CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

n-Hexane is a hydrocarbon that is refined from crude oil and is primarily used as a volatile, non-polar solvent in industry. *n*-Hexane is also used in special glues and adhesives and is present in gasoline. Pure *n*-hexane is widely used in laboratories as an extractant, while most commercial/industrial hexanes are a mixture of aliphatic hydrocarbons, including other hexane isomers. Major uses for solvents containing *n*-hexane include as cleaning agents in the printing, textile, furniture, and shoemaking industries, and for extracting vegetable oils from crops such as soybeans.

Because of the high volatility of *n*-hexane, the most likely route of human exposure is inhalation. Low-level exposures to *n*-hexane can possibly occur for much of the U.S. population, especially those who live in urban areas or those that commute in areas with heavy traffic, due to emissions of *n*-hexane associated with motor fuel use. As such, the general population will be exposed to very low levels at all times, while those living in urban centers may be exposed to slightly higher levels. Ambient air concentrations of *n*-hexane are in the parts per billion (ppb) range, with values between 0.05 and 4 ppb (EPA 2022a).

1.2 SUMMARY OF HEALTH EFFECTS

The health effects of *n*-hexane have been evaluated in observational occupational and population-based epidemiological studies, case reports/series, and experimental animal studies. Exposure to *n*-hexane occurs mainly through inhalation, although oral and dermal exposures may also occur. Most human studies have evaluated chronic-duration inhalation exposure, while animal studies have focused on acute- and intermediate-duration inhalation and oral exposures. Both human and animal studies were located for the majority of the endpoints evaluated in this profile. The available information suggests that adverse neurological, respiratory, developmental, and reproductive effects are the most important health concerns related to exposure to *n*-hexane (Figures 1-1 and 1-2). Muscle atrophy and decreased body weight are also common findings after exposure to *n*-hexane in experimental animals, but they are possibly secondary to the neurotoxicity that results in muscle denervation and decreased ability to move.

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

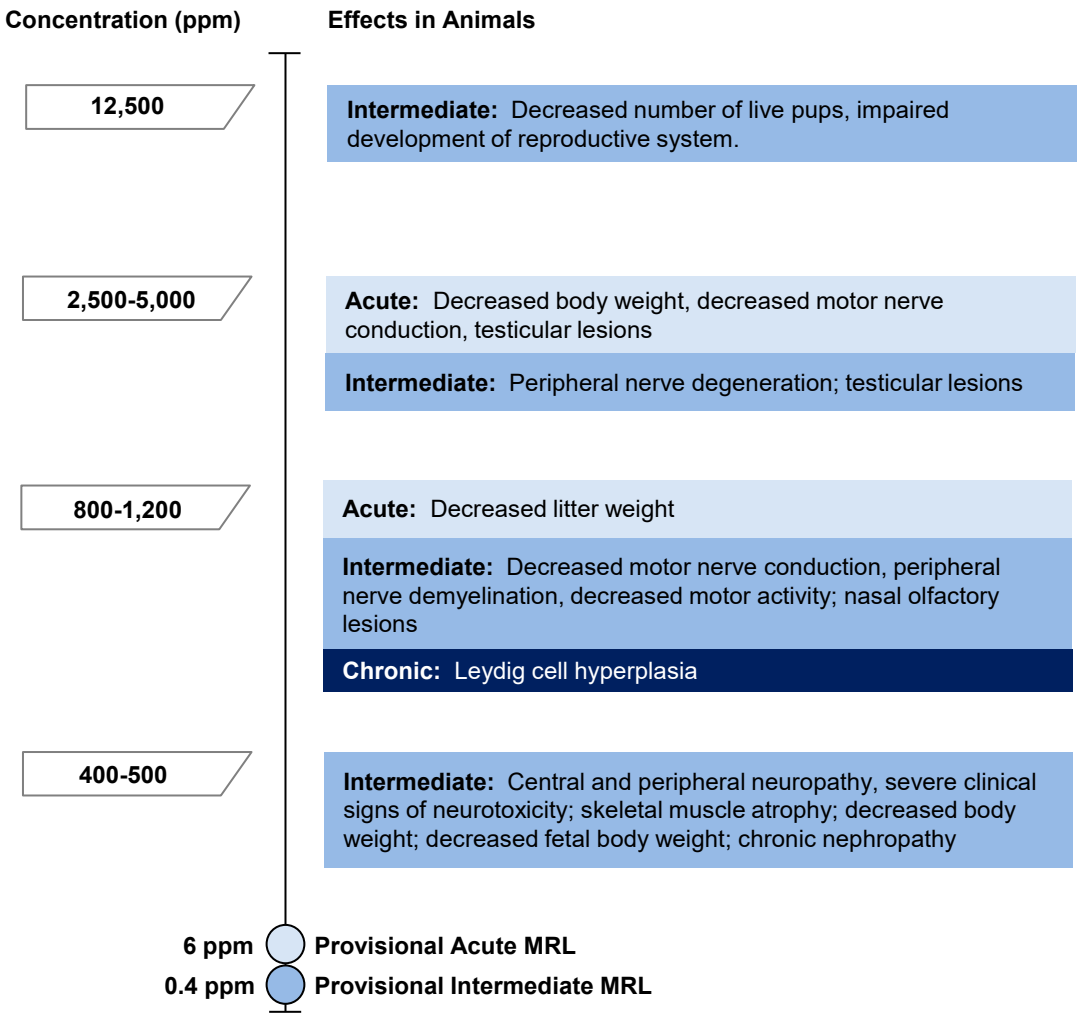
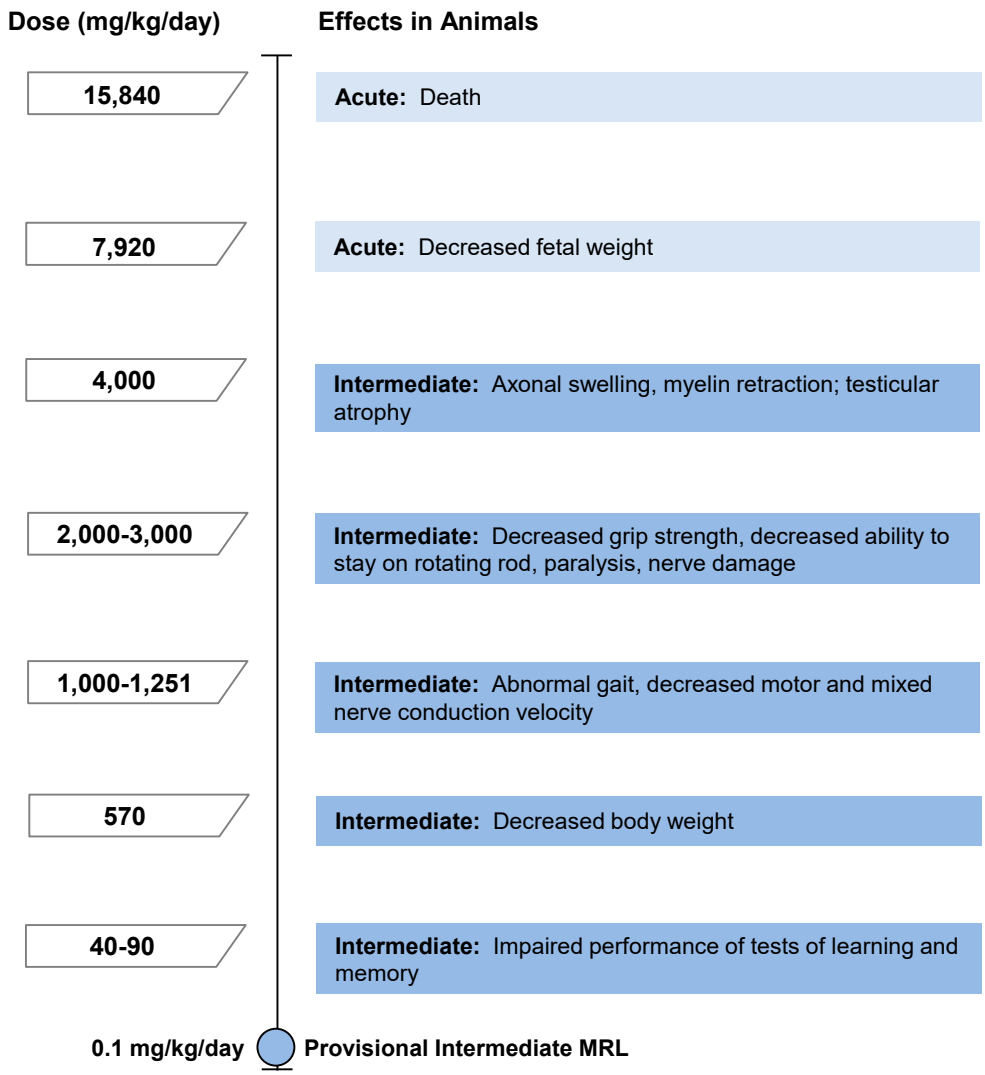


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to *n*-Hexane



Neurological Effects. The major public health concern regarding *n*-hexane exposure is the potential for the development of neurotoxicity. Occupational studies have documented that human exposure to *n*-hexane can result in peripheral neuropathy that in severe cases can lead to paralysis (Altenkirch et al. 1977; Wang et al. 1986; Yamamura 1969); observed clinical signs include paresthesia and leg weakness. The dose-duration relationship has not been well characterized in humans, but concentrations ≥500 ppm, and exposure for ≥2 months have been associated with human neurotoxicity. Clinical signs of peripheral neuropathy have been observed in rat studies via the inhalation and oral routes (Altenkirch et al. 1982; API 1981; De Martino et al. 1987; Huang et al. 1989; Krasavage et al. 1980; Schaumburg and Spencer 1976; Takeuchi et al. 1980). Clinical signs of neurotoxicity have not been observed in mice following intermediate-duration inhalation exposure.

Respiratory Effects. Very few studies have examined the potential respiratory effects of *n*-hexane in animals and humans. *n*-Hexane was not irritating to the eyes, nose, or throat in humans at concentrations up to 500 ppm for 3–5 minutes (Nelson et al. 1943). Higher incidences of self-reported respiratory symptoms have been observed in workers exposed to *n*-hexane (Mustajbegovic et al. 2000; Nijem et al. 2001), while reduced lung function has been reported in children residing near point sources (Wichmann et al. 2009). Respiratory effects including rales, gasping, and mouth breathing were reported in rabbits throughout a 24-week inhalation exposure to 3,000 ppm *n*-hexane (Lungarella et al. 1984). Histopathological examination revealed serious effects in the lung, including centrilobular emphysema and fibrosis. Respiratory effects were also seen in mice exposed via inhalation to up to 10,000 ppm *n*-hexane for 13 weeks (NTP 1991). Mild effects were seen in the olfactory epithelium at 1,000 ppm, and in both the olfactory and respiratory tracts at 10,000 ppm. In contrast to the findings in mice, no histopathological changes were observed in the nasal cavity of male and female rats exposed up to 10,000 ppm for 13 weeks (Cavender et al. 1984) or in male rats exposed to 500 ppm for 6 months (API 1981).

Developmental Effects. Associations have been reported between *n*-hexane exposure in humans and low birth weight (Gong et al. 2018) and alterations of the neonatal immune system (Lehmann et al. 2002). Rodent studies have reported decreased fetal/litter weights following inhalation (Bus et al. 1979; NIEHS 1987, 1988c; Stoltenburg-Didinger et al. 1990) or oral exposure (Marks et al. 1980) to *n*-hexane. Inhalation studies using concentrations ≥5,000 ppm have also observed more severe effects, including decreases in the number of live fetuses and increases in skeletal malformations (Li et al. 2014, 2015; NIEHS 1987, 1988c).

Body Weight Effects. Data on body weight effects in humans exposed to *n*-hexane are very limited. In an offset printing factory in Hong Kong, weight loss of >5 pounds was reported in 11 out of 20 employees who developed peripheral neuropathy after exposure to solvents containing *n*-hexane, and in 5 out of 26 asymptomatic workers who were considered to have subclinical peripheral neuropathy (Chang et al. 1993). Marked decreases in body weight gain were observed at doses associated with outward clinical signs of neurotoxicity (Huang et al. 1989; API 1981; Takeuchi et al. 1980). Less severe body weight effects were observed in animal species that are less susceptible to *n*-hexane-induced neurotoxicity, such as mice (NTP 1991). In contrast, in a cross-sectional study conducted in Portugal, exposure to indoor *n*-hexane was associated with obesity in children (Paciencia et al. 2019).

Reproductive Effects. Longer menstrual cycles, longer times to get pregnant, lower serum follicle-stimulating hormone (FSH) concentrations, and higher risks of spontaneous abortion and preeclampsia have been reported in human epidemiological studies evaluating exposure to *n*-hexane (Agnesi et al. 1997; Mendola et al. 2016; Nobles et al. 2019; Ruiz-García et al. 2020; Sallmen et al. 2008). Female reproductive effects have not been thoroughly examined in experimental animal studies, although several studies have reported effects in the male reproductive system. Decreased testis weights or altered testis and epididymis histopathology have been observed in rats following intermediate-duration inhalation exposure (De Martino et al. 1987; Howd et al. 1983; Nylen et al. 1989). Testicular atrophy was also noted in rats after intermediate-duration oral exposure (Krasavage et al. 1980).

Cancer Effects. There is currently little information on the carcinogenic potential of *n*-hexane. A single epidemiological study identified a potential correlation between *n*-hexane exposure and intracranial tumors, but this study was extremely limited due to the small number of cases and large number of co-exposures. Papillary tumors were reported in the bronchiolar epithelium of rabbits after a 24-week exposure to 3,000 ppm *n*-hexane, but the incidence was not reported (Lungarella et al. 1984). The U.S. Environmental Protection Agency (IRIS 2005) concluded that there is inadequate information to assess the carcinogenic potential of *n*-hexane, while the Department of Health and Human Services (HHS) and the International Agency for Research on Cancer (IARC) have not assessed the carcinogenicity of *n*-hexane.

1.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs. The inhalation database was considered adequate for derivation of acute- and intermediate-duration provisional MRLs for *n*-hexane. The chronic-duration data were insufficient for

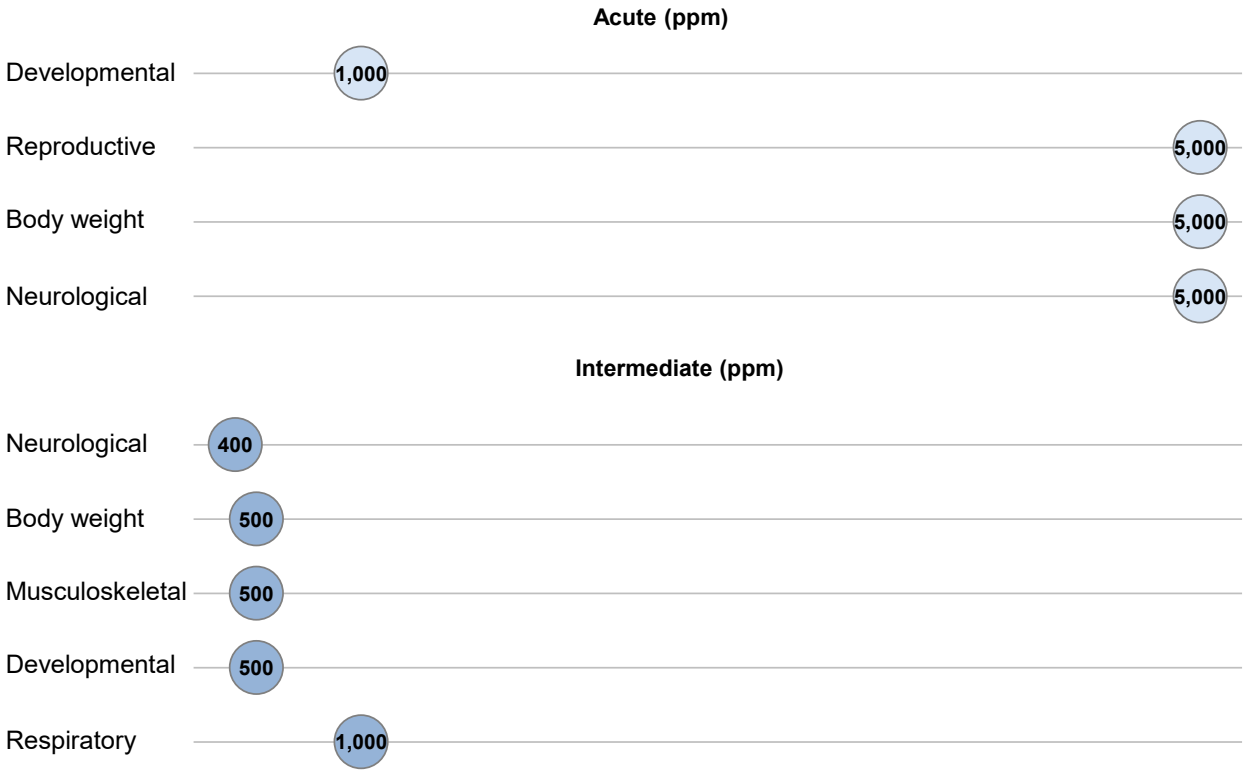
deriving a chronic-duration inhalation MRL. As illustrated in Figure 1-3, the most sensitive target of *n*-hexane toxicity following inhalation exposure is the neurological system. When air concentrations are expressed as human equivalent concentrations (HECs), the developmental and respiratory systems are the most sensitive targets. Body weight and musculoskeletal effects also have relatively low LOAEL values. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Oral MRLs. The oral database was considered adequate for derivation of a provisional intermediate-duration MRL for *n*-hexane. The acute- and chronic-duration data were insufficient for deriving provisional MRLs. As illustrated in Figure 1-4, the neurological system and body weight effects appear to be the most sensitive targets of *n*-hexane toxicity following oral exposure. 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 *n*-Hexane – Inhalation

The neurological and musculoskeletal systems* are the most sensitive targets of *n*-hexane inhalation exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.



*When exposure levels were expressed as human equivalent concentrations, the developmental and respiratory systems were the most sensitive targets.

Figure 1-4. Summary of Sensitive Targets of *n*-Hexane – Oral

Available data indicate that the nervous system and body weight changes are the most sensitive targets of *n*-hexane oral exposure.

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

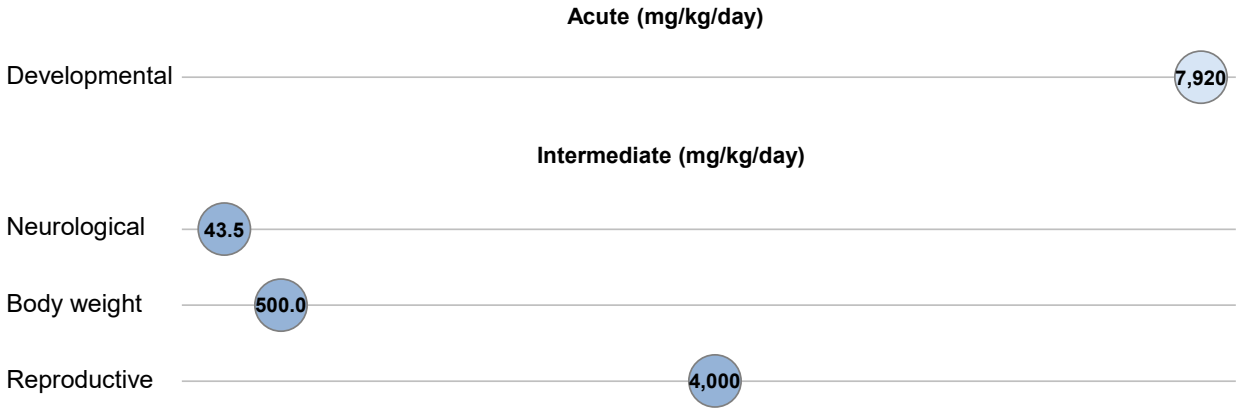


Table 1-1. Minimal Risk Levels (MRLs) for *n*-Hexane[a]

Exposure route	Exposure duration	Provisional MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	**Acute**	**6 ppm** (21 mg/m^3)	Decreased fetal body weight	$NOAEL_{HEC}$	167 ppm	UF: 30	NIEHS 1987
	Intermediate	**0.4 ppm** (1.4 mg/m^3)	Nasal cavity lesions	$LOAEL_{HEC}$	111 ppm	UF: 300	NTP 1991
	Chronic	None	–	–	–	–	–
Oral	**Acute**	None	–	–	–	–	–
	Intermediate	**0.1 mg/kg/day**	Impaired performance of a test of memory	LOAEL	43.5 mg/kg/day	UF: 300	Gao et al. 2019
	Chronic	None	–	–	–	–	–

[a]See Appendix A for additional information.

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; UF = uncertainty factor