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.

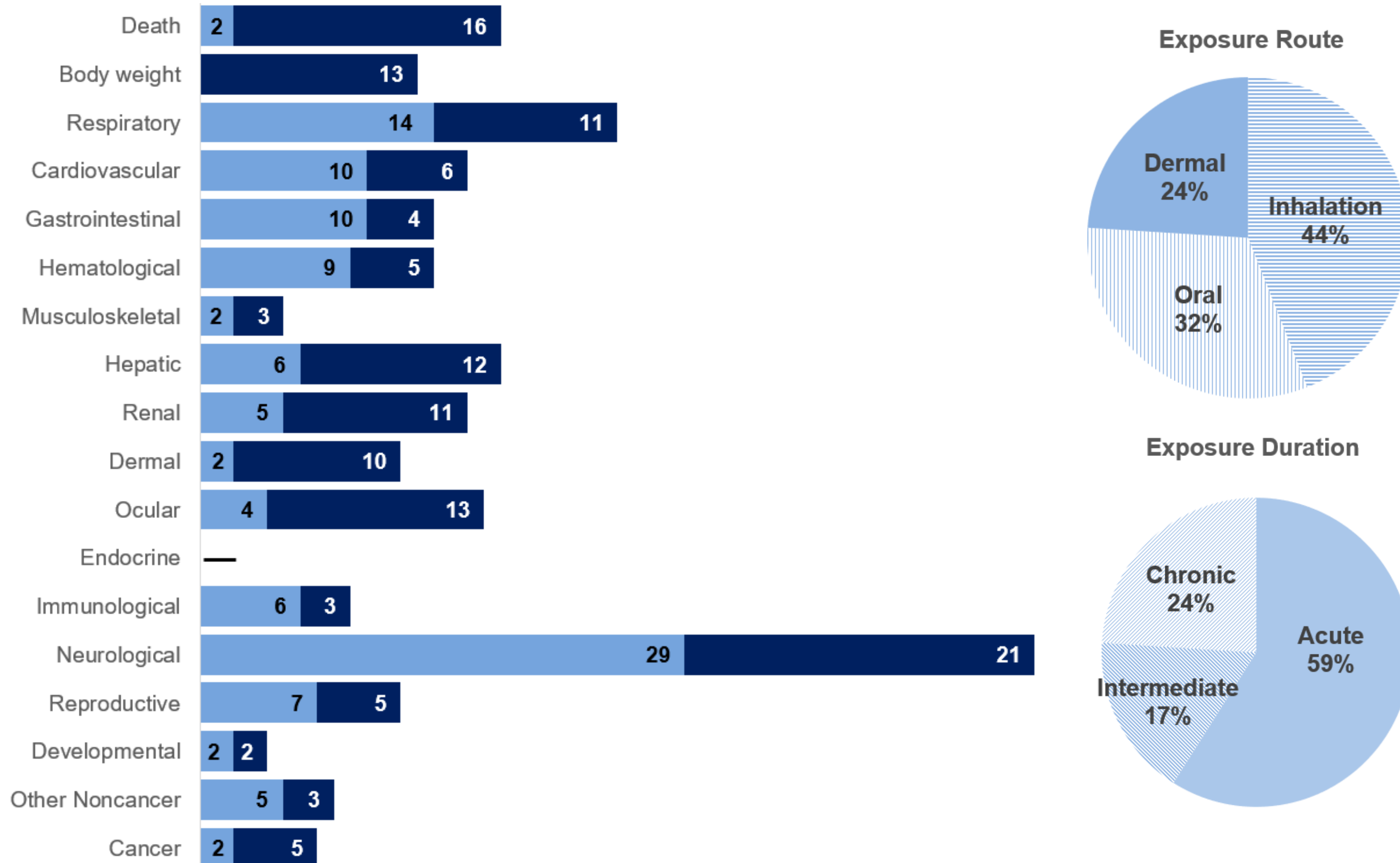
- **Ocular endpoints.** Acetone is also a known eye irritant, based on occupational studies in humans and animal studies of direct dermal/ocular application.

- **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

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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≤0.05)
					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	1,070			
					Hepatic	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

Acute (≤14 days)

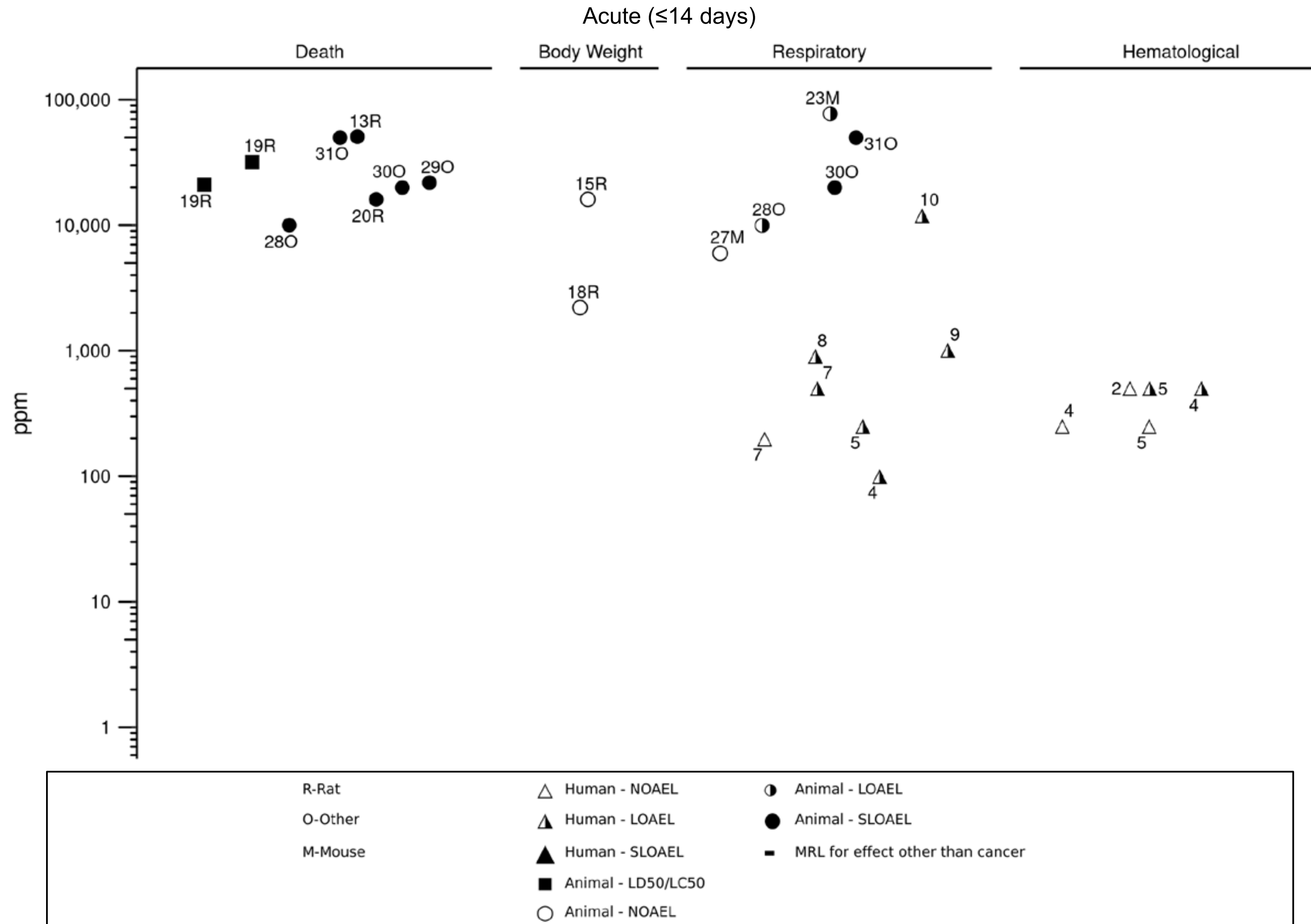


Figure 2-2. Levels of Significant Exposure to Acetone – Inhalation
Acute (≤14 days)

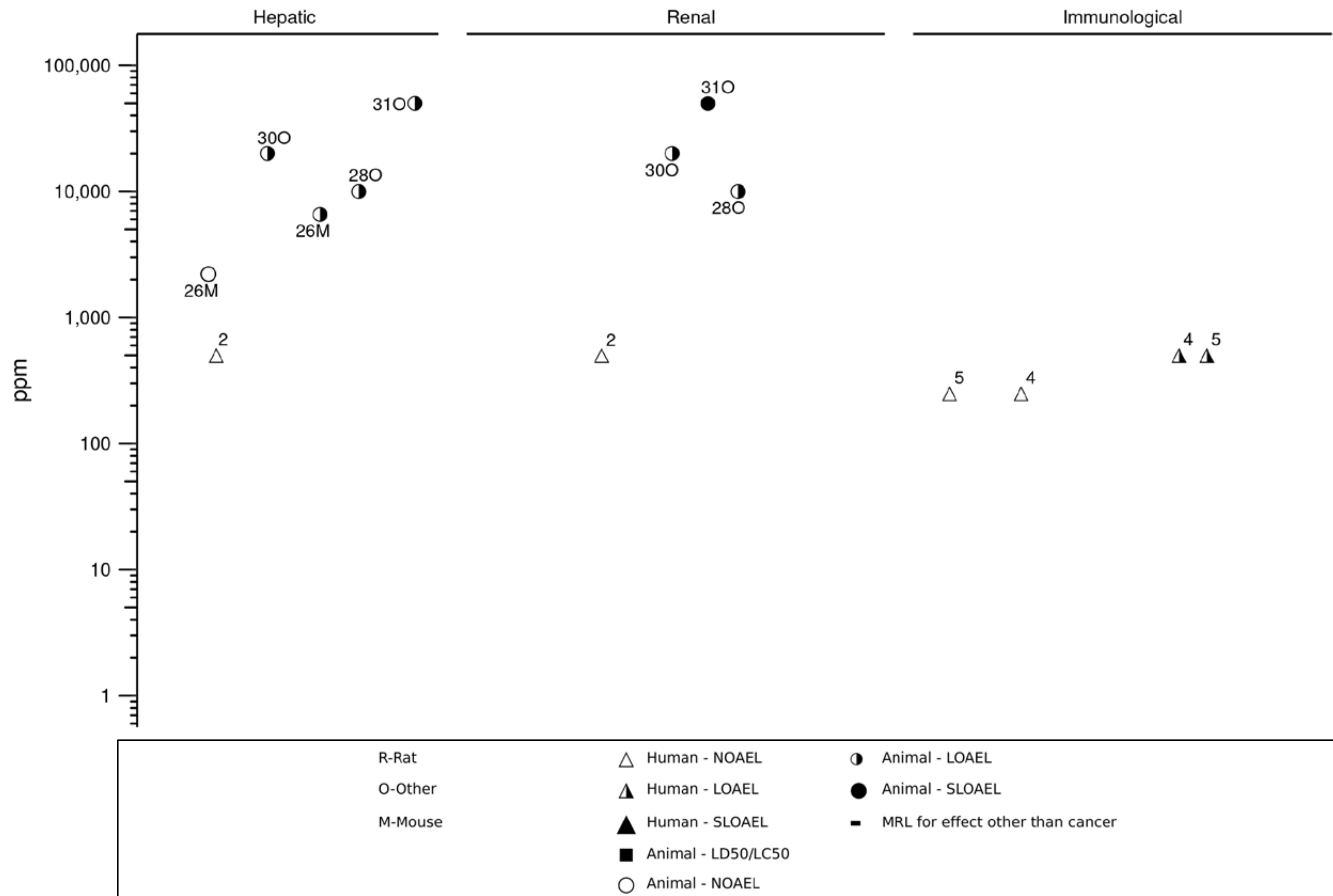
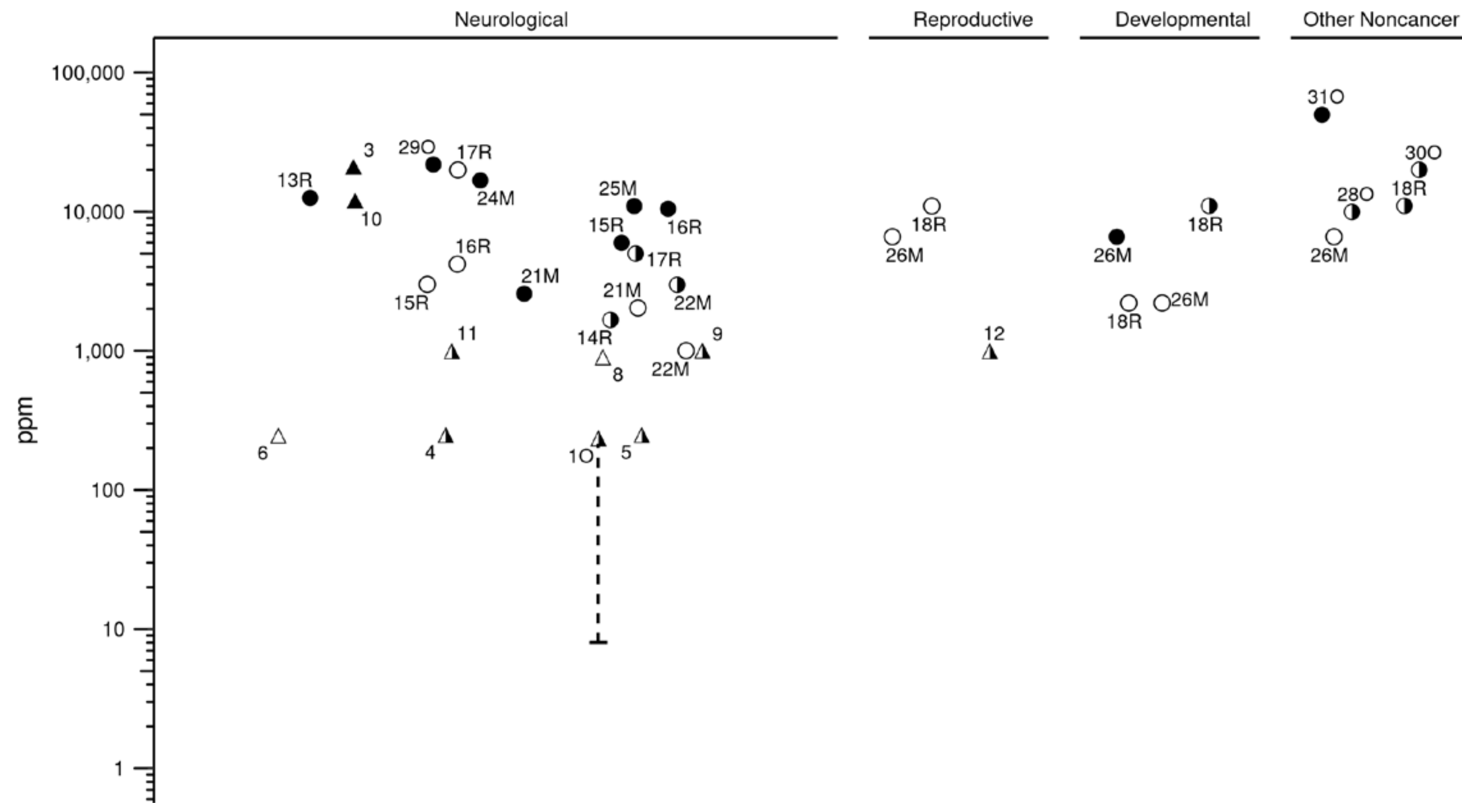


Figure 2-2. Levels of Significant Exposure to Acetone – Inhalation
Acute (≤14 days)



R-Rat	△ Human - NOAEL	◑ Animal - LOAEL
O-Other	Human - LOAEL	● Animal - SLOAEL
M-Mouse	▲ Human - SLOAEL	▬ MRL for effect other than cancer
	■ Animal - LD50/LC50	
	○ Animal - NOAEL	

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

Intermediate (15–364 days)

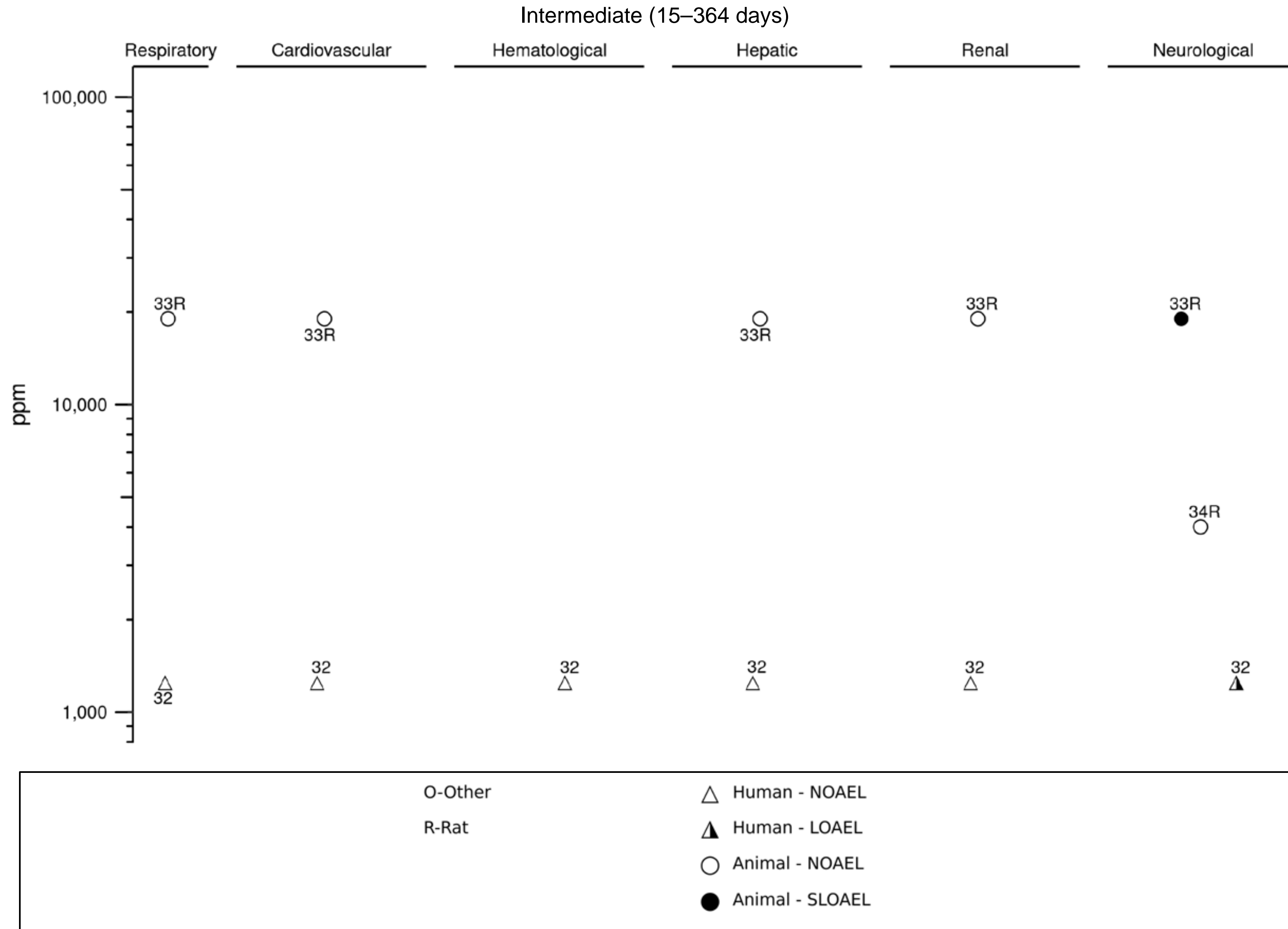


Figure 2-2. Levels of Significant Exposure to Acetone – Inhalation

Chronic (≥365 days)

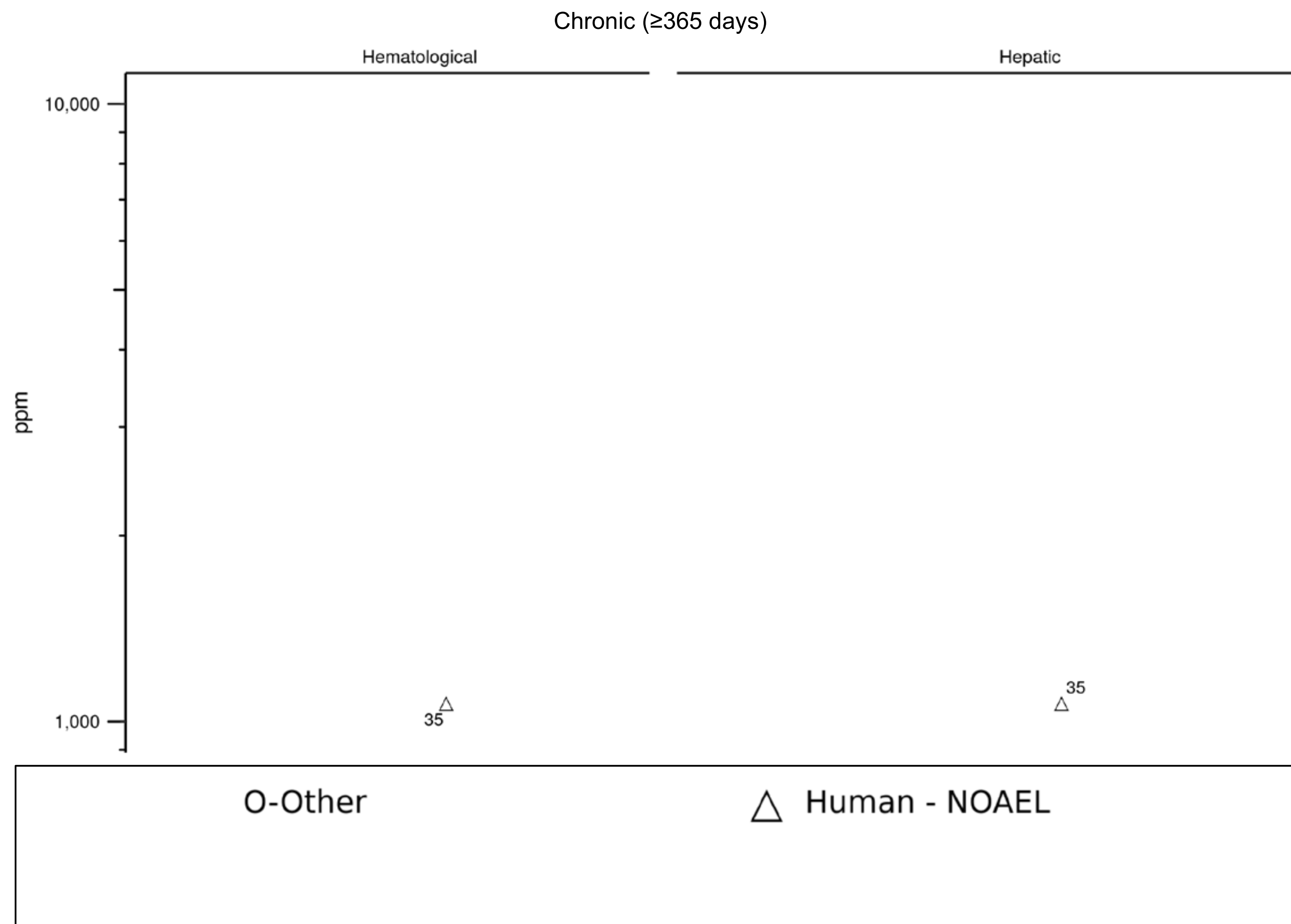


Table 2-3. Levels of Significant Exposure to Acetone – Oral

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

Acute (≤14 days)

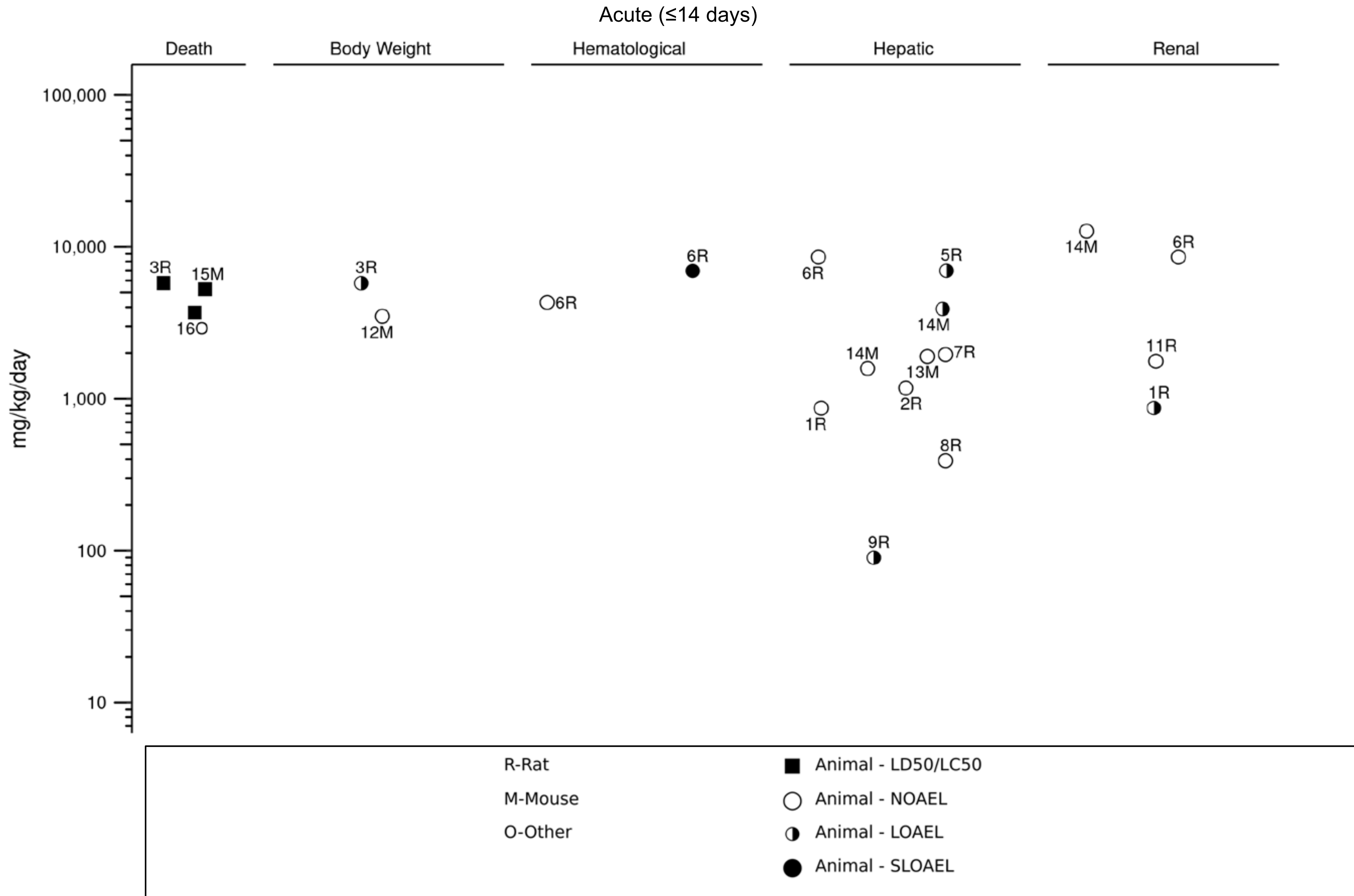


Figure 2-3. Levels of Significant Exposure to Acetone – Oral

Acute (≤14 days)

Neurological Reproductive Developmental Other Noncancer

mg/kg/day

100,000
10,000
1,000
100
10

3R
4R
12M
12M
14M
6R
10R
11R

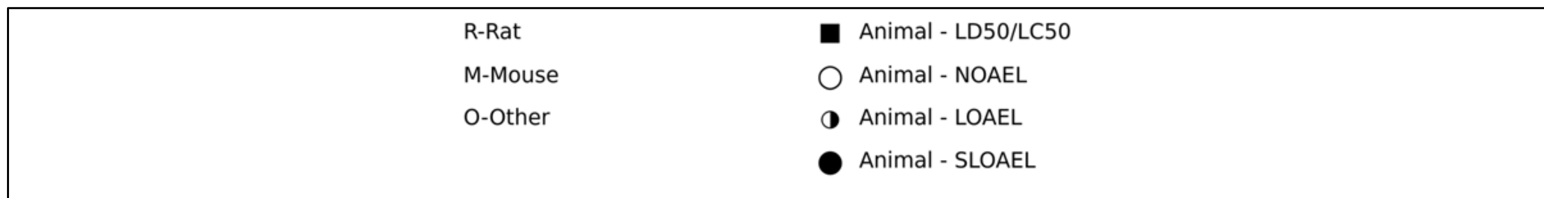


Figure 2-3. Levels of Significant Exposure to Acetone – Oral

Intermediate (15–364 days)

Respiratory Cardiovascular Gastrointestinal Hematological

mg/kg/day

100,000
10,000
1,000
100
10
1
0.1

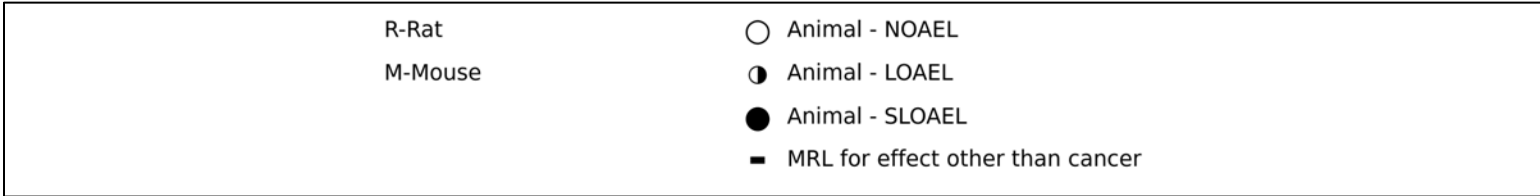


Figure 2-3. Levels of Significant Exposure to Acetone – Oral

Intermediate (15–364 days)

Musculoskeletal
Hepatic
Renal
Dermal

mg/kg/day

100,000
10,000
1,000
100
10
1
0.1

25M
18R
22R
25M
22R
18R
17R
17R
18R
25M
22R
22R
18R
18R
25M
18R
22R

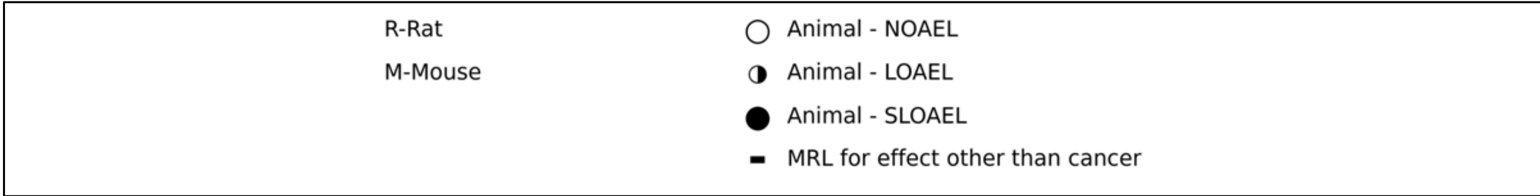


Figure 2-3. Levels of Significant Exposure to Acetone – Oral

Intermediate (15–364 days)

Immunological Neurological Reproductive Other Noncancer

mg/kg/day

100,000 10,000 1,000 100 10 1 0.1

26M 25M 22R 18R 17R 23R 18R 19R 17R 24M 24M 21R 21R 20R 21R 25M 22R 17R 18R 23R 19R

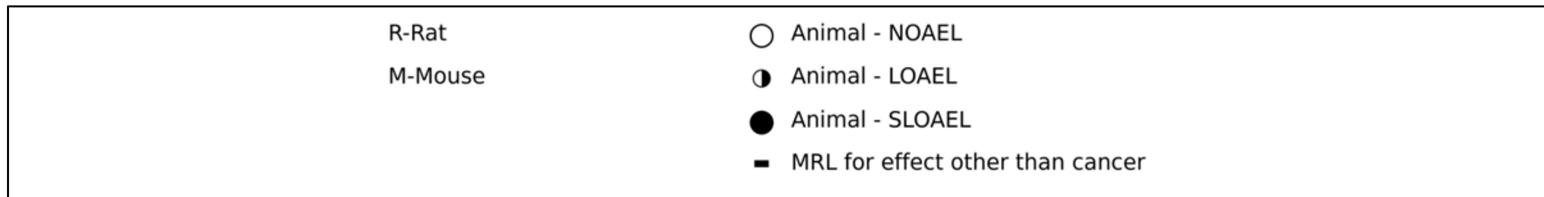


Table 2-4. Levels of Significant Exposure to Acetone – Dermal

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 $\mu g/m^3$. Acetone was one of the most commonly emitted VOCs at 70ºC, being measured in concentrations of 50 $\mu g/m^3$ in ceiling tile, 102 $\mu g/m^3$ in Spanished wallcovering, and 2,591 $\mu g/m^3$ 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: Activation With	Results: Activation Without	Reference
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 (WPs(λ))	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.