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-butanone 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-butanone.

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.

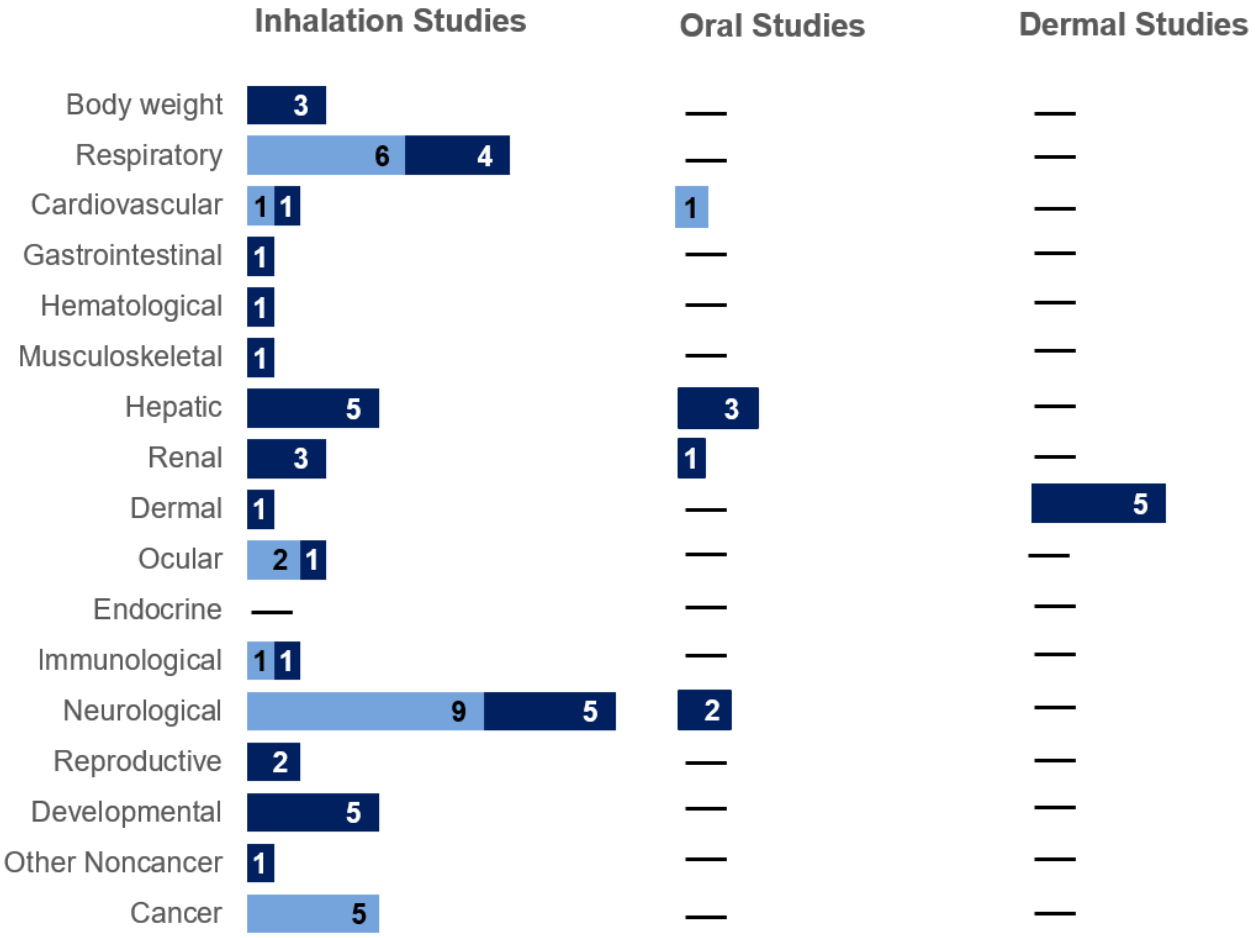
6.1 INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to 2-butanone 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-butanone. 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 of the data on the toxicity of 2-butanone come from inhalation studies in humans and laboratory animals. The most commonly examined endpoints were respiratory and neurological effects. Developmental effects and liver toxicity were also studied in animals only. A small number of oral studies in animals evaluated hepatic, renal, and neurological effects. No reports of systemic toxicity are available for dermal exposure.

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

Potential respiratory, hepatic, and neurological effects were the most studied endpoints
The majority of the studies examined inhalation exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2. The number of studies include those finding no effect; many studies examined more than one 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. A number of studies have evaluated the acute-duration toxicity of inhaled 2-butanone in humans, primates, rats, mice, and guinea pigs. The data were considered adequate for derivation of an acute-duration inhalation MRL. The acute oral toxicity of 2-butanone was evaluated in rats; most of these studies involved a single gavage exposure. An acute-duration oral MRL was not derived because the oral database was considered inadequate to identify target organs or establish dose-response relationships.

Intermediate-Duration MRLs. A comprehensive 90-day inhalation study in rats showed that 2-butanone did not have adverse effects in the respiratory, cardiovascular, gastrointestinal, musculoskeletal, hematological, hepatic, renal, or dermal/ocular systems (Cavender and Casey 1981; Cavender et al. 1983). The most serious effect was slightly increased liver weight at the highest concentration tested, 5,000 ppm. Occupational exposures to concentrations this high are unlikely since humans find 350 ppm 2-butanone intolerable (Nelson et al. 1943). No signs of neurotoxicity, either clinical or histological, were observed in several studies of intermediate exposures to high concentrations of 2-butanone up to 6,000 ppm (Altenkirch et al. 1978, 1979; Cavender and Casey 1981; Cavender et al. 1983). Therefore, most organs and tissues in humans probably would not be adversely affected by intermediate 2-butanone exposures either occupationally or near toxic waste sites. An intermediate-duration inhalation MRL was not derived because neurological symptoms (i.e., headache, fatigue, feeling of intoxication) and nose and throat irritation occurred in humans at acute inhalation exposure levels lower than the NOAEL values for intermediate-duration inhalation exposure in animals. No intermediate oral or dermal studies investigated the systemic toxicity of 2-butanone by these routes, and the available pharmacokinetic data are not sufficient to predict whether target organs would be similar by the various routes of exposure. 2-Butanone has been detected in air, water, food, and soil (see Section 5.5); therefore, exposures by the inhalation, oral, and dermal routes are possible. From a public health perspective, exposure to solvent mixtures is more likely than exposure to a single pure chemical. Therefore, intermediate exposure studies of 2-butanone mixed with other solvents (hexacarbons and haloalkanes),

the toxicity of which is potentiated by 2-butanone, would provide valuable information on neurotoxicity and systemic toxicity. This information is important since these chemicals are often found together in solvents used occupationally, and they might be stored together at hazardous waste sites where surrounding populations could be exposed for intermediate durations.

Chronic-Duration MRLs. No studies were located regarding the health effects of chronic exposure to 2-butanone by any route in humans or animals. Pharmacokinetic data are insufficient to predict the possible target organs of chronic exposure by any route. Since 2-butanone has been detected in air, water, food, and soil (see Section 5.5), exposures by the inhalation, oral, and dermal routes are possible. 2-Butanone is often found in formulations with other chemicals, such as chloroform, carbon tetrachloride, n-hexane, and methyl-n-butyl ketone, the toxicities of which 2-butanone potentiates. These chemicals may be stored together at hazardous waste sites. Chronic inhalation, oral, and dermal studies in which animals are administered these chemicals in combination with 2-butanone may provide dose-response information for the potentiation of the neurotoxicity and hepatotoxicity of these chemicals by 2-butanone. This information is important because there are populations surrounding hazardous waste sites that might be exposed to these chemicals for similar durations.

Although no cancer bioassays were available, preliminary epidemiological studies suggest that occupational exposure to 2-butanone does not increase the development of neoplasms. Furthermore, genotoxic effects including gene mutation, chromosome aberration, micronucleus frequency, DNA damage, cell transformation, and unscheduled DNA synthesis were primarily negative (see Section 2.20). Three studies reported evidence for 2-butanone induction of chromosome effects in yeast, but the findings were inconsistent with other studies evaluating similar endpoints. On the basis of this information, 2-butanone does not appear to be carcinogenic.

Health Effects.

Reproductive Toxicity. No studies were located regarding effects on reproductive capacity or reproductive organs and tissues in humans following exposure to 2-butanone. The authors of a health hazard evaluation report for NIOSH concluded that a perceived increase in the number of spontaneous abortions among female workers believed to result from exposure to 2-butanone and several other volatile chemicals at a shoe factory was not related to exposure (NIOSH 1982). No histopathological lesions were found in male or female reproductive organs of rats exposed to 5,000 ppm 2-butanone for 90 days (Cavender and Casey 1981; Cavender et al. 1983), but reproductive function was not assessed. Further studies of the reproductive function of

2-butanone by all durations and routes would provide valuable information, particularly if the studies include histological examination of the organs and tissues of the reproductive system. If reproductive organs were identified as targets of 2-butanone toxicity, single or multigeneration reproductive studies probably would be warranted. Since 2-butanone potentiates the neurotoxicity or hepatotoxicity of certain chemicals, it would be valuable to investigate the reproductive effects of mixed solvent exposures that include 2-butanone. This investigation would be useful because 2-butanone is often found in mixtures with other solvents in occupational settings, and these mixtures may be found together at or near hazardous waste sites.

Developmental Toxicity. Information regarding developmental toxicity of 2-butanone in humans was not located. 2-Butanone was slightly fetotoxic in rats (Deacon et al. 1981; Saillenfait et al. 2006; Schwetz et al. 1974) and mice (NTP 1989; Schwetz et al. 1991) following inhalation exposure of pregnant rats and mice to 3,000 or 4,000 ppm. The fetotoxicity was related to delayed development. Furthermore, five of eight pregnant rats exposed continuously to 800 ppm throughout gestation failed to deliver litters and brain development was delayed in offspring of rats that delivered pups (Stoltenburg-Didinger 1991; Stoltenburg-Didinger 1990). In addition, developmental effects were more pronounced in pups born to rat dams exposed to a mixture of n-hexane and 2-butanone than in pups born to dams exposed to n-hexane alone (Stoltenburg-Didinger et al. 1990). This study, however, was very poorly reported, with very little information provided on exposure to 2-butanone alone. No developmental or distribution studies have been conducted by the oral route, but there is no reason to believe that 2-butanone or its metabolites could not cross the placenta after administration by the oral route. Therefore, it is likely that orally administered 2-butanone would be fetotoxic in these species. Determination of the doses needed to produce the fetotoxicity by the oral route would provide valuable information. Since 2-butanone potentiates the neurotoxicity or hepatotoxicity of certain chemicals, it would be valuable to further investigate the developmental effects of mixed solvent exposures that include 2-butanone. Such a study would be useful because 2-butanone is often found in mixtures with other solvents in occupational settings, and these mixtures may be found at or near hazardous waste sites.

Immunotoxicity. There are limited data on the potential immunotoxicity of 2-butanone. A case report of an individual reported 2-butanone-induced contact urticaria (Varigos and Nurse 1986). Studies in rats reported no histological alterations of immune and lymphoreticular tissues following intermediate-duration inhalation exposure (Cavender and Casey 1981; Cavender et al.

1983). Because these studies did not evaluate immune function, they are not considered adequate for evaluating potential immunotoxicity of 2-butanone. Studies evaluating potential impairment of immune function (thymus, lymph nodes, peripheral blood lymphocytes, etc.) would provide valuable information regarding the immunotoxicity of 2-butanone.

Neurotoxicity. 2-Butanone was not neurotoxic at a concentration of 200 ppm in several acute inhalation exposure studies in male volunteers (Dick et al. 1984, 1988, 1989, 1992). However, symptoms of neurotoxicity (headache, fatigue, feeling of intoxication) were reported by subjects exposed to 100 ppm (Tomicic et al. 2011). Neurobehavioral effects have been observed in mice (1,602 ppm) (De Ceaurriz et al. 1983) and baboons (100 ppm) (Geller et al. 1979) exposed acutely by inhalation. Guinea pigs displayed narcosis and incoordination after acute inhalation exposure to high concentrations (Patty et al. 1935). Clinical signs of neurotoxicity were also observed in rats treated acutely by gavage with a high dose of 2-butanone (Stillmeadow Inc. 1978). Most of the available information on the neurotoxicity of 2-butanone is derived from studies conducted over 30 years ago when neurobehavioral screening tests were not as sensitive as currently available tests. Additional studies using sensitive measures could provide information on potential subtle neuropathological alterations. 2-Butanone is not generally regarded as being highly neurotoxic when administered alone. In acute and intermediate exposure studies, 2-butanone markedly potentiated the neurotoxicity of n-hexane and methyl-n-butyl ketone both in humans and animals. A comprehensive study of acute, intermediate, and chronic exposures to mixtures of 2-butanone, n-hexane, and methyl-n-butyl ketone by inhalation, oral, and dermal routes would provide valuable information regarding the neurotoxicity of these compounds. Such a study would be particularly valuable because 2-butanone is often found occupationally in mixtures containing n-hexane and methyl-n-butyl ketone, and these chemicals would probably be found together at hazardous waste sites.

Epidemiology and Human Dosimetry Studies. Studies with male and female volunteers determined that inhalation exposure to 100 ppm produced neurological symptoms (i.e., headache, fatigue, feeling of intoxication) (Tomicic et al. 2011) and was irritating to the eyes, nose, and throat (Nelson et al. 1943; Tomicic et al. 2011). Other studies reported the absence of neurological and irritation effects in volunteers at concentrations up to 200 ppm (Muttray et al. 2002; Seeber et al. 2002; van Thriel et al. 2002); however, these studies were conducted in male subjects only. Female subjects were reported to be more sensitive than males to neurological symptoms and the respiratory and eye irritation effects of 2-butanone (Tomicic et al. 2011). In four separate studies, volunteers exposed to 200 ppm had no

neurobehavioral effects (Dick et al. 1984, 1988, 1989, 1992). Several epidemiological studies of occupational workers exposed to 2-butanone showed inconclusive results regarding increased risk of cancer (Alderson and Rattan 1980; Blair et al. 1998; Radican et al. 2008; Wen et al. 1985). Two case-control studies evaluating the relationship between 2-butanone exposure and childhood leukemia were also inconclusive (Gao et al. 2014; Infante-Rivard et al. 2005). No epidemiological studies regarding other health effects of 2-butanone exposure were located. Therefore, valuable epidemiological information could be obtained from further studies of cancer and other health effects, particularly neurotoxicity and reproductive and developmental toxicity.

Biomarkers of Exposure and Effect. The only known biomarkers of 2-butanone exposure are blood, breath, and urinary concentrations of 2-butanone and its metabolites (Brown et al. 1986; Brugnone et al. 1983; Ghittori et al. 1987; Miyasaka et al. 1982). 2-Butanone is rapidly cleared from the body, and existing studies show that accumulation of 2-butanone in tissues does not occur to a significant extent. Furthermore, 2-butanone alone is relatively free of adverse health effects. Therefore, development of biomarkers of exposure to a battery of solvents often used occupationally in combination with 2-butanone would be more valuable than development of biomarkers for 2-butanone alone.

2-Butanone exposure has no specific effects that can be used as biomarkers for exposure by any route or for any duration of exposure.

Absorption, Distribution, Metabolism, and Excretion. 2-Butanone is absorbed by inhalation (Liira et al. 1988a, 1988b, 1990a, 1991) and oral exposure (Brown and Hewitt 1984; Dietz and Traiger 1979; Dietz et al. 1981; Hewitt et al. 1983; Sakata et al. 1989). Net retention of inhaled 2-butanone is approximately 50% in humans (Liira et al. 1988a, 1988b). Studies of absorption after dermal exposure would provide valuable information on this occupationally significant route of entry. Available data regarding the relative rates or extent of absorption, metabolism, distribution, and excretion by the three routes of exposure are not sufficient to draw meaningful conclusions. 2-Butanone is equally soluble in all tissues and organs measured (Perbellini et al. 1984). Therefore, 2-butanone is probably evenly distributed throughout the body. The primary route of excretion appears to be the lungs. The metabolic pathways for 2-butanone have been thoroughly studied in rats (Dietz and Traiger 1979; Dietz et al. 1981) and guinea pigs (DiVincenzo et al. 1976). Similar metabolites have been identified in humans (Liira et al. 1988a, 1988b; Miyasaka et al. 1982). In rats, 30% of an oral dose of 2-butanone was converted to 2,3-butanediol (Dietz et al. 1981). Potentiation of the neurotoxicity of ethanol, n-hexane, and methyl-n-butyl ketone and the hepatotoxicity of haloalkanes by 2-butanone may involve interactions in the biotransformation of

these compounds (Brady et al. 1989; Cunningham et al. 1989; Raunio et al. 1990; Robertson et al. 1989; Traiger et al. 1989). Further studies regarding the interaction of hexacarbons, haloalkanes, and 2-butanone at the metabolic level may provide valuable information.

Comparative Toxicokinetics. Available human data show that 2-butanone is metabolized primarily to 2,3-butanediol and 3-hydroxy-2-butanone, but the extent of metabolism appears to be small (Liira et al. 1988a, 1988b). In an occupational exposure study of 2-butanone, only 3-hydroxy-2-butanone was observed (Brugnone et al. 1983). In rats and guinea pigs, a third metabolite, 2-butanol, was observed (Dietz et al. 1981; DiVincenzo et al. 1976). About 30% of an oral dose of 2-butanone in rats later appeared in plasma as 2,3-butanediol (Dietz et al. 1981). 2-Butanol is also a product of 2-butanone metabolism in humans (Liira et al. 1990a). 2-Butanone potentiates the neurotoxicity of n-hexane and methyl-n-butyl ketone and the hepatotoxicity of haloalkanes. The 2-butanone metabolite, 2,3-butanediol, may be more efficacious for potentiating the hepatotoxicity of the haloalkanes than 2-butanone. Therefore, valuable information would be gained by toxicokinetic studies of 2-butanone and its metabolites as they pertain to the toxicity of the hexacarbons and haloalkanes.

Children's Susceptibility. The human blood:air partition coefficient was 2–4% higher in male and female pediatric subjects compared with adults and a similar age-related pattern was observed in rats with a 4–6% higher blood:air coefficient observed in PND 10 males compared with adult and aged male rats (Mahle et al. 2007). These data suggest that pulmonary uptake following inhalation may be slightly higher in children compared to adults. Although several animal studies have evaluated the potential developmental toxicity of 2-butanone, no studies were identified that evaluated potential age-related differences. Additional studies in young animals would be useful to address potential concerns that children may be more susceptible to the toxicity of 2-butanone than adults.

Physical and Chemical Properties. The physical and chemical properties of 2-butanone are well documented. The environmental fate of 2-butanone can be predicted from these properties and compared to experimental results once they are obtained in areas where deficiencies exist.

Production, Import/Export, Use, Release, and Disposal. The significant amounts of 2-butanone produced in the United States, combined with its prevalence in commercial and household products, suggest that large numbers of citizens are potentially exposed to anthropogenic sources of this compound. The production, use, and international trading of 2-butanone is well described in the available literature (Kavaler 1987; Neier and Strehlke 1985; Papa and Sherman 1981; USITC 1987, 1988, 1989). Methods

for the disposal of 2-butanone are established (OHM/TADS 1989), but the amounts processed by each method cannot be ascertained. Therefore, disposal of 2-butanone cannot be compared to the regulations controlling this practice. Knowing the amount of 2-butanone released to the environment and its disposal pattern will aid in determining routes and levels of exposure to the general population by indicating which media should be monitored carefully.

Environmental Fate. There is sufficient predictive information to indicate that 2-butanone is not likely to partition from water (Hansch et al. 1995; Lyman et al. 1982; Roy and Griffin 1985); yet, there are few field studies to verify these predictions. Similarly, 2-butanone's transport, transformation, and degradation in the environment can be predicted (Atkinson 1985; Babeu and Vaishnav 1987; Cox et al. 1980; Delfino and Miles 1985), but has not yet been experimentally substantiated in all areas. Experimental studies in this area would allow the determination of 2-butanone's lifetime in the environment and aid in determining levels and routes of human exposure.

Bioavailability from Environmental Media. Numerous toxicokinetic and toxicity studies in humans and animals have demonstrated the bioavailability of 2-butanone from air, ingestion of food and water, and dermal contact. Absorption of 2-butanone after inhalation is well-established, and it appears to be adsorbed after ingestion. These mechanisms are consistent with what one would expect, based on 2-butanone's physical and chemical properties (Lyman et al. 1982). Given the potential for exposure to 2-butanone because of its prevalence in commercial products available to the public, further research on the bioavailability of this compound will allow the quantification of human exposure and risk.

Food Chain Bioaccumulation. 2-Butanone is not believed to appreciably bioconcentrate in fish and aquatic organisms (Hansch et al. 1995; Lyman et al. 1982). It is also not expected to biomagnify in the food chain. Quantitative data supporting these conclusions are not available in the literature. Additional information on bioconcentration and biomagnification would be useful in confirming the predicted behavior of this compound.

Exposure Levels in Environmental Media. Data are available regarding the level of 2-butanone in environmental media (Grosjean and Wright 1983; EPA 1988) and foods (Dumont and Adda 1978; Grey and Shrimpton 1967; Kinlin et al. 1972; Lovegren et al. 1979; Takeoka et al. 1988); however, the data available are often qualitative and only generalized trends regarding the occurrence of this compound can be derived. Quantitative determination of the levels of 2-butanone in environmental media and foods will allow the estimation of human intake levels of this compound from each media. Studies evaluating

potential exposure via vapor intrusion or volatilization during showering/bathing would provide valuable information regarding potential human exposure pathways.

Exposure Levels in Humans. 2-Butanone has been found in the human blood samples of urban dwellers, but the observed levels have not been correlated with personal activities. Studies on the level of 2-butanone in human tissues near hazardous waste sites are not complete. A study is needed to evaluate the levels of 2-butanone in humans with their personal activities or the areas where they live will allow an assessment of potential exposure to the general population. Similarly, correlations of occupational exposure by profession will aid in the determination of human exposure levels.

Exposures of Children. No studies are available to assess whether children are at a higher exposure risk than adults to 2-butanone. Studies examining potential exposure sources for children would be useful.

6.3 ONGOING STUDIES

No ongoing studies of 2-butanone were identified by the National Institutes of Health (NIH) (RePORTER 2020).