CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 2-butanone. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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

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

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to 2-butanone, but may not be inclusive of the entire body of literature.

Animal inhalation studies are presented in Table 2-1 and Figure 2-2, and animal oral studies are presented in Table 2-2 and Figure 2-3. Animal dermal studies are presented in Table 2-3.

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

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

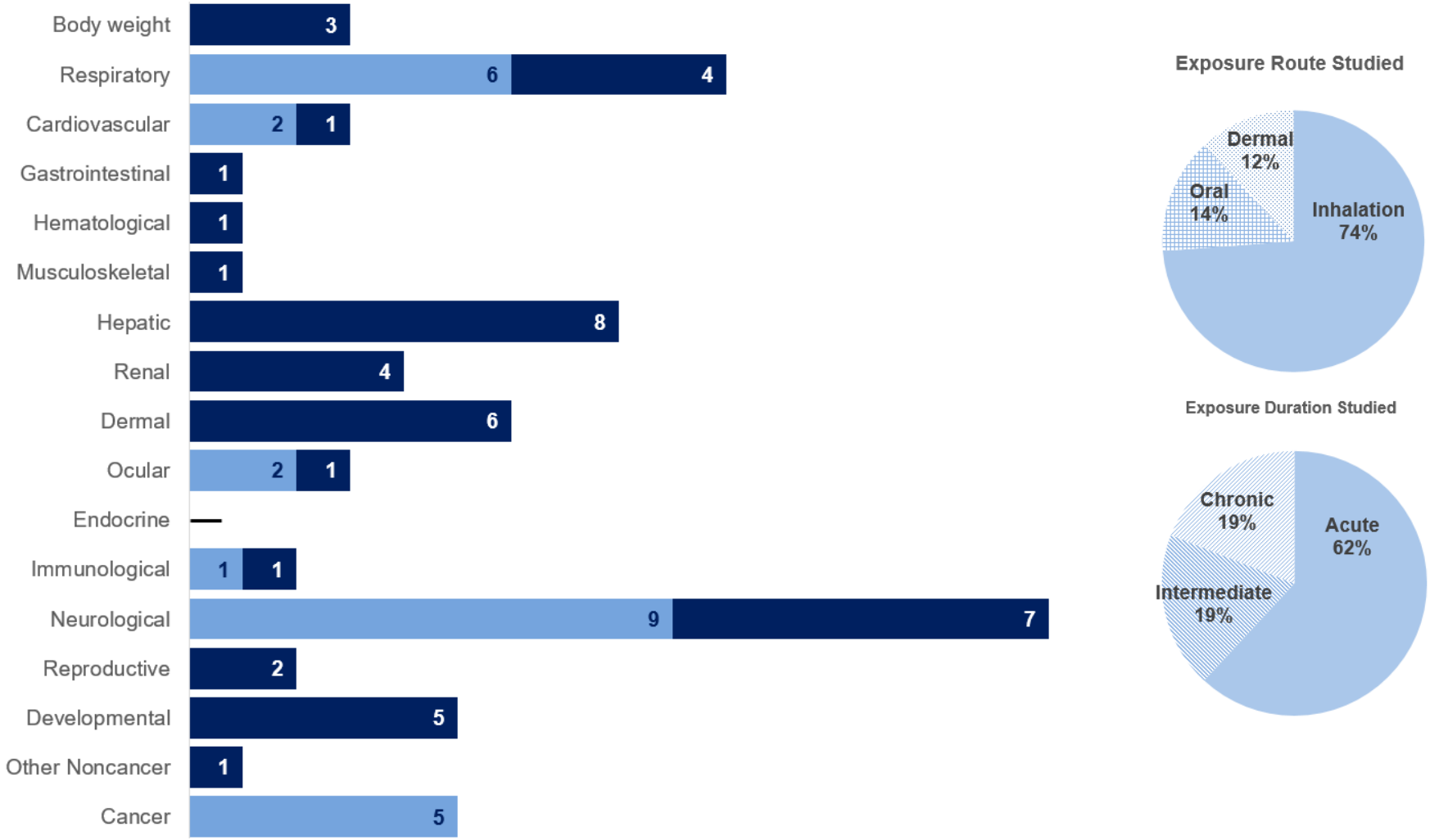
A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

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

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

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

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



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

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

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

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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)	Effect
8	Rat (Sprague-Dawley) 25 F (35 F controls)	10 days GDs 6–15, 7 hours/day	0, 400, 10,00, 3,000	BW, OW, FI, WI, CS, FX, DX, MX, TG	Bd wt	1,000	3,000		Decreased maternal body weight
					Develop	1,000	3,000		Extra ribs, delayed ossification
Deacon et al. 1981									
9	Rat (NS) 3 M, F	1 day 3 hours/day	92,239	LE	Death			92,239	
Klimisch 1988									
10	Rat (albino) 8 M	1 day 4 hours/day	0, 7,850, 9,090, 9,060, 12,200, 13,150, 18,100, 20,200	LE	Death			11,700	LC_{50}
LaBelle and Brieger 1955									
11	Rat (Wistar) 6–7 F	7 days 8 hours/day	0, 300	BC, BI	Hepatic	300			
Li et al. 1986									
12	Rat (Sprague-Dawley) 19–23 F	GDs 6–20 6 hours/day	0, 1,000, 2,000, 4,000, 6,000	BW, DX, FI, FX, OW, MX, TG	Bd wt	2,000	4,000		Reduced food consumption (12%) and maternal body weight gain (52%)
					Develop	2,000	4,000		Decreased fetal body weight (15% in males); incomplete ossification of the sternebrae
Saillenfait et al. 2006									

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

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

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

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

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

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

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

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

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

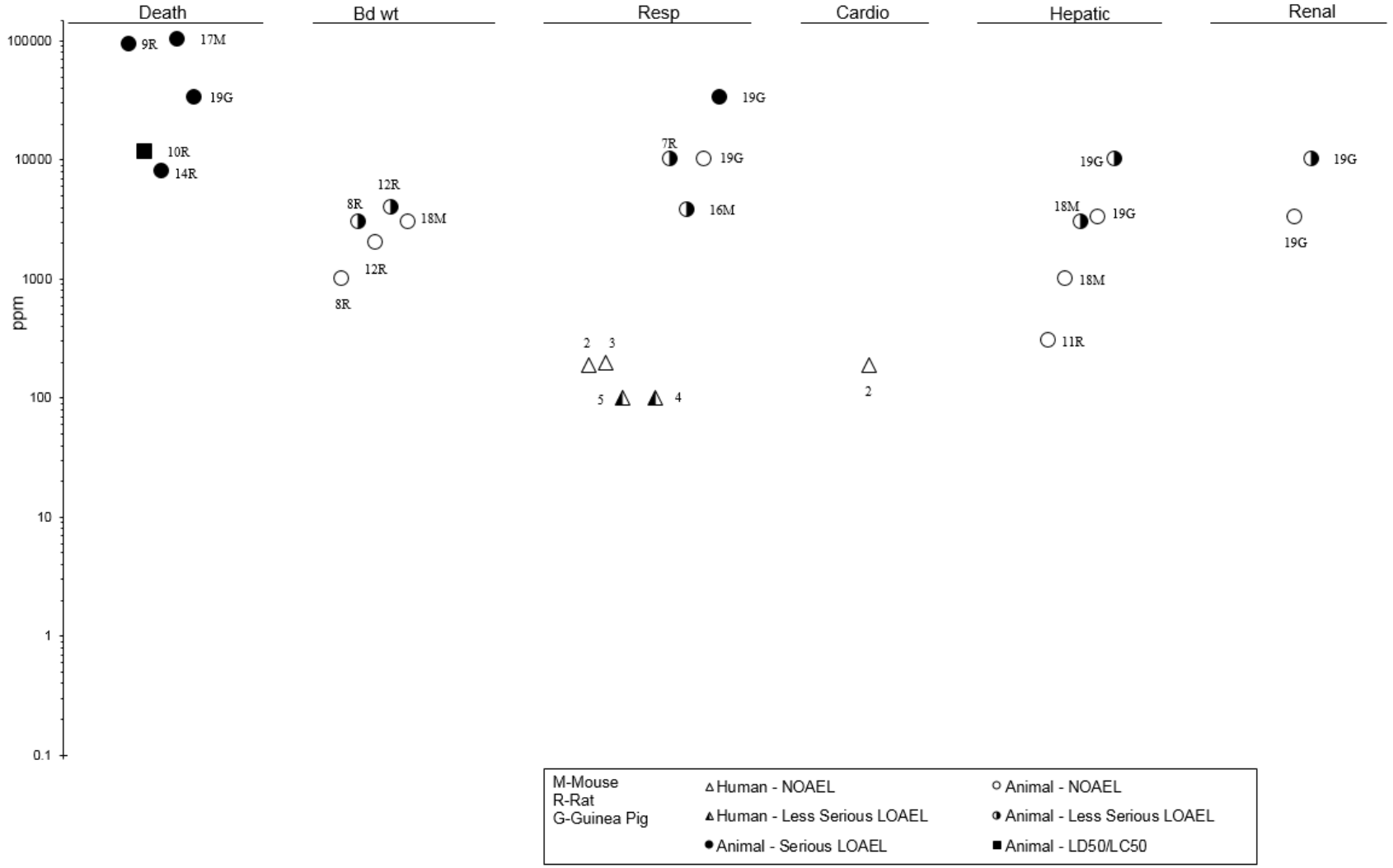

Figure 2-2. Levels of Significant Exposure to 2-Butanone – Inhalation
Acute (≤14 days)

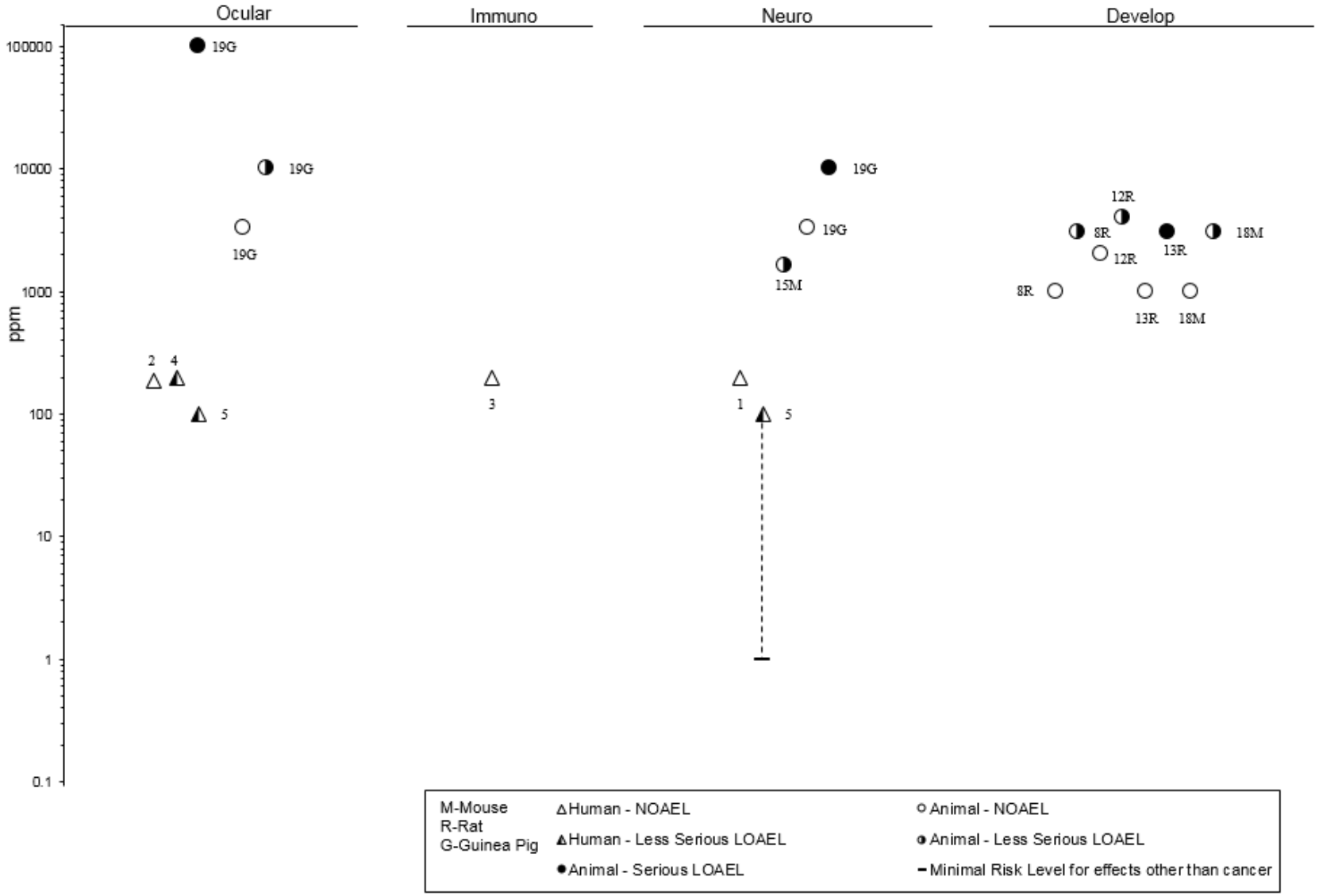

Figure 2-2. Levels of Significant Exposure to 2-Butanone – Inhalation
Intermediate (15-364)

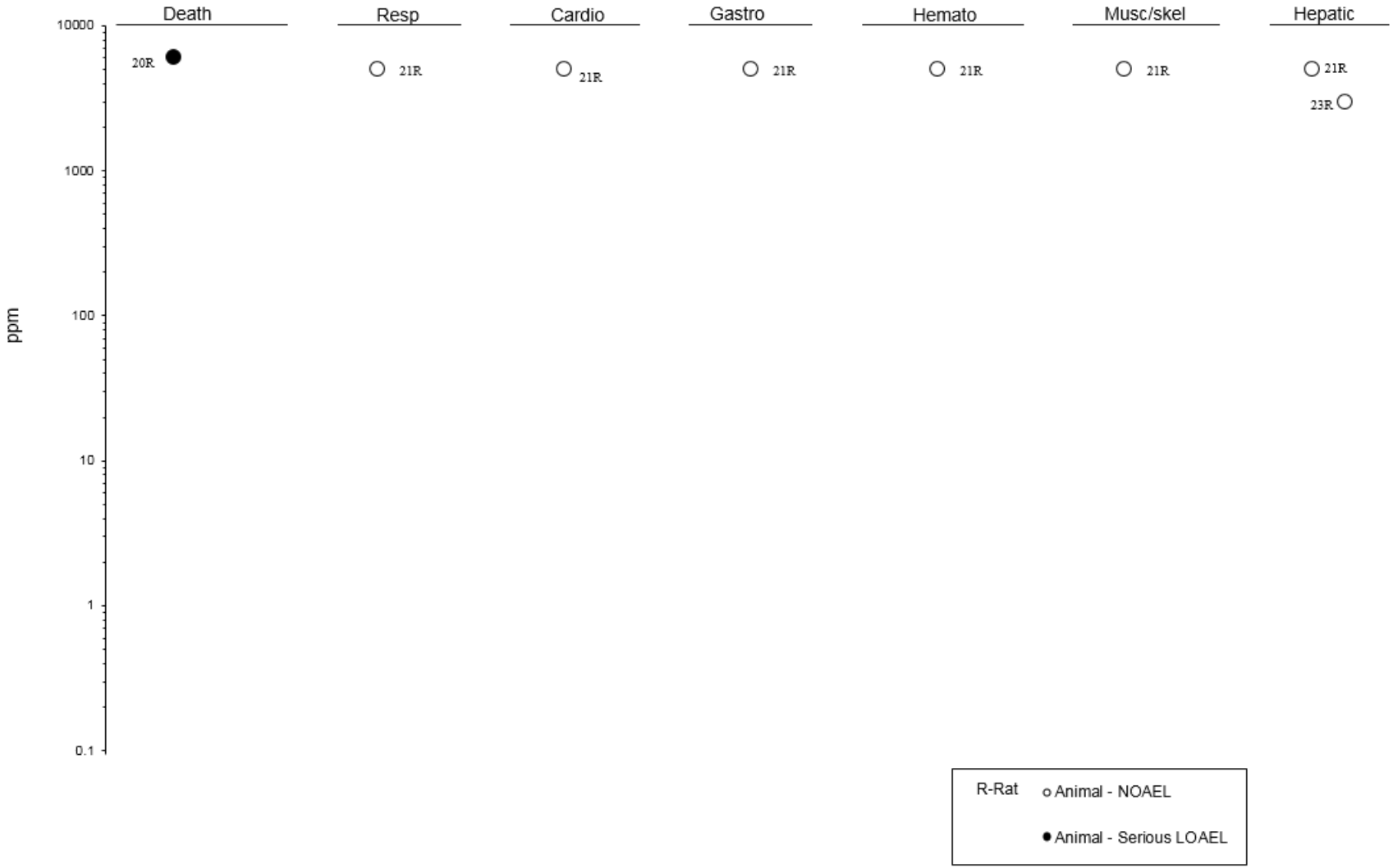

Figure 2-2. Levels of Significant Exposure to 2-Butanone – Inhalation
Intermediate (15-364)

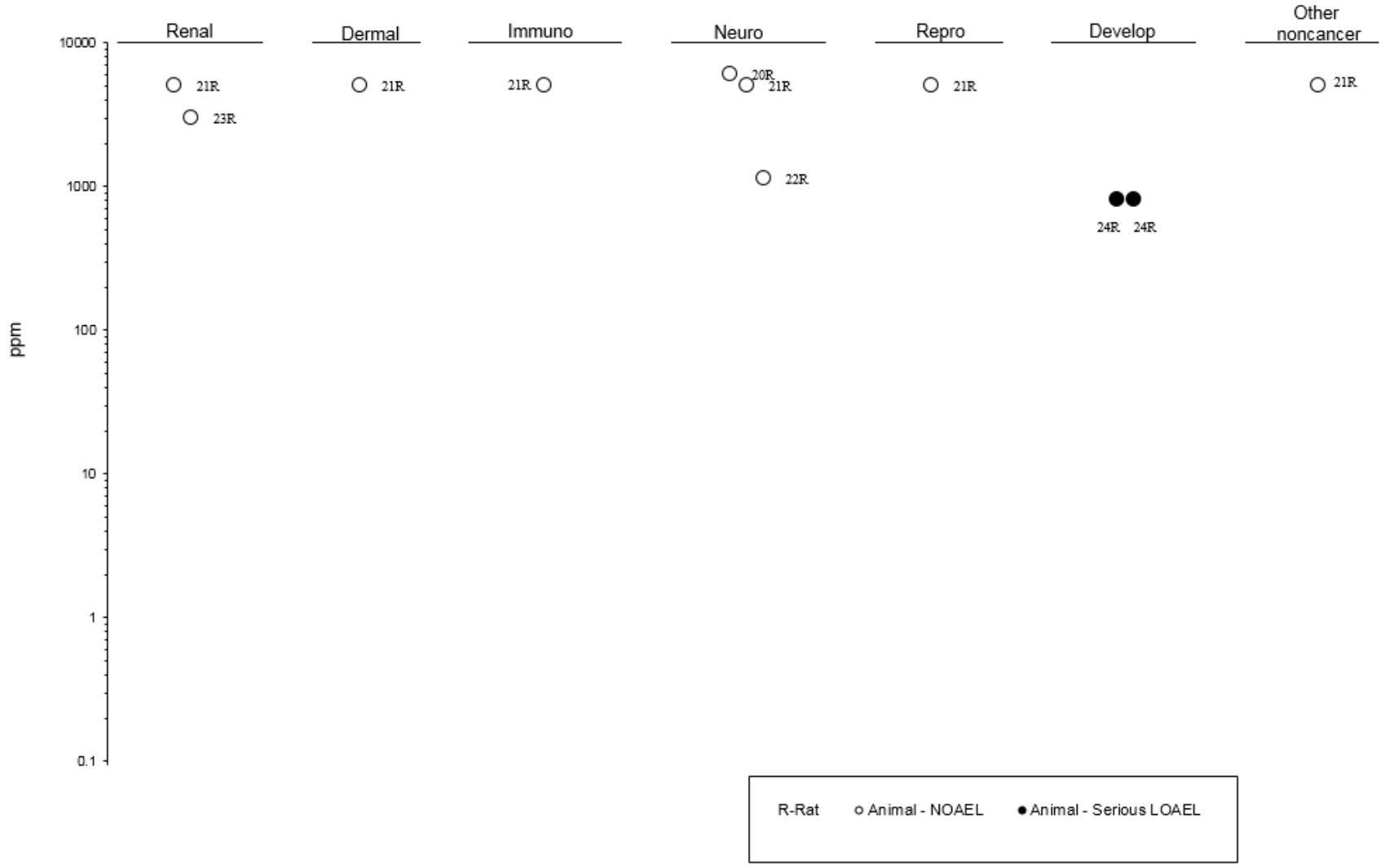

Table 2-2. Levels of Significant Exposure to 2-Butanone – Oral

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

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

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

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

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

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

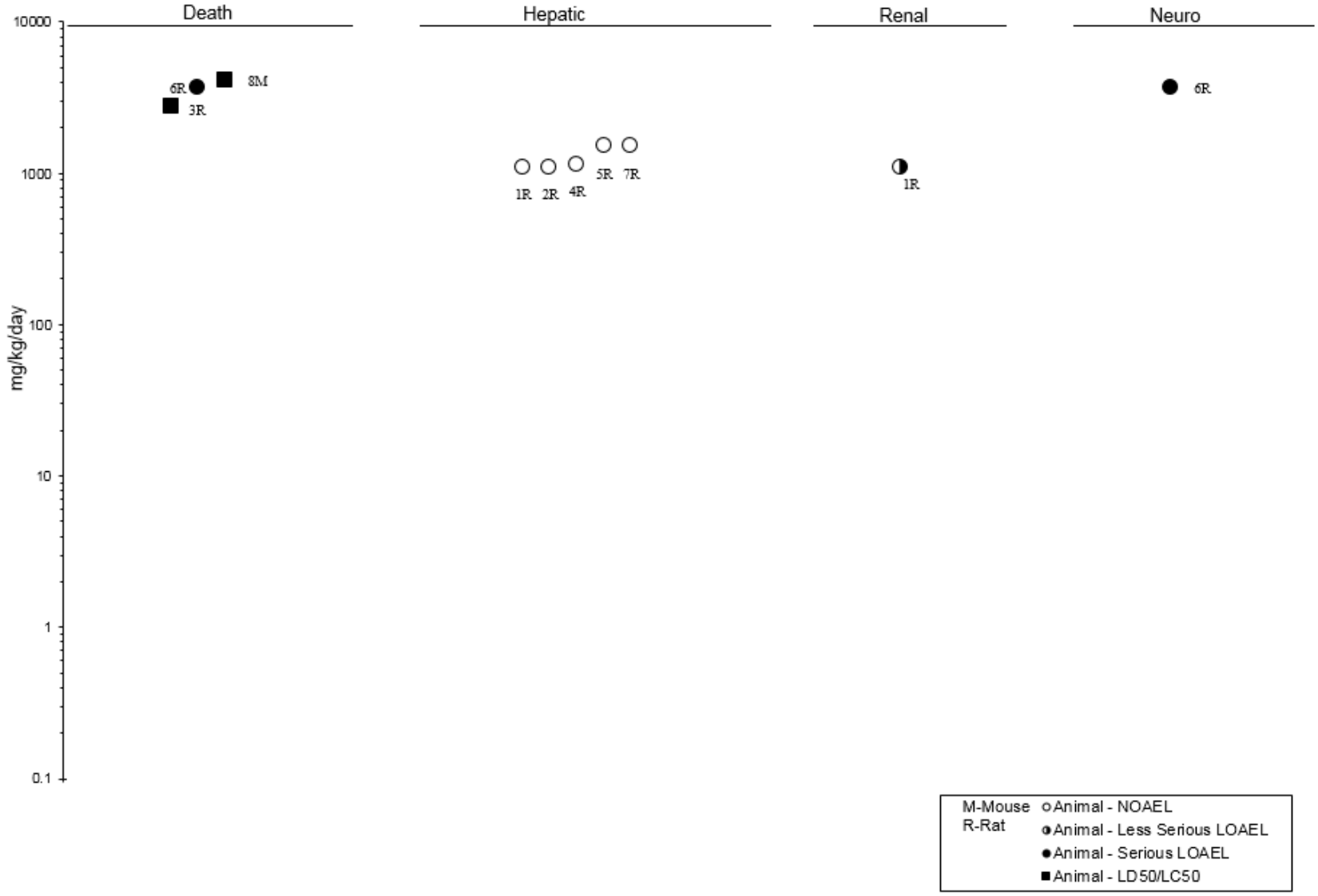

Figure 2-3. Levels of Significant Exposure to 2-Butanone – Oral
Intermediate (15-364 days)

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

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

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

2.2 DEATH

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

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

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

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

2.3 BODY WEIGHT

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

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

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

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

2.4 RESPIRATORY

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

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

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

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

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

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

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

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

2.5 CARDIOVASCULAR

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

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

2.6 GASTROINTESTINAL

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

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

2.7 HEMATOLOGICAL

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

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

2.8 MUSCULOSKELETAL

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

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

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

2.9 HEPATIC

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

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

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

2.10 RENAL

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

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

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

2.11 DERMAL

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

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

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

2.12 OCULAR

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

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

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

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

2.13 ENDOCRINE

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

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

2.14 IMMUNOLOGICAL

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

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

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

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

2.15 NEUROLOGICAL

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

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

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

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

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

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

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

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

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

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

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

2.16 REPRODUCTIVE

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

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

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

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

2.17 DEVELOPMENTAL

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

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

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

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

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

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

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

2.18 OTHER NONCANCER

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

2.19 CANCER

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

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

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

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

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

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

2.20 GENOTOXICITY

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

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

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

– = negative result

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

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

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

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

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