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 isophorone 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 isophorone.

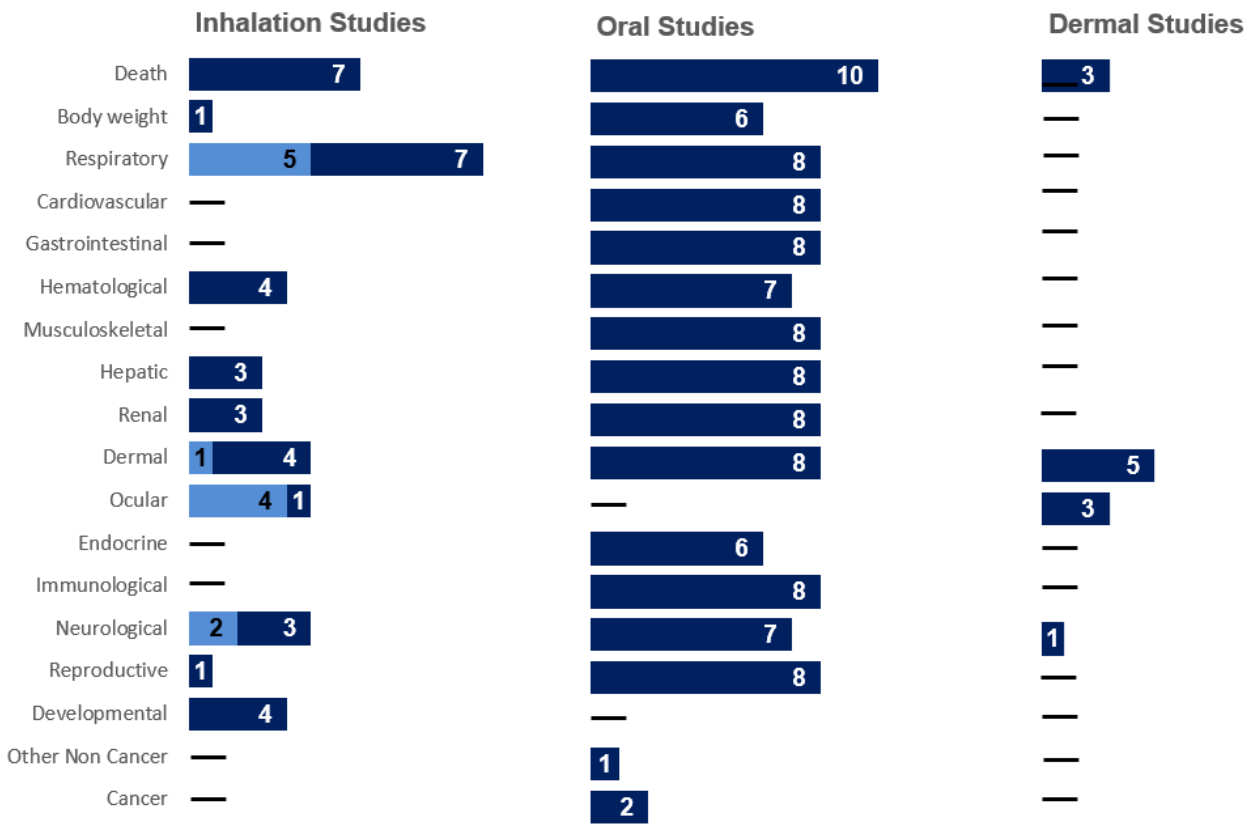
Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will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

As illustrated in Figure 6-1, most studies evaluated toxicity of oral exposure to isophorone. The most commonly examined endpoints were respiratory, dermal, hematological, and neurological effects. Two oral exposure studies evaluated a wide range of potential endpoints of intermediate- and chronic-duration exposure to isophorone in several animal species (AME Inc. 1972a, 1972b; NTP 1986). In addition, eight studies examined the acute lethality of isophorone following inhalation, oral, or dermal exposure.

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



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.

Acute-Duration MRLs. The acute-duration inhalation database was not considered suitable for derivation of MRLs for isophorone. Acute inhalation studies in human subjects identify NOAEL and LOAEL values for irritation of the nose and eyes; however, study exposures were very short (≤15 minutes). Studies in animals also identified respiratory tract irritation as the most sensitive effect of exposure to isophorone in air; however, none of the available studies evaluated comprehensive toxicological endpoints. Acute oral exposure studies were designed to assess lethality and did not conduct evaluations of a wide range of potential targets of toxicity. Acute-duration inhalation and oral studies are needed to fully define the effects of acute exposure, identify sensitive targets of toxicity, and establish dose-response relationships.

Intermediate-Duration MRLs. The database for intermediate-duration oral exposure to isophorone was considered adequate for derivation of an MRL. The intermediate-duration inhalation database was not sufficient to derive an MRL because available studies evaluated only single exposure levels and did not assess comprehensive endpoints. Intermediate-duration inhalation studies are needed to fully define the effects of acute exposure, identify sensitive targets of toxicity, and establish dose-response relationships.

Chronic-Duration MRLs. The database for chronic-duration oral exposure to isophorone was considered adequate for derivation of an MRL. Similar to the intermediate-duration inhalation database, chronic inhalation studies were not sufficient to derive an MRL because available studies evaluated only single exposure levels and did not assess comprehensive endpoints. Chronic-duration inhalation studies are needed to fully define the effects of acute exposure, identify sensitive targets of toxicity, and establish dose-response relationships.

Health Effects.

Reproductive. Reproductive effects of isophorone in animal studies have not been well-studied. One inhalation study reported no effect on pregnancy rate following intermediate-duration inhalation exposure. Other studies conducting gross and histopathological evaluations of reproductive tissues have not identified effects of exposure to isophorone. However, no rigorous assessments of reproductive function have been conducted. Such data would be important to more fully explore potential reproductive effects of isophorone.

Developmental. Developmental effects of inhaled expose to isophorone in animals have been evaluated in a few studies (Bio/dynamics 1984a, 1972b; Dutertre-Catella 1976); however, studies examining comprehensive developmental endpoints were not available. Additional studies investigating developmental effect are needed to fully evaluate the potential for isophorone to adversely affect the developing organism.

Immunological. Studies conducting histopathological assessments of immune system tissues have not identified adverse effects of exposure to isophorone. However, none of these studies conducted specific tests of immune function. Such tests of immune function are needed to evaluate potential effects of isophorone. Isophorone is a skin irritant in rabbits, guinea pigs, and humans, but tests for sensitization were not identified in publicly available literature. Such tests might provide information on whether an allergic response to isophorone is likely.

Neurological. Isophorone has been shown to produce signs of neurotoxicity (lethargy, depression) in acute- and intermediate-duration exposure studies. However, only one study evaluated the effects of isophorone on neurobehavioral outcomes. Additional information, including dose-response information, is needed to provide a full evaluation of the neurological effects of isophorone.

Epidemiology and Human Dosimetry Studies. A limited number of epidemiological studies examining respiratory, dermal, and neurological endpoints were identified for isophorone. Additional studies could be helpful in evaluating the chronic human health risk from isophorone exposure, including the potential for isophorone to induce cancer.

Biomarkers of Exposure and Effect. No biomarkers of exposure to isophorone were located. Studies evaluating whether levels of isophorone or one of its metabolites in biological fluids are reflective of exposure levels would be useful.

Absorption, Distribution, Metabolism, and Excretion. Studies evaluating the toxicokinetics of isophorone provide information to general descriptions of the absorption, distribution, metabolism, and excretion of isophorone. However, studies to determine quantitative estimates for these parameters have not been determined. Additional studies providing quantitative estimates of toxicokinetic parameters would provide important information for isophorone.

Comparative Toxicokinetics. Available information on toxicokinetics of isophorone is from studies conducted in rats and rabbits. However, as discussed above, comparisons between these species are only qualitative. Therefore, additional studies providing quantitative information on toxicokinetics is needed to provide comparisons between species. In addition, because toxicity studies on isophorone also have been in mice, toxicokinetic studies in mice may provide essential information regarding differences in toxicological responses between species. In addition, studies of the pattern of isophorone degradation products in human urine would be helpful in evaluating whether isophorone is metabolized in humans as it is in rats.

Children's Susceptibility. No studies have evaluated the toxicity of isophorone in children or young animals. Studies in young animals and/or children would be useful to address potential concerns of that children may be more susceptible to the toxicity of isophorone than adults.

Physical and Chemical Properties. Many physical and chemical properties are available for isophorone, but most do not have extensive experimental descriptions accompanying the data; therefore, an evaluation of the accuracy of the data is difficult. Specifically, measured vapor pressure, K_{oc}, and Henry's Law constant at environmentally significant temperatures would help to remove doubt regarding the accuracy of the estimated data. The data on physical properties form the basis of much of the input requirements for environmental models that predict the behavior of a chemical under specific conditions, including hazardous waste landfills. The data on the chemical properties, on the other hand, can be useful in predicting certain environmental fates of this chemical.

Production, Import/Export, Use, Release, and Disposal. Data on current uses and disposal practices would be valuable in determining whether industrial activities pose an important source of human exposure to isophorone.

Environmental Fate. Sensitized photolysis studies in water and oxidation/reduction studies in both air and water are lacking, as are biodegradation studies in surface water and groundwater. These kinds of studies are important, since they represent the fundamental removal mechanisms available to isophorone in the environment. In addition, the kinetic studies for the atmospheric reactions are important for understanding the significance of a removal mechanism and predicting the reactions that may control the fate of a chemical in the environment.

Bioavailability from Environmental Media. No studies were located regarding the bioavailability of isophorone from environmental media. Furthermore, no reports were located indicating that isophorone or its metabolites have been detected in human tissues or fluids. Since the monitoring literature reports that isophorone is present in the environment as well as in environmental organisms, the lack of data does not necessarily indicate a lack of bioavailability. Fish may be the only source of isophorone in the environment that is not subject to large spatial and temporal variations in concentration, as appears to be the case with drinking water. In particular, fish in the Lake Michigan area are known to contain isophorone (Camanzo et al. 1987), and analysis of the body fluids of people who consume the fish may allow a determination of the existence of exposure and an estimation of the degree of exposure.

Food Chain Bioaccumulation. No studies were located regarding the food chain bioaccumulation of isophorone from environmental media. The monitoring literature reports that isophorone is present in the environment as well as in environmental organisms. The monitoring data further suggest that isophorone levels in fish do not correlate well with the lipid content of the fish. Thus, structure-activity relationships developed to estimate levels in biological media based on the partitioning properties of a chemical may not provide accurate information for isophorone. Furthermore, only one bioaccumulation study was available. In this study, which indicated a low potential for bioaccumulation, fish were exposed to isophorone in water rather than in food. From these data, it appears that food chain bioaccumulation may be occurring, and a clearer understanding of the potential for this would aid in determining how levels in the environment affect the food chain and potentially impact on human exposure levels.

Exposure Levels in Environmental Media. Environmental monitoring data are not available for soil and air, and the data available for water, sediments, and biota are not sufficient to determine ambient

concentrations. These data would be helpful in determining the ambient concentrations of isophorone so that exposure estimates of the general population and the bioconcentration factor of this chemical in aquatic organisms can be made.

Exposure Levels in Humans. After the establishment of biomarkers of exposure, a program involving analyses of human tissues would be useful in assessing the magnitude of environmental exposures. Monitoring of human tissues from different locations and seasons and using different category of the population would be helpful so that the effects of such variables as occupational, geographical, and seasonal can be assessed.

Exposures of Children. No studies are available to assess whether children are at a higher exposure risk than adults to isophorone. Studies examining potential exposure sources for children would be useful.

6.3 Ongoing Studies

No ongoing studies were identified for isophorone.