 ppb and 95th percentile of 3.8 ppb.	Environment Canada 2014
Greece, Cyprus, the Netherlands, Hungary, Belgium, Italy, Ireland, Finland, and Denmark	Urban	2004–2008	0.1–5.4	0.1	Measured 66 samples from 11 different cities; median of 2.6 ppb	Geiss et al. 2011
New York		1997–2003	No data	No data	Measured 114 samples for 2-hour periods; 6.1% of samples were non-detectable; median of 2.7 ppb; 25th, 75th, and 90th percentiles of 1.4, 5.9, and 18.5 ppb, respectively	NYSDOH 2005
Caribbean Sea		1988	0.18 – 0.95	0.38	Sea-level sampling	Zhou and Mopper 1993
Portland, Oregon	Urban	1987–1988		7.4	Sampling of air outside of newly constructed office buildings	Hodgson et al. 1991
Houston, Texas	Urban, industrial	1987–1988	No data	6.1	Measured 60 samples during 24-hour sampling intervals	Lagrone 1991
Ontario	Rural	1988	No data	1.7		Shepson et al. 1991

Table 5-5. Outdoor Air Monitoring Data for Acetone

Location(s)	Geographic type	Date(s)	Range (ppb)	Mean concentration (ppb)	Notes	Reference
United States		1975–1986	Lower quartile of 0.0 and upper quartile of 2.8	6.9	Measured 17 sample; median of 0.9 ppb	Shah and Singh 1988
Germany		1984–1985	No data	0.47	Ground-level sampling	Arnold et al. 1986
Germany		1984–1985	No data	0.12	Upper troposphere and lower stratosphere; altitudes of 5,900–11,300 m	Arnold et al. 1986
Tucson, Arizona	Urban	1982	No data	12.0	Measured 17 samples; standard deviation = 4.0 ppb	Snider and Dawson 1985
Santa Rita and Mt. Lemmon, Arizona	Rural	1982	No data	2.8	Measured 18 samples; standard deviation = 0.8 ppb	Snider and Dawson 1985
Troposphere (lower)		No data	No data	0.7		Dilling et al. 1984
Point Barrow, Alaska	Arctic conditions	1967	No data	1.1	Measured 25 samples over a 24-hour period	Cavanagh et al. 1969

WQP = Water Quality Portal

Table 5-6. Indoor Air Monitoring Data for Acetone

Location(s)	Geographic type	Date(s)	Mean concentration (ppb)	Notes	Reference
New Jersey	Suburban and rural	2003–2006	36.1	Measured 100 homes, 94 of which had detectable levels of acetone; median of 14.3 ppb; range of <5.0–1,201.1 ppb	Weisel et al. 2008
Ottawa, Canada	Urban and suburban	2002–2003	18.4	Measured 75 homes with 99% detection frequency; median of 11.8 ppb; range of 0.006 to 188.8 ppb; 75th and 90th percentiles of 19.4 and 31.6 ppb, respectively	Zhu et al. 2005
New York	Not specified, homes were mostly near the Albany area	1997–2003	Not reported	227 samples of fuel oil heated homes. Median of 8.7 ppb; 25th, 75th, and 90th percentiles were 4.1, 21.5, and 45.6 ppb, respectively	NYSDOH 2005
United States	Not specified. Sampling of 56 office buildings	1995–1998	Not reported	Range of 7.1–220 ppb' median of 29 ppb; 168 samples (3 per building) collected over summer or winter months	Girman et al. 1999
New Jersey and Pennsylvania	Non-tobacco smoking homes	1992	20.8	Sampled 60 home; range of 1.2–161.4 ppb; median of 14.0 ppb; SD of 24.2 ppb	Heavner et al. 1996
New Jersey and Pennsylvania	Tobacco smoking homes	1992	29.5	Sampled 29 homes; range of 8.2–275.4 ppb; median of 16.3 ppb; SD of 48.9 ppb	Heavner et al. 1996
New Jersey and Pennsylvania	Non-tobacco smoking workplaces	1992	24.7	Sampled 52 workplaces; range of 2.3–171.6 ppb; median of 11.8 ppb; SD of 33.0 ppb.	Heavner et al. 1996
New Jersey and Pennsylvania	Tobacco smoking workplaces	1992	394.7	Sampled 28 workplaces; range of 3.4– 8732.3 ppb; median of 25.1 ppb; SD of 1,651.8 ppb	Heavner et al. 1996
Portland, Oregon	Urban	1987–1988	12.1–28.1	Samples from newly constructed office buildings collected August and October 1987 and January and October 1988	Hodgson et al. 1991
California and New Jersey	Residential and occupational sites	1981–1984	8.0	Measured 4 samples; median of 8.57 ppb; lower quartile of 4.5 ppb and upper quartile of 11.4 ppb	Shah and Singh 1988

SD = standard deviation

SHOWER model is available by sending a request to showermodel@cdc.gov. Vapor intrusion may also be a potential source of acetone exposure, as vapor intrusion has been observed for several VOCs with similar properties (Burk and Zarus 2013). Indoor air measurements in a review of 16 vapor intrusion sites (Table 5-7) fell within the range of those found at sites with no known hazardous waste (Table 5-6). However, only 2 of the 16 vapor intrusion sites had sufficient data (indoor air, outdoor air, and soil gas) to fully evaluate the vapor intrusion pathway. EPA's compilation of six studies of background indoor air concentrations found a 94–99% detection rate for acetone in 937 U.S. resident samples between 1996 and 2006 (EPA 2011). The background medians ranged from 21 to 49 µg/m^3, 95th percentiles ranged from 140 to 190 µg/m^3, and maximum values ranged from 257 to 2,900 µg/m^3. The potential for intrusion of acetone present as soil gas into a house adjacent to a landfill by diffusive and advective routes was found to be low (Hodgson et al. 1992). However, only a single house was studied. Two separate measurements were made, and basement air concentrations were found to be 12 and 82 ppb (v/v). Table 5-7 lists maximum measured values of acetone in various environmental media in U.S. hazardous waste sites.

5.5.2 Water

Data for water monitoring and drinking water monitoring for acetone are summarized in Tables 5-8 and 5-9, respectively. In 50,125 groundwater samples collected in the United States for the Water Quality Portal (WQP) between 2000 and 2021, 13,903 contained detectable levels of acetone ranging from 0 to 42,000 µg/L with an average concentration of 55.6 µg/L (WQP 2021). Several U.S. Geological Survey (USGS) studies have detected acetone in groundwater. A study of 54 wells in Clinton County, Pennsylvania in 2017 found acetone in 1 of 54 samples at a maximum concentration of 45.9 µg/L, and the concentration did not exceed the EPA drinking-water standards (USGS 2020). A study of 12 carbonate aquifers across the United States from 1993 to 2005 found that acetone was one of the most frequently detected volatile organic compounds and was most often found in urban and mixed land-use locations (USGS 2009). The maximum concentration was 6.97 µg/L (USGS 2009). The National Water Quality Assessment Program conducted sampling of acetone in groundwater and finished water in 24 community water systems in the United States and found non-detectable levels of acetone (<6 or <7 µg/L) in the majority of samples (USGS 2007). The highest concentration observed was 68 ppb in an aquifer in Florida (USGS 2007). In 103 finished water samples collected for WQP between 2002 and 2009, 30 samples contained detectable levels of acetone ranging from 1.4 to 20.2 µg/L (WQP 2021). In a National Organics Reconnaissance Survey (NORS) by EPA involving drinking water supplies from 10 cities in the United States, acetone was qualitatively detected in all 10 water samples. The 10 cities in

Table 5-7. Maximum Measured Values of Acetone at Selected Hazardous Waste Sites with Potential for Vapor Intrusion

Site name	Location	Date	Environmental medium	Maximum measured value (ppb)	Reference
Laugh and Learn Daycare	Ashville, Ohio	6/18/07	Indoor air	10.0	ATSDR 2007a
			Soil gas	3.5	
			Outdoor air	6.3	
Krouts Creek HC	Huntington, West Virginia	6/14/07	Soil gas	140.3	ATSDR 2007b
Sal's Auto Repair	Neptune City, New Jersey	4/4/07	Soil gas	88.6	ATSDR 2007c
Gorham	Providence, Rhode Island	12/4/06	Soil gas	69.6	ATSDR 2006a
Chevron	Hooven, Ohio	11/27/06	Soil gas	5,110.5	ATSDR 2006b
Brewer Brothers	Cardwell, Missouri	9/30/06	Soil gas	29.5	ATSDR 2006c
Brookhaven Landfill	Brookhaven, New York	11/29/05	Outdoor air	50.6	ATSDR 2005a
McCook VOC Vapor Intrusion Site	McCook, Nebraska	9/7/05	Indoor air	13.9	ATSDR 2005b
Bagley Bank	Bagley, Minnesota	7/13/05	Indoor air	16.3	ATSDR 2005c
Bachman Spill Site	Washington Township, Pennsylvania	6/21/05	Indoor air	51.1	ATSDR 2005d
Silver Creek Subdivision	Tucson, Arizona	6/3/05	Indoor air	0.2	ATSDR 2005e
Pemaco Superfund Site (VI Eval)	Maywood, California	4/29/05	Indoor air	160.3	ATSDR 2005f
			Soil gas	1,302.6	
			Outdoor air	674.9	
Matchbox Daycare	Warsaw, Indiana	3/15/05	Indoor air	26.5	ATSDR 2005g
Cooper's Poynt Elementary	Camden, New Jersey	2/9/05	Indoor air	12.2	ATSDR 2005h
			Outdoor air	5.1	
Sunoco	Greensburg, Pennsylvania	10/18/04	Indoor air	13.9	ATSDR 2004a
Freeland Garland	Freeland, Pennsylvania	8/9/04	Indoor air	21.0	ATSDR 2004b
Trichloroethylene Site			Outdoor air	10.0	
		6/26/03	Indoor air	42.1	ATSDR 2003

this survey were Cincinnati, Ohio; Miami, Florida; Ottumwa, Indiana; Philadelphia, Pennsylvania; Seattle, Washington; Grand Forks, North Dakota; Lawrence, Kansas; New York, New York; Terrebonne Parrish, Louisiana; and Tucson, Arizona (Bedding et al. 1982; Coleman et al. 1976; Keith et al. 1976). The determined concentration of acetone in one of the drinking water samples (Seattle, Washington) was 1 ppb (Keith et al. 1976). Acetone has also been detected in water from several artesian wells adjacent to a landfill in Wilmington, Delaware at a concentration of 0.3 ppb in finished drinking water from one of the wells (DeWalle and Chian 1981). The concentration of acetone was 3,000 ppb in a contaminated drinking water well in New Jersey (Burmaster 1982; Steelman and Ecker 1984).

Acetone was detected in 1,238 of 3,970 surface water samples in the United States collected for WQP between 2000 and 2021 at concentrations ranging from 0 to 25,000 µg/L (0–25,000 ppb) with an average concentration of 35.2 µg/L (35.2 ppb) (WQP 2021). Acetone has been detected at low levels (median of 2.6 ppb) in streams in New York and New Jersey (USGS 1997). Higher concentrations (>100 ppb) have been reported in several samples of storm water runoff from industrial sites (Line et al. 1997). The concentration of acetone in open ocean water (Tongue of the Ocean, Bahamas) was 6 nM (0.35 ppb) (Kieber and Mopper 1990), whereas the reported mean concentrations in seawater from the Straits of Florida and the Eastern Mediterranean were 20 and 30 ppb, respectively (Corwin 1969). The concentration of acetone in the Potomac River, Virginia was below the detection limit of 40 ppb (Hall et al. 1987).

Acetone in one sample of industrial effluent in the United States from 2009 reported in the WQP was below the detection level of 0.05 mg/L (WQP 2021). In 89 samples of leachate collected between 2002 and 2020 in the United States, 12 samples contained acetone at detectable levels ranging from 0.028 to 360 mg/L (WQP 2021). In five samples of wastewater treatment plant effluent in the United States from 2003 to 2007, acetone was detected in two samples, at concentrations of 0.041 and 0.044 mg/L, while the other three samples were below the detection limit of 0.0012 mg/L (WQP 2021). Acetone has been detected in the effluent from a textile plant (Gordon and Gordon 1981) and in effluent water from a specialty- chemicals manufacturing plant at a concentration of 200–230 ppm (Jungclaus et al. 1978). The compound has also been detected in groundwater, leachate, and run-off waters from landfill sites (Brown and Donnelly 1988; Connecticut Agricultural Experiment Station 1986; DeWalle and Chian 1981; Gould et al. 1983; Stonebraker and Smith 1980). The concentration of acetone in an industrial landfill leachate in Michigan was in the range of 0.05–62.0 ppm (Brown and Donnelly 1988). However, the quality of the reported data is uncertain. Acetone was detected at a mean concentration of 56 ppb in a landfill leachate in Orange County, Florida (Hallbourg et al. 1992).

Table 5-8. Water Monitoring Data for Acetone

Location(s)	Geographic type	Date(s)	Range (ppb)	Mean concentration (ppb)	Notes	Reference
New York and New Jersey	Streams	1997	Not reported	Not reported	Detectable levels in 64% of samples; detection limit of 5 ppb; median concentration of 2.6 ppb and maximum concentration of 6.6 ppb	USGS 1997
North Carolina	Industrial	1993–1994	Not reported	Not reported	Storm water runoff from industrial sites. Acetone not detectable (less than the minimum detection limit of 100 ppb) in seven of nine first-flush samples; detectable levels (>100 ppb) in two samples	Line et al. 1997
Tongue of the Ocean, Bahamas	Open ocean	Not reported	Not reported	0.35	Sampling depth: 200 m	Kieber and Mopper 1990
Potomac River, Virginia	River surface water	1986	Not reported	<40	Composite samples collected from three field stations	Hall et al. 1987
Straits of Florida	Sea water	February 1968	14–52	23.3	11 total samples (1 non-detect, <5 ppb); collected at depths of 0–518 m	Corwin 1969
Eastern Mediterranean	Sea water	August 1965	18–53	32.9	16 samples measured; collected at depths 0–1,200 m	Corwin 1969

Table 5-9. Drinking Water Monitoring Data for Acetone

Location(s)	Geographic type	Date(s)	Range (ppb)	Mean concentration (pbb)	Notes	Reference
United States	Groundwater (15 principal aquifers)	2002–2005	<6–68.36	<6 or 7	Majority of samples were too low to be quantified (<6 or <7 ppb), non-detects; however, Florida aquifer system (unconfined unit) contained 68.36 ppb	USGS 2007
New Jersey	Drinking water well	1980		3,000		Burmaster 1982; Steelman and Ecker 1984
Wilmington, Delaware	Drinking water wells	Mid-1977	0.2–0.7	0.35	Six samples from wells (including finished water); wells located adjacent to a landfill	DeWalle and Chian 1981
Seattle, Washington	Finished drinking water	1975	Not reported	1 ppb		Keith et al. 1976

5.5.3 Sediment and Soil

There are few data regarding the level of acetone in soil and sediment. In 811 samples of soil collected between 2000 to 2015 in the United States, acetone was detected in 245 at concentrations ranging from 1 to 5,300 µg/kg and averaging 141.8 µg/kg (WQP 2021). The maximum concentration of acetone in soils from Vega Alta Public Supply well sites in Puerto Rico was 9,500 ppb (ATSDR 1988). The mean concentration of acetone in soil from Summit National Site, Ohio, was 9,484 ppb (dry weight) (EPA 1988b). In 3,265 samples of sediment in the United States from 2000 to 2020, acetone was detected in 2,134 samples with concentrations ranging from 2 to 8,820,000 µg/kg and averaging 6,785 µg/kg (WQP 2021). Acetone has been qualitatively detected in river sediment that received effluents from a specialty chemicals manufacturing plant (Hites and Lopez-Avila 1980). A concentration of 6 ppb acetone was detected in the sediment of a creek adjacent to a landfill in Louisville, Kentucky (Stonebraker and Smith 1980). Because of its high water solubility and low sediment adsorption coefficient, most acetone in an aquatic system will be found in water, rather than in sediment.

5.5.4 Other Media

Acetone has been qualitatively detected as a volatile component of a number of foods including blue cheese (Day and Anderson 1965), baked potatoes (Coleman et al. 1981), roasted filbert nuts (Kinlin et al. 1972), meat (Grey and Shrimpton 1967; Shahidi et al. 1986), and nectarines (Takeoka et al. 1988). In kiwi fruit, the acetone concentration comprised 0.2% of total volatile components (Bartley and Schwede 1989). The concentrations of acetone in dry legumes, such as beans (mean of several varieties), split peas, and lentils were 880, 530, and 230 ppb, respectively (Lovegren et al. 1979). The level of acetone in headspace volatiles of Bisbee Delicious apples ranged from 111 to 912 pL/kg-hour (Mattheis et al. 1991). The percent of acetone (of the total) in commercial concentrated aqueous orange essences ranged from 0.003 to 0.009% (Moshonas and Shaw 1990).

Acetone is also found naturally in dairy milk and breastmilk, as it is produced endogenously in both cows and humans. In a study carried out in Czechoslovakia, the concentrations of acetone in samples of milk and cream culture were 0.8 and 0.001 ppm, respectively (Palo and Ilkova 1970). Acetone also has been qualitatively detected in breast milk of working mothers, although the study did not identify whether the concentrations of acetone were higher than normal physiologic levels (Giroux et al. 1992). Acetone has been qualitatively detected in 8 of 12 mothers' milk samples collected from two locations in New Jersey; Bridgeville, Pennsylvania; and Baton Rouge, Louisiana (Pellizzari et al. 1982). More recent studies of

volatile organic compounds in human breastmilk did not measure acetone concentrations (Blount et al. 2010; Kim et al. 2007).

Acetone has been detected in occasional rain samples collected in Hanover, Germany (Levsen et al. 1990). The authors were not sure whether the detection of acetone in the rain water was due to contamination of samples during analysis. The concentration of combined acetone and acrolein was 0.05 ppm in a rain water sample from Los Angeles, California (Grosjean and Wright 1983). The investigators could not separate acetone from acrolein by the method used for the determination of carbonyl compounds.

5.6 GENERAL POPULATION EXPOSURE

Acetone is endogenously produced by all humans. The general population is exposed to acetone by inhaling ambient air, ingesting food, and drinking water containing acetone. A recent study reported acetone emissions from children's 3-D pens and 3-D printer toys, with a range of acetone air concentrations of 1.5−9.4 ppb (3.1−22.4 µg/m^3) (Yi et al. 2019). Dermal exposure to acetone may result from skin contact with certain consumer products (e.g., certain nail polish removers, paint removers, and household cleaning and waxing products) (see Section 5.2.3). However, no quantitative data for dermal exposure to acetone from consumer products were located. Inhalation and daily intake rates for the general population can be estimated using monitoring data (see Section 5.5.1 and 5.5.2). Considering a high exposure scenario, the concentration of acetone is 36.1 ppb (85.75 µg/m^3) in indoor air (Weisel et al. 2008), and 6.9 ppb (16.38 µg/m^3) in outdoor air. Then assuming that a person inhales 15 m^3/day of indoor air and 5 m^3/day of outdoor air, the estimated inhalation rate of acetone is 1.64 mg/day. No experimental or estimated data were located regarding the daily intake of acetone in the general population in the United States from ingestion of drinking water and food. However, the daily intake for acetone (assuming a person consumes 2 L of drinking water/day) from this source would be <approximately 0.012 mg/day based on the assumption that the level of acetone in drinking water is <6 ppb (Section 5.5.2).

The acetone concentrations in body fluids and expired air of healthy and diabetic individuals are given in Table 5-10. The concentration of acetone in whole blood does not differ from that in plasma (Gavino et al. 1986). Even in healthy subjects, the level of acetone in blood/plasma varies with fasting or nonfasting conditions and depends on the weight of the subject. Generally, the blood/plasma acetone concentrations are higher in fasted than nonfasted subjects and higher in subjects who are not obese, compared to obese

subjects (Haff and Reichard 1977). An analysis of data from the Third National Health and Nutrition Examination Survey (NHANES III) found that the mean concentration of acetone in whole blood was 3.1 mg/L (Ashley et al. 1994). Blood acetone concentrations varied widely: the 5th percentile was 0.64 mg/L and the 95th percentile was 6.0 mg/L.

Table 5-10. Concentrations of Acetone in Human Biomarkers Collected in the United States

Medium	Concentration	Subjects	Reference
Whole blood	3.1 mg/L	NHANES III sample	Ashley et al. 1994
Whole blood	0.84 mg/L	Healthy	Wang et al. 1994
Whole blood	1.26 mg/L	Healthy	Jones et al. 1993
Whole blood	1.90 mg/L	Diabetic	Jones et al. 1993
Whole blood	2.03 mg/L	Drunk drivers	Jones et al. 1993
Whole blood	0.93 mg/L	Healthy (nonfasted)	Gavino et al. 1986
Plasma	46.5 mg/L	Healthy (fasted)	Haff and Reichard 1977
Plasma	1.74 mg/L	Healthy (nonfasted)	Trotter et al. 1971
Plasma	290 mg/L	Ketoacidotic	Haff and Reichard 1977
Plasma	424 mg/L	Ketoacidotic	Trotter et al. 1971
Urine	0.84 mg/L	Healthy	Wang et al. 1994
Urine	0.76 mg/L	Healthy	Pezzagno et al. 1986
Urine	0.23–0.41 mg/L	Healthy	Kobayashi et al. 1983
Urine	0.64–9.0 mg/L	Diabetic	Kobayashi et al. 1983
Expired air	1.3 µg/L	Healthy	Phillips and Greenberg 1987
Expired air	0.1 µg/L	Healthy	Krotoszynski et al. 1979
Expired air	1.16 µg/L	Healthy	Trotter et al. 1971
Expired air	1.23 µg/L	Healthy	Jansson and Larsson 1969

NHANES = National Health and Nutrition Examination Survey

5.7 OPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in industries that manufacture or use acetone are one segment of the population at an especially high risk of acetone exposure compared to the general population (see Section 5.6). Professional painters, salon workers, factory workers, and commercial and household cleaners (who use certain detergents, cleansers, waxes, or polishes that contain acetone) are also likely to be exposed to acetone at higher concentrations than the general population. In a small printing factory in the United States, employees were exposed to short-term average concentrations of acetone ranging from 11.4 to 41.4 ppm during printing and cleaning activities, respectively (Lee et al. 2009). The concentration of acetone in the

breathing zone air of a solvent recycling plant in the United States ranged from not detected to 43 mg/m^3 (Kupferschmid and Perkin 1986). Several studies of workplaces in foreign countries have measured acetone concentrations in breathing zone air. The concentrations of acetone in the breathing zone air in a paint factory, a plastics factory, and an artificial fiber factory in Italy were >3.48 mg/m^3 (Pezzagno et al. 1986). The concentration of acetone in the breathing zone air of a fiber-reinforced plastic plant in Japan, where bathtubs were produced, was <108 mg/m^3 (Kawai et al. 1990a). The inhalation exposure for workers to acetone in a shoe factory in Finland ranged from 25.4 to 393.4 mg/m^3 (Ahonen and Schimberg 1988). Concentrations of acetone in the breathing zone air in shoe factories in Italy were also high (Brugnone et al. 1978). High levels of acetone were also detected in the ambient air in other industries including chemical, plastic button, and paint manufacturing industries in Italy (Ghittori et al. 1987).

Several studies have measured indoor air concentrations of acetone in nail salons across the United States to analyze exposures of nail salon workers. One study found that salon workers are exposed to acetone while painting nails, and nail polish samples contained 0.56 to 8.07 ppm acetone (Heaton et al. 2019). In a study of salons in New York City, Philadelphia, and southern New Jersey, the mean personal chemical exposure ranged from 3.30 to 58.47 ppm across 25 salons; the total mean personal exposure for acetone was 18.51 ppm (Ma et al. 2019). The median personal exposure to acetone in 6 salons in Colorado ranged from 8.0 to 30 ppm, with an overall range of 3.6–45 ppm (Lamplugh et al. 2019). In 12 randomly selected nail salons in Salt Lake County, Utah, the concentration of acetone ranged from 1.6 to 13 ppm with a mean of 6.1 ppm (Alaves et al. 2013). The concentration of a control sample taken from a single family residence with no nail products was 0.011 ppm (Alaves et al. 2013). The range of acetone concentrations in 3 Alameda County, California air salons was 0.31 to 6.60 ppm, with a mean concentration of 3.10±3.20 ppm (Quach et al. 2011). NIOSH (2019a) found that the mean full-shift personal air concentrations of acetone in air across three salons was 9.06 ppm. The concentration ranged from 2.7 to 29 ppm (NIOSH 2019a). One study of nail salons in Norway found mean acetone concentrations of 3.50 ppm (range 0.05–16.4 ppm) in breathing zones of the 32 technicians sampled (Gjølstad et al. 2006). Exposure to acetone in nail salons can be limited by using dispensers that reduce spills, not leaving acetone in open bowls or containers, not heating acetone, and using gloves when handling acetone (NIOSH 2019a).

Among the general population, high exposure to acetone may occur among several subgroups. Cigarette smoke contains acetone, and a cigarette may generate 50 to 550 µg of acetone (Counts et al. 2005; HHS 2010; Polzin et al. 2007). In Juul electronic cigarettes, the mean concentration of acetone in aerosols was 0.20±0.05 µg/puff, with no significant differences among flavors (Reilly et al. 2019). People who smoke

cigars (both filtered and little cigars) may be exposed to higher levels of acetone per cigar than those who smoke cigarettes (Reilly et al. 2018a). Using the International Organization of Standards method to detect acetone in smoke, acetone concentrations were: 11.8±0.1–18.0±1.1 µg/puff in cigarettes, 23.2±1.0–23.3±0.3 µg/puff in filtered cigars, and 32.9±4.3–41.2±5.0 µg/puff in little cigars (Reilly et al. 2018a, 2018b). While the concentrations measured using the Health Canada Intense machine-smoking protocols were higher, a similar distribution was observed between the types of product sampled (Reilly et al. 2018a, 2018b). Concentrations of acetone in workplaces with tobacco smoking have been found to be significantly higher than in workplaces with no tobacco smoking (Heavner et al. 1996). Therefore, people who smoke tobacco and individuals exposed to environmental tobacco smoke are exposed to higher concentrations of acetone than those in non-tobacco smoking environments. The content of acetone in certain nail polish removers is high; the concentration of acetone in one brand of remover used in Michigan nail salons was 413.5±4.4 g/m^3 (Zhong et al. 2019a, 2019b), and nail polish removers used in salons in the Greater Boston Area were all 100% acetone (Ceballos et al. 2019). Therefore, individuals who frequently use nail polish removers are exposed to higher levels of acetone than the general population. People who live near landfill sites that emit acetone or those who live near industrial sources of emission (e.g., refinery, incinerator, close to high vehicular traffic areas) are also susceptible to higher exposure concentrations of acetone than the general population that does not reside near these sites. People who consume contaminated well water (see Section 5.5.2) as drinking water are subject to higher exposures. People who consume food containing acetone excessively would also be subject to high exposure, especially if associated with other risks. Those who choose a ketogenic diet or take ketone supplements may be at increased risk of exposure to greater levels of ketones than are endogenously produced, though limited literature outlines the long-term effects of ketogenic diets (Masood et al. 2020).

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 acetone 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 acetone.

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 acetone 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 acetone. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

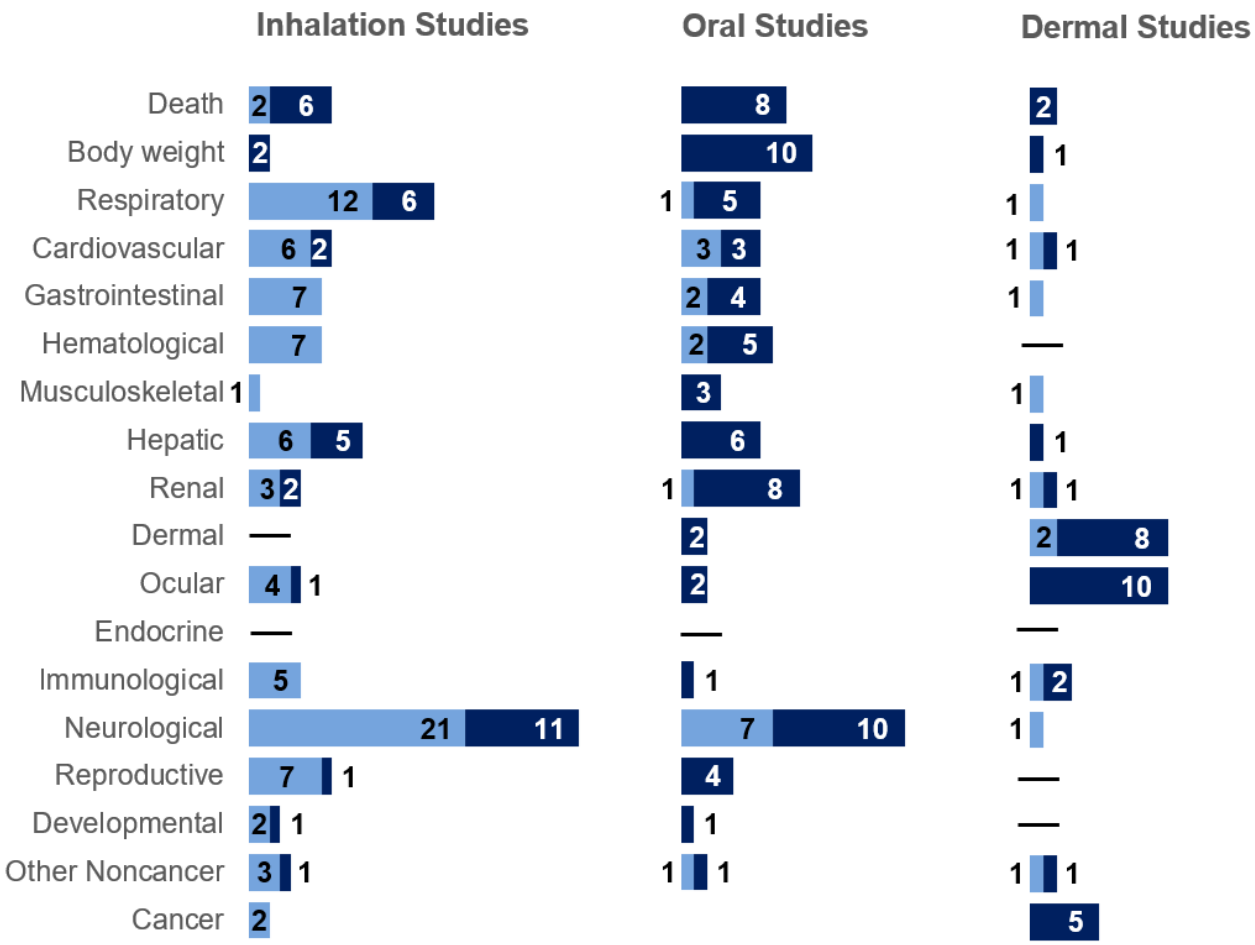
6.2 IDENTIFICATION OF DATA NEEDS

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

Acute-Duration MRLs. The data for acute effects in animals were sufficient to derive an acute-duration inhalation MRL of 8 ppm for neurobehavioral effects and altered auditory tone discrimination in humans exposed for 4 hours (Dick et al. 1989). Further studies are needed to derive an acute-duration oral MRL for acetone.

Figure 6-1. Summary of Existing Health Effects Studies on Acetone by Route and Endpoint*

Potential neurological and respiratory effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** or inhalation exposure in **humans**.



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

Intermediate-Duration MRLs. There are insufficient data for derivation of an intermediate-duration inhalation MRL, due to a lack of high-quality studies at lower exposure levels. An intermediate-duration oral MRL of 0.6 mg/kg/day was derived based on a $BMDL_{1SD}$ of 57.0 mg/kg/day from a rat study published in Dietz et al. (1991) and NTP (1991) in which evidence of anemia was observed with decreased reticulocyte counts. Additional high-quality studies would strengthen this MRL.

Chronic-Duration MRLs. Further studies are needed to derive chronic-duration inhalation and oral MRLs for acetone.

Health Effects. In general, there is a need for further epidemiological studies that are specific to acetone exposure; many of the identified studies examined exposure to a mixture of solvents, making it difficult to distinguish the effects of acetone alone. Because studies of acetone exposure in humans are limited, there is also little understanding of interindividual variance in human responses to acetone exposure.

Cardiovascular. Human studies on the cardiovascular effects of acetone have reported mixed results. Tachycardia has been observed in patients after application of casts for which acetone was used in the setting solution (Chatterton and Elliott 1946; Hift and Patel 1961). High pulse rates and blood pressure have also been observed following ingestion of acetone, although it is difficult to attribute these effects to acetone alone given the medical histories and co-exposures found in these case studies (Herman et al. 1997; Kumarvel and Da Fonseca 2007; Slutzman et al. 2015). One epidemiological study of workers exposed to solvents observed increases in hypertension; however, workers were co-exposed to several chemicals, and concentrations of acetone were low (Attarchi et al. 2013). No effects on cardiac function were observed in a controlled study of volunteers exposed to acetone (Stewart et al. 1975). An epidemiology study of workers using acetone as the only solvent (Ott et al. 1983a, 1983b) failed to find any significant effects on cardiovascular mortality. Animal studies have indicated little evidence for cardiovascular effects (Specht et al. 1939; Bruckner and Peterson 1981b). Further research is needed to elucidate the cardiovascular effects of acetone.

Hematological. There is evidence of hematological effects of acetone from human studies of occupationally exposed workers (Ott et al. 1983a, 1983c) and volunteers (Matsushita et al. 1969a, 1969b). However, evidence is mixed, and several studies have failed to find any significant associations following inhalation exposures (DiVincenzo et al. 1973; Satoh et al. 1996; Stewart et

al. 1975). No epidemiological studies on the hematological effects of oral exposures were identified. In animals, associations between acetone exposure and hematological effects have been found in rats but not in mice (Dietz et al. 1991; NTP 1991). Additionally, hematological effects were more pronounced in male than female rats (Dietz et al. 1991; NTP 1991). Studies on the hematological effects of acetone are needed to provide clarification on differences by species and sex.

Musculoskeletal. There is limited evidence on the musculoskeletal effects of acetone. One epidemiological study of occupational exposures found a significant association with rheumatic symptoms (Mitran et al. 1997) and one case study found rhabdomyolysis (Piatkowski et al. 2007). However, animal studies have failed to find significant associations between acetone and musculoskeletal effects (American Biogenics Corp. 1986; Dietz et al. 1991; NTP 1991). There is a need for more studies to elucidate the musculoskeletal effects of acetone.

Renal. Evidence on the renal effects of acetone in humans is mixed: case studies have reported effects such as renal insufficiency and failure (Chen et al. 2002; Kostusiak et al. 2003; Piatkowski et al. 2007), but controlled studies of volunteers have failed to find any significant effects (DiVincenzo et al. 1973; Stewart et al. 1975). Animal studies have shown differences in susceptibility to the renal effects of acetone by sex. For example, kidney weight decreases were observed at lower doses in female rats than male rats, but histopathological lesions in the kidney were observed in male rats at lower doses than in females (Dietz et al. 1991; NTP 1991). Further research is needed on the renal effects of acetone in humans, and to elucidate the sex differences observed in animals.

Endocrine. There is a need for research on the endocrine effects of acetone, as no studies in humans or animals were located.

Immunological. There is limited evidence on the immunological effects of acetone. Increases in white blood cell counts were observed in some studies of volunteers exposed to acetone (Matsushita et al. 1969a, 1969b), but not others (DiVincenzo et al. 1973; Stewart et al. 1975). One case study showed immunological effects in a woman after chronic dermal exposure to acetone (Tosti et al. 1988). No studies were located regarding immunological effects in humans after oral exposure. Evidence from animal studies is limited to one intermediate oral exposure study that observed no significant effects (Woolhiser et al. 2006). However, there is some

evidence that dermal exposure to animals may modulate humoral immunity (Singh et al. 1996) and increase cytokine production (Denda et al. 1996). Further epidemiological research is needed to assess the immunological effects of acetone exposure in humans.

Reproductive. There are few studies on the reproductive effects of acetone in humans. One study found evidence of an association between pregnancy complications including miscarriage in workers exposed to acetone, but no conclusions can be drawn from this report due to poor reporting quality (Nizyaeva 1982). It is additionally difficult to draw conclusions from other epidemiological studies of occupational exposures, because the women examined were exposed to several solvents (Agnesi et al. 1997; Axelsson et al. 1984; Beaumont et al. 1995; Swan et al. 1995). Evidence from animal studies is mixed. Decreased fertility was observed in mice exposed to acetone (EHRT 1987), but not rats (Larsen et al. 1991). There is some evidence of adverse effects on the male reproductive system, such as decreased sperm motility (Dietz et al. 1991; NTP 1991). Given the limited data in humans and results from animal studies, further research is needed to assess the reproductive effects of acetone in humans.

Developmental. Information on the developmental effects of acetone is limited. Of the two epidemiological studies in occupationally exposed women located, one found evidence of a significant association between acetone and increases in developmental effects (Nizyaeva 1982) and one did not (Axelsson et al. 1984). However, the Nizyaeva (1982) study did not report pertinent details such as number of women studied, and therefore no conclusions can be drawn from the report. An animal study of rats and mice exposed to acetone found evidence of decreased fetal weights (NTP 1988). Additionally, gestational exposures in mice were associated with increased resorptions and malformations (NTP 1988) as well as reduced postnatal pup survival (EHRT 1987). Further research is needed to assess whether acetone is associated with malformations and other developmental effects, and to elucidate potential differences in susceptibility between species.

Cancer. Only two epidemiological studies investigated the association between acetone and cancer in humans. A retrospective mortality study found no excess risk of death from cancer in exposed workers (Ott et al. 1983a, 1983b). A case-control study found an association between risk of neuroblastoma in children and maternal exposure to acetone, though recall bias may have affected these results (Kerr et al. 2000). No studies in animals were identified, though acetone has been used as the solvent control in several studies on the carcinogenicity of other chemicals

and has not been associated with any increases in neoplastic lesions or cancer (De Pass et al. 1989; Roe et al. 1972; Van Duuren et al. 1971, 1978; Weiss et al. 1986). Further research on this endpoint would help confirm that acetone is not carcinogenic.

Genotoxicity. Evidence from numerous *in vitro* studies of bacteria and cultured animal cells, as well as several *in vivo* studies of human fibroblasts and skin epithelial cells, indicate that acetone is likely not genotoxic in humans. However, additional studies on the peripheral lymphocytes, fibroblasts, and skin epithelial cells of exposed workers would help confirm that acetone is not genotoxic.

Epidemiology and Human Dosimetry Studies. Several controlled human exposure studies were identified which have helped to characterize the effects of acetone exposures. However, many of the epidemiological studies identified on various health endpoints examined the effects of occupational exposure to solvents. Therefore, because exposure to additional solvents such as toluene occurred in addition to exposures to acetone, it is difficult to attribute observed effects to acetone exposures. Further studies on occupational exposures to acetone alone would help to elucidate its health effects.

Biomarkers of Exposure and Effect. Acetone has been extensively measured in the expired air, blood, and urine of individuals in the general population and occupationally exposed workers. Because acetone can be directly measured in breath and urine samples, no additional biomarkers of exposure to acetone are required. Biomarkers of effect for acetone have not been identified for acetone, because similar effects are observed following exposure to several other chemicals. Therefore, additional research is unlikely to identify a specific biomarker of effect.

Absorption, Distribution, Metabolism, and Excretion. Evidence suggests that acetone is readily absorbed through the lungs and gastrointestinal tract. Studies in animals have found conflicting results on the effects of vehicle on gastrointestinal absorption; further research on this topic would help clarify absorbed doses. Based on evidence from animal studies and chemical properties, acetone is expected to distribute throughout body tissues in humans, particularly to tissues with high water content. However, studies in humans, as well as studies of absorption in animals following dermal exposures, are limited and further research would help confirm patterns of distribution. The metabolism of acetone is well-characterized, appears to be independent of both the species examined and the route of administration, and involves three separate gluconeogenic pathways (Casazza et al. 1984; Hallier et al. 1981; Hetenyi and Ferrarotto 1985; Johansson et al. 1986; Koop and Casazza 1985; Kosugi et al. 1986a, 1986b; Mourkides

et al. 1959; Price and Rittenberg 1950; Puccini et al. 1990; Rudney 1954; Sakami 1950; Sakami and LaFaye 1951; Skutches et al. 1990). Elimination of acetone in humans has been well-studied following inhalation exposures, but information on elimination following oral and dermal exposures is lacking.

Comparative Toxicokinetics. As above, the toxicokinetics of acetone have been characterized in animals and humans. There appear to be few differences across species in the toxicokinetics of acetone exposure. Therefore, additional studies on comparative toxicokinetics are not needed at this time.

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

Biomonitoring studies indicate that maternal-fetal and maternal-infant transfer of acetone is possible. Levels of acetone in blood tend to be higher in children than in adults, due to their higher energy expenditures (Peden 1964). No studies in humans were located regarding whether children are more or less susceptible than adults to adverse health effects from a given amount or duration of exposure to acetone. In a lethality study among newborn rats, 14-day-old rats, and adult rats, susceptibility to the lethal effects of acetone generally decreased with increasing maturity (Kimura et al. 1971). Humans may have similar susceptibility, but further research on this topic is needed, especially given evidence from biomonitoring studies.

Physical and Chemical Properties. Information regarding the physical and chemical properties of acetone necessary to predict its environmental fate and transport processes in the environment is available (see Table 4-2). However, experimental determination of a value for the soil sorption coefficient of acetone from water would be helpful in assessing the potential for leaching and volatility of acetone in different soils.

Production, Import/Export, Use, Release, and Disposal. Production methods for acetone are known and there does not appear to be a need for further information.

The use pattern of acetone is known. Most acetone is used as an intermediate in the production of other chemicals or as a solvent. Detailed information on the uses of acetone in consumer products is available from Chemical Data Reporting (CDC 2012, 2016). Additional data on the uses of acetone are not needed.

There is no information on releases of acetone from manufacturing and processing facilities to air, water, or soil because these releases were not required to be reported prior to 2020 (EPA 2005). Therefore, there is a data need for information on releases of acetone. As of 2020, facilities are required to report atmospheric releases of acetone in volumes of 5,000 pounds or more (EPA 2020).

The regulations governing the disposal of acetone are well defined. However, more information about the proportion of discarded acetone recovered from recycling, and the proportion lost due to evaporation, ground burial, and incineration, would be useful in determining the relative importance of the different routes of exposure.

Industries are not required to submit chemical release and off site transfer information on acetone to the EPA. The TRI does not contain data on acetone because atmospheric releases of acetone were not required to be reported prior to 2020 (EPA 2005, 2020).

Environmental Fate. The environmental fate of acetone, for the most part, has been well studied (see Section 5.4). Acetone will undergo transport from one environmental medium to another (Grosjean and Wright 1983; Rathbun et al. 1982). Due to its reasonably long half-life in air (22 days) (Meyrahn et al. 1986) and restricted volatilization from groundwater, the atmosphere and groundwater may act as sinks for acetone. More experimental data regarding the rate of sorption and biodegradation of acetone in soil and its biodegradability in groundwater would be useful to assess the relative importance of the different fate processes.

Bioavailability from Environmental Media. Acetone is readily absorbed in the lung and gastrointestinal tract following inhalation and ingestion. Acetone can also be absorbed from the skin (see Section 3.1.1). The low value for K_{oc} (see Table 4-1) and a moderate value for Henry's law constant (Rathbun and Tai 1987) suggest that bioavailability of acetone from contaminated water and soil as a result of skin contact may be significant. However, quantitative data regarding the rate and extent of dermal absorption of acetone from contaminated water and soil are lacking. The high water solubility and low K_{oc} value for acetone suggest that bioavailability from ingested soil (e.g., children playing at or near contaminated sites) will be high, but quantitative absorption data are lacking. Data on bioavailability of acetone from ingested plant food were not located, but would be helpful.

Food Chain Bioaccumulation. Acetone does not bioaccumulate in aquatic organisms. There is no indication of biomagnification of acetone along the aquatic food chain. Studies of the potential for

acetone transfer from soil and plants and biomagnification in terrestrial food chains would be useful to ascertain its potential for food chain bioaccumulation.

Exposure Levels in Environmental Media. Data regarding the level of acetone in ambient air are available (EPA 2021; Lagrone 1991; Shah and Singh 1988; Snider and Dawson 1985). There is a paucity of data regarding the level of acetone in drinking water (Bedding et al. 1982; Coleman et al. 1976; Keith et al. 1976). More comprehensive data on the levels of acetone in the air and water consumed by people who live near acetone-containing hazardous waste sites would be useful in estimating the daily intake from these sources. Although the levels of acetone in the volatile components of several fruits and vegetables are available (see Section 5.5.4), development of data regarding the level of acetone in the total diet would be useful. There are few data regarding the level of acetone in background soil samples. Reliable monitoring data for the levels of acetone in contaminated media at hazardous waste sites are needed so that the information obtained on levels of acetone in the environment can be used in combination with the known body burden of acetone to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. The levels of acetone in blood/plasma and urine of healthy people, occupationally exposed groups, and diabetic patients are available (see Section 5.6). However, data on the levels of acetone in body fluids or tissues of general populations living near sites with higher (than normal) exposure potential (e.g., hazardous waste sites) were not located. This information could inform the need to conduct health studies on these populations.

Exposures of Children. There are limited data on exposures to acetone in children. However, studies have shown that acetone can be transferred via the placenta and breastmilk. Further research is needed to characterize exposures in children.

6.3 ONGOING STUDIES

No on-going study that would fill the data gaps regarding the transport and fate of acetone in the environment or that evaluates its exposure potential in general population groups susceptible to higher levels of exposure was located.

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2021) database.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding acetone 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 acetone.

Table 7-1. Regulations and Guidelines Applicable to Acetone

Agency	Description	Information	Reference
	Air		
EPA	RfC	Value not estimated	EPA 2003
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories	Not listed	EPA 2018a
	National primary drinking water regulations	Not listed	EPA 2009
	RfD	0.9 mg/kg/day	EPA 2003
WHO	Drinking water quality guidelines	No data	WHO 2017
FDA	Substances added to food[a]	Permitted under several color additive, indirect, and secondary direct food additive regulations	FDA 2022
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2021
EPA	Carcinogenicity classification	Data are inadequate for an assessment of the human carcinogenic potential	EPA 2003
IARC	Carcinogenicity classification	No data	IARC 2021
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	1000 ppm (2400 mg/m^3)	OSHA 2018a 29 CFR 1910.1000 Table Z-1; OSHA 2018b 29 CFR 1915.1000 Table Z; OSHA 2018c 29 CFR 1926.55 Appendix A
NIOSH	REL (up to 10-hour TWA)	250 ppm (590 mg/m^3)	NIOSH 2019b

Table 7-1. Regulations and Guidelines Applicable to Acetone

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air		EPA 2018b
	AEGL 1[b]		
	10-minute	200 ppm	
	30-minute	200 ppm	
	60-minute	200 ppm	
	4-hour	200 ppm	
	8-hour	200 ppm	
	AEGL 2[b]		
	10-minute	9,300 ppm[c]	
	30-minute	4,900 ppm[c]	
	60-minute	3,200 ppm[c]	
	4-hour	1,400 ppm	
	8-hour	950 ppm	
	AEGL 3[b]		
	10-minute	16,000 ppm[d]	
	30-minute	8,600 ppm[c]	
	60-minute	5,700 ppm[c]	
	4-hour	2,500 ppm	
	8-hour	1,700 ppm	
DOE	PACs-air		DOE 2018a
	PAC-1[e]	470 mg/m^3	
	PAC-2[e]	7,600 mg/m^3	
	PAC-3[e]	14,000 mg/m^3	

[a]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS (Generally Recognized As Safe) substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited from use in food, delisted color additives, and some substances "no longer FEMA GRAS".
[b]Definitions of AEGL terminology are available from U.S. Environmental Protection Agency (EPA 2018c).
[c]Safety considerations against the hazard of explosion must be taken into account.
[d]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 2018b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; 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 Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acetone
CAS Numbers: 67-64-1
Date: June 2022
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL: 8 ppm
Critical Effect: Altered auditory tone discrimination and neurobehavioral effects
Reference: Dick et al. 1989
Point of Departure: Minimal LOAEL of 237 ppm
Uncertainty Factor: 30
LSE Graph Key: 1
Species: Human

MRL Summary: The acute-duration inhalation MRL of 8 ppm is based on a minimal LOAEL of 237 ppm for neurobehavioral effects (altered auditory tone discrimination and neurobehavioral effects) in humans exposed for 4 hours (Dick et al. 1989). An uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability) was applied.

Selection of the Critical Effect: Numerous studies have evaluated the neurological effects of acetone. Neurological effects in humans exposed to acetone range from dizziness and headaches (Pomerantz 1950; Raleigh and McGee 1972) to dulling of reflexes (Chen et al. 2002; Haggard et al. 1944) and unconsciousness (Ross 1973). Narcotic effects were found in animals exposed to high doses of acetone (NTP 1988; Specht et al. 1939). These effects are found after both inhalation and oral exposures of varying durations. Table A-1 summarizes relevant NOAEL and LOAEL values following acute inhalation exposures to acetone.

Table A-1. Summary of Relevant NOAEL and LOAEL Values Following Acute Duration Inhalation Exposure to Acetone

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Neurological effects					
Human	4 hours	None	237	Altered auditory tone discrimination; increases in anger and hostility	Dick et al. 1989
Human	4.5 hours	247	None	Tests of reaction time and vigilance	Muttray et al. 2005
Human	Two 3-hour sessions with 45-minute interval break	100	250	Self-reports of weakness, tension, lack of energy	Matsushita et al. 1969a
Human	6 hours/day 6 days	None	250	Decreased reaction time; self-reports of weakness, tension, lack of energy	Matsushita et al. 1969b

Table A-1. Summary of Relevant NOAEL and LOAEL Values Following Acute Duration Inhalation Exposure to Acetone

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Respiratory irritation					
Human	Two 3-hour sessions with 45-minute interval break	None	100	Self-report of irritation of the mucous membrane (nose, throat and trachea)	Matsushita et al. 1969a
Human	6 hours/day 6 days	250	500	Self-report of irritation of the mucous membrane (nose, throat, and trachea)	Matsushita et al. 1969b
Human	3–5 minutes	200	500	Irritation in the majority of subjects (n≈10)	Nelson et al. 1943

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

Neurobehavioral effects were observed in humans exposed to acetone at 237 ppm for 4 hours (Dick et al. 1989). Similar effects have also been observed in humans exposed to 250 ppm acetone for 6 hours or repeatedly for 6 hours/day for 6 days (Matsushita et al. 1969a, 1969b). Effects included lack of energy, general weakness, delayed visual reaction time, and headache. Although irritation of the nose, throat, and trachea was reported in one of five subjects exposed to 100 ppm for two 3-hour exposures (with 45-minute interval break) (Matsushita et al. 1969a), other studies in humans reported respiratory irritation only at higher levels (>250 ppm) for longer durations (Matsushita et al. 1969b; Nelson et al. 1943; Raleigh and McGee 1972; Ross 1973). Furthermore, the reporting of these irritating effects was subjective, and only five volunteers were exposed to 100 ppm (Matsushita et al. 1969a). Therefore, neurological effects were preferentially selected as the critical effect.

Selection of the Principal Study: Matsushita et al. (1969a) reported a NOAEL of 100 ppm and in a subsequent study, Matsushita et al. (1969b) observed neurological effects including lack of energy, weakness, headache, and delayed reaction times after exposure in volunteers to 250 ppm of acetone for 6 hours/day for 6 days. The effects observed in Dick et al. (1989) occurred at a slightly lower concentration of acetone (237 ppm) with a shorter exposure duration of 4 hours. Another study by Muttray et al. (2005) examined the neurological effects of acetone exposures in male volunteers at 247 ppm for 4.5 hours. However, this study involved co-exposure to toluene at 25 ppm. Due to study quality (i.e., small sample size) of Matsushita et al. (1969a) and given the other relevant acute inhalation studies under consideration, Dick et al. (1989) was selected as the key study for its sensitive endpoint (i.e., minimal LOAEL).

Summary of the Principal Study: Dick RB, Setzer JV, Taylor BJ, et al. 1989. Neurobehavioural effects of short duration exposures to acetone and methyl ethyl ketone. Occup Environ Med 46(2):111-121.

Dick et al. (1989) exposed 11 male and 11 female volunteers to a concentration of 237 ppm of acetone (note: the target concentration for participants was 250 ppm acetone, but monitoring of acetone concentrations during the 4-hour exposures indicated a mean concentration of 237 ppm). Additional participants were exposed to either methyl ethyl ketone (MEK) at a target concentration of 200 ppm, a combination of acetone at 125 ppm and MEK at 100 ppm, or ethanol solution. Two control groups were also examined. Participants were aged 18–32 years old and did not have pre-existing medical conditions or substance use disorders. Neurobehavioral testing occurred during six test sessions: one session on the

day before the exposures occurred, four sessions on the day of exposure, and one final session on the day after exposure. Psychomotor, sensorimotor, and psychological tests were administered to participants to assess a variety of neurobehavioral tasks.

Participants exposed to acetone at a mean concentration of 237 ppm showed significant differences on two neurobehavioral tasks as compared to controls. Acetone-exposed participants showed significant increases in response time ($p < 0.05$) and significantly greater false alarm percentages ($p < 0.005$) on the auditory tone discrimination task compared to controls. The changes in performance on this task were persistent and mirrored the measured blood concentrations of acetone, indicating that tolerance to acetone did not occur. In addition, significant increases in measures of anger and hostility were observed in males, but not females, exposed to acetone ($p < 0.001$). However, the study authors noted that this finding may be due to chance, given the small sample size and absence of any other significant changes in tests of mood.

Selection of the Point of Departure for the MRL: The MRL was derived from the minimal LOAEL of 237 ppm for neurological effects (auditory tone discrimination task and neurobehavioral effects) in humans exposed to acetone for 4 hours (Dick et al. 1989). Benchmark dose (BMD) modeling could not be performed as only one dose of exposure to acetone alone was examined.

Adjustment for Intermittent Exposure: Because acetone is evenly distributed in blood after absorption, an adjustment for intermittent to continuous exposure was deemed not necessary. Henry's law indicates that acetone has a high blood to air partition coefficient and will therefore dissolve in blood upon pulmonary gas exchange.

Adjustments for Animal to Human Exposure: Not applicable.

Uncertainty Factor (UF): The LOAEL of 237 was divided by a total uncertainty factor of 30.

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

MRL = LOAEL ÷ UF = 237 ppm ÷ 30 = 8 ppm

Other Additional Studies or Pertinent Information that Lend Support: A second minimal LOAEL of 250 ppm for neurobehavioral effects (Matsushita et al. 1969b) was considered for derivation of an acute inhalation MRL. Using an uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability), the resulting MRL would be 8 ppm, which is equivalent to the proposed MRL.

Agency Contacts (Chemical Managers): Obaid Faroon

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acetone
CAS Numbers: 67-64-1
Date: June 2022
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL due to extremely high exposure levels and limitations in study design. Table A-2 indicates the breadth of the data available.

Table A-2. Summary of Relevant NOAEL and LOAEL Values Following Intermediate Duration Inhalation Exposure to Acetone

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Neurological effects					
Human	1, 3, or 7.5 hours/day, 4 days/week, 6 weeks	1,000	1,250	Significantly increased amplitude of the visual evoked response	Stewart et al. 1975
Rat (Sprague-Dawley)	3 hours/day, 5 days/week, 8 weeks	None	19,000	Significant decreases in brain weight	Bruckner and Peterson 1981b
Rat (Crl:CD BR)	6 hours/day, 5 days/week, 13 weeks	4,000	None	Schedule-controlled operant conditioning	Christoph et al. 2003

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

Rationale for Not Deriving an MRL: Bruckner and Peterson (1981b) only examined high-dose acetone exposure (19,000 ppm). This exposure level resulted in a serious LOAEL for significant decreases in brain weights of rats; therefore, it is not appropriate for derivation of an MRL. Christoph et al. (2003) observed that exposure of male rats to acetone vapor concentrations as high as 4,000 ppm for 6 hours/day, 5 days/week for 13 weeks did not cause lasting effects on schedule-controlled operant performance. The study authors noted that their study design was not intended to investigate the operant processes that have been associated with occupational exposures to acetone in humans (e.g., decreased digit-span retention); conclusions of the study only "serve to increase confidence that prolonged exposures within specified limits are unlikely to have enduring effects on the expression of previously well-learned behaviors" (p. 797). Therefore, other unmeasured neurological effects may have occurred at the concentrations examined and the study is not appropriate for derivation of the MRL. Stewart et al. (1975) examined adults exposed to varying durations of acetone at concentrations of 0, 200, 1,000, and 1,250 ppm. No significant neurological effects were observed, apart from increases in visual evoked response in two of four males exposed to 1,250 ppm. However, multiple studies of acute exposure suggest that acetone causes neurological effects in humans at levels around 250 ppm (Dick et al. 1989; Matsushita et al. 1969a, 1969b). Additionally, the Stewart et al. (1975) study only examined a maximum of four participants per dosage and contains poor reporting of methodology and results; it was not considered to be of sufficient quality for derivation of an MRL.

Agency Contacts (Chemical Managers): Obaid Faroon

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acetone
CAS Numbers: 67-64-1
Date: June 2022
Profile Status: Final
Route: Inhalation
Duration: Chronic

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

Rationale for Not Deriving an MRL: A chronic-duration inhalation MRL was not derived for acetone because a suitable NOAEL or LOAEL for a sensitive endpoint was not sufficiently characterized. The only studies located were three epidemiological studies. Ott et al. (1983a, 1983c) observed no hematological or hepatic effects in workers exposed 5 days/week, 8 hours/day to up to 1,070 ppm for months to years. However, the study did not monitor all endpoints that are known to be sensitive endpoints of acetone exposure, such as neurological effects; other endpoints may have been affected at this exposure level. Additionally, this study has significant limitations: there was no true reference group for the acetone-exposed workers and high potential for misclassification of exposure. Two occupational studies found evidence of neurological and behavioral effects (lack of energy, general weakness, delayed visual reaction time, and headache) associated with exposures to acetone (Mitran et al. 1997; Satoh et al. 1996). Mitran et al. (1997) examined 71 workers at a coin printing factory who were exposed to TWA concentrations of acetone ranging from 416 to 980 ppm for a mean duration of 14 years. Acetone-exposed workers showed significant decreases in measures of attention and delays in tests of nerve conduction velocity and visual reaction time relative to controls. In addition to neurological effects, the workers self-reported a higher prevalence of respiratory irritation, eye irritation, and gastrointestinal symptoms relative to matched controls. Satoh et al. (1996) reported symptoms of heavy, vague, or faint feelings in the head, along with impaired neurobehavioral responses, in a group of 110 male workers at an acetate fiber manufacturing plant where acetone was used for production. Controls consisted of 67 unexposed workers at the same facility. Acetone levels at the end of the work shift measured 5–1,212 ppm in the breathing zone (mean of 361.4 ppm). It is difficult to establish a NOAEL and LOAEL for effects observed in the occupational studies by Mitran et al. (1997) and Satoh et al. (1996), as the occupational exposures observed varied widely in concentration and duration. Therefore, these studies were deemed inappropriate for derivation of an MRL for chronic inhalation exposures to acetone.

Agency Contacts (Chemical Managers): Obaid Faroon

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acetone
CAS Numbers: 67-64-1
Date: June 2022
Profile Status: Final
Route: Oral
Duration: Acute

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

Rationale for Not Deriving an MRL: An acute-duration oral MRL was not derived for acetone because a suitable NOAEL or LOAEL for a sensitive endpoint was not sufficiently characterized. Brown and Hewitt (1984) found a renal LOAEL of 871 mg/kg/day in rats; however, this study was a one-time gavage exposure and is therefore not considered to be applicable to human exposure scenarios. Additionally, other studies failed to find renal effects in rats following 2 days of gavage exposure to 1,766 mg/kg/day acetone (Valentovic et al. 1992) or 14 days of drinking water exposure at concentrations of 8,560 mg/kg/day (Dietz et al. 1991; NTP 1991). Mice also tolerated doses up to 12,725 mg/kg/day without renal effect (Dietz et al. 1991; NTP 1991). Similarly, Ross et al. (1995) found increased liver weights in eight rats administered 90 mg/kg/day of acetone in drinking water for 14 days. However, other studies have only observed these effects at higher levels of exposure. Moreover, available evidence from epidemiological and human controlled studies suggests that acetone is not associated with hepatic endpoints in humans.

The other acute studies located showed effects above 2,241 mg/kg/day, which is a serious effect level for neurological and metabolic effects for human exposures (Gitelson et al. 1966). Therefore, these studies cannot be used as they would not be the most sensitive endpoint nor species in the current dataset.

Agency Contacts (Chemical Managers): Obaid Faroon

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acetone
CAS Numbers: 67-64-1
Date: June 2022
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.6 mg/kg/day
Critical Effect: Anemia with decreased reticulocyte count
Reference: Dietz et al. (1991); NTP (1991)
Point of Departure: $BMDL_{1SD}$ of 57.0 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 22
Species: Rat

MRL Summary: The intermediate-duration oral MRL of 0.6 mg/kg/day is based on a $BMDL_{1SD}$ of 57.0 mg/kg/day for anemia with decreased reticulocyte count in rats treated with acetone in the drinking water for 13 weeks (Dietz et al. 1991; NTP 1991). An uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability) was applied.

Selection of the Critical Effect: Table A-3 summarizes relevant NOAEL and LOAEL values following intermediate oral exposures to acetone. The available data indicate that hematological effects are the most sensitive endpoint associated with intermediate duration oral exposure to acetone. Additionally, there is evidence of the hematological effects of acetone from human and animal studies. Hematological effects have been observed in humans exposed by inhalation to acetone (Matsushita et al. 1969a, 1969b), in rats exposed to 200 mg/kg/day in the drinking water for 14 days (Dietz et al. 1991; NTP 1991), and in rats treated by gavage with 2,500 mg/kg/day for 93–95 days (American Biogenics Corp. 1986).

Table A-3. Summary of Relevant NOAEL and LOAEL Values Following Intermediate Duration Oral Exposure to Acetone

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurological effects					
Rat	6 weeks	None	650	Decreased motor nerve conduction velocity	Ladefoged et al. 1989
Hematological effects					
Rat (F344/N)	13 weeks	200	400	Anemia with decreased reticulocyte counts	Dietz et al. 1991; NTP 1991
Rat (Crl:CD BR)	93–95 days, 1 time/day	500	2,500	Increased hemoglobin, hematocrit, mean cell hemoglobin, mean cell volume, decreased platelets	American Biogenics Corp. 1986

Table A-3. Summary of Relevant NOAEL and LOAEL Values Following Intermediate Duration Oral Exposure to Acetone

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Reproductive effects					
Rat (F344/N)	13 weeks	200	3,400	11.7% decreased sperm motility	Dietz et al. 1991; NTP 1991[a]

[a]Dietz et al. (1991) and NTP (1991) refer to the same study.

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

The critical hematological effect observed by Dietz et al. (1991) and NTP (1991) is anemia with decreased reticulocyte count (Table A-3). Reticulocytes are necessary for bone marrow to regenerate in response to anemia. The absence of reticulocytes in an anemic subject indicates that the bone marrow is not regenerating in response to the anemia, a condition known as non-regenerative anemia. Dietz et al. (1991) and NTP (1991) also observed statistically significantly increased relative kidney weight in female rats, along with decreased sperm motility and increased mean corpuscular hemoglobin in male rats. However, each of these results was not consistent as doses increased. Further, Dietz et al. (1991) and NTP (1991) observed kidney nephropathy in male rats exposed to doses as low as 200 mg/kg/day, with increasing incidence and severity as doses increased up to 3,400 mg/kg/day; however, the male control group developed minimal and mild severity kidney nephropathy similar to the 200 mg/kg/day dose group, and no similar kidney nephropathy effects were observed in the female rats. American Biogenics Corp. (1986) also observed severe kidney nephropathy in male rats at doses of 500 and 2,500 mg/kg/day via oral gavage, in addition to an accentuation of hyaline droplet accumulation, with no observed kidney effects in female rats. It is widely known that male rats have a high likelihood of developing chronic progressive kidney nephropathy as a part of their natural aging process, which often confounds intermediate and chronic studies of kidney nephropathy in these animals (Hard and Khan 2004; Hard et al. 2009). The accentuation of hyaline droplet accumulation observed in the American Biogenics Corp. (1986) study is often a biomarker of one mechanism of this kidney nephropathy that is not considered relevant for extrapolation to humans, specifically pointing to α2-μglobulin induced renal pathology (ATSDR 2018). Additionally, chronic progressive nephropathy that only occurs in male rats and not female rats, as was the case in Dietz et al. (1991) and NTP (1991), is generally considered to be age-related, even if the test chemical is shown to potentially exacerbate this age-related effect (ATSDR 2018). ATSDR does not use lesions of chronic progressive nephropathy where there was no concurrent enhancement in females as endpoints in MRL derivation (ATSDR 2018).

Selection of the Principal Study: Hematological effects are considered to be a sensitive endpoint associated with acetone exposure. Of the two intermediate-duration studies identified (American Biogenics Corp. 1986; Dietz et al. 1991; NTP 1991), the study published by Dietz et al. (1991) and NTP (1991) had the lowest NOAEL and LOAEL identified.

Summary of the Principal Study:

Dietz DD, Leininger JR, Rauckman EJ, et al. 1991. Toxicity studies of acetone administered in the drinking water of rodents. Toxicol Sci 17(2):347-360. https://doi.org/10.1093/toxsci/17.2.34.

NTP. 1991. National Toxicology Program - technical report no. 3. Toxicity studies of acetone in F344/N rats and B6C3F, mice (drinking water studies). U.S. Department of Health and Human Services, Public Health Service, National Institute of Health. NIH publication no. 91-3122.

Dietz et al. (1991) and NTP (1991) examined exposures to acetone in the drinking water of F344/N rats and B6C3F1 mice (10 males and 10 females per dose per species). In the 13-week study, rats and female mice were continuously exposed to acetone in drinking water at 0, 2,500, 5,000, 10,000, 20,000 or 50,000 ppm. Concentrations examined in male mice were 0, 1,250, 2,500, 5,000, 10,000 or 20,000 ppm of acetone. The authors calculated TWA doses (mg/kg/day) associated with each concentration.

Clinical examinations of exposed animals occurred twice daily throughout the 13-week exposure period. At the end of the exposure period, animals were sacrificed, and histopathological and hematological examinations were conducted.

No hematological effects or histologically observable lesions in hematopoietic tissues were found in male or female mice (Dietz et al. 1991; NTP 1991). In contrast to the mouse data, Dietz et al. (1991) and NTP (1991) found evidence of macrocytic anemia in male, but not female, rats exposed to acetone in drinking water for 13 weeks. This evidence consisted of significantly ($p<0.05$ or $p<0.01$) decreased hemoglobin concentration, increased mean corpuscular hemoglobin and mean corpuscular volume, decreased erythrocyte counts, decreased reticulocyte counts and platelets, and splenic hemosiderosis. The LOAEL for these effects was 400 mg/kg/day, and the NOAEL was 200 mg/kg/day. The number of affected parameters increased as the dose increased. Table A-4 displays results for the most sensitive hematological effect observed: decreased reticulocyte counts in male rats. The data were amenable to BMD modeling and were fit to the continuous models in EPA's Benchmark Dose Modeling Software (BMDS; version 3.1.2).

Table A-4. Reticulocyte Counts in Male Rats Administered Acetone via Drinking Water for 13 Weeks (Dietz et al. 1991; NTP 1991)

Dose (mg/kg/day)	Reticulocyte count mean (10^6/µL)	Reticulocyte count standard deviation
0	225	34.8
200	195	46.5
400	171[a]	47.1
900	179[b]	47.4
1,700	168[a]	34.8
3,400	152[a]	29.4

[a]$p \leq 0.01$.
[b]$p \leq 0.05$.

Selection of the Point of Departure for the MRL: BMD modeling was conducted to identify a point of departure (POD) using the data from Dietz et al. (1991) and NTP (1991) displayed in Table A-4. The data were fit to all available continuous models in EPA's BMDS (version 3.1.2) using a benchmark response (BMR) of 10% extra risk and the default settings for the application of restrictions. Adequate model fit was judged by four criteria: chi-square goodness-of-fit p-value ($p \geq 0.1$), visual inspection of the dose-response curve, BMDL <10 times the lowest non-zero dose, and scaled residual (>-2 and <+2) at the data point (except the control) closest to the predefined BMR. Among models providing adequate fit to the data, the lowest $BMDL_{1SD}$ was selected as the POD when the difference between the BMDLs estimated from these models was >3 fold; otherwise, the $BMDL_{1SD}$ from the model with the lowest

Akaike's Information Criterion (AIC) was chosen. Table A-5 presents only those BMD/BMDL values considered for MRL derivation. The MRL was based on a $BMDL_{1SD}$ of 57.0 mg/kg/day for a decrease in reticulocytes in rats treated with acetone in the drinking water for 13 weeks (Dietz et al. 1991; NTP 1991).

Table A-5. Results from BMD Analysis of Decreased Reticulocyte Counts in Sprague-Dawley Rats After Intermediate Oral Exposure via Drinking Water for 13 Weeks (Dietz et al. 1991; NTP 1991)

					Scaled residuals[c]	
Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	P Value[b]	AIC	Dose below BMD	Dose above BMD
Exponential (2-degree)[d]	2,422.23	1,495.34	0.12	621.93	-0.20	1.90
Exponential (3-degree)[d]	2,419.46	1,495.34	0.12	621.93	-0.20	1.90
Exponential (5-degree)[d]	281.18	119.84	0.48	619.01	0.16	0.01
Hill[e,f]	**263.80**	**57.02**	**0.60**	**618.41**	**0.11**	**-0.21**

[a]BMDLs <10 times the lowest non-zero dose and their corresponding BMDs are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Selected model. The exponential and Hill models provided adequate fit to the data. BMDLs for models providing adequate fit differed by >3-fold; therefore, the model with the lowest $BMDL_{1SD}$ was selected (Hill).

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{1SD}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 1SD = dose associated with 1 standard deviation from the mean); DF = degree of freedom

Adjustment for Intermittent Exposure: Because acetone is evenly distributed in blood after absorption, an adjustment for intermittent to continuous exposure was deemed not necessary. Henry's law indicates that acetone has a high blood to air partition coefficient and therefore will dissolve in blood upon pulmonary gas exchange.

Uncertainty Factor (UF): The $BMDL_{1SD}$ of 57.0 mg/kg/day was divided by a total uncertainty factor of 100.

- 10 for interspecies extrapolation
- 10 for human variability

$$MRL = BMDL_{1SD} \div UF = 57.0 \text{ mg/kg/day} \div 100 = 0.6 \text{ mg/kg/day}$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Not applicable.

Agency Contacts (Chemical Managers): Obaid Faroon

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acetone
CAS Numbers: 67-64-1
Date: June 2022
Profile Status: Final
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: A chronic-duration oral MRL was not derived for acetone because no chronic-duration oral exposure studies were identified.

Agency Contacts (Chemical Managers): Obaid Faroon

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR ACETONE

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 acetone.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for acetone. 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 acetone 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 acetone are presented in Table B-1.

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

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

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

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

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for acetone released for public comment in 2021; thus, the literature search was restricted to studies published between March 2019 and November 2021. The following main databases were searched in November 2021:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for acetone. 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 acetone 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	
11/2021	("acetone"[MeSH Terms] OR (("2-Propanone"[tw] OR "acetona"[tw] OR "Acetone"[tw] OR "beta-Ketopropane"[tw] OR "Dimethyl ketone"[tw] OR "Dimethylformaldehyde"[tw] OR "Dimethylketal"[tw] OR "Dimethylketone"[tw] OR "Ketone propane"[tw] OR "Ketone, dimethyl"[tw] OR "Methyl ketone"[tw] OR "Propan-2-one"[tw] OR "Propanone"[tw] OR "Pyroacetic acid"[tw] OR "Pyroacetic ether"[tw] OR "β-Ketopropane"[tw]) NOT medline[sb])) AND (2018/01/01:3000[dp] OR 2019/01/01:3000[mhda] OR 2019/01/01:3000[crdat] OR 2019/01/01:3000[edat])
NTRL	
11/2021	"2-Propanone" OR "acetona" OR "Acetone" OR "beta-Ketopropane" OR "Dimethyl ketone" OR "Dimethylformaldehyde" OR "Dimethylketal" OR "Dimethylketone" OR "Ketone propane" OR "Ketone, dimethyl" OR "Methyl ketone" OR "Propan-2-one" OR "Propanone" OR "Pyroacetic acid" OR "Pyroacetic ether" OR "β-Ketopropane"
Toxcenter	
11/2021	FILE 'TOXCENTER' ENTERED AT 16:32:34 ON 18 NOV 2021 CHARGED TO COST=EH038.13.01.LB.04 ACT ACETONE/A --------- L1 (47903)SEA FILE=TOXCENTER 67-64-1 L2 (47712)SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 (28488)SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 (22419)SEA FILE=TOXCENTER L3 AND PY>1991 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))

Table B-2. Database Query Strings

Database search date	Query string
	L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L20 QUE (ENDOCRIN? AND DISRUPT?) L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L27 QUE (NEPHROTOX? OR HEPATOTOX?) L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L33 QUE L30 OR L31 OR L32 L34 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L35 QUE L33 OR L34 L36 (9567)SEA FILE=TOXCENTER L4 AND L35 L37 (2307)SEA FILE=TOXCENTER L36 AND PY>2017 L38 (79)SEA FILE=TOXCENTER L37 AND MEDLINE/FS L39 (2228)SEA FILE=TOXCENTER L37 NOT MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	L40 (2232)DUP REM L38 L39 (75 DUPLICATES REMOVED) L41 (79)SEA FILE=TOXCENTER L40 L42 (2153)SEA FILE=TOXCENTER L40 L43 2153 SEA FILE=TOXCENTER (L41 OR L42) NOT MEDLINE/FS --------- D SCAN L43

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
11/2021	Compound searched: 67-64-1
NTP	
11/2021	Limited to 2018-present 67-64-1 "Acetone" "Propanone" "Dimethyl Ketone" "Methyl Ketone" "2-Propanone" "Pyroacetic Acid" "Pyroacetic Ether" "Dimethylformaldehyde" "Beta-ketopropane" "Dimethyl Formaldehyde" "Ketone Propane"
Regulations.gov	
11/2021	Limited to 2018-present in dockets, documents, EPA notices 67-64-1 Acetone "Dimethyl Ketone" "Methyl Ketone" "2-Propanone" "Pyroacetic Acid" "Pyroacetic Ether" "Dimethylformaldehyde" "Beta-ketopropane" "Dimethyl Formaldehyde" "Ketone Propane" "Propanone"
NIH RePORTER	
12/2021	Search Criteria Fiscal Year: Active ProjectsText Search: "2-Propanone" OR "acetona" OR "Acetone" OR "beta-Ketopropane" OR "Dimethyl ketone" OR "Dimethylformaldehyde" OR "Dimethylketal" OR "Dimethylketone" OR "Ketone propane" OR "Ketone, dimethyl" OR "Methyl ketone" OR "Propan-2-one" OR "Propanone" OR "Pyroacetic acid" OR "Pyroacetic ether" OR "β-Ketopropane" (advanced)Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2021 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 4,590
- Number of records identified from other strategies: 10
- Total number of records to undergo literature screening: 4,600

B.1.2 Literature Screening

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

- 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.

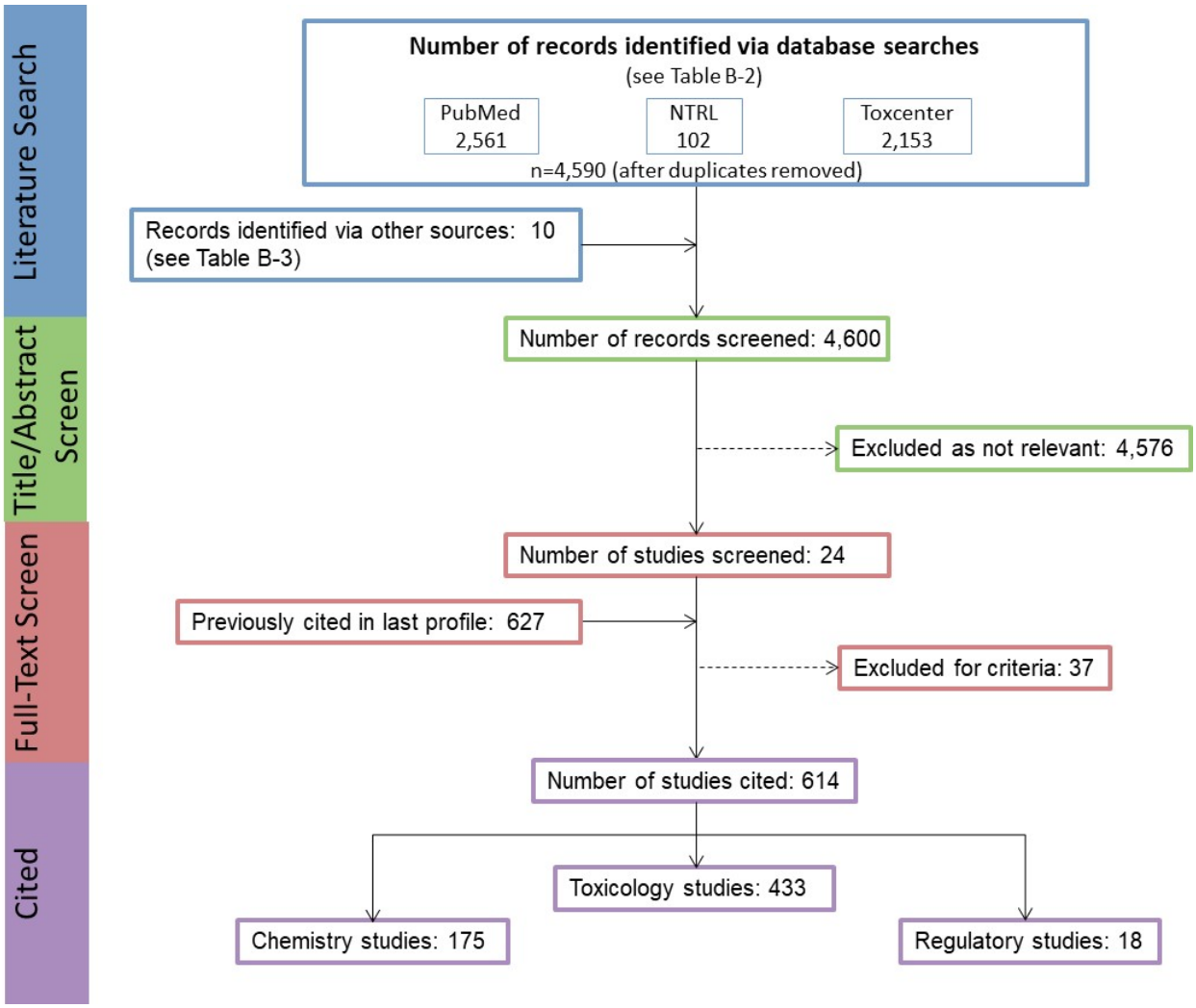
- Number of titles and abstracts screened: 4,600
- Number of studies considered relevant and moved to the next step: 24

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: 24
- Number of studies cited in the pre-public draft of the toxicological profile: 627
- Total number of studies cited in the profile: 614

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

Figure B-1. November 2021 Literature Search Results and Screen for Acetone



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), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), 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.

(12) 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.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) 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.

(15) 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).

(16) 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.

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

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

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

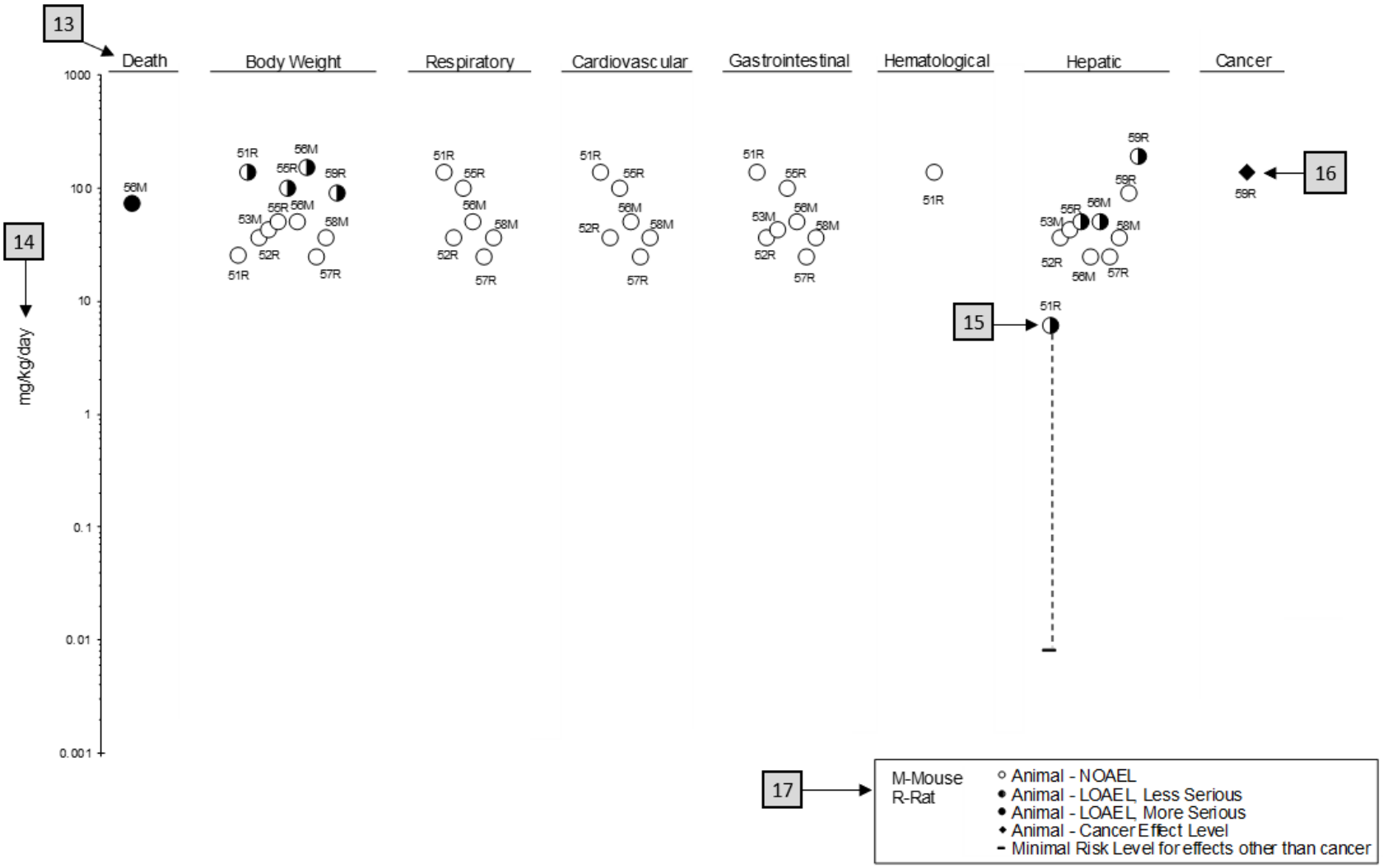
[a]The number corresponds to entries in Figure 2-x.

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

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

APPENDIX C

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



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

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

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

Pediatrics:

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

ATSDR Information Center

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

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

https://www.atsdr.cdc.gov/emes/health_professionals/index.html for more information on resources for clinicians.

Managing Hazardous Materials Incidents is a 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.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

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

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

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

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

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

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

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

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

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

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

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

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

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

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

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

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

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

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

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

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

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

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

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

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

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

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

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

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

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

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

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

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

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure 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
SLOAEL	serious lowest-observed-adverse-effect level
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