

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 acetone 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 acetone.

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 acetone 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 acetone. 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

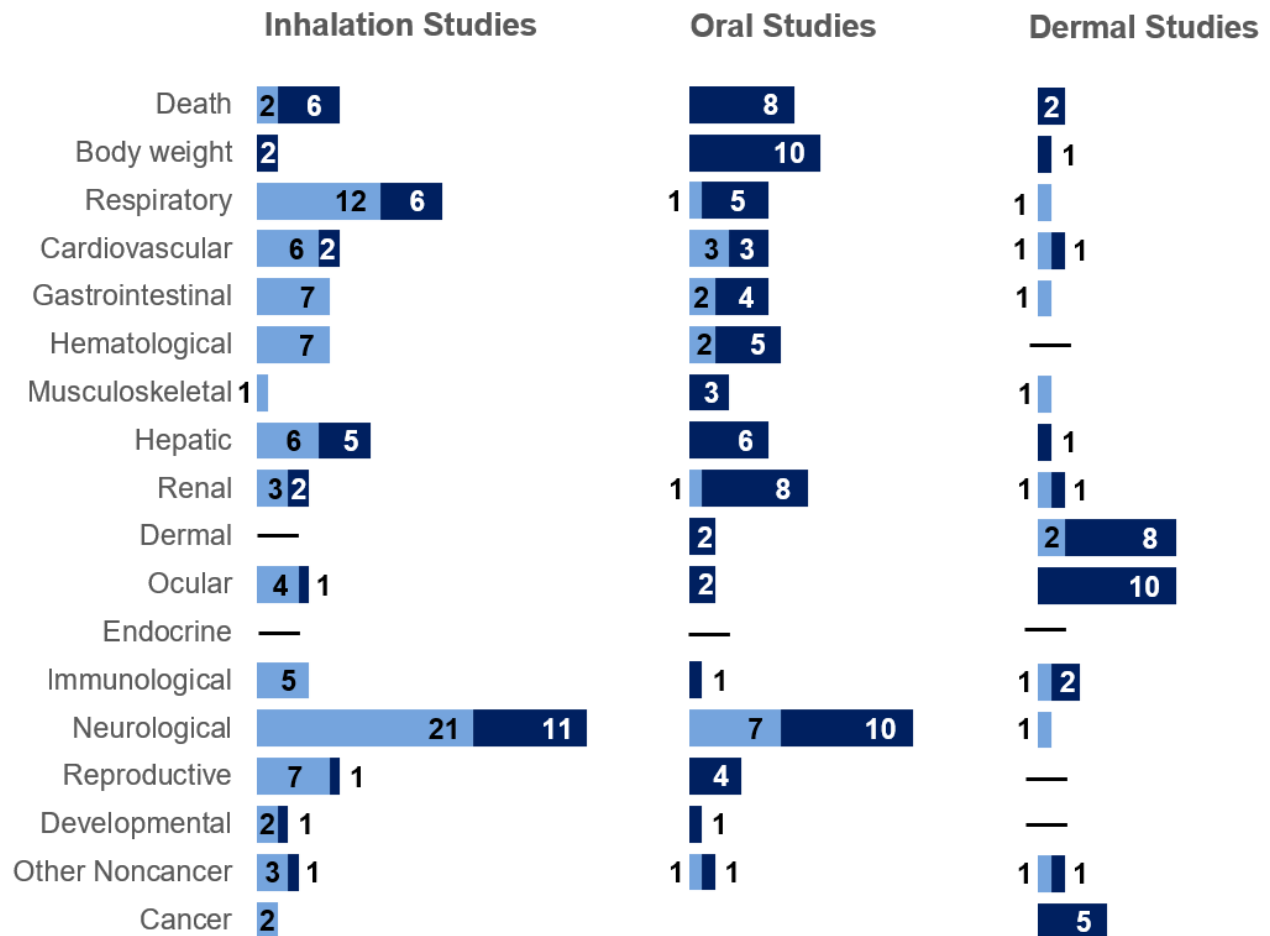
Missing information in Figure 6-1 should not be interpreted as a “data need.” A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health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

Acute-Duration MRLs. The data for acute effects in animals were sufficient to derive an acute-duration inhalation MRL of 8 ppm for neurobehavioral effects and altered auditory tone discrimination in humans exposed for 4 hours (Dick et al. 1989). Further studies are needed to derive an acute-duration oral MRL for acetone.

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Figure 6-1. Summary of Existing Health Effects Studies on Acetone by Route and Endpoint*

Potential neurological and respiratory effects were the most studied endpoints
 The majority of the studies examined oral exposure in **animals** or inhalation exposure in **humans**.



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

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Intermediate-Duration MRLs. There are insufficient data for derivation of an intermediate-duration inhalation MRL, due to a lack of high-quality studies at lower exposure levels. An intermediate-duration oral MRL of 0.6 mg/kg/day was derived based on a $BMDL_{1SD}$ of 57.0 mg/kg/day from a rat study published in Dietz et al. (1991) and NTP (1991) in which evidence of anemia was observed with decreased reticulocyte counts. Additional high-quality studies would strengthen this MRL.

Chronic-Duration MRLs. Further studies are needed to derive chronic-duration inhalation and oral MRLs for acetone.

Health Effects. In general, there is a need for further epidemiological studies that are specific to acetone exposure; many of the identified studies examined exposure to a mixture of solvents, making it difficult to distinguish the effects of acetone alone. Because studies of acetone exposure in humans are limited, there is also little understanding of interindividual variance in human responses to acetone exposure.

Cardiovascular. Human studies on the cardiovascular effects of acetone have reported mixed results. Tachycardia has been observed in patients after application of casts for which acetone was used in the setting solution (Chatterton and Elliott 1946; Hift and Patel 1961). High pulse rates and blood pressure have also been observed following ingestion of acetone, although it is difficult to attribute these effects to acetone alone given the medical histories and co-exposures found in these case studies (Herman et al. 1997; Kumarvel and Da Fonseca 2007; Slutzman et al. 2015). One epidemiological study of workers exposed to solvents observed increases in hypertension; however, workers were co-exposed to several chemicals, and concentrations of acetone were low (Attarchi et al. 2013). No effects on cardiac function were observed in a controlled study of volunteers exposed to acetone (Stewart et al. 1975). An epidemiology study of workers using acetone as the only solvent (Ott et al. 1983a, 1983b) failed to find any significant effects on cardiovascular mortality. Animal studies have indicated little evidence for cardiovascular effects (Specht et al. 1939; Bruckner and Peterson 1981b). Further research is needed to elucidate the cardiovascular effects of acetone.

Hematological. There is evidence of hematological effects of acetone from human studies of occupationally exposed workers (Ott et al. 1983a, 1983c) and volunteers (Matsushita et al. 1969a, 1969b). However, evidence is mixed, and several studies have failed to find any significant associations following inhalation exposures (DiVincenzo et al. 1973; Satoh et al. 1996; Stewart et

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al. 1975). No epidemiological studies on the hematological effects of oral exposures were identified. In animals, associations between acetone exposure and hematological effects have been found in rats but not in mice (Dietz et al. 1991; NTP 1991). Additionally, hematological effects were more pronounced in male than female rats (Dietz et al. 1991; NTP 1991). Studies on the hematological effects of acetone are needed to provide clarification on differences by species and sex.

Musculoskeletal. There is limited evidence on the musculoskeletal effects of acetone. One epidemiological study of occupational exposures found a significant association with rheumatic symptoms (Mitran et al. 1997) and one case study found rhabdomyolysis (Piatkowski et al. 2007). However, animal studies have failed to find significant associations between acetone and musculoskeletal effects (American Biogenics Corp. 1986; Dietz et al. 1991; NTP 1991). There is a need for more studies to elucidate the musculoskeletal effects of acetone.

Renal. Evidence on the renal effects of acetone in humans is mixed: case studies have reported effects such as renal insufficiency and failure (Chen et al. 2002; Kostusiak et al. 2003; Piatkowski et al. 2007), but controlled studies of volunteers have failed to find any significant effects (DiVincenzo et al. 1973; Stewart et al. 1975). Animal studies have shown differences in susceptibility to the renal effects of acetone by sex. For example, kidney weight decreases were observed at lower doses in female rats than male rats, but histopathological lesions in the kidney were observed in male rats at lower doses than in females (Dietz et al. 1991; NTP 1991). Further research is needed on the renal effects of acetone in humans, and to elucidate the sex differences observed in animals.

Endocrine. There is a need for research on the endocrine effects of acetone, as no studies in humans or animals were located.

Immunological. There is limited evidence on the immunological effects of acetone. Increases in white blood cell counts were observed in some studies of volunteers exposed to acetone (Matsushita et al. 1969a, 1969b), but not others (DiVincenzo et al. 1973; Stewart et al. 1975). One case study showed immunological effects in a woman after chronic dermal exposure to acetone (Tosti et al. 1988). No studies were located regarding immunological effects in humans after oral exposure. Evidence from animal studies is limited to one intermediate oral exposure study that observed no significant effects (Woolhiser et al. 2006). However, there is some

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evidence that dermal exposure to animals may modulate humoral immunity (Singh et al. 1996) and increase cytokine production (Denda et al. 1996). Further epidemiological research is needed to assess the immunological effects of acetone exposure in humans.

Reproductive. There are few studies on the reproductive effects of acetone in humans. One study found evidence of an association between pregnancy complications including miscarriage in workers exposed to acetone, but no conclusions can be drawn from this report due to poor reporting quality (Nizyaeva 1982). It is additionally difficult to draw conclusions from other epidemiological studies of occupational exposures, because the women examined were exposed to several solvents (Agnesi et al. 1997; Axelsson et al. 1984; Beaumont et al. 1995; Swan et al. 1995). Evidence from animal studies is mixed. Decreased fertility was observed in mice exposed to acetone (EHRT 1987), but not rats (Larsen et al. 1991). There is some evidence of adverse effects on the male reproductive system, such as decreased sperm motility (Dietz et al. 1991; NTP 1991). Given the limited data in humans and results from animal studies, further research is needed to assess the reproductive effects of acetone in humans.

Developmental. Information on the developmental effects of acetone is limited. Of the two epidemiological studies in occupationally exposed women located, one found evidence of a significant association between acetone and increases in developmental effects (Nizyaeva 1982) and one did not (Axelsson et al. 1984). However, the Nizyaeva (1982) study did not report pertinent details such as number of women studied, and therefore no conclusions can be drawn from the report. An animal study of rats and mice exposed to acetone found evidence of decreased fetal weights (NTP 1988). Additionally, gestational exposures in mice were associated with increased resorptions and malformations (NTP 1988) as well as reduced postnatal pup survival (EHRT 1987). Further research is needed to assess whether acetone is associated with malformations and other developmental effects, and to elucidate potential differences in susceptibility between species.

Cancer. Only two epidemiological studies investigated the association between acetone and cancer in humans. A retrospective mortality study found no excess risk of death from cancer in exposed workers (Ott et al. 1983a, 1983b). A case-control study found an association between risk of neuroblastoma in children and maternal exposure to acetone, though recall bias may have affected these results (Kerr et al. 2000). No studies in animals were identified, though acetone has been used as the solvent control in several studies on the carcinogenicity of other chemicals

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and has not been associated with any increases in neoplastic lesions or cancer (De Pass et al. 1989; Roe et al. 1972; Van Duuren et al. 1971, 1978; Weiss et al. 1986). Further research on this endpoint would help confirm that acetone is not carcinogenic.

Genotoxicity. Evidence from numerous *in vitro* studies of bacteria and cultured animal cells, as well as several *in vivo* studies of human fibroblasts and skin epithelial cells, indicate that acetone is likely not genotoxic in humans. However, additional studies on the peripheral lymphocytes, fibroblasts, and skin epithelial cells of exposed workers would help confirm that acetone is not genotoxic.

Epidemiology and Human Dosimetry Studies. Several controlled human exposure studies were identified which have helped to characterize the effects of acetone exposures. However, many of the epidemiological studies identified on various health endpoints examined the effects of occupational exposure to solvents. Therefore, because exposure to additional solvents such as toluene occurred in addition to exposures to acetone, it is difficult to attribute observed effects to acetone exposures. Further studies on occupational exposures to acetone alone would help to elucidate its health effects.

Biomarkers of Exposure and Effect. Acetone has been extensively measured in the expired air, blood, and urine of individuals in the general population and occupationally exposed workers. Because acetone can be directly measured in breath and urine samples, no additional biomarkers of exposure to acetone are required. Biomarkers of effect for acetone have not been identified for acetone, because similar effects are observed following exposure to several other chemicals. Therefore, additional research is unlikely to identify a specific biomarker of effect.

Absorption, Distribution, Metabolism, and Excretion. Evidence suggests that acetone is readily absorbed through the lungs and gastrointestinal tract. Studies in animals have found conflicting results on the effects of vehicle on gastrointestinal absorption; further research on this topic would help clarify absorbed doses. Based on evidence from animal studies and chemical properties, acetone is expected to distribute throughout body tissues in humans, particularly to tissues with high water content. However, studies in humans, as well as studies of absorption in animals following dermal exposures, are limited and further research would help confirm patterns of distribution. The metabolism of acetone is well-characterized, appears to be independent of both the species examined and the route of administration, and involves three separate gluconeogenic pathways (Casazza et al. 1984; Hallier et al. 1981; Hetenyi and Ferrarotto 1985; Johansson et al. 1986; Koop and Casazza 1985; Kosugi et al. 1986a, 1986b; Mourkides

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et al. 1959; Price and Rittenberg 1950; Puccini et al. 1990; Rudney 1954; Sakami 1950; Sakami and LaFaye 1951; Skutches et al. 1990). Elimination of acetone in humans has been well-studied following inhalation exposures, but information on elimination following oral and dermal exposures is lacking.

Comparative Toxicokinetics. As above, the toxicokinetics of acetone have been characterized in animals and humans. There appear to be few differences across species in the toxicokinetics of acetone exposure. Therefore, additional studies on comparative toxicokinetics are not needed at this time.

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

Biomonitoring studies indicate that maternal-fetal and maternal-infant transfer of acetone is possible. Levels of acetone in blood tend to be higher in children than in adults, due to their higher energy expenditures (Peden 1964). No studies in humans were located regarding whether children are more or less susceptible than adults to adverse health effects from a given amount or duration of exposure to acetone. In a lethality study among newborn rats, 14-day-old rats, and adult rats, susceptibility to the lethal effects of acetone generally decreased with increasing maturity (Kimura et al. 1971). Humans may have similar susceptibility, but further research on this topic is needed, especially given evidence from biomonitoring studies.

Physical and Chemical Properties. Information regarding the physical and chemical properties of acetone necessary to predict its environmental fate and transport processes in the environment is available (see Table 4-2). However, experimental determination of a value for the soil sorption coefficient of acetone from water would be helpful in assessing the potential for leaching and volatility of acetone in different soils.

Production, Import/Export, Use, Release, and Disposal. Production methods for acetone are known and there does not appear to be a need for further information.

The use pattern of acetone is known. Most acetone is used as an intermediate in the production of other chemicals or as a solvent. Detailed information on the uses of acetone in consumer products is available from Chemical Data Reporting (CDC 2012, 2016). Additional data on the uses of acetone are not needed.

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There is no information on releases of acetone from manufacturing and processing facilities to air, water, or soil because these releases were not required to be reported prior to 2020 (EPA 2005). Therefore, there is a data need for information on releases of acetone. As of 2020, facilities are required to report atmospheric releases of acetone in volumes of 5,000 pounds or more (EPA 2020).

The regulations governing the disposal of acetone are well defined. However, more information about the proportion of discarded acetone recovered from recycling, and the proportion lost due to evaporation, ground burial, and incineration, would be useful in determining the relative importance of the different routes of exposure.

Industries are not required to submit chemical release and off site transfer information on acetone to the EPA. The TRI does not contain data on acetone because atmospheric releases of acetone were not required to be reported prior to 2020 (EPA 2005, 2020).

Environmental Fate. The environmental fate of acetone, for the most part, has been well studied (see Section 5.4). Acetone will undergo transport from one environmental medium to another (Grosjean and Wright 1983; Rathbun et al. 1982). Due to its reasonably long half-life in air (22 days) (Meyrahn et al. 1986) and restricted volatilization from groundwater, the atmosphere and groundwater may act as sinks for acetone. More experimental data regarding the rate of sorption and biodegradation of acetone in soil and its biodegradability in groundwater would be useful to assess the relative importance of the different fate processes.

Bioavailability from Environmental Media. Acetone is readily absorbed in the lung and gastrointestinal tract following inhalation and ingestion. Acetone can also be absorbed from the skin (see Section 3.1.1). The low value for K_{oc} (see Table 4-1) and a moderate value for Henry's law constant (Rathbun and Tai 1987) suggest that bioavailability of acetone from contaminated water and soil as a result of skin contact may be significant. However, quantitative data regarding the rate and extent of dermal absorption of acetone from contaminated water and soil are lacking. The high water solubility and low K_{oc} value for acetone suggest that bioavailability from ingested soil (e.g., children playing at or near contaminated sites) will be high, but quantitative absorption data are lacking. Data on bioavailability of acetone from ingested plant food were not located, but would be helpful.

Food Chain Bioaccumulation. Acetone does not bioaccumulate in aquatic organisms. There is no indication of biomagnification of acetone along the aquatic food chain. Studies of the potential for

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acetone transfer from soil and plants and biomagnification in terrestrial food chains would be useful to ascertain its potential for food chain bioaccumulation.

Exposure Levels in Environmental Media. Data regarding the level of acetone in ambient air are available (EPA 2021; Lagrone 1991; Shah and Singh 1988; Snider and Dawson 1985). There is a paucity of data regarding the level of acetone in drinking water (Bedding et al. 1982; Coleman et al. 1976; Keith et al. 1976). More comprehensive data on the levels of acetone in the air and water consumed by people who live near acetone-containing hazardous waste sites would be useful in estimating the daily intake from these sources. Although the levels of acetone in the volatile components of several fruits and vegetables are available (see Section 5.5.4), development of data regarding the level of acetone in the total diet would be useful. There are few data regarding the level of acetone in background soil samples. Reliable monitoring data for the levels of acetone in contaminated media at hazardous waste sites are needed so that the information obtained on levels of acetone in the environment can be used in combination with the known body burden of acetone to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. The levels of acetone in blood/plasma and urine of healthy people, occupationally exposed groups, and diabetic patients are available (see Section 5.6). However, data on the levels of acetone in body fluids or tissues of general populations living near sites with higher (than normal) exposure potential (e.g., hazardous waste sites) were not located. This information could inform the need to conduct health studies on these populations.

Exposures of Children. There are limited data on exposures to acetone in children. However, studies have shown that acetone can be transferred via the placenta and breastmilk. Further research is needed to characterize exposures in children.

6.3 ONGOING STUDIES

No on-going study that would fill the data gaps regarding the transport and fate of acetone in the environment or that evaluates its exposure potential in general population groups susceptible to higher levels of exposure was located.

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2021) database.