CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

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

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

1.2 SUMMARY OF HEALTH EFFECTS

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

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

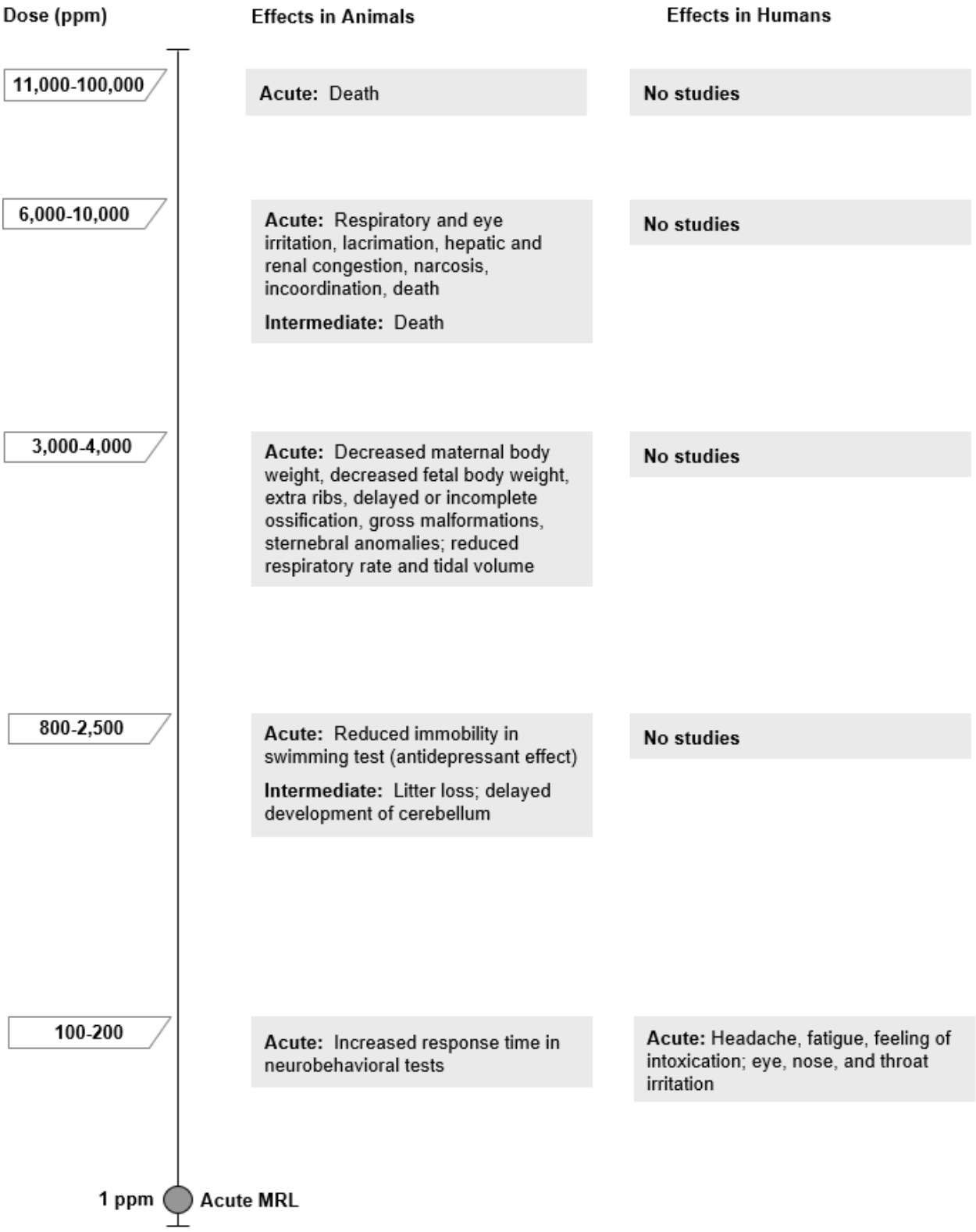
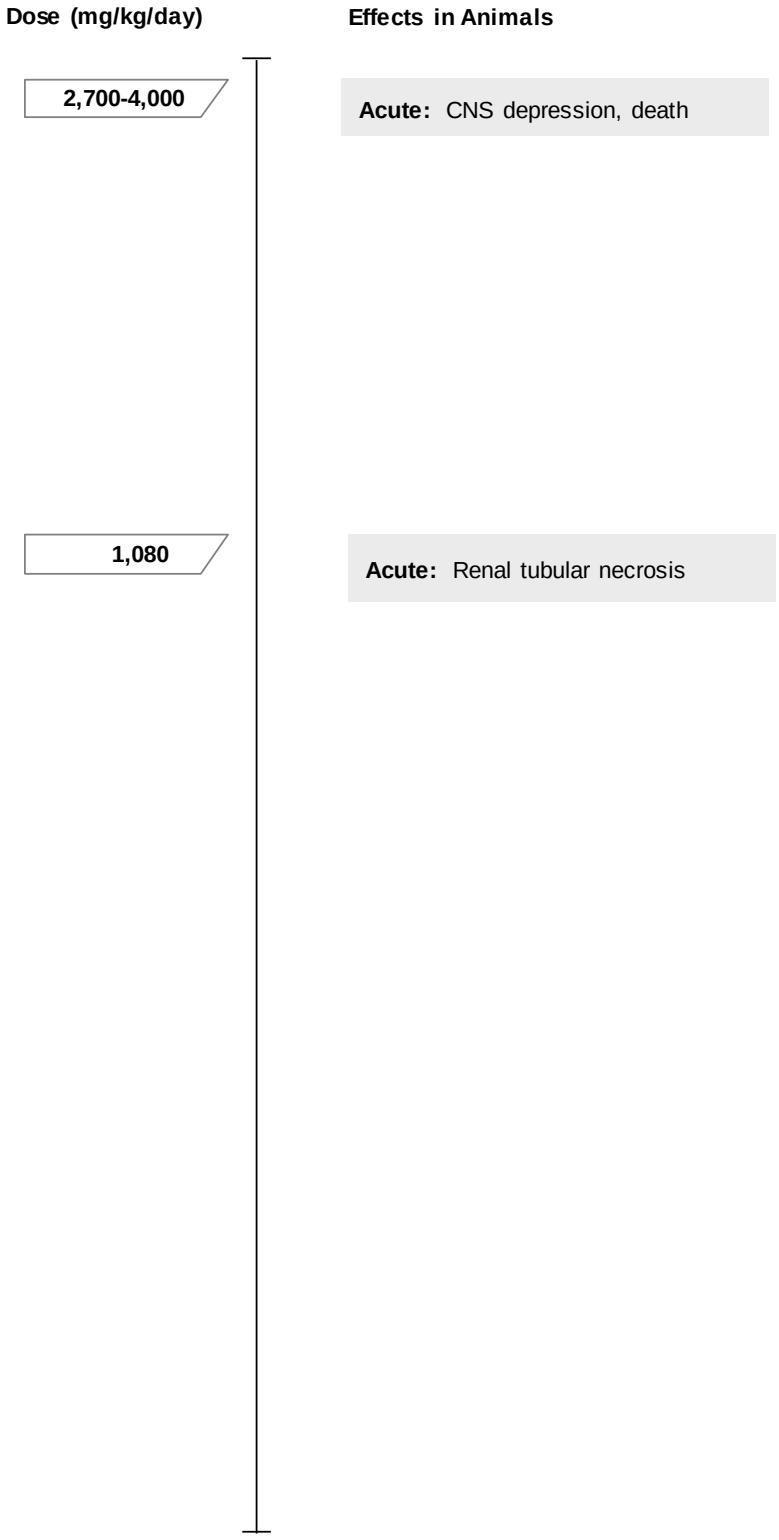


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 2-Butanone



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

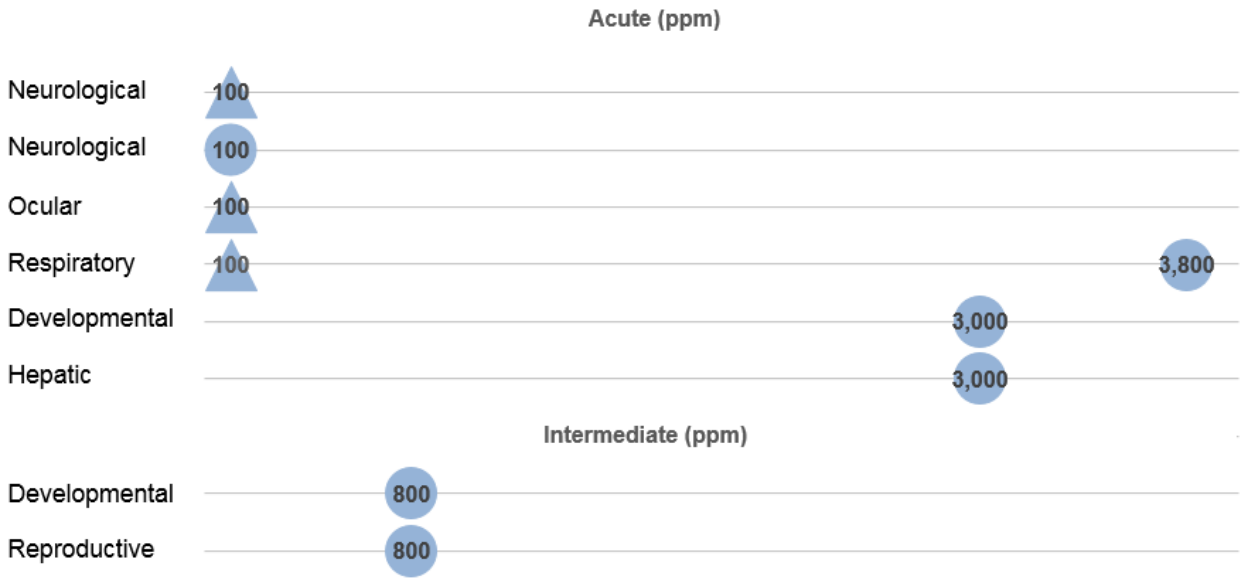
1.3 MINIMAL RISK LEVELS (MRLs)

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

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

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

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

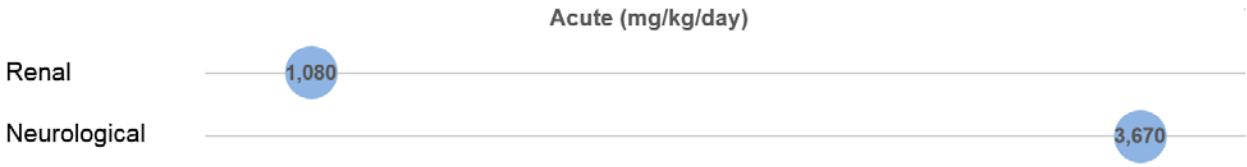


No acute, intermediate-, or chronic-duration oral MRLs were derived for 2-butanone. In the case of acute-duration oral exposure, target organs have not been sufficiently identified (see Figure 1-4). The paucity of information on toxic effects after intermediate- and chronic-duration oral exposure likewise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

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

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

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



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

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

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

[a]See Appendix A for additional information.

LOAEL = lowest-observed-adverse-effect level; UF = uncertainty factor