# CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

## 1.1 OVERVIEW AND U.S. EXPOSURES

2-Hexanone (Chemical Abstracts Service [CAS] Registry Number: 591-78-6; common synonym: methyl-n-butyl ketone) is a waste product of wood pulping, coal gasification, and *in situ* oil shale operations (Pellizzari et al. 1979). 2-Hexanone dissolves very easily in water and can evaporate rapidly into the air as a vapor. Once it is introduced into the environment, 2-hexanone may be degraded by atmospheric photooxidation and direct photolysis or degraded by biodegradation mediated by microorganisms found in most sediment, soils, and water (Atkinson 1989; Babeu and Vaishnav 1987; Calvert and Pitts 1966). 2-Hexanone is likely to migrate through the soil and into groundwater since it is expected to have very high mobility in soils. Volatilization of 2-hexanone from water surfaces has been observed. A large fraction of vapor-phase 2-hexanone will dissolve in water droplets in the atmosphere, and precipitation may be an important physical removal mechanism (Thomas 1990). Bioconcentration of this compound in aquatic organisms is not expected to occur (Lande et al. 1976).

Significant exposure of the general population to 2-hexanone is not likely at present, as it is no longer manufactured, processed, or used for commercial purposes in the United States. 2-Hexanone was formerly used as a solvent in lacquers and varnish removers, and in various chemical substances. Due to the harmful health effects of this chemical, the lone U.S. producer of 2-hexanone discontinued its production in 1979 and sold its remaining reserves by 1981 (EPA 1987). However, while 2-hexanone is no longer manufactured or used in the United States, it may be indirectly generated as a waste product during processing at coal gasification plants, *in situ* oil shale operations, and wood pulping mills (Pellizzari et al. 1979; TCEQ 2011); therefore, human exposure to 2-hexanone may occur. 2-Hexanone has been detected in drinking water and soil near hazardous waste sites, so the general population living near an industry or hazardous waste site that releases the liquid into waste water or the gas form into the surrounding air has an increased risk of exposure (CLPSD 1989; Lucas 1984). In the past decade, there has been an increase in oil and natural gas production from shale in the United States (EIA 2016), and 2-hexanone has been detected at low levels (Grinberg 2014; Hawthorne and Sievers 1984; Pellizzari et al. 1979) in air samples near these operations and aqueous samples related to these processes. Exposure to small amounts of 2-hexanone may also occur by ingestion of foods in which it occurs. It is possible that exposure to small amounts of 2-hexanone may occur through imported products containing 2-hexanone. Individuals may still be exposed from consumer products manufactured prior to 1982, such as lacquers, primers, sealers, and thinners that contain 2-hexanone.

When 2-hexanone was still being manufactured, occupational exposure may have occurred through inhalation and dermal contact. It is unlikely that many persons are currently occupationally exposed to 2-hexanone, other than as a degradation product resulting from wood pulping, *in situ* oil shale processing, or coal gasification operations (EPA 1987; RTECS 2009).

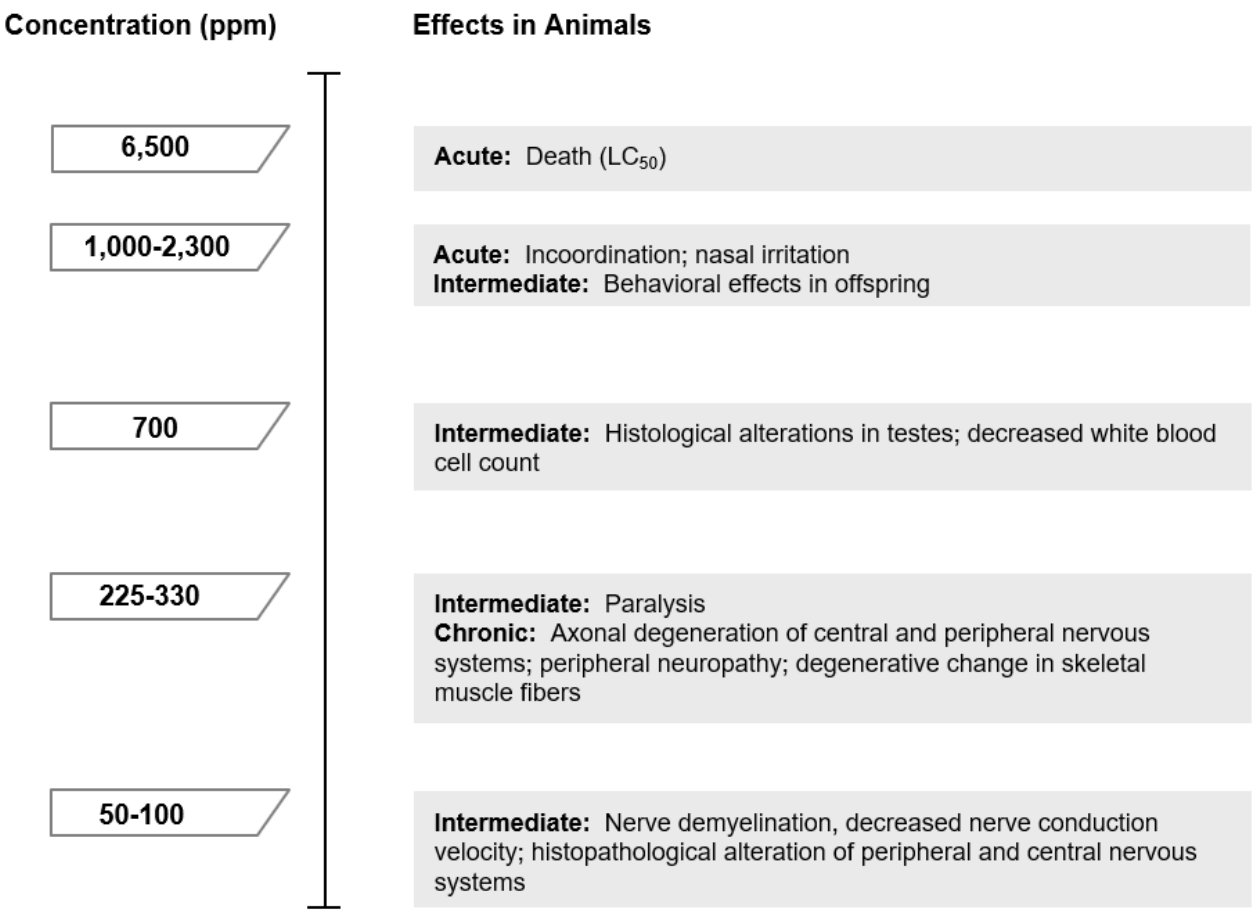
No biomarkers specific to 2-hexanone are currently identified to indicate if exposure to 2-hexanone has occurred.

## 1.2 SUMMARY OF HEALTH EFFECTS

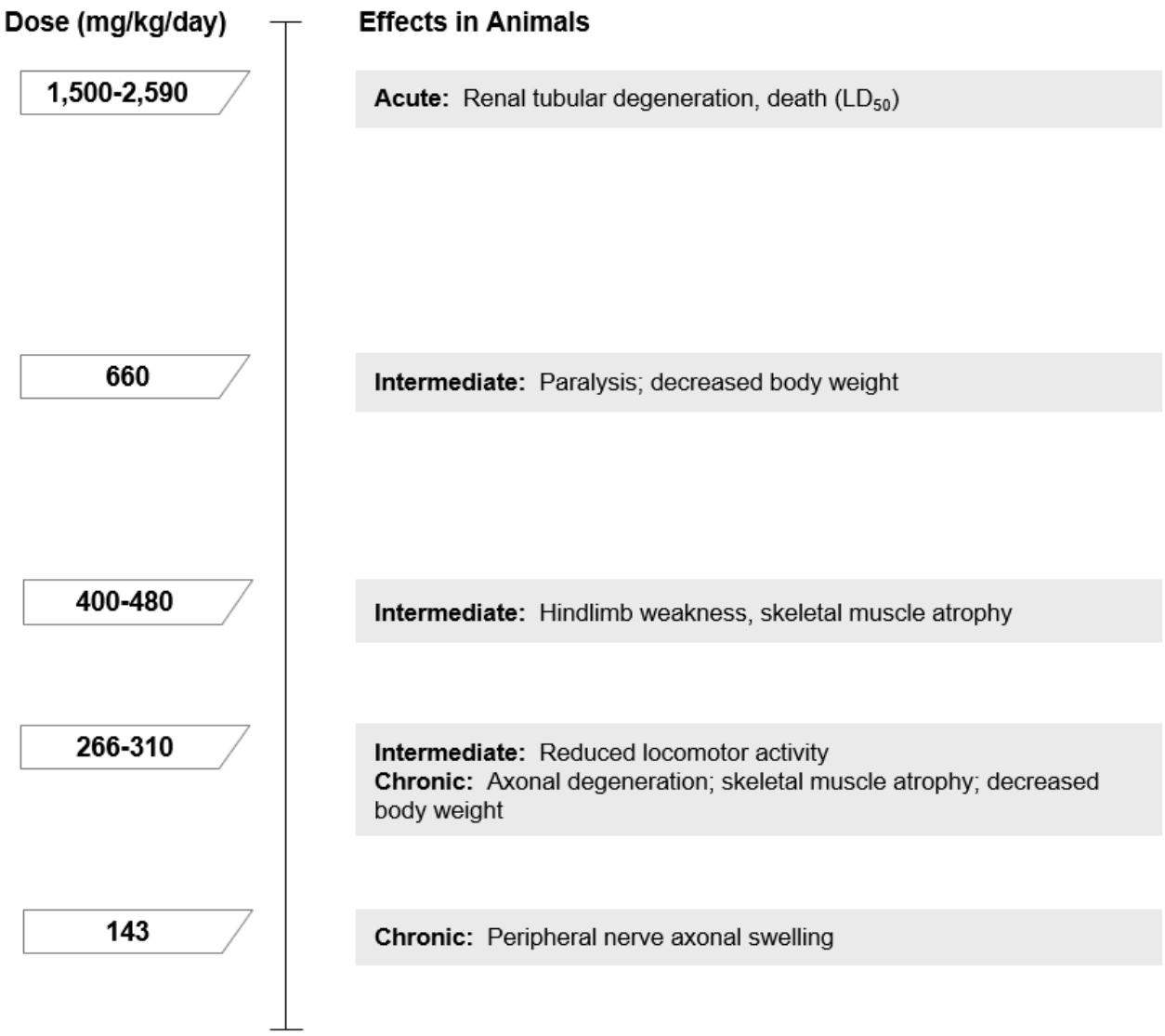
Information on the toxicity of 2-hexanone primarily comes from inhalation and oral studies in laboratory animals, with some limited information on effects in humans. Results of these studies provide strong evidence that the nervous system is the most sensitive target of 2-hexanone (Figures 1-1 and 1-2). Other targets include toxicity to male reproductive organs, decreased body weight, possible developmental effects, and effects to the musculoskeletal systems. As stated in Section 1.1, significant exposure of the general population to 2-hexanone is not likely because it is no longer manufactured, processed, or used for commercial purposes in the United States.

It should be noted that most animal studies tested only one concentration/dose of 2-hexanone; therefore, little information on dose-response relationships was provided in these studies. Furthermore, very few studies stated the purity of the 2-hexanone tested, with purity of commercial grade 2-hexanone ranging from 70-96% (Topping et al. 2001); contaminants may include methyl isobutyl ketone (MiBK). This is of concern because MiBK has been shown to potentiate the neurotoxicity of 2-hexanone through induction of hepatic microsomal cytochrome P-450 enzymes, resulting in increased production of the 2-hexanone active metabolite, 2,5-hexanedione (ATSDR 1999).

## Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to 2-Hexanone



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



***Neurological Effects.*** In humans, information on 2-hexanone neurotoxicity is from studies on a population of workers exposed to 2-hexanone in a fabric finishing plant (Allen et al. 1975; Billmaier et al. 1974). Neurological effects attributed to 2-hexanone include peripheral neuropathy characterized by axon and myelin disruption, axonal swellings involving motor and sensory nerves, alterations in nerve conduction velocity, ataxia, sensory deficits, and skeletal muscle weakness accompanied by electromyographic abnormalities. However, lack of reliable exposure data and co-exposure to other chemicals limit the usefulness of these findings other than for hazard identification. In laboratory animals, inhalation and oral exposure to 2-hexanone results in effects to the peripheral nervous system similar to those reported in humans (Abdo et al. 1982; Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Mendell et al. 1974; O'Donoghue and Krasavage 1979; O'Donoghue et al. 1978; Saida et al. 1976; Union Carbide 1977). Involvement of the central nervous system has also been reported in animals (Egan et al. 1980; O'Donoghue and Krasavage 1979). The 2-hexanone metabolite, 2,5-hexanedione, is the toxicologically active chemical responsible for the neurotoxic effects of 2-hexanone (Abdel-Rahman et al. 1978; DiVincenzo et al. 1976; Eben et al. 1979; Krasavage et al. 1980).

***Musculoskeletal Effects.*** Musculoskeletal effects of 2-hexanone appear to be secondary to neurological damage. Muscle weakness has been observed in workers exposed to 2-hexanone, with findings accompanied by electromyographic abnormalities (Allen et al. 1975; Billmaier et al. 1974). 2-Hexanone induced skeletal muscle pathology of neurogenic origin was found in rats following repeated inhalation (Krasavage and O'Donoghue 1977) or oral (O'Donoghue et al. 1978; Union Carbide 1977) exposures. Alterations generally consisted of atrophy and degenerative changes.

***Body Weight Effects.*** In workers exposed to 2-hexanone in a fabric finishing plant, body weight was reduced in some workers with moderate to severe neurological impairment (Allen et al. 1975; Billmaier et al. 1974). However, there was no information regarding the subjects' appetite and/or actual food consumption. These workers regained weight when exposure to 2-hexanone was discontinued. In animal studies, exposure to 2-hexanone also resulted in decreased weight gain in inhalation studies in rats and monkeys (Johnson et al. 1977; Katz et al. 1980; Peters et al. 1981) and in oral studies in rats (Krasavage et al. 1980; O'Donoghue et al. 1978; Union Carbide 1977). However, without data on food consumption in most of these studies, the usefulness of this information is limited.

***Reproductive Effects.*** The evaluation of potential reproductive toxicity of 2-hexanone yielded mixed results. Intermediate-duration inhalation exposure of male rats to 2-hexanone resulted in reduced testes

weight and atrophy of the testicular germinal epithelium of male rats (Katz et al. 1980). However, chronic inhalation exposure of male rats and female cats did not induce microscopic alterations in the reproductive organs of either species (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979). In oral studies, 2-hexanone induced testicular toxicity in male rats when given by gavage (Krasavage et al. 1980), but not when given in the drinking water (O'Donoghue et al. 1978) in comparable doses. Fertility was not assessed in any of these studies.

***Developmental Effects.*** Available data are inadequate to determine if 2-hexanone produces developmental effects, as only one developmental study was identified. In this study, inhalation exposure of rats to 2-hexanone during gestation resulted in reduced maternal weight during gestation, reduced birth weight, and reduced pups per litter, and induced behavioral alterations in the offspring tested at various times between weaning and the geriatric stage (Peters et al. 1981). The investigators concluded that the results suggest that exposure to 2-hexanone may be associated with hyperactivity in the young and subsequent decreased activity in older animals; however, definite conclusions could not be made.

***Cancer Effects.*** Available chronic-duration studies in animals evaluating comprehensive toxicological endpoints did not report any findings of cancer following inhalation or oral exposure (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979; O'Donoghue et al. 1978).

Neither the Department of Health and Human Services (HHS) nor the International Agency for Research on Cancer (IARC) have classified 2-hexanone regarding its carcinogenicity (IARC 2019; NTP 2016). The U.S. Environmental Protection Agency (EPA) stated that "there is inadequate information to assess the carcinogenic potential" of 2-hexanone (EPA 2009a).

## 1.3 MINIMAL RISK LEVELS (MRLs)

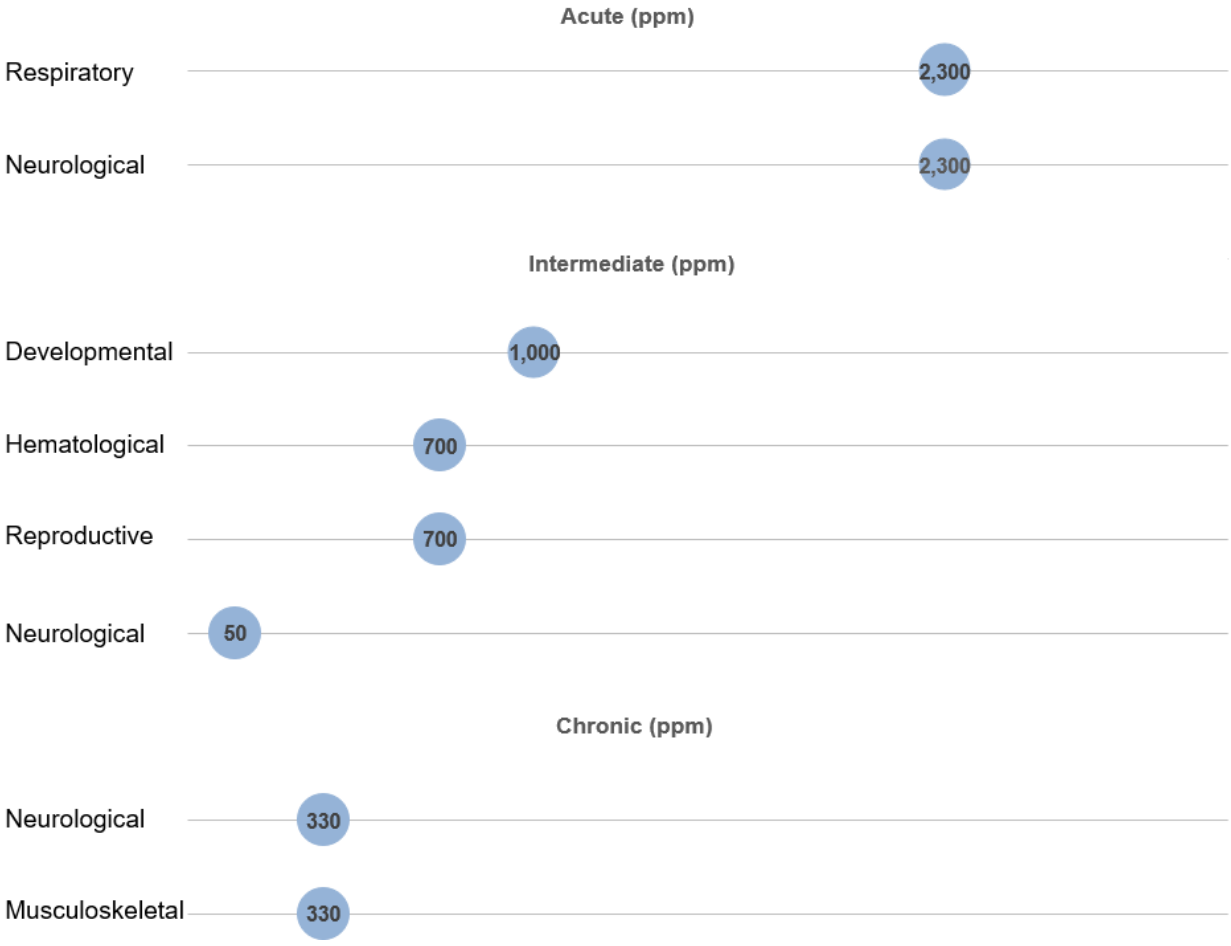
The inhalation database for 2-hexanone was not considered adequate for deriving inhalation MRLs. As presented in Figure 1-3, available inhalation data for 2-hexanone in laboratory animals indicate that the nervous system is the most sensitive toxicity target for all exposure durations.

For oral MRLs, adequate data were available for derivation of a chronic-duration MRL, but not for acute- or intermediate-duration MRLs. Similar to inhalation exposure, available oral exposure data identify the

neurological system as the most sensitive target (Figure 1-4). The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

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

**The neurological system is the most sensitive target of 2-hexanone inhalation exposure.**
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.



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

**The neurological system is the most sensitive target of 2-hexanone oral exposure.**
Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

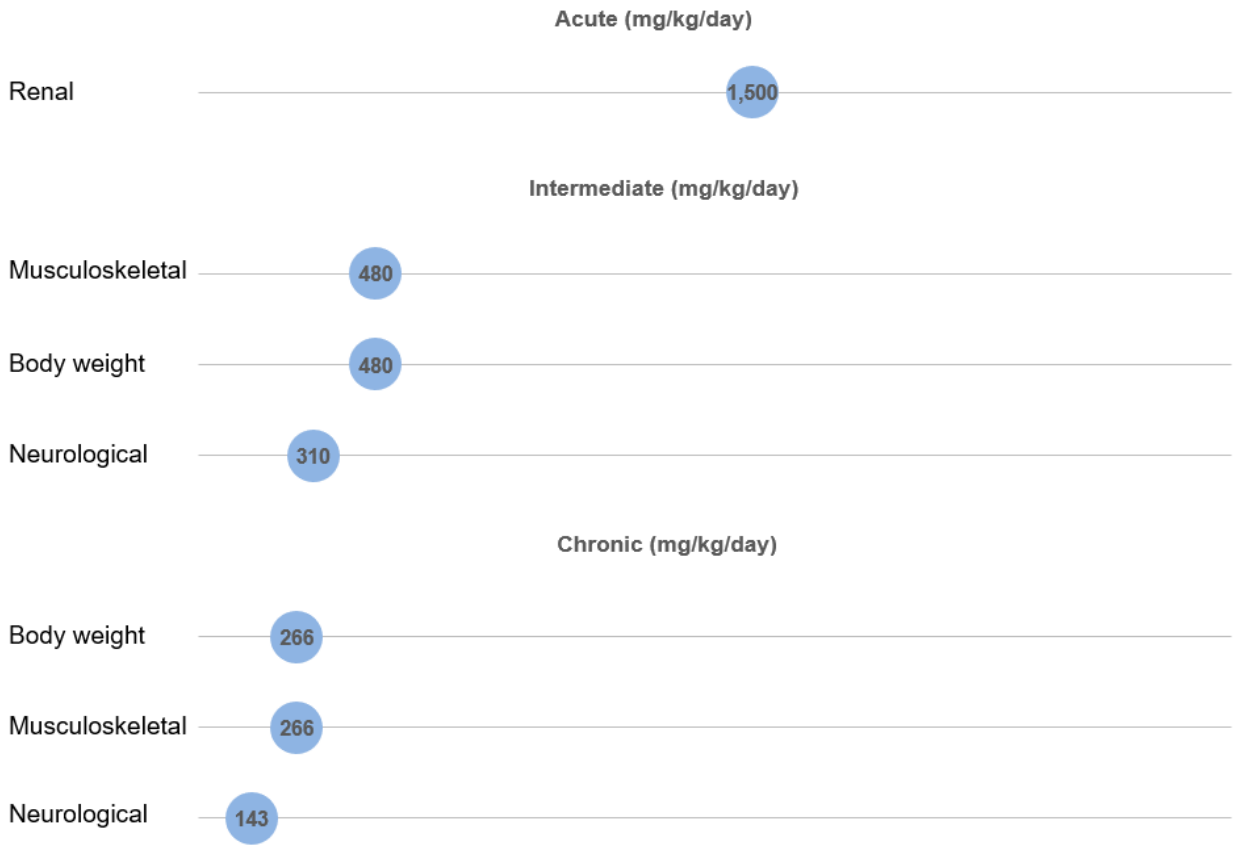


**Table 1-1. Minimal Risk Levels (MRLs) for 2-Hexanone[a]**

| Exposure duration | MRL | Critical effect | Point of departure | Uncertainty factor and modifying factor | Reference |
|---|---|---|---|---|---|
| **Inhalation exposure (ppm)** | | | | | |
| Acute | Insufficient data for MRL derivation | | | | |
| 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 | 0.05 | Axonal swelling in spinal cord and peripheral nerves | 143 (LOAEL) | UF 1,000 MF 3 | O'Donoghue et al. 1978 |

[a]See Appendix A for additional information.

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