CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 2-hexanone is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of 2-hexanone.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 INFORMATION ON HEALTH EFFECTS

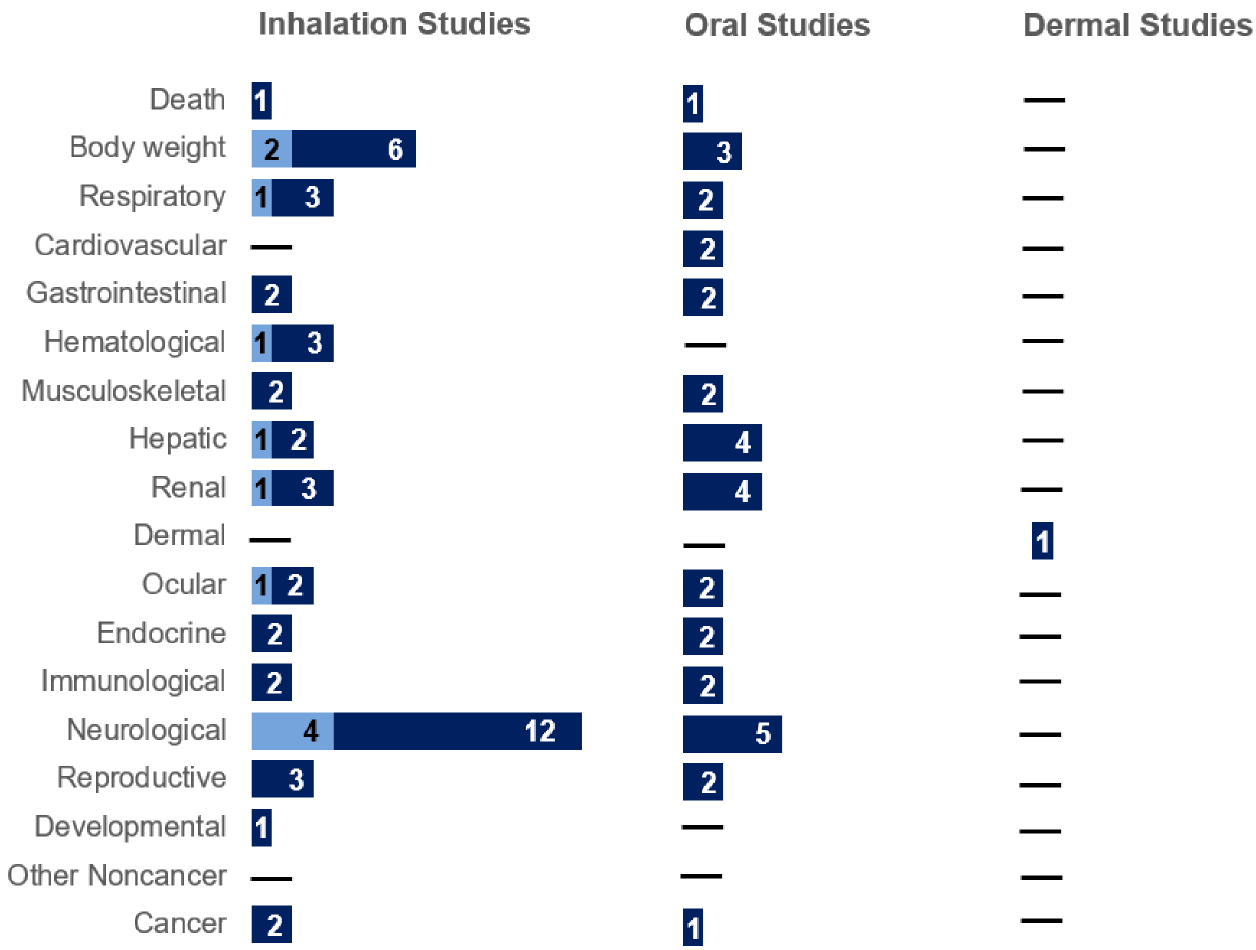
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to 2-hexanone that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of 2-hexanone. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 6-1. Summary of Existing Health Effects Studies on 2-Hexanone By Route and Endpoint*

Potential neurological and body weight effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the numbers of studies include those finding no effect. Studies may have evaluated multiple endpoints.

Acute-Duration MRLs. The only acute-duration data available on humans is that exposure to concentrations ≥2,300 ppm 2-hexanone in the air caused irritation of the eyes and nasal passages in men (Schrenk et al. 1936). Acute inhalation exposure to ≥2,300 ppm caused nose and eye irritation in guinea pigs (Schrenk et al. 1936). Acute lethality data are available for guinea pigs via inhalation exposure (Schrenk et al. 1936) and for rats via the oral route (Smyth et al. 1954). Neither an acute-duration inhalation nor oral MRL could be derived due to lack of adequate studies. Acute-duration studies would be useful for determining minimal doses and exposure durations that can induce neurological effects of short-term exposure.

Intermediate-Duration MRLs. The currently available data on humans exposed to 2-hexanone for intermediate durations is based on a study of workers exposed to 2-hexanone for ≥5 weeks (Allen et al. 1975; Billmaier et al. 1974). Peripheral neuropathy and weight loss were the major observations. Several limitations including exposure to other chemicals and possibly significant oral and dermal exposure precluded using this study for derivation of an intermediate-duration inhalation MRL. Repeated-dose studies in rats, cats, monkeys, and guinea pigs indicate that the nervous system is the primary target of 2-hexanone exposure via inhalation (Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Mendell et al. 1974; Saida et al. 1976; Spencer et al. 1975) or orally (Abdel-Rahman et al. 1978; Eben et al. 1979; Krasavage et al. 1980; Union Carbide 1977). Most intermediate-duration studies tested only one exposure concentration or dose level and many did not provide information regarding the purity of the test material. Because the lowest exposure levels tested were serious LOAELs for neurological effects, no intermediate-duration MRLs were derived. Intermediate-duration inhalation and oral studies that examine multiple endpoints, including neurotoxicity, would be valuable for establishing dose-response relationships and deriving MRLs.

Chronic-Duration MRLs. Some of the workers exposed to 2-hexanone who developed peripheral neuropathy studied by Allen et al. (1975) had been exposed to the chemical for chronic durations. No additional chronic-duration studies in humans were located. As mentioned above, however, confounders in the Allen et al. (1975) study precluded its use for MRL derivation. There are two chronic-duration inhalation studies in animals (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979). Both studies examined multiple endpoints and the lowest exposure concentration tested, 100 ppm, was a NOAEL for neurological effects. Because the exposure level of 100 ppm was a serious LOAEL for neurological effects in intermediate-duration studies, a chronic-duration inhalation MRL for 2-hexanone could not be derived based on the studies by Krasavage and O'Donoghue (1977) and O'Donoghue and Krasavage (1979). There is one chronic-duration oral study available in rats exposed to pure 2-hexanone

that examined multiple endpoints (O'Donoghue et al. 1978); this study was used to derive a chronic-duration oral MRL for 2-hexanone. Additional chronic-duration studies providing data to derive a chronic-duration inhalation MRL would be valuable.

Health Effects.

Neurotoxicity. The nervous system has been clearly established as the major target for 2-hexanone in humans exposed via inhalation (Allen et al. 1975; Billmaier et al. 1974) and in animals exposed via any route of exposure (Abdel-Rahman et al. 1978; Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Krasavage et al. 1980; Krasavage and O'Donoghue 1977; O'Donoghue et al. 1978; O'Donoghue and Krasavage 1979; Saida et al. 1976; Spencer et al. 1975; Union Carbide 1977). However, most of the available information is derived from studies using 2-hexanone of low or unknown purity or using it at a single dosage level, so its usefulness is limited. Animal data that would clearly establish dose-response relationships for neurological effects, including histopathological damage as well as clinical manifestations, as a result of exposure to pure 2-hexanone via all routes of exposure and using a range of exposure durations would be useful. This information would be valuable in assessing the potential risks of neurotoxicity in persons exposed to 2-hexanone in the vicinity of hazardous waste sites. In addition, continued research aimed at determining the mode of action of 2,5-hexanedione, the active neurotoxic metabolite at the molecular level, would be valuable.

Reproductive Toxicity. There is no information on the effects of 2-hexanone on reproductive parameters in exposed humans via any route of exposure. Limited studies in animals have not produced conclusive results. Reduced testes weight and induced atrophy of the testicular germinal epithelium of male rats were reported in an intermediate-duration inhalation study (Katz et al. 1980); however, chronic exposure of male rats and female cats to ≤330 ppm 2-hexanone of unreported purity did not induce gross or 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 to male rats (O'Donoghue et al. 1978) in comparable doses. Exposure to 2,5-hexanedione can result in testicular damage (increased spermatid heads) in rats (Bryant et al. 2008). None of the available 2-hexanone studies assessed fertility. A 2-generation reproductive toxicity study could provide useful data.

Developmental Toxicity. There is no information on the effects of exposure to 2-hexanone via any route on human development. There are no animal studies using the oral or dermal routes. The currently available data for animals is based on a single inhalation study in pregnant rats in which relatively high 2-hexanone exposure resulted in decreased litter size and pup weight and in behavioral effects in the offspring tested later in life (Peters et al. 1981). Additional studies would be useful to confirm or refute the findings of Peters et al. (1981).

Immunotoxicity. There are currently no data on the effects of 2-hexanone on the human immune system via any route of exposure. 2-Hexanone did not induce morphological alterations in lymphoreticular organs or tissues of rats or cats in long-term inhalation or oral studies (Krasavage and O'Donoghue 1977; O'Donoghue and Krasavage 1979; O'Donoghue et al. 1978; Union Carbide 1977). However, none of these studies examined parameters of immunocompetence. A screening (Tier I) study using a battery of tests (immunopathology, humoral- and cell-mediated immunity, nonspecific immunity) (Luster et al. 1988) would provide valuable results.

Epidemiological and Human Dosimetry Studies. The only epidemiological information that is currently available is the study of workers in a plant producing plastic-coated and color-printed fabrics (Allen et al. 1975; Billmaier et al. 1974). Some workers developed peripheral neuropathy whose origin was traced to exposure to 2-hexanone, although exposure to other chemicals also occurred. Because 2-hexanone is no longer manufactured or used commercially in the United States, 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. Identification and evaluation of populations having long-term exposure to 2-hexanone due to, for example, contamination of drinking water, for neurological, reproductive, developmental, and cancer effects would be useful.

Biomarkers of Exposure and Effect.

Exposure. Measurement of 2-hexanone and its metabolites in blood or urine may not provide an adequate indication of exposure to this substance, since these metabolites may also result from exposure to *n*-hexane (Fedtke and Bolt 1986; Nomeir and Abou-Donia 1985; White et al. 1979). Further work in the characterization of the neurofilament protein adduct produced by the active metabolite, 2,5-hexanedione, would be useful.

Effect. The major target organ of 2-hexanone in humans is the nervous system (Allen et al. 1975), and morphological effects may occur before clinical manifestations of toxicity (Egan et al. 1980). Development of noninvasive imaging procedures that can identify morphological alterations in peripheral nerves and in central tracts would be useful.

Absorption, Distribution, Metabolism, and Excretion. Although some information is available on each of these topics from studies conducted in several species, more information in each of these areas would be useful. In addition, because most of these studies were conducted by the same group of researchers, further studies in other laboratories in each of these areas would be useful in confirming the available data.

Available data indicate that 2-hexanone is readily absorbed by humans and various animal species after inhalation, oral, or dermal administration (DiVincenzo et al. 1977, 1978). Estimates are available regarding the rates of absorption via the inhalation and oral routes in humans (DiVincenzo et al. 1978), but information is lacking regarding rates of dermal absorption. Also lacking is information regarding possible mechanism(s) by which 2-hexanone is absorbed through the lungs, gastrointestinal tract, and skin.

Limited information on distribution of 2-hexanone is available. An inhalation study in rats reported distribution of 2-hexanone and metabolites to the lungs and liver but did not examine any other organ or tissue (Duguay and Plaa 1995). It also appeared that some accumulation occurred in the lungs at exposure concentrations ≥150 ppm. Further studies, particularly longer-term studies that examine potential distribution to additional tissues, especially the nervous system would be valuable. An environmentally relevant route of exposure (i.e., oral, dermal) is preferred over parenteral dosing.

The proposed metabolic pathway for 2-hexanone is based on blood metabolites identified during intraperitoneal studies in guinea pigs (DiVincenzo et al. 1976) and oral studies in rats (DiVincenzo et al. 1977). The metabolite, 2,5-hexanedione, has also been found in human serum after inhalation exposure (DiVincenzo et al. 1978). Because studies in rats exposed to 2-hexanone have indicated a strong relationship between the concentration of 2,5-hexanedione in the urine and the onset of neuropathic signs (Eben et al. 1979), it would be useful to also have this information for humans. In addition, information on specific enzymes involved in phase I metabolic reactions and details on phase II conjugation reactions would provide important information to advance the understanding of 2-hexanone metabolism in humans.

Limited excretion data are available in humans receiving 2-hexanone via inhalation, oral, and dermal exposure, in dogs via inhalation exposure, and in rats via oral exposure (DiVincenzo et al. 1977, 1978). However, human data on excretion of 2-hexanone via feces are not available, and the available information in dogs concerns excretion via exhaled breath only. In these and any other studies, information on all routes of excretion would help to evaluate the potential for 2-hexanone clearance in the exposed species. Excretion data in rats receiving 2-hexanone via inhalation and dermal application and in other species receiving 2-hexanone via all three routes would be useful for comparison with the human data and to assess the comparative risks of exposure by each route. In addition, information on excretion rates in each species via each route would be helpful in understanding how long 2-hexanone and its metabolites may persist in the body.

Comparative Toxicokinetics. The toxicokinetic studies available in both humans and animals (dogs, rats, and guinea pigs) suggest that there may not be any major differences in the kinetics of this compound across certain species. Metabolites of 2-hexanone in the expired breath (carbon dioxide) of humans and rats exposed via the oral route and the presence of 2,5-hexanedione in the serum of humans exposed via inhalation, as well as in the blood and urine of orally exposed rats and the intraperitoneally exposed guinea pigs, suggest that there is a similar metabolic pathway in humans and experimental animals (DiVincenzo et al. 1976, 1977, 1978). Confirmation of this assumption would be useful. Similar toxic effects, neuropathy and weight loss, have been noted in several species (humans, monkeys, rats, cats, hens, and guinea pigs) (Abdel-Rahman et al. 1978; Allen et al. 1975; Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Krasavage et al. 1980; O'Donoghue et al. 1978; Saida et al. 1976; Spencer et al. 1975). Therefore, it would also be useful to investigate patterns of distribution, to identify target organs, and to measure rates of excretion in several species and to identify blood metabolites in humans in order to investigate interspecies similarities and differences. Studies in this area would be valuable for predicting toxic effects in humans and for studying the mechanisms of action of this chemical.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There are no studies of children exposed to 2-hexanone or animal studies that compare the susceptibility of animals of various ages to 2-hexanone. Any research in this area could provide valuable information.

Physical and Chemical Properties. The physical and chemical property data available for 2-hexanone are sufficient to allow a limited estimation of the potential environmental fate of this chemical. The estimated Henry's law constant (EPA 2012a) and K_{oc} (Thomas 1990) need to be verified experimentally to help confirm the estimates of partitioning in environmental media.

Production, Import/Export, Use, Release, and Disposal. No information is available in the TRI database on facilities that manufacture or process 2-hexanone because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005).

2-Hexanone is no longer produced, imported, or used commercially in the United States (EPA 1987). Any future manufacture or use is required to be reported to EPA (EPA 1987). No data on disposal of 2-hexanone were located. Information on disposal practices for wastes containing 2-hexanone is necessary for estimations of human exposure from this source. No regulations govern the disposal of 2-hexanone.

Environmental Fate. The probable transport and partitioning of 2-hexanone in environmental media have been predicted based on estimated partition coefficients. Experimental confirmation of these values would help to increase the accuracy of transport and partitioning assessments. The loss mechanisms of 2-hexanone transformations in the atmosphere are fairly-well understood (Atkinson et al. 1985; Calvert and Pitts 1966; Laity et al. 1973; MacLeod et al. 1984), but the reaction pathways and environmental fates of the transformation products are not known. Very little is known about the fate of 2-hexanone in water or soil (Babeu and Vaishnav 1987; Lande et al. 1976; Lowery et al. 1968; Lukins and Foster 1963; Perry 1968). Data on photodegradation and biodegradation of 2-hexanone in surface water and biodegradation of 2-hexanone in groundwater and soil may be helpful in assessing the persistence of 2-hexanone in these media.

Bioavailability from Environmental Media. Information on absorption by humans and other animal species indicates that it is well absorbed via the oral and dermal routes (DiVincenzo et al. 1977, 1978). 2-Hexanone has also been demonstrated to be well absorbed by humans and animals following inhalation exposure (DiVincenzo et al. 1978). Information on its bioavailability from contaminated soils would be useful in assessing the risk from exposure to this medium by populations in the vicinity of hazardous waste sites likely contaminated with 2-hexanone.

Food Chain Bioaccumulation. There are no data on the bioaccumulation of 2-hexanone in food chains. This lack of data may not be a major limitation in the database because it is unlikely that 2-hexanone is bioconcentrated by plants, aquatic organisms, or animals at lower trophic levels based on its high water solubility (Lande et al. 1976). However, data confirming that bioconcentration does not occur would help to more accurately assess the probability of bioaccumulation of 2-hexanone.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of 2-hexanone in contaminated media at hazardous waste sites are needed so that the information obtained on levels of 2-hexanone in the environment can be used in combination with the known body burden of 2-hexanone to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Very few data are available regarding the presence of 2-hexanone in any environmental media (CLPSD 1989; Lucas 1984; Myers 1983). Although high levels of this compound are not expected to occur in ambient air, water, or soil, concentrations of 2-hexanone in these media near effluent sources or hazardous waste sites would be helpful in assessing the potential extent and magnitude of human exposures.

Exposure Levels in Humans. No specific biomarkers for 2-hexaonone exposure have been identified. It would be useful to collect information on levels of exposure to 2-hexanone in the environment and associated blood, urine, or tissue levels of 2-hexanone and/or its metabolites in the exposed populations. Additional information relating those levels to the subsequent development of health effects would also be extremely useful.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. No information has been located on exposure levels of children to 2-hexanone in the vicinity of hazardous waste sites. It would be useful to collect information on levels of exposure to 2-hexanone in the environment and associated blood, urine, or tissue levels of 2-hexanone and/or its metabolites in the exposed populations. Additional information relating those levels to the subsequent development of health effects would also be extremely useful.

6.3 ONGOING STUDIES

Relevant ongoing research regarding 2-hexanone identified in the National Institutes of Health (NIH) RePORTER (2019) database is presented in Table 6-1.

Table 6-1. Ongoing Studies on 2-Hexanone

Investigator	Affiliation	Research description	Sponsor
Boekelheide, K	Brown University	Study to develop sperm molecular biomarkers to improve detection and monitoring of toxicant-induced testicular injury	NIEHS

NIEHS = National Institute of Environmental Health Sciences

Source: RePORTER (2019)