2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO 2-HEXANONE IN THE UNITED STATES

2-Hexanone is a waste product of wood pulping, coal gasification, and in situ oil shale operations. 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. 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. Bioconcentration of this compound in aquatic organisms is not expected to occur.

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. 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; 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. In the past decade, there has been an increase in oil and natural gas production from shale in the United States; and 2-hexanone has been detected at low levels 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. However, the levels detected in foods are far below the levels that have caused harmful effects in animals. 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, \textit{in situ} oil shale processing, or coal gasification operations.

Children are exposed to 2-hexanone by the same routes that affect adults. Ingestion of foods contaminated with small amounts of 2-hexanone is the most likely route of exposure for children. No data were located regarding 2-hexanone in breast milk; therefore, an adequate determination of the importance of this route of child exposure has not been made.

See Chapter 6 for more detailed information regarding concentrations of 2-hexanone in environmental media.

2.2 SUMMARY OF HEALTH EFFECTS

Limited information is available regarding the effect of 2-hexanone in humans. An early study reported that men exposed to $\geq 2,300$ ppm vapors of a commercial-grade 2-hexanone for brief periods of time (25–60 seconds) found the contaminated air extremely disagreeable due to a strong odor and irritation of the eyes and nasal passages.

Information, from workers in an Ohio fabric finishing plant, indicates that exposure to 2-hexanone affects mainly the nervous system. The study involved the screening of 1,157 employees. The effects consist of a peripheral neuropathy characterized by axon and myelin disruption and axonal swellings involving motor and sensory nerves and resulting in alterations in nerve conduction velocity, ataxia, sensory deficits, and skeletal muscle weakness accompanied by electromyographic abnormalities. Air samples collected at locations in the plant showed that the workers could have been exposed to mean concentrations ranging from 9.2 to 36 ppm 2-hexanone. These exposure levels should be interpreted with caution since there was also exposure to other chemicals and there may have been significant oral and dermal exposure to solvents due to practices such as eating on/in work areas or washing the hands in solvent. Exposure to 2-hexanone was presumably responsible for adverse neurological effects in a furniture finisher and in three painters. No exposure data were available in these cases, plus the subjects had also been exposed to other chemicals.
Studies have shown that 2,5-hexanedione, a metabolite of 2-hexanone, is the toxicologically active chemical responsible for the neurotoxic effects of 2-hexanone. 2,5-Hexanedione is also a metabolite of n-hexane, a chemical with extensive industrial use, so considerably more information regarding effects of exposure to 2,5-hexanedione in humans can be found in documents regarding n-hexane.

Aside from the neurotoxic effects, there was little evidence of adverse effects in the affected workers at the Ohio plant. Results of clinical tests used to assess liver and kidney function, as well as results of hematological assessments, were within normal ranges. Body weight was reduced in some workers found to have moderate to severe neurological impairment. However, there was no information regarding the subject’s appetite and/or actual food consumption. The study stated that the workers regained weight when the use of 2-hexanone was discontinued.

Exposure of most animal species to 2-hexanone by any route of exposure results in neurotoxic effects similar to those reported in humans. Comparative studies also have shown the relative species sensitivity to 2-hexanone as chicken > cat > dog > primate > rat. Involvement of the central nervous system has also been reported in studies in animals; detailed studies regarding central nervous system involvement have been conducted in animals exposed directly to 2,5-hexanedione. The lowest lowest-observed-adverse-effect level (LOAEL) for neurotoxicity in an inhalation study with 2-hexanone was 50 ppm in rats and hens exposed intermittently for several months. It should be noted, however, that the purity of the 2-hexanone used in the rat study was not reported and, in the study in hens, the test material was 70% 2-hexanone and 30% methyl isobutyl ketone (MiBK). This is important because MiBK has been reported to induce total cytochrome P-450 in the liver, thus potentially increasing the formation of 2,5-hexanedione, the neurotoxic metabolite of 2-hexanone.

Limited systemic toxicity of 2-hexanone was reported in inhalation and oral studies in animals. It should be mentioned that many studies tested only one concentration/dose of 2-hexanone, so no information on dose-response was provided. In addition, very few studies stated the purity of the 2-hexanone tested, so there is uncertainty regarding whether the reported effects were caused by 2-hexanone or by the interactive action of 2-hexanone with other chemicals, possibly MiBK.

2-Hexanone induced skeletal muscle pathology of neurogenic origin in rats following repeated inhalation (≥330 ppm) or oral exposure (≥480 mg/kg/day). Alterations generally consisted of atrophy and degenerative changes. Exposure to 2-hexanone also resulted in decreased weight gain in inhalation
2-HEXANONE

2. RELEVANCE TO PUBLIC HEALTH

studies (≥700 ppm) in rats and monkeys and in oral studies in rats (≥266 mg/kg/day). However, without data on food consumption in most of these studies, the usefulness of this information is limited.

2-Hexanone did not induce histological alterations in lymphoreticular organs or tissues of rats or cats in long-term inhalation or oral studies. However, none of these studies examined parameters of immunocompetence, so no firm conclusions regarding immunotoxicity of 2-hexanone can be made.

The evaluation of potential reproductive toxicity of 2-hexanone yielded mixed results. Exposure to 700 ppm pure 2-hexanone for 11 weeks reduced testes weight and induced atrophy of the testicular germinal epithelium of male rats, whereas chronic exposure of male rats and female cats to ≤330 ppm 2-hexanone of unreported purity did not induce microscopic alterations in the reproductive organs of either species. In oral studies, 2-hexanone induced testicular toxicity in male rats when given by gavage but not when given in the drinking water to male rats in comparable doses. Fertility was not tested in any of these studies. It seems that a 2-generation reproductive study could provide useful data.

There are not enough data to determine whether 2-hexanone is a developmental toxicant. In the only developmental study available, exposure of rats to ≥1,000 ppm 2-hexanone (unknown purity) during gestation resulted in reduced maternal weight during gestation, reduced birth weight, reduced pups per litter, and behavioral alterations in the offspring tested at various times between weaning and the geriatric stage. The investigators concluded that the results suggested 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 drawn.

There are no studies of cancer from exposure to 2-hexanone in humans or in animals. The EPA has stated that “there is inadequate information to assess the carcinogenic potential” of 2-hexanone. Neither the Department of Health and Human Services (DHHS) nor the International Agency for Research on Cancer (IARC) have classified 2-hexanone regarding its carcinogenicity.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been established for 2-hexanone. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the
most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

An acute-duration inhalation MRL for 2-hexanone was not derived due to lack of appropriate studies in humans or in animals. The only information located regarding effects in humans is that men (unknown number) exposed to $\geq 2,300$ ppm vapors of a commercial-grade 2-hexanone for brief periods of time (25–60) seconds found the contaminated air extremely disagreeable due to a strong odor and irritation of the eyes and nasal passages (Schrenk et al. 1936). The same group of investigators reported that an unspecified number of guinea pigs exposed to 2,300 ppm 2-hexanone showed signs of eye and nose irritation after 1 minute of exposure and lacrimation after 10 minutes of exposure; no such signs were reported in guinea pigs exposed to 1,000 ppm 2-hexanone. Exposure to 6,500 ppm for 540 minutes caused lethality. This information is insufficient for MRL derivation.

An intermediate-duration inhalation MRL for 2-hexanone was not derived due to inadequacies of the human database and the fact that the lowest LOAELs in animal studies were classified as serious LOAELs, and ATSDR does not derive MRLs based on serious LOAELs (Chou et al. 1998). Pertinent human data are available from a study of workers at a coated fabric plant (Allen et al. 1975; Billmaier et al. 1974). Eighty-six cases of distal polyneuropathy were reported among 1,157 workers exposed to 2-hexanone and other chemicals. The time worked in the print department by persons with peripheral neuropathy ranged from 5 weeks to 27 years. The mean concentration of 2-hexanone in an area where operators spent 60–80% of their time was 9.2 ppm. However, this exposure level is not a reliable LOAEL for the following several reasons. In that same working area, the mean concentration of methyl ethyl
2. RELEVANCE TO PUBLIC HEALTH

Ketone (MEK) was 331 ppm, and MEK has been shown to potentiate the effects induced by 2,5-hexanedione, the toxic metabolite of 2-hexanone (Saida et al. 1976; Yu et al. 2002). In addition, workers reportedly exhibited poor work practices, such as eating in work areas, washing hands with solvent, and using solvent-soaked rags to clean equipment and machinery. It was also noted that no respirators were worn, and gloves were rarely used. All of these issues may have contributed to considerable oral and dermal exposure to 2-hexanone. Results of clinical tests used to assess liver and kidney function, as well as results of hematological assessments, were within normal ranges. Body weight was reduced in some workers found to have moderate to severe neurological impairment. Because of serious confounders, this study is not appropriate for MRL derivation.

There are several intermediate-duration studies in animals that identified the nervous system as the target for 2-hexanone. Species examined include rats, monkeys, cats, and hens. While hens have proved to be a good, sensitive model for 2-hexanone-induced neuropathy and studies in this species are useful for hazard identification, they are not useful for risk assessment. Because the digestive and respiratory systems are different from mammals, it is not known whether the dose-response in hens is applicable to humans.

Additional limitations of the animal database include the fact that several of the studies available tested only one exposure concentration, thus not allowing the construction of dose-response relationships, and not providing information regarding the purity of the 2-hexanone tested. As previously mentioned, knowing the purity of the 2-hexanone tested is important because commercial grades of 2-hexanone may vary in purity from 70 to 96% and up to 30% may be MiBK (Topping et al. 2001). MiBK has been shown to potentiate the neurotoxicity of ketogenic chemicals such as n-hexane by inducing microsomal cytochrome P-450 content in liver, resulting in increased production of the n-hexane and the 2-hexanone active metabolite, 2,5-hexanedione (Abou-Donia et al. 1985c, 1991; Lapadula et al. 1991).

While the limitations mentioned above do not totally preclude derivation of an intermediate-duration inhalation MRL for 2-hexanone, such an MRL would carry low confidence. However, the main reason for not deriving an intermediate-duration inhalation MRL for 2-hexanone is that the lowest exposure concentrations tested induced serious neurological effects in rats that were classified as serious LOAELs. For example, Duckett et al. (1979) reported the lowest LOAEL at 50 ppm (only exposure concentration tested) for widespread demyelination of the sciatic nerve in 32 out of 40 rats exposed intermittently to 2-hexanone for 6 months. In another study, exposure of rats almost continuously to 100 ppm pure 2-hexanone caused peripheral and central nervous system histopathology (Egan et al. 1980). The exposure regime did not induce clinical signs during the first 4 months of the study; however, alterations
in the peripheral and central nervous system became evident around this time. Changes consisted of axonal swelling and secondary demyelination in axons from peripheral nerves and axonal swelling in the medulla oblongata and cerebellum in the central nervous system. By 6 months, changes became more severe; nerve fiber damage by 6 months was described by the investigators as “strikingly advanced.” Therefore, the 100 ppm exposure level in the Egan et al. (1980) study represents a serious LOAEL. It is very likely that if exposure had continued, degeneration would have kept progressing and clinical signs would have been apparent.

In another intermediate-duration inhalation study, rats were exposed intermittently to 100 ppm (lowest levels tested) of a commercial-grade 2-hexanone for 29 weeks (Johnson et al. 1977). Measurements of sciatic-tibial nerve conduction velocity on week 28 showed a 45% decrease in conduction velocity compared to measurements performed on week 24 (from 45 to 22 m/second), making the 100 ppm exposure level a serious LOAEL. In the same study, exposure of monkeys to 100 ppm 2-hexanone for 41 weeks induced a significant decrease in sciatic-tibial nerve conduction velocity (about 12%) compared to controls, although data presented in a figure seemed to show that a significant reduction relative to controls already occurred after 4 months of exposure. Monkeys exposed to 330 ppm 2-hexanone showed a progressive decrease in motor conduction velocity relative to controls beginning at 3 months of exposure. In this group, after 6 months, mean conduction velocity was 63% of the mean measured in controls. No histological examinations of nervous system tissues were performed in this study. Other intermediate-duration inhalation studies in rats and cats showed severe neuropathy occurring at exposure levels ≥225 ppm 2-hexanone (Katz et al. 1980; Mendell et al. 1974b; Saida et al. 1976; Spencer et al. 1975). In conclusion, an intermediate-duration inhalation MRL for 2-hexanone was not derived because the lowest exposure levels tested, 50 ppm in Duckett et al. (1979) and 100 ppm in Egan et al. (1980) and Johnson et al. (1977), caused neurological effects in rats that were classified as serious LOAELs.

A chronic-duration inhalation MRL for 2-hexanone was not derived due to lack of adequate data. An occupational study reported that some workers exposed to 2-hexanone developed peripheral neuropathy (Allen et al. 1975; Billmaier et al. 1974). However, as summarized above, confounders such as exposures to other chemicals, as well as likely multi-route exposure, preclude using this study for MRL derivation.

Two chronic-duration inhalation studies have been conducted, one in rats exposed intermittently to 2-hexanone for 72 weeks (Krasavage and O'Donoghue 1977) and one in cats similarly exposed for 2 years (O'Donoghue and Krasavage 1979). In both studies, the animals were exposed to 0, 100, or 330 ppm 2-hexanone of unknown purity. In rats, exposure to 330 ppm 2-hexanone induced equivocal
2-HEXANONE

2. RELEVANCE TO PUBLIC HEALTH

signs of neuropathy as stated by the investigators based on manifestation of clinical signs and histopathological examinations of peripheral and central neural tissues. However, poor reporting of the results made it difficult to define a no-observed-adverse-effect level (NOAEL) and LOAEL. Specifically, in some cases, the control and low-exposure groups may have been combined, which made it difficult to ascertain whether effects were treatment-related. In cats, exposure to 330 ppm 2-hexanone induced axonal degeneration in the peripheral and central nervous system below the level of the cerebellum and pons; cats in the 100 ppm exposure group were not affected. Even if the 100 ppm exposure level were considered a NOAEL for neurological effects in rats and cats in these chronic-duration studies, a chronic-duration inhalation MRL could not be derived because severe neurological effects were reported in rats exposed to 100 ppm 2-hexanone in two intermediate-duration studies (Egan et al. 1980; Johnson et al. 1977) and in rats exposed to an even lower concentration of 50 ppm 2-hexanone in another intermediate-duration study (Duckett et al. 1979).

**Oral MRLs**

An acute-duration oral MRL was not derived for 2-hexanone because of an insufficient database. There are no human data and the database in animals consists of a report of an oral LD_{50} in rats (Smyth et al. 1954) and a study of the potentiation action of 2-hexanone on liver and kidney toxicity caused by chloroform (Brown and Hewitt 1984). In that study, a single high dose of 1,500 mg pure 2-hexanone/kg alone (only dose tested) did not induce morphological alterations in the liver, but produced epithelial degeneration in proximal tubules of the kidneys. This information is insufficient for MRL derivation.

An intermediate-duration oral MRL for 2-hexanone was not derived due to lack of relevant data in humans and the fact that the lowest dose tested in an animal study induced serious neurological effects in guinea pigs that were classified as serious LOAELs, and ATSDR does not derive MRLs based on serious LOAELs (Chou et al. 1998). There are several animal studies that identified the nervous system as the target for 2-hexanone. For example, Abdel-Rahman et al. (1978) reported an approximately 40% reduction in locomotor activity in guinea pigs dosed with approximately 310 mg 2-hexanone/kg/day in the drinking water for 24 weeks, pupillary responses to light stimuli were also significantly reduced at this dose level. No information was provided regarding results obtained with a lower dose of approximately 124 mg/kg/day. Union Carbide (1977) reported peripheral neuropathy in rats dosed with ≥480 mg 2-hexanone/kg/day in the drinking water for 120 days. Eben et al. (1979) reported hindlimb weakness in rats dosed by gavage with 400 mg 2-hexanone/kg/day (only dose tested) for 40 weeks; no histological examinations were conducted in this study. Krasavage et al. (1980) reported clinical signs and
2-HEXANONE

2. RELEVANCE TO PUBLIC HEALTH

microscopic evidence of neuropathy in rats dosed by gavage with 660 mg 2-hexanone/kg/day (only dose tested) for 90 days. In both Eben et al. (1979) and Krasavage et al. (1980), the true LOAEL was probably lower than the doses tested. Because the lowest dose tested for which there is information on induced effects (310 mg/kg/day) is considered a serious LOAEL, an intermediate-duration oral MRL was not derived for 2-hexanone.

- A provisional MRL of 0.05 mg/kg/day has been derived for chronic-duration oral exposure (365 days or longer) to 2-hexanone.

The MRL is based on adverse neurological effects in male Sprague-Dawley rats exposed to 2-hexanone in the drinking water for 13 months (O’Donoghue et al. 1978). No human studies were located and the only relevant information in animals is that from the study by O’Donoghue et al. (1978). In that study, male Sprague-Dawley rats exposed to ≥143 mg 2-hexanone/kg/day (96.1% pure) in the drinking water developed peripheral neuropathy; the first clinical signs appearing in rats dosed with 560 mg 2-hexanone/kg/day, the highest dose tested. At termination, histological examination of neural tissues showed that rats from all treated groups (143, 266, and 560 mg/kg/day) had “giant” axonal neuropathy. Neurogenic skeletal muscle atrophy in proximal and distal hindlimb musculature was also evident. Relevant incidence data are shown in Table 2-1. A more detailed summary of O’Donoghue et al. (1978) study is presented in Appendix A.

Inspection of Table 2-1 shows that the most sensitive neural tissues for developing axonal swellings were the spinal cord and peripheral nerve. Of these two data sets, the incidence of axonal swelling in peripheral nerve is preferred for MRL derivation because 10 rats were included for analysis in the three treated groups and in the control group, as opposed to the data set for the lesion in the spinal cord. It should be noted that atrophy of the muscle fibers is a phenomenon secondary to damage to the innervating axons, reflecting “Wallerian-type” degeneration.

Benchmark dose (BMD) modelling of the incidence data for axonal swelling in peripheral nerve of rats in the O’Donoghue et al. (1978) study was considered, but was rejected because a nearly maximum response level (80%) was reached with the lowest dose tested. In such cases, there is great uncertainty because the BMD may be just below the first dose or orders of magnitude lower (EPA 2012a). Therefore, the NOAEL/LOAEL approach was used for MRL derivation. Applying a combined uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for animal to human extrapolation, and 10 for human variability) and a modifying factor of 3 (to account for an 80% response rate at the lowest dose) to the LOAEL of 143 mg/kg/day results in a chronic-duration oral provisional MRL of 0.05 mg/kg/day for 2-hexanone.
### Table 2-1. Incidence Data for Neuropathological Lesions in Rats Exposed to 2-Hexanone for 13 Months

<table>
<thead>
<tr>
<th>Dose (mg/kg/day)</th>
<th>Brain</th>
<th>Spinal cord</th>
<th>Dorsal root ganglia</th>
<th>Peripheral nerve</th>
<th>Quadriceps muscle</th>
<th>Calf muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0/10</td>
<td>0/5</td>
<td>0/5</td>
<td>0/10</td>
<td>0/10</td>
<td>0/10</td>
</tr>
<tr>
<td>143</td>
<td>2/10</td>
<td>7/10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0/7</td>
<td>8/10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1/10</td>
<td>2/10</td>
</tr>
<tr>
<td>266</td>
<td>4/10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5/5&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>10/10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10/10&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>p<0.05 per Fisher Exact Test conducted by SRC, Inc.

Source: O’Donoghue et al. 1978