PRIORITY DATA NEEDS FOR ACROLEIN

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NOTE TO THE READER

The Priority Data Needs documents are intended to characterize substance-specific priority data needs determined via the ATSDR Decision guide for identifying substance-specific data needs related to toxicological profiles (54 Federal Register 37618, September 11, 1989). The identified priority data needs reflect the opinion of the Agency, in consultation with other federal programs, of the research necessary for fulfilling its statutory mandate under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (Superfund) or CERCLA. They are not intended to represent the priority data needs for any other program.

We plan to revise these documents in response to public comments and as additional data becomes available. Therefore, we encourage comments that will make these documents of the greatest use.

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Substance-Specific Applied Research Program

Priority Data Needs for:

ACROLEIN

Prepared by: Agency for Toxic Substances and Disease Registry/
Division of Toxicology and Environmental Medicine (ATSDR/DTEM)

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I. Executive Summary

Acrolein is included in the priority list of hazardous substances identified by ATSDR and the Environmental Protection Agency (EPA) (ATSDR 2005a, 2005b). This list contains substances that have been identified at National Priorities List (NPL) sites and determined to pose a human health risk based on (1) known or suspected human toxicity, (2) frequency of occurrence at NPL sites or other facilities, and (3) the potential for human exposure to the substance. An updated Toxicological Profile for Acrolein (Draft for Public Comment) was published in September 2005. Currently, the updated toxicological profile is being finalized.

Acrolein is a volatile, clear or yellow liquid with a burnt, sweet, pungent odor that occurs naturally in the environment as a result of combustion of wood. Acrolein is highly soluble in water and miscible with many organic solvents (e.g., lower alcohols, ketones, benzene, diethyl ether, crude oil, and petroleum fuels). Currently, there are three manufacturers of acrolein in the United States, and its domestic production in 2002 was estimated to be 100–500 million pounds. Acrolein is used largely as an unisolated intermediate in the manufacture of acrylic acid, most of which is converted to its lower alkyl esters. Acrolein is also used in the manufacture of allyl alcohol, pyridines, tetrahydrobenzaldehyde, modified starch, synthetic glycerine, acrolein polymers, polyurethanes, and polyester resins and as a biocide. As a biocide, acrolein is intentionally released into the environment as an herbicide and algicide to control the growth of aquatic plants in irrigation waters, drainage ditches, and processing waters, and as a microbiocide in the control of sulfide producing bacteria and the removal of hydrogen sulfide and iron sulfide from oil production and injection wells. Acrolein has also found use as a component in military poison gas mixtures.

Acrolein's production and use will result in its release to the environment, with the vast majority emitted to air. In air, acrolein undergoes degradation through reactions with photochemically produced hydroxyl radicals, ozone, and nitrate radicals. The lifetime of acrolein in air is determined predominantly by the reaction of the compound with hydroxyl radicals, with a half-life of 15–20 hours. Degradation of acrolein in air also results from direct photolysis of the compound and through reactions with ozone and nitrate radicals; however, these modes of degradation play a much less significant role in determining the fate of acrolein in air based on half-lives of 10, 59, and 10 days, respectively, for the three degradation pathways. If released to soil or water, acrolein is expected to volatilize rapidly based on a measured Henry's law constant of 1.22×10^{-4} atm-m^3/mol at 25 °C and a measured vapor pressure of 274 mm Hg at 25 °C. Based on measured log K_{oc} values of 51–270 and an estimated log K_{oc} value of 24, acrolein is expected to be highly to moderately mobile in soil and has the potential to leach significantly. However, leaching of acrolein through soil is expected to be significantly retarded by irreversible sorption of acrolein to components in soil in addition to biodegradation, hydration, and volatilization of the compound. In water and soil, volatilization and degradation are expected to be the main removal processes.

The predominant route of environmental exposure is inhalation of smoke or automotive exhaust. Ingesting food containing acrolein is another route of exposure for the general population given that acrolein is formed in food as a result of the ripening of fruit, fermentation, and the overheating of fats. Occupational exposures to acrolein occur through inhalation and dermal contact in the workplace where it is produced or used. These external exposures to acrolein are in addition to endogenous exposure to small amounts of acrolein that are formed as a consequence of peroxidation of lipid membranes and metabolism of α-hydroxy amino acids and polyamines or as the consequence of some diseases, such as Alzheimer's disease and atherosclerosis. Populations residing near waste disposal sites may be subject to higher than average levels of acrolein in air since acrolein is volatile, or in drinking water obtained from groundwater wells. Children are expected to be exposed to acrolein by the same route as adults. The primary route of exposure for children in the general population is inhalation of ambient and indoor air, especially from environmental tobacco smoke. Ingestion of contaminated food items is also a route of exposure for children in the general population. Children who live near hazardous waste sites or municipal landfills may be subject to higher levels of acrolein in air and drinking water obtained from groundwater wells.

Acrolein is a highly reactive compound that rapidly binds to the sulfhydryl groups in proteins and other cellular molecules. Human and animal studies indicate that the primary target of acrolein toxicity following inhalation, oral, and dermal exposure is the tissue at the site of contact, as shown by irritation to the respiratory and gastrointestinal tracts, eyes, and skin. Systemic effects observed in animal inhalation and oral studies were essentially minor, not clearly toxicologically significant, and/or occurred at exposure levels similar to or higher than those causing respiratory or gastrointestinal irritation; effects included decreased body weight gain, increased relative organ weights, and hematological alterations. Available animal data are insufficient to assess the carcinogenic potential of acrolein, due to experimental design limitations in inhalation studies and an inconsistent cancer finding in oral studies. Effects on alveolar macrophages and neurological signs occurred in animals at high levels of inhalation and oral exposure, respectively, but these findings do not necessarily indicate that acrolein is directly neurotoxic and immunotoxic. Animal studies also found that the developing fetus may be a target of acrolein, but only at oral doses that were maternally toxic. It is not known if children are more susceptible to the toxicity of acrolein than adults.

On the basis of the available data, ATSDR has identified the following priority data needs:

Exposure

- Evaluation of existing data on concentrations of acrolein in contaminated environmental media at hazardous waste sites
- Exposure levels in humans living near hazardous waste sites
- Exposure levels of children

Toxicity

- Dose-response data for chronic-duration via inhalation exposure

II. Introduction: ATSDR's Substance-Specific Applied Research Program

A. Legislative

Section 104(i)(5) of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) directs the Administrator of ATSDR (ihpn 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 acrolein is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects. Such program shall include, to the extent necessary to supplement existing information, but shall not be limited to--

- laboratory and other studies to determine short, intermediate, and long-term health effects;
- laboratory and other studies to determine organ-specific, site-specific, and system-specific acute and chronic toxicity;
- laboratory and other studies to determine the manner in which such substances are metabolized or to otherwise develop an understanding of the biokinetics of such substances; and
- where there is a possibility of obtaining human data, the collection of such information.

Section 104(i)(5)(C): In the development and implementation of the research program ATSDR is required to coordinate with EPA and NTP to avoid duplication of research being conducted in other programs and under other authorities.

Section 104(i)(5)(D): It is the sense of Congress that the costs for conducting this research program be borne by private industry, either under the Toxic Substances Control Act (TSCA), the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), or cost recovery under CERCLA.

B. Impact on Public Health

The major purpose of this research program is to supplement the substance-specific informational needs of the public and the scientific community. More specifically for ATSDR, this program

will supply necessary information to improve the database to conduct public health assessments. This is more fully described in the ATSDR Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (54 Federal Register 37618) [henceforth referred to as the ATSDR Decision Guide].

Experience from ATSDR health assessments shows the need for more information for select substances, on both exposure and toxicity, so the Agency can more completely assess human health effects. Exposure data collected from this substance-specific research will complement data being collected on a site-specific basis by ATSDR's Division of Health Studies and the Division of Health Assessment and Consultation. More specifically, the Agency will use the exposure data to help identify populations that need follow-up exposure or health-outcome studies.

Regarding substance toxicity, the collected data will be used to characterize the toxicity of the substance for public and scientific community. For ATSDR, the data are necessary and essential to improve the design and conduct of follow-up health studies.

C. Procedures

Section 104(i)(2) of CERCLA, as amended, requires that ATSDR (1) with EPA develop a list of hazardous substances found at NPL sites (in order of priority), (2) prepare toxicological profiles of those substances, and (3) assure the initiation of a research program to fill identified data needs associated with the substances.

The first step in implementing the ATSDR substance-specific research program for acrolein occurred when the data needs for acrolein were determined in the ATSDR Toxicological Profile for Acrolein. Considered a subset of all information gaps on acrolein, these data needs were reviewed by scientists from ATSDR and other federal agencies. They were peer reviewed by an external review panel and made available for public comment. All comments received by ATSDR on the identification of data needs for acrolein were addressed before the toxicological profile was finalized. In preparing the priority data needs document, a literature search was conducted to provide updated information on acrolein.

The purpose of this paper is to take the data needs identified in the Toxicological Profile for Acrolein and subject them to further scientific evaluation. This will lead to priorities and ultimately to ATSDR's substance-specific research agenda. To affect this step, ATSDR developed and presented a logical scientific approach to priority setting in its Decision Guide.

Briefly, data needs are categorized as exposure or toxicity and are then subcategorized across three levels (Tables 1 and 2). Level I research is a base set of exposure and toxicity information to identify basic characteristics of each substance. Level II research is conducted to confirm the toxicity and exposure indicated by Level I data. Level III research will improve the application of the results of Level II research to people.

The Decision Guide recognized three general principles for setting priorities:

- Not all information gaps identified in toxicological profiles are data needs.
- All data needs are not the same priority.
- Substances should be considered individually, but may be grouped, because of structural similarity or other relevant factors.

Other considerations spelled out in the Decision Guide include:

- All levels of data should be considered in selecting priority data needs.
- Level I gaps are not automatically in the priority grouping. In general, Level I data have priority when there are no higher level data for the same category, and when data are insufficient to make higher level priority testing decisions. For example, priority would generally not be assigned multigenerational animal studies (Level II) if an adequate subchronic study (Level I) had not been conducted that evaluated reproductive organ histopathology.
- Priority for either exposure or toxicity data requires thorough evaluation of research needs in other areas to help achieve a balanced research program for each substance.

The Decision Guide listed the following eight tenets to determine research priorities:

- Development and/or confirmation of appropriate analytical methods.
- Determination of environmental and human exposure levels when analytical methods are available.
- Bioavailability studies for substances of known significant toxicity and exposure.

- Studies available to characterize target organs and dose response.
- Disposition studies and comparative physiologically-based pharmacokinetics when a toxic end point has been determined and differences in species response have been noted.
- Mechanistic studies on substances with significant toxicity and substantial human exposure.
- Investigation of methods to mitigate toxicity for substances when enough is known about mode of action to guide research.
- Epidemiologic studies designed to link human disease with a substance of known significant toxicity.

These last three "prioritizing" tenets address Level III research. When Level III research is identified as priority, ATSDR will not develop detailed methods to successfully fulfill the data needs. Because there are no standard "testing guidelines" for Level III research, we expect considerable discussion between ATSDR and parties interested in conducting this research. Thus, ATSDR will only announce that its scientists believe that the accumulation of Level III research is appropriate, and it is a priority at this time. ATSDR will state the reasons why this is so.

D. Selection Criteria

ATSDR prepares toxicological profiles on substances that are most commonly found at facilities on the NPL sites and which, in its sole discretion, pose the most significant threat to human health because of their known or suspected toxicity and potential for human exposure.

Briefly, the rationale is as follows:

1. Frequency of Occurrence

Finding: Acrolein is included in the priority list of hazardous substances identified by ATSDR and EPA (ATSDR 2005a, 2005b).

Acrolein has been detected in at least 31 of 1,662 National Priorities List (NPL) hazardous waste sites in the United States (HazDat 2005). Exposure to acrolein at these sites may occur by contacting contaminated air, water, soil, or sediment. ATSDR is presently evaluating the extent of media-specific contamination at these and other sites.

2. Potential for Human Exposure

***Finding*:** ATSDR scientists have determined that there has been significant past human exposure and that the potential exists for current human exposure to acrolein via inhalation, ingestion, and skin contact.

The following is a brief summary of the potential for human exposure to acrolein. For a more detailed discussion of available information, refer to the ATSDR Toxicological Profile for acrolein, Chapter 6, on Potential for Human Exposure (ATSDR 2005c).

Acrolein is a volatile, clear or yellow liquid with a burnt, sweet, pungent odor that occurs naturally in the environment as a result of combustion of wood. Acrolein is highly soluble in water and miscible with many organic solvents (e.g., lower alcohols, ketones, benzene, diethyl ether, crude oil, and petroleum fuels). Acrolein is used largely as an unisolated intermediate in the manufacture of acrylic acid, most of which is converted to its lower alkyl esters (IARC 1995). Acrolein is also used in the manufacture of allyl alcohol, pyridines, tetrahydrobenzaldehyde, modified starch, synthetic glycerine, acrolein polymers, polyurethanes, and polyester resins. Isolated and refined acrolein is used in the manufacture of the nutritional supplement methionine and as a biocide. As a biocide, acrolein is intentionally released into the environment as an herbicide and algicide to control the growth of aquatic plants in irrigation waters, drainage ditches, processing waters, and as a microbiocide in the control of sulfide producing bacteria and the removal of hydrogen sulfide and iron sulfide from oil production and injection wells. Acrolein has also found use as a component in military poison gas mixtures.

Acrolein is an important substance for research because of its widespread environmental contamination. According to the Toxics Release Inventory (TRI), 41 facilities manufactured or processed acrolein in 2002 (TRI02 2005). It was estimated that 265,716 pounds of acrolein, amounting to 66% of the total environmental release, was discharged to air from manufacturing and processing facilities in the United States in 2002 (TRI02 2005). Approximately 34% of the total release of acrolein to the environment is through underground injection (TRI02 2005). Smaller amounts, 1,500 and 10 pounds, were released to water and land, respectively (TRI02 2005). Natural sources of acrolein release are fermentation and ripening processes, forest fires and incomplete combustion of organic matter, and photochemical oxidation of hydrocarbons in

the atmosphere (Ghilarducci and Tjeerdema 1995; Lipari et al. 1984). Releases of this compound to the environment may result from the manufacture, use, storage, distribution, and disposal of acrolein. The major anthropogenic releases of this compound to the environment are into air from combustion processes within stationary (e.g., waste incinerators, furnaces, fireplaces, power plants, etc.) and mobile (e.g., automobiles, trucks, buses, airplanes, construction equipment, etc.) sources (EPA 1998a, 2001b).

Acrolein largely partitions into air where it undergoes degradation through reactions with photochemically produced hydroxyl radicals, ozone, and nitrate radicals. The lifetime of acrolein in air is predominantly determined by the reaction of the compound with hydroxyl radicals. An estimated half-life of 15–20 hours for acrolein is based on experimental reaction rate constants ranging between 1.90×10^{-11} and 2.53×10^{-11} cm^3/molecules-sec (25–26 °C) and an average ambient hydroxyl radical concentration of 5.0×10^5 molecules/cm^3 (Atkinson 1985). Based on experimental data, the reaction of acrolein with ozone ($k=2.8 \times 10^{-19}$ cm^3/molecules-sec at 25 °C; half-life 59 days) and nitrate radicals ($k=5.9 \times 10^{-16}$ cm^3/molecules-sec; half-life 16 days) in the troposphere are too slow to be environmentally significant (Atkinson 1985; Atkinson et al. 1987). Direct photolysis of acrolein occurs but is expected to be of minor importance in the degradation of acrolein in the atmosphere, based on a half-life of 10 days in the lower troposphere and <5 days in the upper troposphere (Gardner et al. 1987). If released to soil or water, acrolein is expected to volatilize rapidly based on a measured Henry's law constant of 1.22×10^{-4} atm-m^3/mol at 25 C (Gaffney et al. 1987) and a measured vapor pressure of 274 mm Hg at 25 C (Daubert and Danner 1987). Based on measured log K_{oc} values of 51–270 (Irwin 1988) and an estimated value of 24 (Lyman 1982), acrolein is expected to be highly to moderately mobile in soil and has a significant potential to leach through soil (Swann et al. 1983). However, leaching of acrolein through soil is expected to be significantly retarded by irreversible sorption of acrolein to components in soil (Irwin 1988), in addition to biodegradation, hydration, and volatilization of the compound. In water and soil, volatilization and degradation are expected to be the main removal processes. In water, acrolein undergoes hydration to form 3-hydroxypropanal, which undergoes aerobic biodegradation that occurs optimally with acclimated cultures (Bowmer and Higgins 1976). This was demonstrated by Bowmer and Higgins (1976) when they reported a 100-hour lag period in the biodegradation of 3-hydroxypropanal followed by a period of rapid degradation after the concentration of acrolein fell below 2–3 ppm. Based on the results in aquatic systems (Bowmer and Higgins 1976), the degradation of acrolein in soil is suggested to occur through hydration, biodegradation, and irreversible binding to organic components in soil.

Acrolein has been identified in at least 31 of the 1,662 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2005). However, the number of sites evaluated for acrolein is not known. Acrolein has been identified in air samples collected at 5 sites, surface water samples collected at 4 sites, groundwater samples collected at 15 sites, soil samples collected at 1 site, and sediment samples collected at 2 of the 31 NPL hazardous waste sites where acrolein was detected in some environmental media (HazDat 2005).

The general population is exposed to acrolein primarily through the inhalation of air, especially indoor air containing environmental tobacco smoke (Environment Canada 2000). The concentration of acrolein in ambient air within the United States averaged 0.20 and 0.12 μg/m^3 (0.086 and 0.052 ppb) for urban and rural locations, respectively (EPA 1998b). Based on measured acrolein concentrations in ambient and indoor air, it is estimated that the Canadian population is exposed to an average acrolein concentration in air of 1.3 μg/m^3 (0.56 ppb) (Environment Canada 2000). For an average adult, this amounts to an intake of 26 μg of acrolein per day, assuming a daily inhalation volume of 20 m^3/day. Ingesting food containing acrolein is another route of exposure given that acrolein is formed in food as a result of the ripening of fruit, fermentation, and the overheating of fats. Due to a lack of monitoring data for acrolein in food and water, the average daily intake of acrolein and the relative importance of each source of exposure cannot be determined. Endogenous exposure to small amounts of acrolein occurs in the general population. Endogenous acrolein is formed as a consequence of peroxidation of lipid membranes and metabolism of α-hydroxy amino acids and polyamines (Alarcon 1970; Uchida et al. 1998a) or as a consequence of certain diseases, such as Alzheimer's disease and atherosclerosis (Anderson et al. 1997; Calingasan et al. 1999; Gómez-Ramos et al. 2003; Uchida et al. 1998b). Populations residing near waste disposal sites may be subject to higher than average levels of acrolein in air since acrolein is volatile. Exposure to acrolein in drinking water is not expected to be a problem for these individuals due to the volatilization of acrolein from soils and of the retention or degradation of acrolein in soils. However, data of exposures of residents living near hazardous waste sites through inhalation of air or ingestion of drinking water could not be located.

Children are exposed to acrolein through inhalation of ambient and indoor air, particularly in indoor air containing environmental tobacco smoke, and ingestion of food containing acrolein. However, no studies could be located describing these exposures for children in the United States.

Occupational exposure to acrolein may occur through inhalation and dermal contact at workplaces where this compound is produced or used. Data from a workplace survey conducted by NIOSH from 1980 to 1983 indicated that 1,298 workers (including 5 females) in 37 facilities in the United States are occupationally exposed to acrolein (NIOSH 1988; RTECS 2004).

3. Toxicity

***Finding*:** ATSDR considers that short, intermediate, and long-term health effects can result from inhalation, ingestion, and dermal contact of acrolein. Target organs or systems known to be affected include the respiratory tract, gastrointestinal tract, eyes, and skin.

The following is a brief summary of the toxicology of acrolein. Refer to the ATSDR Toxicological Profile for Acrolein chapter on "Health Effects" for a more detailed discussion of available information (ATSDR 2005c).

Acrolein is toxic following inhalation, oral, and dermal exposure primarily at the site of contact with tissues, causing irritation to the respiratory and gastrointestinal tracts and eyes and skin. Inhalation exposure to acrolein can affect the entire respiratory tract. Nasal irritation appears to be the most sensitive acute-duration respiratory effect based on observations of nose and throat irritation in volunteers (Weber-Tschopp et al. 1977) and nasal cellular changes (e.g., mild epithelial dysplasia and necrosis) in rats (Cassee et al. 1996). Higher acute inhalation exposure levels caused more severe effects in animals, including moderate to severe histological alterations of the nasal, tracheal, and bronchial epithelium, bronchial epithelial destruction, pulmonary edema, and lung hemorrhage in mice, rats, and guinea pigs (Buckley et al. 1984; Catilina et el. 1966; Dahlgren et al. 1972; Hales et al. 1988; Kilburn and Mckenzie 1978; Murphy et al. 1964; Skog 1950). Similar effects occurred in human cases of massive acute inhalation exposures, including dyspnea, coughing, foamy expectoration, cyanosis, pulmonary edema, and death (Bauer et al. 1977; Champeix et al. 1966; Gosselin et al. 1979; Mahut et al. 1993). No information is available on respiratory effects of longer-term inhalation exposures to acrolein in humans. Effects observed in animals following intermediate- and chronic-duration inhalation exposures included inflammation and histological alterations in the entire respiratory tract of rats, monkeys, guinea pigs, dogs, rabbits, and hamsters (Costa et al. 1986; Feron et al. 1978; Kutzman et al. 1984, 1985; Lyon et al. 1970).

Irritation of the gastrointestinal mucosa appears to be the primary effect of oral exposure to acrolein. Oral toxicity data in humans are not available, and there is essentially no information on effects of low-level acute oral exposures in animals. Acute- and intermediate-duration exposures to high oral doses caused effects that included severe mucosal inflammation, ulceration, focal hemorrhage, and edema in mice, rats, and rabbits (King 1984; NTP 1995; Parent et al. 1993; Sakata et al. 1989). Effects from low intermediate-duration oral doses included glandular and forestomach squamous epithelial hyperplasia in mice and rats, respectively (NTP 1995). In contrast, chronic oral exposure to low levels of acrolein produced no significant gross or histopathological effects in rats (Parent et al. 1992a), mice (Parent et al. 1991), or dogs (Parent et al. 1992b). The reported differences in gastrointestinal sensitivity are not well understood, but responses in the dogs suggest that adaptation to irritating effects might occur during low chronic exposures.

The eye appears to be the most sensitive target for dermal exposure to acrolein vapor or liquid. At low vapor levels, humans experienced rapid-onset mild to moderate stinging of the eyes accompanied by increased blinking, and appear to adapt to ocular irritation (Weber-Tschopp et al. 1977). Exposure to higher concentrations caused lacrimation with increased severity of irritant sting (Sim and Pattle 1957). Dogs and monkeys appear to be more sensitive to the ocular effects of acrolein than rodents, as evidenced by lacrimation and blinking or closing of the eyes during intermediate-duration exposures that caused no observable ocular effects in guinea pigs or rats (Lyon et al. 1970). No information is available on whether ocular exposure to acrolein can cause structural damage (histopathological changes) to the eye. Acute dermal exposure to a 10% solution of acrolein caused irritation, edema, and epidermal necrosis in the skin of volunteers (Lacroix et al. 1976).

No information is available regarding the systemic toxicity of acrolein in humans. Systemic effects in animals were observed in inhalation and oral studies, but were essentially minor, not clearly toxicologically significant, and/or occurred at exposure levels similar to or higher than those causing respiratory or gastrointestinal irritation. Systemic effects of inhalation included increases in serum levels of liver enzymes in rats following acute exposure (Murphy 1965; Murphy et al. 1964), and reduced body weight gain in several species (Bouley et al. 1975; Feron et al. 1978; Kutzman et al. 1985; Leach et al. 1987; Lyon et al. 1970), increased relative heart weight in hamsters and rats (Feron et al. 1978), and hematological alterations in hamsters (Feron

et al. 1978) following intermediate-duration exposure. Systemic effects of oral exposure included reduced body weight gain in mice (Parent et al. 1991) following intermediate-duration exposure.

No information is available on the immunotoxicity and neurotoxicity of acrolein in humans, and batteries of tests have not been conducted to investigate these end points in animals. Acute- and intermediate-duration inhalation studies found that exposure to acrolein caused a reduction in numbers of alveolar macrophages, suggesting that acrolein might increase the risk of bacterial infections in the respiratory tract (Aranyi et al. 1986), but this effect could be due to a direct cytotoxic effect rather than an immunotoxic response. No data were located regarding possible immunological effects in animals after oral or dermal exposure. Animal data also do not suggest that the nervous system is a major target of acrolein. The only clinical signs of neurotoxicity in animals exposed to acrolein by inhalation or ingestion were central nervous system depression in rodents after acute oral exposure to lethal doses (Sprince et al. 1979). Increased relative brain weight and inflammatory responses in the brain were found in several species in intermediate-duration inhalation studies, but these were nonspecific effects not necessarily indicative of neurotoxic action of acrolein (Feron et al. 1978; Kutzman et al. 1985; Lyon et al. 1970).

No information is available on the reproductive and developmental effects of acrolein in humans. No reproductive effects were observed in rats after inhalation or oral exposure to acrolein (Bouley et al. 1975; King 1984; Parent et al. 1992c). Developmental toxicity was not tested by inhalation, but occurred in orally exposed animals at doses that were generally maternally toxic; effects included reduced fetal body weight gain, skeletal anomalies, and delayed ossification in rats and fetal resorptions in rabbits (King 1982; Parent et al. 1991, 1992c).

No studies were located regarding the carcinogenicity of acrolein in humans, and evidence in animals is inconclusive. No increases in tumor incidence were observed in two chronic inhalation studies in rats and hamsters (Feron and Kruysse 1977; Le Bouffant et al. 1980), but the designs of these studies were inadequate for proper evaluation of carcinogenicity. No carcinogenic effects were found in rats, mice, or dogs in chronic oral studies (Parent et al. 1991, 1992a, 1992b), although a questionable increased incidence of adrenocortical adenomas occurred in rats in another chronic oral study (Lijinsky and Reuber 1987). Acrolein has not been tested for complete carcinogenicity by the dermal route, although it showed no skin tumor initiating activity in a mouse study that used croton oil as the promoter (Salaman and Roe 1956). The Department of Health and Human Services (DHHS) has not classified acrolein as to its carcinogenicity. The

International Agency for Research on Cancer (IARC) and the EPA have determined that the potential carcinogenicity of acrolein in humans is not classifiable based on an inadequate database.

No studies were located regarding the genotoxicity of acrolein in humans or animals following inhalation, oral, or dermal exposure. Acrolein was not mutagenic in vivo in a dominant lethal assay in mice exposed by intraperitoneal injection (Epstein et al. 1972) or in a sex-linked recessive lethal test in Drosophila exposed by feeding or injection (Zimmering et al. 1985). In vitro studies have shown some evidence of mutagenicity in bacteria, yeast, and mammalian cells, as well as chromosomal and DNA damage in mammalian cells.

Populations that might be unusually susceptible to acrolein include people whose respiratory function is compromised, such as individuals with emphysema or asthma, due to the strong respiratory irritant effects of the chemical. It is not known whether children are more sensitive than adults. Adults have been shown to reduce their respiration rate in the presence of airborne acrolein (Weber-Tschopp et al. 1977), but children will not necessarily react in the same or similar manner. Since point-of-contact irritation is the main toxic action of acrolein, children are not likely to be more susceptible to acrolein's effects at the tissue level.

III. Identification of Data Needs

In evaluating the exposure and toxicity testing needs for acrolein, ATSDR considered all available published and unpublished information that has been peer-reviewed. From its evaluation of these data, ATSDR is recommending the conduct of specific research or testing.

A. Exposure Data Needs (Table 1)

Three of the eight "prioritizing" tenets presented in the Decision Guide directly address exposure data needs:

- Development and/or confirmation of appropriate analytical method;
- Determination of environmental and human exposure levels when analytical methods are available; and
- Bioavailability studies for substances of known significant toxicity and exposure.

The progressive accumulation of exposure information begins with developing suitable analytical methods to analyze the compound in all relevant biological and environmental media, followed by confirmation of exposure information, before the conduct of any Level III research. However, in order to know what analytes are available to monitor, some basic environmental fate information is generally required and becomes a priority if it is lacking.

Bioavailability and food chain bioaccumulation studies are appropriately placed in Level II, and should be undertaken after analytical methods are developed and the substance has been confirmed at many hazardous waste sites and in environmental media.

1. Levels I & II Data Needs

a. Analytical Methods

***Purpose*:** To determine if available methods are adequate to detect and quantify levels of acrolein in environmental and biological matrices. The methods should be sufficiently specific and sensitive to measure (1) background levels in the environment and the population; and (2) levels at which biological effects might occur.

***Finding*:** A data need has not been identified. Analytical methods exist for the detection of acrolein in human biological samples and environmental media. These methods are sufficiently sensitive and are reliable enough to measure background levels in the general population as well as levels at which health effects might occur after short- or long-term exposure.

Analytical methods for determining acrolein in biological samples are available and involve the detection of acrolein itself or the products that are formed in the reaction of acrolein with thiol-containing proteins or glutathione. Methods exist for the detection of acrolein in urine (Al-Rawithi et al. 1993; Sakura et al. 1998), plasma (Paci et al. 2000), and tissues (Boor and Ansari 1986). Detection sensitivities for acrolein and its metabolites in urine are at or below the ppb level. Recoveries are variable but are optimal (99–104.1%) when acrolein is quantified through the use a derivatizing agent (Al-Rawithi et al. 1993). In plasma, the detection limit for the derivatized form of acrolein is 5.6 ng/mL with recoveries ranging from 78 to 82% (Paci et al. 2000). Detection sensitivities for acrolein in tissues when using an extraction procedure are

<0.2 ng in the extract. However, the assay is limited by the low (4.6–43.8%) recoveries of acrolein (Boor and Ansari 1986).

Methods have been developed for the detection and quantification of biomarkers of acrolein exposure. The urinary metabolite of acrolein, 3-hydroxypropyl-L-cysteine, is quantified directly with a sensitivity limit of 1.25 µg/mL (Sanduja et al. 1989). The metabolite, 3-hydroxypropyl-mercapturic acid, is converted to, and quantified as, 3-hydroxypropylmercapturic after hydrolysis in HCl (Alarcon 1976). Exposure of the enzyme, glucose-6-phosphate dehydrogenase (which is found in red blood cells) to acrolein results in changes in the activity of the enzyme (Trieff et al. 1993). The formation of acrolein-albumin adducts in blood are another measure of the presence of acrolein *in vivo* (Li et al. 2004). However, the changes in the levels of these biomarkers in blood and urine have not been correlated with exposures to acrolein. Also, these biomarkers are formed as a consequence of the endogenous production of acrolein that occurs through peroxidation of lipid membranes and the metabolism of α-hydroxy amino acids and polyamines. The endogenous production of acrolein is likely to complicate the use of biomarkers to quantitatively assess external exposures of humans to acrolein.

A number of methods exist for measuring the concentration of acrolein in air (EPA 1996; Hurley and Ketchum 1978; Kennedy et al. 1984; Koostra and Herbold 1995; NIOSH 1994; Nishikawa et al. 1986; Sakuragawa et al. 1999). Methods also exist for measuring acrolein in water (EPA 1984, 1994, 2001a; Kissel et al. 1978; Nishikawa et al. 1987; Ogawa and Fritz 1985). The greatest source of exposure to acrolein for the general population in the United States is inhalation of contaminated air. Other potential routes of human exposure include ingestion of drinking water or food that contains acrolein. For most assays, acrolein can be measured in the sub-ppb to ppb in air and water with recoveries generally >75%. For measurements of acrolein in air, the compound is collected through reactions with a trapping agent and the resulting reaction product is analyzed using gas chromatography (GC) techniques (coupled with nitrogen specific detectors or electron capture detectors [ECDs]) or high performance liquid chromatography (HPLC)-ultraviolet detector (UV) techniques. The detection limits range from 4 ppb (Rietz 1985) to 0.02 ppb (Koostra and Herbold 1995) using HPLC methods. For measurements of acrolein in water, GC coupled with flame ionization detectors (FID) or mass spectrometers (MS) has detection limits of 0.7and 50ug/L, respectively, for acrolein (EPA 1984, 2001a). The sensitivity of the methods for detecting acrolein in air and water are sufficient for detecting levels of the compound that may be of human health concern.

***Priority Recommendation*:** A data need has not been identified.

b. Physical/Chemical Properties

***Purpose*:** To determine whether adequate data on the chemical and physical properties of acrolein are available to permit estimation of its environmental fate under various conditions of release, and evaluation of its pharmacokinetics under different exposure durations and routes.

***Finding*:** A data need has not been identified. The relevant physical and chemical properties of acrolein including solubility in water (Seidell 1941) and organic solvents (Tomlin 2003), vapor pressure (Daubert and Danner 1987), K_{ow} (Hansch and Leo 1985), K_{oc} (Irwin 1988), and Henry's law constant (Gaffney et al. 1987) have been measured experimentally or have been estimated accurately enough to permit evaluating the environmental fate and transport of acrolein.

***Priority Recommendation*:** A data need has not been identified.

c. Exposure Levels

(1) Environmental Media

***Purpose*:** To determine whether adequate data are available on the levels of acrolein in the ambient and contaminated environments for purposes of conducting meaningful follow-up exposure and health studies.

Finding: A data need to evaluate existing data on concentrations of acrolein in contaminated environmental media at hazardous waste sites has been identified.

The concentrations of acrolein in ambient air are typically in the sub to low ppb range. Slightly higher concentrations are found near point sources, such as areas with high traffic density and urban areas. Data for 2004 obtained from EPA's Air Quality System (AQS) database show average concentrations of acrolein at various monitoring stations ranging from 0.3 to 2.048 ppb carbon (0.5–3.186 ppbv), with maximum values ranging from 0.3 to 3.6 ppb carbon (0.5–5.6 ppbv) (EPA 2004). Data obtained for 1996 show similar average concentrations for acrolein,

ranging from 0.05 to 3.2 ppb carbon (0.08–5.6 ppbv) with maximum values ranging from 0.5 to 11.46 ppb carbon (0.8–17.82 ppbv). Lower average concentrations of 0.05–0.64 ppb carbon (0.08–1.00 ppbv) for acrolein (maximum values ranging from 0.05 to 9.9 ppb carbon [0.08–15 ppbv]) were found for 2000. The National Air Quality and Emissions Trend Report for 1998 reported mean concentrations of acrolein of 0.086 and 0.052 ppb in urban and rural locations in the United States, respectively (EPA 1998b). Populations residing near hazardous waste sites may be subject to above average levels of acrolein in the ambient air. Acrolein has been detected in air samples collected at 5 of the 31 hazardous waste sites where acrolein has been detected in some environmental medium (HazDat 2005). The HazDat information includes data from both NPL and other Superfund sites. Concentrations of acrolein in outdoor air ranged from 0.03–6 to 0.013–42.4 ppbv in onsite and offsite sampling, respectively (HazDat 2005).

Data from the EPA STORET Database indicate that acrolein has a low frequency of occurrence in waste water streams, ambient surface water, and groundwater in the United States (EPA 1988; Staples et al. 1985). Acrolein has not been found as a contaminant of drinking water (EPA 1980; Krill and Sonzogni 1986; Otson 1987). Grosjean and Wright (1983) detected acrolein, in combination with acetone, at a concentration of 0.05 μg/mL (50 ppb) in rain water collected in Los Angeles, California; however, these compounds were not detected in rain water samples collected in four less densely populated sites in California. Acrolein is registered for use as a biocide for controlling aquatic plants and mollusks in irrigation canals. Concentrations of 15 ppm are typically encountered in water when acrolein is applied as a biocide. Acrolein has been detected in surface water and groundwater samples collected at 4 and 15 of the 31 hazardous waste sites, respectively, where acrolein has been detected in some environmental medium (HazDat 2005). The HazDat information includes data from both NPL and other Superfund sites. Concentrations of acrolein in landfill leachate ranged from 2.1 to 234 ppm (HazDat 2005; Sabel and Clarke 1984). In groundwater collected at 15 NPL and other Superfund sites, the concentrations of acrolein ranged from 1.3 to 75 ppm, with the highest concentrations generally obtained from onsite monitoring wells (HazDat 2005).

Data on acrolein concentrations in soil are limited. Acrolein was identified in sediment/soil/water samples collected from Love Canal in Niagara Falls, New York (Hauser and Bromberg 1982); however, no quantitative data were available. More recently, acrolein has been detected in soil and sediment samples collected at 1 and 2 of the 31 hazardous waste sites, respectively, where acrolein has been detected in some environmental medium (HazDat 2005). The HazDat

information includes data from both NPL and other Superfund sites. One soil sample site was found to have an acrolein concentration of 100 ppm (HazDat 2005).

***Priority Recommendation*:** The identified data need is considered priority. Reliable and current monitoring data for the levels of acrolein in contaminated media at hazardous waste sites are needed so that the information obtained on levels of acrolein in the environment and the resulting body burden of acrolein can be used to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

ATSDR has developed a hazardous substance release/health effects database (HazDat) that includes the extant data for the 31 NPL sites at which acrolein has been found. This database includes maximum concentrations of acrolein in on- and off-site media, and an indication of relevant routes of exposure. This database will be evaluated before the need to collect additional media-specific data is assigned priority.

(2) Humans

***Purpose*:** To determine whether adequate data are available on the levels of acrolein in human tissues for the general population and exposed populations for purposes of conducting meaningful follow-up exposure and health studies.

Finding: A data need has been identified. No data are available on the levels of acrolein in body tissues or fluids for people living near hazardous waste sites. Also, there are no data regarding acrolein levels in various human tissues and body fluids for the general population. Because of the lack of recent comprehensive monitoring data for acrolein in water and food, the average daily intake of acrolein and the relative importance of each source of exposure cannot be determined. However, probabilistic estimates of 24-hour time-weighted concentrations of acrolein in air have been used to assess human exposures to acrolein in the Canadian population (Environment Canada 2000). Mean and median estimates of acrolein concentration of 1.3 and 0.6 $\mu g/m^3$ (0.56 and 0.26 ppb), respectively, were derived, with a 95% percentile value of 5.0 $\mu g/m^3$ (2.1 ppb). The estimate uses measured data on acrolein concentrations obtained between 1989 and 1996 for outdoor air in rural, suburban, and urban sites and indoor air measurements taken in 40 homes between 1991 and 1993. The exposure estimate assumes that both a mean time of 3 hours is spent outdoors and that the general population is exposed to

concentrations of acrolein similar to those in indoor air of their homes. Based on the mean estimate for acrolein concentration and an inhalation volume of 20 m^3 of air per day, it is estimated that an average adult will inhale 26 µg acrolein/day.

Environmental tobacco smoke (ETS) is a major source of acrolein exposure for many individuals in the general population. Nazaroff and Singer (2004) estimate that in 2000, between 31 and 53 million nonsmokers in the United States were exposed to acrolein concentrations in indoor air ranging from 1.6 to 3.6 µg/m^3 in households where ETS is generated by one or more individuals residing in the same household. Between 15 and 25 million of the affected number of nonsmokers are adults. Based on the lifetime average for the volume of inspired air of 14 m^3/day for males and 10 m^3/day for females, it is estimated that the inhalation intake of acrolein through inspiration of ETS over a lifetime is 22–50 µg/day for males and 16–36 µg/day for females. Assuming that the exposure data obtained from the Canadian study (Environment Canada 2000) discussed above are representative of exposures of residents in the United States to acrolein in households without ETS, then it is estimated that the inhalation intake of acrolein for nonsmokers exposed to ETS in the residence is 2.2–3.8 times greater for both males and females than in households without ETS. This comparison is based on inhalation intakes of acrolein for males and females in non-ETS households of 18 and 13 µg/day, respectively, that are based on an estimated mean acrolein concentration in air of 1.6 µg/L taken from the Canadian study (2000) and on the average daily inhalation volumes of air for males and females given by Nazaroff and Singer (2004).

In addition, acrolein is formed endogenously through the normal metabolism of α-hydroxy amino acids and polyamines (Alarcon 1970; Uchida et al. 1998a). Therefore, it is expected that a range of basal levels of acrolein will exist within the general population.

***Priority Recommendation*:** The identified data need to collect additional information is considered priority. For a sound database to serve as a solid foundation for higher level environmental or toxicological research, it should contain exposure information on the levels of acrolein in body tissues or fluids, particularly in populations living near hazardous waste sites. This information is necessary to better define exposure estimates in the general population and the workforce, and to examine the relationship between levels of acrolein in the environment, human tissues levels, and the subsequent development of health effects.

ATSDR has developed a hazardous substance release/health effects database (HazDat) that includes the extant data for the 31 NPL sites at which acrolein has been found. This database includes maximum concentrations of acrolein in on- and off-site media, and an indication of relevant routes of exposure. This database will not, however, supply information on the levels of acrolein (or its metabolites) in the tissues of individuals living near hazardous waste sites or other exposed populations such as workers.

d. Exposures of Children

Purpose: To determine if adequate data on exposures of children to acrolein are available for the purpose of conducting meaningful follow-up exposure and health studies.

***Finding*:** A data need to conduct additional studies to assess exposures of children to acrolein has been identified. There are no exposure studies or body burden measurements of acrolein in children, but it is likely that children are exposed to this compound in the same manner as adults. Based on all available data, the primary route of exposure for children to acrolein is through environmental tobacco smoke (ETS) generated by smokers living within the child's residence. Children are not likely to be exposed to acrolein from parent's clothing or other items removed from the work place. There have been no documented exposures of children to acrolein from pica, and children are unlikely to be exposed to acrolein from pica since the majority of acrolein released to the environment is emitted to the atmosphere. Based on the available data in aquatic systems (Bowmer and Higgins 1976), the release of acrolein to soil is expected to either volatilize or become inactivated through irreversible binding to soil. Because the primary route of exposure of children to acrolein is through inhalation, it is expected that intake of acrolein will be greater than an adult's due to greater ventilation rate per body weight or pulmonary surface area in children than in adults (Ginsberg et al. 2005).

***Priority Recommendation*:** The identified data need to conduct additional studies to assess exposures of children to acrolein is considered priority. Collecting information on the levels of acrolein in children is important in order to determine the extent of a child's exposure to acrolein through inhalation as well as to identify ways to reduce the potential sources for exposure risks.

e. Environmental Fate

***Purpose*:** To determine whether the available data are adequate to estimate exposure to acrolein under various conditions of environmental release for purposes of planning and conducting meaningful follow-up exposure and health studies.

***Finding*:** A data need to determine the persistence of acrolein in soil and groundwater has been identified. Based on a Henry's law constant of 1.22×10^{-4} atm-m^3/mol (Gaffney et al. 1987) and a vapor pressure of 274 mm Hg (Daubert and Danner 1987), acrolein is expected to partition primarily to the atmosphere. In the atmosphere, acrolein is degraded through reactions with photochemically produced hydroxyl radicals and ozone. Based on experimental rate constants ranging between 1.90×10^{-11} and 2.53×10^{-11} cm^3/molecule-sec at 25–26 °C and an ambient hydroxyl radical concentration of 5.0×10^5 molecules/cm^3, the half-life for acrolein in air is estimated to be 15–20 hours (Atkinson 1985). The products of this reaction include carbon monoxide, formaldehyde, glyoxal, and glycolaldehyde (Grosjean 1990). These reaction products are expected to also degrade in the atmosphere through reactions with hydroxyl radicals and direct photolysis. Degradation of acrolein through direct photolysis, ozone, or nitrate radicals is not expected to play a significant role in the degradation of acrolein in the atmosphere in comparison to degradation of the compound through reactions with hydroxyl radicals. Estimated half-lives for degradation of acrolein through photolysis is 10 days in the lower troposphere and <5 days in the upper troposphere (Gardner et al. 1987). Half-lives for acrolein in reactions with ozone ($k=2.8 \times 10^{-19}$ cm^3/molecules-sec at 25 °C) and nitrate radicals ($k=5.9 \pm 2.8 \times 10^{-16}$ cm^3/ molecules-sec at 25 °C) are estimated to be 59 and 16 days, respectively (Atkinson 1985; Atkinson et al. 1987).

Low concentrations of acrolein may degrade in natural water by either aerobic biodegradation, especially by acclimated cultures, or reversible hydration to β-hydroxypropionaldehyde, which subsequently undergoes aerobic biodegradation (Bowmer and Higgins 1976; Callahan et al. 1979; Ghilarducci and Tjeerdema 1995; Tabak et al. 1981). Acrolein at a concentration of 5–10 mg/L was completely degraded in 7–10 days in a static culture flask screening procedure (Tabak et al. 1981). Acrolein applied to surface waters at application rates suggested for herbicidal use (for example, 15 ppm) can persist up to 6 days (WSSA 1983). Bowmer and Higgins (1976) measured acrolein removal in both laboratory water and in field experiments using irrigation channels. Their studies suggested that the degradation of the hydration product of acrolein, 3-hydroxy-

propanal, occurs after the concentration of acrolein falls below 2–3 ppm. The degradation of 3-hydroxypropanal was also preceded by a 100-hour lag period, suggesting that biodegradation was occurring through the action of acclimated cultures. Data could not be located for the degradation of acrolein in groundwater.

Based on a log K_{oc} of 51–270, acrolein is expected to be mobile in soil and would have the potential to contaminate groundwater (Irwin 1988; Swann et al. 1983). However, there are competing factors that limit the potential for acrolein to migrate into groundwater including volatilization, reversible hydration, aerobic biodegradation, and irreversible binding to soil. The data in the literature are not adequate to determine to what extent these factors contribute to the fate of acrolein in soil. However, data collected from groundwater samples showing the presence of acrolein in 15 of 31 hazardous waste sites (HazDat 2005) suggest that these factors do not entirely limit the migration of acrolein through soil and into groundwater.

***Priority Recommendation*:** The identified data need is not considered priority. Although it is important to understand the contribution of volatilization, biodegradation, reversible hydration to β-hydroxypropionaldehyde (which biodegrades readily), and irreversible binding to soil to the fate of acrolein in soil, it is recognized that the primary release medium of acrolein in the environment is to air and surface water. The environmental fate in air is well understood. In surface water, the persistence of acrolein has been studied. However, it is not entirely certain to what extent volatilization, reversible binding, and aerobic biodegradation contribute to the lifetime of acrolein in surface water.

f. Bioavailability and Bioaccumulation Potential

***Purpose*:** To determine whether adequate data are available to predict the potential of acrolein to be taken up by people exposed via contaminated air, soil, water, and the food chain, in order to plan and conduct meaningful follow-up exposure and health studies.

***Finding*:** A data need to determine the bioavailability of acrolein from ambient air, drinking water, food, and fermented beverages has been identified. Acrolein is predominantly released into air and to a lesser extent into surface water as a biocide. Based on the Henry's law constant for acrolein (Gaffney et al. 1987), it is expected that acrolein will readily volatilize from water. Therefore, inhalation exposure is expected to represent the most likely route of exposure for the

general population. Because acrolein is mobile in soil, leaching into groundwater may occur at hazardous waste sites where it has been discarded and at sites of major spills. Ingestion of contaminated drinking water, and more importantly, inhalation of ambient air represent the most likely routes of exposure for residents living near hazardous waste sites. Based on the Henry's law constant, inhalation exposure is also probable given that acrolein is likely to volatilize from water during showering, bathing, washing laundry, dish washing, and other similar activities, especially when hot water is used. There are some data suggesting that acrolein is effectively absorbed in the upper and lower respiratory tracts in animals (Egle 1972). However, not as much is known about the absorption of acrolein by the gastrointestinal tract or skin. Information of the uptake and absorption of acrolein from ambient air, food, drinking water, and fermented beverages is needed to evaluate the potential for human exposure.

From a study of acrolein bioconcentration in fish, the experimental bioconcentration factor (BCF) value of 344 was determined in bluegill sunfish (Veith et al. 1980). However, because the study used ^{14}C-labeled acrolein, it was suggested that this BCF may be high given that acrolein metabolites may also have been measured. An estimated BCF of 0.6 was calculated using a linear regression equation based on a log octanol/water partition coefficient (K_{ow}) of -0.01 (Bysshe 1982; Hansch and Leo 1985). Based on these data and the physicochemical properties of acrolein, bioconcentration and bioaccumulation of the compound are not expected to occur.

Priority Recommendation: The identified data need is not considered a priority. Information on bioavailability from air is available. Air has been identified as the major release medium in the environment for acrolein and studies in animals have shown that acrolein is readily absorbed following inhalation exposure (Egle 1972, Morris et al. 1996, 2003) the primary exposure route for populations at hazardous waste sites. In addition, available information indicates that acrolein reacts at the point of contact in the nasal passages and lungs following inhalation exposure. Furthermore, the uptake and absorption of acrolein from drinking water, food, and fermented beverages is not considered the primary route of exposure for populations living near hazardous sites. Therefore, the need to further assess the bioavailability of acrolein from ambient air, drinking water, food, and fermented beverages is not assigned priority at this time.

2. Level III Data Needs

a. Registries of Exposed Persons

***Purpose*:** To help assess long-term health consequences of exposure to acrolein in the environment. The ATSDR Division of Health Studies will be asked to consider this substance for selection as a primary contaminant to establish an acrolein subregistry of the National Exposure Registry.

***Finding*:** A data need has been identified. Acrolein has been found in at least 31 NPL hazardous waste sites. At this time, no formal registries exist that identify people known to have been exposed to acrolein. The development of an exposure registry should provide an important reference tool to help assess long-term health consequences of exposure to acrolein. It should also facilitate the conduct of epidemiologic or health studies to assess any increased incidence of chronic disease or late-developing effects such as cancer. An effort is currently under way at ATSDR to identify those sites where humans have been exposed to site contaminants. From those identified sites, ATSDR can determine which sites list acrolein as a contaminant and the size of the potentially exposed population.

***Priority Recommendation*:** The identified data need is not considered priority. The development of an acrolein subregistry at this time would not contribute significantly to the current database. The development of an exposure subregistry should await the results of needed studies including information on levels in populations living near hazardous waste sites.

B. Toxicity Data Needs (Table 2)

The five remaining "prioritizing" tenets presented in the Decision Guide address toxicity data needs.

- Studies available for all toxicological profile substances to characterize target organs and dose response.
- Disposition studies and comparative physiologically-based pharmacokinetics when a toxic end point has been determined and differences in species response have been noted.
- Mechanistic studies on substances with significant toxicity and substantial human exposure.

- Investigation of methods for mitigation of toxicity for substances where enough is known about mode of action to guide research.
- Epidemiologic studies that will provide a direct answer on human disease for a substance of known significant toxicity.

The following is a brief summary of the toxicity data needs for acrolein. Please refer to the ATSDR Toxicological Profile for Acrolein, chapter on "Health Effects" for a more detailed discussion of available information (ATSDR 2005c). Generally, ATSDR believes that the most relevant route of human exposure to acrolein at waste sites is inhalation, thus ATSDR scientists believe that the proposed toxicity studies should be conducted via the inhalation route. Additionally, animal testing should be conducted on the species with metabolism most similar to humans or the most sensitive species.

1. Levels I & II Data Needs

ATSDR determines Minimal Risk Levels (MRLs) which are defined as estimates of daily human exposure to a chemical that are likely to be without appreciable risk of deleterious effects over a specified duration. In order to derive MRLs for acute, intermediate, and chronic exposure durations, ATSDR evaluates the substance-specific database to identify studies of the appropriate route and duration of exposure. Thus, in order to derive acute MRLs, ATSDR evaluates studies of 14 days or less duration that identify the target organs and levels of exposure associated with these effects. Similar studies are identified for intermediate and chronic duration exposures.

Currently, ATSDR is using tools such as physiologically-based pharmacokinetic modeling and pharmacodynamic modeling to extrapolate data across routes or durations of exposure. ATSDR acknowledges that such extrapolations may be done on a substance-by-substance basis after adequate toxicokinetics information has been collected.

As reflected in the Decision Guide, ATSDR assigns priorities to identified data needs for acute/intermediate (Level I) studies by the most relevant route of exposure at Superfund sites. Regarding the need to conduct studies by other routes of exposure, ATSDR usually first requires toxicokinetic studies for the three routes of exposure to determine the need for the additional route-specific information.

Regarding chronic studies, ATSDR acknowledges that appropriately conducted 90-day studies can generally predict the target organs for chronic exposure. However, they might fall short in accurately predicting the levels of exposure associated with these effects. Although ATSDR acknowledges this fact, it will generally await the results of prechronic and toxicokinetic studies before assigning priority to chronic toxicity studies. Note: Chronic toxicity studies may be separated from cancer bioassays; they require a 1-year exposure.

a. Acute-Duration Exposure

***Purpose*:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause acute human health effects.

***Finding*:** A data need to conduct additional studies via inhalation, oral, and dermal exposure has been identified. Information on the acute toxicity of acrolein in humans comes primarily from experimental studies of upper respiratory tract and eye irritation in volunteers (Sim and Pattle 1957; Weber-Tschopp et al. 1977). These studies identified effect levels for respiratory and ocular irritation in various vapor exposure scenarios of up to 60 minutes in duration, and are supported by similar findings in animals (Cassee et al. 1996; Lyon et al. 1970). Observed respiratory effects included nasal irritation, discomfort, and reduction in respiratory rate in humans (Weber-Tschopp et al. 1977), reduced respiratory rate in rats and mice (Buckley et al. 1984; Cassee et al. 1996; Kane and Alarie 1977), histological changes in nasal epithelium of rats and mice (Cassee et al. 1996), and reduced bactericidal activity in lungs of mice (Aranyi et al. 1986). More severe respiratory effects included dyspnea, coughing, foamy expectoration, cyanosis, tracheal and alveolar epithelial destruction, pulmonary edema, and lung hemorrhage in humans, mice, rats, guinea pigs, hamsters, and dogs (Buckley et al. 1984; Catilina et el. 1966; Champeix et al. 1966; Dahlgren et al. 1972; Hales et al. 1988; Kilburn and Mckenzie 1978; Murphy et al. 1964; Skog 1950).

The human and animal data clearly indicate that the respiratory tract is the primary target of acrolein toxicity via acute inhalation exposure, and a lowest-observed-adverse-effect level (LOAEL) of 0.3 ppm for nasal and throat irritation and decreased respiratory rate in humans exposed for 60 minutes (Weber-Tschopp et al. 1977) was used as the basis for an acute-duration inhalation MRL. No reliable human no-observed-adverse-effect level (NOAEL) was identified. A LOAEL of 0.1 ppm was reported for reduced lung bactericidal activity in rats (Aranyi et al.

1986), but the toxicological significance of this finding is unclear. A LOAEL of 0.25 ppm was reported for nasal histopathology in rats (Cassee et al. 1996), but this level is essentially the same as the human LOAEL of 0.3 ppm. The human LOAEL was the preferred basis for the Minimal Risk Level (MRL) because it eliminated the introduction of uncertainty from interspecies extrapolation. Additional studies are needed to better characterize the exposure-response relationship, particularly for identification of a NOAEL and to provide data on effect levels for acute-duration inhalation exposures longer than 60 minutes (e.g., 14 days). These studies could also be used to provide information on systemic toxicity at exposure levels below those causing nasal irritation, as well as a comparison of young and adult animals (to address children's susceptibility as discussed in that section).

No data are available on effects of acute oral exposure to acrolein in humans. Information regarding acute oral toxicity in animals is essentially limited to maternal data in developmental toxicity studies in rats and rabbits (King 1982; Parent et al. 1993) and observations during the early part of a chronic study in dogs (Parent et al. 1992b). Effects in these studies included severe stomach ulceration, edema, and death in pregnant rabbits at 4 mg/kg/day (Parent et al. 1993), and vomiting in dogs shortly after daily dosing with 0.5 mg/kg/day during the first 4 weeks of the chronic study (Parent et al. 1992b). The relevance of the 0.5 mg/kg/day LOAEL in dogs is questionable because the effect might have been impacted by the capsule method of oral treatment and because of a lack of information on statistical significance. Derivation of an acute oral MRL was precluded by the identification of a higher NOAEL of 0.75 mg/kg/day for forestomach histopathology in rats in a well-conducted intermediate-duration oral gavage study (NTP 1995). The available data indicate that the gastrointestinal tract is a sensitive target of acute oral toxicity, but additional studies are needed to determine a suitable NOAEL and LOAEL for MRL derivation. Studies using nonpregnant animals and gastrointestinal histological examinations to identify sensitive irritant effects would be particularly useful.

Acute dermal exposure to liquid acrolein caused skin irritation, burns, and epidermal necrosis in humans (Champeix et al. 1966; Lacroix et al. 1976; Schöning 1966), but no data are available on skin effects in dermally exposed animals. Eye irritation is a particularly sensitive dermal effect of acute vapor exposure to acrolein, occurring in volunteers at concentrations as low as 0.3–0.5 ppm for 10–40 minutes (i.e., in the range of the LOAEL for respiratory irritation) (Kane and Alarie 1977; Sim and Pattle 1957; Weber-Tschopp et al. 1977). Ocular irritative effects in animals are qualitatively similar to those in humans and have been observed in dogs and monkeys at vapor

concentrations in the range of 1.8–3.7 ppm (Lyon et al. 1970). Additional studies are needed to identify a NOAEL for ocular irritation, provide data on ocular effect levels for longer acute-duration exposures (e.g., for 14 days), and determine NOAELs and LOAELs for local and systemic effects of skin exposure.

***Priority Recommendation*:** The identified data needs to conduct additional studies via inhalation, oral, and dermal exposure are not considered priority. Inhalation is the primary exposure route for acrolein at hazardous waste sites. Additional studies are needed to identify thresholds for nasal and ocular irritation and systemic target organs, particularly for longer-duration acute exposures, but these are not priority because the available data provide a sufficient basis for inhalation MRL derivation. The needs for additional oral and dermal data are not priority because oral and dermal exposures are not considered primary routes for populations living near hazardous waste sites.

b. Intermediate-Duration Exposure

***Purpose*:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause subchronic human health effects.

Finding: A data need to conduct additional studies via inhalation, oral, and dermal exposure has been identified. No data are available for effects of intermediate-duration inhalation exposure to acrolein in humans. Studies in animals indicate that the respiratory tract is the most sensitive target of toxicity for inhaled acrolein. Exposures to acrolein concentrations between 0.4 and 5.0 ppm for up to 180 days caused a continuum of histological alterations, inflammation, and severe tissue destruction across the entire respiratory tract of rats (Costa et al. 1986; Feron et al. 1978; Kutzman et al. 1984, 1985; Lyon et al. 1970), rabbits (Feron et al. 1978), guinea pigs (Lyon et al. 1970), and monkeys (Lyon et al. 1970). The most sensitive effects were nasal epithelial metaplasia and bronchial inflammation, which occurred in rats exposed to 0.4 ppm for 6 hours/day, 5 days/week for 13 weeks (Feron et al. 1978). The 0.4 ppm LOAEL for nasal metaplasia was used to derive an intermediate-duration inhalation MRL. Additional studies are needed to identify the toxicity threshold (NOAEL region) for respiratory effects and to verify that there are no sensitive systemic effects for intermediate-duration inhalation (e.g., neurotoxicity and immunotoxicity, as discussed in those sections).

No data were located on effects of intermediate-duration oral exposure to acrolein in humans. Information in animals is available from 13-week toxicity studies in rats and mice (NTP 1995) and two-generation reproduction studies in rats (King 1984; Parent et al. 1992c) exposed by gavage. Although the number of oral animal studies for this exposure duration is limited, the findings provide consistent evidence that the stomach is the most sensitive target of toxicity. The lowest LOAEL was 1.25 mg/kg/day for squamous epithelial hyperplasia of the forestomach in rats and glandular stomach in mice exposed for 13 weeks (NTP 1995). A NOAEL of 0.75 mg/kg/day was associated with the LOAEL in rats, but no NOAEL was identified in the mice because the LOAEL was the lowest tested dose in this species. The rat NOAEL was used as the basis for deriving an intermediate-duration oral MRL. Additional testing is needed to identify a NOAEL in mice (i.e., to establish that there are no adverse gastrointestinal effects in mice at or below the NOAEL in rats used to derive the MRL), as well as to verify that the stomach is the most sensitive target of toxicity.

No data are available on effects of intermediate-duration dermal exposure to acrolein in humans. Dermal exposure information in animals is essentially limited to observations of ocular irritation (lacrimation and blinking or closing of the eyes) in dogs and monkeys during intermittent intermediate-duration exposures to 1.8-3.7 ppm of acrolein vapor for 6 weeks; no observable ocular changes were found in similarly exposed rats and guinea pigs (Lyon et al. 1970). No data are available on effects of intermediate-duration skin exposure to acrolein in animals. Additional studies are needed to assess the potential for dermal toxicity and species differences by identifying intermediate-duration NOAELs and LOAELs for eye, skin, and systemic effects.

***Priority Recommendation*:** The identified data needs to conduct additional studies via inhalation, oral, and dermal exposure are not considered priority. Inhalation is the primary exposure route for acrolein at hazardous waste sites. Additional studies are needed to better define thresholds for respiratory effects, but these are not priority because the available data were a sufficient basis for MRL derivation. The needs for additional oral and dermal data are not priority because oral and dermal exposure are not considered primary routes for populations living near hazardous waste sites.

c. Chronic-Duration Exposure

(1) Toxicity Assessment

***Purpose*:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause chronic human health effects.

***Finding*:** A data need to conduct additional studies via inhalation, oral, and dermal exposure has been identified. No studies were located regarding toxicity in humans following chronic exposure. In the only chronic inhalation study in animals, respiratory toxicity (epithelial hyperplasia) was observed in rats that were exposed to 8 ppm of acrolein for 1 hour/day, 7 days/week for 18 months (Le Bouffant et al. 1980). Use of this study for chronic-duration inhalation MRL derivation is precluded by the short daily exposure period and single exposure level. Chronic-duration inhalation studies with a longer daily exposure duration, multiple exposure levels sufficient for identifying a NOAEL and LOAEL for respiratory and systemic targets, are needed to derive a chronic-duration inhalation MRL.

Chronic oral studies were conducted in which acrolein was administered daily to rats by gavage in doses up to 2.5 mg/kg/day for 102 weeks (Parent et al. 1992a), mice by gavage in doses up to 4.5 mg/kg/day for 18 months (Parent et al. 1991), and dogs by capsule in doses up to 2 mg/kg/day for 12 months (Parent et al. 1992b). None of these chronic exposures produced unusual gross or histopathological changes to the gastrointestinal tract or other tissues, as have been observed in shorter duration studies at similar and lower dose levels (e.g., gastric lesions in rats and mice in the 13-week NTP [1995] study). Vomiting occurred in the dogs shortly after dosing during the first four weeks of treatment, suggesting gastrointestinal irritation, but adaptation seemed to occur because there was a marked reduction in the frequency of the vomiting later in the study. Systemic effects in the chronic oral studies included decreased serum creatinine phosphokinase levels in rats at 0.05 mg/kg/day and reduced survival in rats at 0.5 mg/kg/day (Parent et al. 1992a) and mice (Parent et al. 1991) at 4.5 mg/kg/day, but the significance and/or cause of these effects is unknown. The inadequacy of the database precluded derivation of a chronic-duration oral MRL for acrolein. Additional studies are needed to better characterize the effects and dose-response relationships (NOAELs and less serious LOAELs) for chronic oral exposure, particularly in the gastrointestinal tract, which has been shown to be a sensitive target of toxicity

in intermediate-duration studies. These studies could also help to determine the reason for the lack of gastrointestinal tract histopathology in the existing chronic oral studies.

No studies were located regarding effects of acrolein in animals following chronic dermal exposure.

***Priority Recommendation*:** The identified data need to conduct additional chronic studies via inhalation exposure is considered priority. An adequately designed chronic inhalation study is needed because the only available study has limitations that preclude its use as the basis for MRL derivation. The data needs for oral and dermal data are not considered priority because oral and dermal exposure are not the primary routes of exposure for populations near hazardous waste sites.

(2) Cancer Assessment

***Purpose*:** To determine whether populations potentially exposed to acrolein are at an increased risk for developing cancer for purposes of conducting meaningful follow-up exposure and health studies. Similar to toxicity end point assessment, when bioassays are indicated because of the potential for substantial exposure and the lack of information on carcinogenicity, ATSDR will generally only assign priority to a bioassay conducted via the most relevant route of human exposure at Superfund sites.

Comparative toxicokinetic information across routes as previously discussed will be assigned priority and conducted before assigning priority to any additional routes of exposure. In cases where the assessment of chronic toxicity and carcinogenicity can be combined, they will.

***Finding*:** A data need to conduct additional studies for the carcinogenicity of acrolein via the inhalation, oral, and dermal routes has been identified. No studies were located regarding the carcinogenicity of acrolein in humans. Two single exposure level studies in animals provide limited information on the carcinogenic potential after inhalation exposure. Feron and Kruysse (1977) found no evidence of tumors in the respiratory tract or other tissues and organs in hamsters exposed to 4 ppm acrolein for 7 hours/day, 5 days/week for 52 weeks. Although the maximum tolerable dose (MTD) appears to have been achieved with the tested concentration, the duration of the study is too short for an adequate determination of carcinogenicity. Le Bouffant et al.

(1980) found no evidence of tumors in the respiratory tract or other tissues and organs in rats exposed to 8 ppm acrolein for 1 hour/day, 7 days/week for 18 months. This study is limited by the single exposure level (and an apparent failure to achieve an MTD), short daily duration of exposure, and less-than-lifetime duration of exposure. A well-designed bioassay in animals, using appropriate dose levels and durations of exposure, is needed to adequately assess the carcinogenicity of acrolein via inhalation exposure.

Information on the carcinogenicity of acrolein in animals following oral exposure is available from four studies. One study reported a slightly increased incidence of adenomas in the adrenal cortex of female rats exposed to 29 mg/kg/day acrolein in drinking water on 5 days/week for 104–124 weeks (Lijinsky and Reuber 1987), but an independent pathology working group concluded that the incidence was within the limits of historical controls and of no biological significance (cited in Parent et al. 1992c). Daily administration of acrolein did not cause an increase in adrenal or other neoplasms in rats exposed to ≤2.5 mg/kg/day by gavage for 102 weeks (Parent et al. 1992a), mice exposed to ≤4.5 mg/kg/day by gavage for 18 months (Parent et al. 1991), or dogs exposed to ≤2 mg/kg/day by capsule for 12 months (Parent et al. 1992b). Additional lifetime testing needs to be performed in order to better assess carcinogenic potential in animals exposed to high doses of acrolein in drinking water (i.e., using a non-bolus method of oral exposure).

A dermal initiation-promotion study was conducted in which acrolein was used as the initiator by weekly application to the skin of mice for 10 weeks (Salaman and Roe 1956). Croton oil was used as the promoter by 18 weekly applications beginning 25 days after the first application of acrolein. Incidences of skin tumors at the application site and lung tumors were not increased at the end of the croton oil treatment, indicating that acrolein had no activity as a tumor initiator. These results should be interpreted with caution since the study duration was too short to evaluate carcinogenic potential and only 15 mice were examined. Additional testing is needed to assess the complete dermal carcinogenicity of acrolein (i.e., exposure in the absence of a tumor promoter).

The DHHS has not classified acrolein as to its carcinogenicity. IARC has determined that acrolein is not classifiable as to carcinogenicity in humans (IARC 2004). The EPA has stated that the potential carcinogenicity of acrolein cannot be determined based on an inadequate database (IRIS 2005).

***Priority Recommendation*:** The identified data need to conduct additional studies by inhalation exposure is not considered priority. Although the available data are insufficient for assessing the potential carcinogenicity of acrolein and a well-designed study would address the limitations of the existing studies, the results of the structure activity relationship (SAR) analyses, conducted by the ATSDR Computational Toxicology Methods Development Unit, do not provide supporting evidence to suggest that acrolein would be carcinogenic (ATSDR 2005d). Therefore, no priority is assigned to the identified data need at this time. The data needs for studies to be conducted via oral and dermal exposure are not considered priority because these two exposure routes are not the primary exposure routes for populations living near hazardous waste sites.

d. Genotoxicity

***Purpose*:** To evaluate the mechanism of acrolein-induced toxicity for purposes of future mitigation activities. Generally, priority is assigned genotoxicity studies if information is lacking to assess the genotoxic potential of this substance both *in vivo* (mouse micronucleus) and *in vitro* (Ames *Salmonella*). This is particularly true if there are human data to suggest that the substance may act by a genotoxic mechanism to cause cancer, reproductive toxicity, etc., or there exists "structural alerts" that suggest that the substance may be genotoxic. Additional studies will not be assigned priority simply to confirm or refute an equivocal database without justification.

***Finding*:** A data need to conduct additional genotoxicity studies has been identified. No studies were located on the genotoxicity of acrolein in humans or laboratory animals exposed by the inhalation, oral, or dermal routes. In the only *in vivo* tests, acrolein did not induce dominant lethal mutations in mice exposed by intraperitoneal injection (Epstein et al. 1972) or sex-linked recessive lethal mutations in *Drosophila* exposed by feeding or injection (Zimmering et al. 1985). The *in vitro* genotoxicity of acrolein has been investigated in prokaryotic and eukaryotic organisms and in mammalian cell systems. The overall evidence in bacteria indicates that acrolein is weakly mutagenic without metabolic activating systems and non-mutagenic in the presence of activating systems, in *Salmonella typhimurium* (Eder et al. 1982; Foiles et al. 1989; Khudoley et al. 1987; Lijinsky and Andrews 1980; Lutz et al. 1982; Marnett et al. 1985; Waegemaekers and Bensink 1984) and *Escherichia coli* (Ellenberger and Mohn 1977; Hemminki et al. 1980; Von der Hude et al. 1988). Acrolein did not induce gene mutations or chromosomal aberrations in the yeast *Saccharomyces cerevisiae* (tested without activation) (Fleer and Brendel

1982; Izard 1973). In mammalian cells, acrolein caused chromosomal breakage and sister chromatid exchange in Chinese hamster ovary cells (Au et al. 1980), gene mutations in Chinese hamster V79 cells and human fibroblasts (Kawanishi et al. 1998; Smith et al. 1990), DNA damage in human myeloid cells and bronchial cells (Crook et al. 1986; Grafstrom et al. 1988; Krokan et al. 1985), inhibition of DNA polymerase activity and DNA and RNA synthesis in rat liver cells (Moule et al. 1971; Munsch et al. 1973, 1974), and inhibition of DNA repair in human fibroblasts (Curren et al. 1988). The mechanism by which acrolein induces genotoxicity in mammalian cells is not known. It has been shown that acrolein can form adducts with DNA (Chung et al. 1984; Foiles et al. 1989; Smith et al. 1990), although testing in human HeLa and xeroderma pigmentosum cells (Yang et al. 2002) and *E. coli* (VanderVeen et al. 2001) indicated an inability of acrolein DNA adducts to cause miscoding errors. Additional *in vivo* studies are needed to provide a more sufficient basis for predicting whether acrolein poses a genotoxic threat to humans.

***Priority Recommendation*:** The identified data need to conduct additional genotoxicity studies is not considered priority. Both *in vivo* and *in vitro* genotoxicity studies for acrolein are available. *In vitro* studies of acrolein have shown evidence of mutagenicity in bacteria and mammalian cells and chromosomal and DNA damage in mammalian cells. Although information on the genotoxicity of acrolein *in vivo* is scant, the two available studies indicated no mutagenic effects in mice and *Drosophila.* Also, there are no human data to suggest that acrolein may act via genotoxic mechanism to cause adverse health effects. Therefore, additional studies to further assess the genotoxic potential of acrolein *in vivo* are not considered a priority at this time.

e. Endocrine Disruption

***Purpose*:** To determine whether populations potentially exposed to acrolein are at an increased risk to develop toxicity of the endocrine system for purposes of conducting meaningful follow-up exposure and health studies. Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the

synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior.

Generally, when considering the need to assign priority, in the absence of all information on this end point, ATSDR will assign priority to screening studies that examine effects on a) male and female reproductive organs, and b) other endocrine organs including hypothalamus, pituitary, thyroid, parathyroid, adrenal, pancreas, paraganglia, and pineal body. Such screening level studies include, but are not limited to, *in vitro* studies (e.g., [1] Estrogen Receptor Binding/Transcriptional Activation Assay, [2] Androgen Receptor Binding/Transcriptional Activation Assay, and [3] Steroidogenesis Assay with Minced Testis), and *in vivo* studies (e.g., [1] Rodent 3-day Uterotropic Assay, [2] Rodent 20-day Pubertal Female Assay with Thyroid, and [3] Rodent 5–7 day Herschberger Assay).

If any of the following is true, then ATSDR will consider assigning Level II priority to 2-generation reproductive studies: if (1) there are suggestions that acrolein may have endocrine disrupting potential from Level I studies; or (2) if there have been human anecdotal reports of endocrine disrupting effects following acrolein exposure; or (3) if there are structurally similar compounds that affect the endocrine system.

As before, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to studies conducted via additional routes of exposure.

***Findings*:** A data need to conduct additional studies on the endocrine system via dermal exposure has been identified. There are no human data on the potential of acrolein to disrupt the endocrine system. No *in vitro* endocrine disruptor screening studies or *in vivo* assays of endocrine function in animals (e.g., measurements of serum hormone levels) are available. Several studies in animals, however, provide data regarding a lack of effect of acrolein on the histology of endocrine tissues and on reproduction. Histological examinations of endocrine tissues were performed in rats, mice, and dogs exposed by inhalation (Feron et al. 1978; Lyon et al. 1970) or oral administration (Lijinsky and Reuber 1987; NTP 1995; Parent et al. 1991, 1992a, 1992b) with negative results. The examinations in these intermediate- and chronic-duration studies generally included the thyroid, adrenals, and pancreas, although the parathyroids and pituitary were also evaluated following oral exposure. Histological examinations of pertinent

reproductive tissues (e.g., testes and ovaries) in the aforementioned inhalation and oral studies showed no changes, and studies of reproductive function in animals exposed by inhalation or oral routes (Bouley et al. 1975; King 1984; Parent et al. 1993) indicate that acrolein is unlikely to impair reproduction. The available oral and inhalation data for noncancer effects in animals do not suggest that acrolein has endocrine disrupting activity. No data are available for the dermal route, indicating a need for screening data (e.g., reproductive and other endocrine histopathology in a dermal study).

***Priority Recommendation*:** The available data on reproductive function and histology of reproductive and endocrine tissues in animals exposed by the inhalation or oral routes do not indicate that acrolein has an endocrine disrupting potential. The identified data need to conduct additional studies on the endocrine system via dermal exposure is not considered priority based on the inhalation and oral findings and because dermal exposure is not a primary route for populations near hazardous waste sites.

f. Reproductive Toxicity

***Purpose*:** To determine whether populations potentially exposed to acrolein are at an increased risk to develop reproductive effects for purposes of conducting meaningful follow-up exposure and health studies. ATSDR scientists believe it is important to acquire reproductive toxicity data in order to consider the needs of susceptible populations. It is desirable to have information on reproductive toxicity before developing MRLs to ensure that target organs have been adequately evaluated.

Generally, when considering the need to assign priority, in the absence of all information on this end point, ATSDR will assign priority to the conduct of 90-day studies with special emphasis on reproductive organ pathology. If any of the following is true, then ATSDR will consider assigning priority to multigeneration animal studies: (1) If any indication is found in these studies that the reproductive system of either male or female animals is a target organ of substance exposure; or (2) if there have been human anecdotal reports of reproductive effects following substance exposure; or (3) if there are structurally similar compounds that affect reproduction.

As before, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to studies conducted via additional routes of exposure.

***Finding*:** A data need to conduct additional reproductive studies via inhalation and dermal exposure has been identified. No studies were located regarding reproductive effects of acrolein in humans. Histological examinations of reproductive organs and tissues showed no effects in rats after intermediate-duration inhalation exposure (Feron et al. 1978), or in rats, mice, or dogs after chronic oral exposure (Parent et al. 1991, 1992a, 1992b). Dominant lethal mutations were not induced in mice exposed to acrolein by inhalation (Epstein et al. 1972). There was no effect on the number of pregnancies and fetuses in rats that were continuously exposed to acrolein by inhalation for 3 days prior to mating through gestation (Bouley et al. 1975), but this study is limited by the short duration of pre-mating exposure and the use of only one exposure level. Additional inhalation testing is needed to address the limitations of the data by this route. Reproductive performance was not impaired in two-generation studies of orally-exposed rats (King 1984; Parent et al. 1992c), indicating that acrolein is unlikely to impair reproduction by oral route. No information is available on reproductive effects in animals after dermal exposure to acrolein, indicating a need for testing by this route.

***Priority Recommendation*:** The identified data need to conduct additional reproductive toxicity studies via inhalation and dermal exposure is not considered priority because the two oral multigeneration studies provide a sufficient indication that acrolein does not impair reproductive performance. Additionally, dermal exposure is not a primary route for populations near hazardous waste sites.

g. Developmental Toxicity

***Purpose*:** To determine whether populations potentially exposed to acrolein are at an increased risk for developmental effects for purposes of conducting meaningful follow-up exposure and health studies. Similar to reproductive toxicity assessment, Agency scientists believe it is important to assess the developmental toxicity data.

In the absence of any reproductive or teratologic information, ATSDR will consider proposals to simultaneously acquire reproductive and teratological information. ATSDR acknowledges that,

in some circumstances, developmental studies may be assigned priority if the following statements are true: (1) if a two-generation reproductive study provides preliminary information on possible developmental toxicity of acrolein, (2) if there are human anecdotal reports of developmental effects following acrolein exposure, *or* (3) if structurally similar compounds have caused developmental effects.

As for reproductive toxicity, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to the conduct of studies via additional routes of exposure.

***Finding*:** A data need to conduct additional developmental studies via inhalation and dermal exposure has been identified. No studies were located regarding developmental effects of acrolein in humans by any route of exposure, or in animals exposed by inhalation or dermally. Information on the developmental toxicity of acrolein after oral exposure is available from studies in rats and rabbits (King 1982; Parent et al. 1992c, 1993). Developmental toxicity was observed in the offspring of rats gestationally exposed to a maternally toxic oral dosage of acrolein; effects included decreased mean fetal and total litter weights and increased incidences of skeletal anomalies and delayed ossification (King 1982). Rats that were exposed to a lower maternally toxic oral dose of acrolein during gestation and lactation in a two-generation study had pups with body weights that were reduced through postpartum day 21, but no effects on litter viability and size, gestation duration, or pup growth and morphology were observed (Parent et al. 1992c). Fetal resorptions were increased in a preliminary dose range-finding study in which rabbits were orally exposed to acrolein during gestation, but this and other developmental toxicity end points were not affected in the main study using similar dose levels and larger numbers of rabbits (Parent et al. 1993); no explanation for the discrepancy was provided. The available data indicate that oral exposure to acrolein may cause developmental toxicity in animals at high doses (e.g., levels that are maternally toxic). Studies by the inhalation and dermal routes would provide data for corroborating the oral findings and establishing dose-response relationships by these routes.

Priority Recommendation: The identified data need to conduct additional developmental toxicity studies via inhalation and dermal exposure is not considered priority. There are no human anecdotal reports of developmental effects following acrolein exposure via any exposure routes. Also, although data from animal studies conducted via oral exposure indicated that acrolein may cause developmental toxicity, the effect was observed only at a maternally toxic

dose (King 1982). In addition, the evidence for developmental toxicity at lower oral doses is inconclusive (Parent et al. 1992c, 1993). Therefore, the identified need to conduct studies by the inhalation route (the primary route of acrolein exposure for populations surrounding hazardous waste sites) to assess the potential for developmental toxicity is not assigned priority. This is because developmental toxicity does not appear to be a primary effect of concern following acrolein exposure based on the available data.

Although developmental data for the dermal route are not available, this need is not considered priority because dermal exposure is not a primary route for populations near hazardous waste sites.

h. Immunotoxicity

Purpose: To evaluate the mechanism of acrolein-induced toxicity for purposes of defining target organs and future mitigation activities. There is evidence to suggest that the immune system might be a susceptible target organ for many environmental contaminants. In the absence of any information on the immune system as a target organ, priority will be assigned to the evaluation of the immune system (lymphoid tissue, blood components) as an end point in 90-day studies (Level I) before assigning priority to an immunotoxicology battery as recently defined by the NTP.

For those substances that either (1) show evidence of immune system effects in 90-day studies, (2) have human anecdotal data to suggest that the immune system may be affected, or (3) are structurally similar to known immunotoxicants, an immunotoxicology battery of tests will be assigned priority.

***Finding*:** A data need to conduct additional immunotoxicity studies via inhalation, oral, and dermal exposure has been identified. No studies were located regarding immunological effects of acrolein in humans by any route of exposure, or in animals exposed orally or dermally. In animals exposed by inhalation, acute- and intermediate-duration studies suggest that acrolein may increase the risk of bacterial infections in the respiratory tract (Aranyi et al. 1986; Astry and Jakab 1983; Bouley et al. 1975; Leach et al. 1987; Sherwood et al. 1986). Exposure to 0.1 ppm acrolein for 3 hours/day for 5 days caused reduced alveolar macrophagic removal of *Klebsiella pneumoniae* bacteria from an aerosol infection in mice (Aranyi et al. 1986). No difference was observed in rats for this same exposure/infection protocol (Sherwood et al. 1986). Eight-hour

exposures to 3 and 6 ppm acrolein in mice similarly caused reduced clearance of *Staphylococcus aureus* from a pulmonary infection, although there was no clear effect at higher concentrations (Astry and Jakab 1983). Rats exposed to 0.55 ppm acrolein had lower alveolar macrophage levels after 10–26 days of exposure, but not after 60–180 days (Bouley et al. 1975). These studies provide no information on whether the effects are toxicologically significant and do not necessarily indicate that inhaled acrolein affects the immune system, because the reduced removal of bacteria from the alveolar spaces could be due to a direct cytotoxic effect of acrolein on the alveolar macrophages present in the respiratory epithelium. The only other information on possible immunological effects of acrolein are negative results of histological examinations of immune system tissues in rats, mice, and dogs exposed by inhalation (Feron et al. 1978; Lyon et al. 1970) or oral administration (Lijinsky and Reuber 1987; NTP 1995; Parent et al. 1991, 1992a, 1992b) in intermediate- and chronic-duration studies. None of the available studies utilized comprehensive immunological testing that might have detected functional effects, indicating that there is a need for additional studies to assess whether low levels of acrolein by the inhalation, oral, and dermal routes represent an immunotoxic concern. Additionally, dermal sensitization studies in animals could provide information on whether acrolein is likely to cause an allergic response.

***Priority Recommendation*:** The identified data need to conduct additional immunotoxicity studies via inhalation exposure is not considered priority. There are no human anecdotal reports of immune system effects following acrolein exposure via any of the exposure routes. Also, although the acute- and intermediate-duration inhalation studies in animals indicate that alveolar macrophages may be a target of acrolein exposure, it is not known if this is due to an immunotoxic response or a nonspecific cytotoxic effect of the chemical. In addition, the only other information on possible immunological effects of acrolein are negative results of histological examinations of immune system tissues in rats, mice, and dogs exposed by inhalation or oral administration in intermediate- and chronic-duration studies. Therefore, the identified need to conduct studies by the inhalation route (the primary route of acrolein exposure for populations surrounding hazardous waste sites) to assess the potential for immunotoxicity is not assigned priority. This is because immunotoxicity does not appear to be a major effect of concern following acrolein exposure based on the available data.

Although immunotoxicity data for the oral and dermal routes are not available, these needs are not considered priority because oral and dermal exposures are not primary routes for populations near hazardous waste sites.

i. Neurotoxicity

***Purpose*:** To evaluate the mechanism of acrolein-induced toxicity to define target organs and future mitigation activities. Similar to immunotoxicity, there is a growing body of data to suggest that the nervous system is a very sensitive target organ for many environmental chemicals. In the absence of any information on the nervous system as a target organ, priority will be assigned to the evaluation of the nervous system as an end point in 90-day studies (Level I) before assigning priority to a neurotoxicology battery.

It may be possible to assign priority to evaluation of demeanor in 90-day studies along with neuropathology. For those substances that either (1) show evidence of nervous system effects in 90-day studies, (2) have human anecdotal data to suggest that the nervous system may be affected, or (3) are structurally similar to known neurotoxicants, a neurotoxicology battery of tests will be assigned priority.

***Finding*:** A data need to conduct additional neurotoxicity studies via inhalation, oral, and dermal exposure has been identified. No information was located regarding neurological effects of acrolein in humans exposed by any route. No behavioral changes or clinical signs of neurotoxicity in animals were observed in acute- and intermediate-duration inhalation studies of acrolein. Intermediate-duration inhalation exposure caused increased brain/body weight ratio and inflammatory responses in the brain in rats, guinea pigs, dogs, and/or monkeys (Feron et al. 1978; Kutzman et al. 1984; Lyon et al. 1970). These effects are not necessarily indicative of acrolein neurotoxicity because the increase in relative brain weight occurred at an exposure level that also caused mortality and a reduction in body weight, and the brain inflammation was a nonspecific response at exposure levels that also caused inflammation in other tissues. Symptoms of central nervous system depression (e.g., slow response to stimuli, body sag, loss of elevation reflexes, poor body tone) were observed in rats after acute oral exposure to acrolein, but only at a dose level that was lethal (Sprince et al. 1979), indicating that it is unclear whether the neurological effects are directly due to acrolein or are nonspecific responses in dying animals. No histological changes were found in the brain, sciatic nerve, or spinal cord of rats, mice, or dogs after chronic

oral exposure to acrolein (Parent et al. 1991, 1992a, 1992b). No studies regarding neurotoxicity of acrolein after dermal exposure were located. None of the available studies utilized comprehensive neurological testing that may have detected subtle neurotoxic effects, indicating that there is a need for additional studies to assess whether low levels of acrolein by the inhalation, oral, and dermal routes represent a neurotoxic concern.

***Priority Recommendation*:** The identified data need to conduct additional neurotoxicity studies via inhalation exposure is not considered priority. There are no human anecdotal reports of nervous system effects following acrolein exposure via any of the exposure routes. Also, although acrolein caused increased relative brain weight and inflammation in the brain after intermediate-duration inhalation exposure in animals, and clinical signs of neurotoxicity in dying animals after acute oral exposure, these effects appear to be nonspecific and not necessarily due to acrolein neurotoxicity. In addition, no histological changes were found in the brain, sciatic nerve, or spinal cord of rats, mice, or dogs after chronic exposure to acrolein. Therefore, the identified need to conduct studies by the inhalation route (the primary route of acrolein exposure for populations surrounding hazardous waste sites) to assess the potential for neurotoxicity is not assigned priority. This is because neurotoxicity does not appear to be a major effect of concern following acrolein exposure based on the available data.

Additional studies by the oral and dermal routes are not considered priority because oral and dermal exposures are not primary routes for populations near hazardous waste sites.

j. Toxicokinetics

***Purpose*:** To evaluate the disposition of acrolein across species and routes of exposure to elucidate target organs and mechanisms of toxicity, and to assess the need to conduct studies by routes other than the primary route of exposure.

***Finding*:** A data need to assess the toxicokinetics of acrolein following inhalation, oral, and dermal exposure has been identified. No information was located regarding the toxicokinetics of acrolein in humans exposed by any route. Toxicokinetic data of acrolein in animals are essentially limited to results from an absorption study in dogs exposed by acute inhalation (Egle 1972), a metabolism study in rats exposed by acute oral administration (Draminski et al. 1983), and *in vitro* metabolism studies using cell preparations from rat liver, kidneys, and lungs (Dawson

et al. 1984; Dupbukt et al. 1987; Esterbauer et al. 1975, 1976; Gurtoo et al. 1981; Patel et al. 1980; Zitting and Heinonen 1980). The inhalation study (Egle 1972) indicates that acrolein is effectively removed from inhaled air by both the upper and lower respiratory tracts, but provides no information on the disposition of the retained acrolein or on whether the uptake rates represent steady-state values. Gastrointestinal uptake of acrolein is assumed to occur based on the observation of toxicological effects after oral administration, but the rate and extent of absorption are not known. Dermal absorption of acrolein is assumed to occur based on mortality observations in acute dermal LD_{50} tests in rabbits (Albin 1962), although permeability of the skin appeared to be low when water was used as the vehicle (as shown by high LD_{50} values). The only information on distribution of acrolein is the identification of the urinary metabolite S-carboxy-ethylmercapturic acid in the rat oral study (Draminski et al. 1983), which provides indirect evidence of distribution of acrolein to the liver or kidneys (i.e., where conjugation most likely occurred). Based on the detection of this urinary metabolite, a metabolic pathway was proposed in which acrolein is first metabolized to acrylic acid with subsequent formation of the methyl ester, which is then conjugated with glutathione to form S-carboxyethylmercapturic acid methyl ester. The *in vitro* metabolism of acrolein seems to be well understood, particularly its reaction with thiol groups in proteins, nucleic acids, glutathione, and cysteine (Patel et al. 1980). The only available information on the excretion of acrolein is the finding of the glutathione urinary metabolite in the orally exposed rats (Draminski et al. 1983). Additional studies are needed to better characterize the toxicokinetics of acrolein. In particular, because the available pharmacokinetic data are insufficient to speculate on possible route-specific target organs, studies describing the pharmacokinetics of acrolein in tissues not directly associated with the respiratory tract, gastrointestinal tract, or skin would be useful to define the existence and extent of target organ toxicity beyond the initial point of contact. Additional studies could also provide information on possible route-specific differences in patterns of metabolism and excretion. No studies were located regarding comparative toxicokinetics of acrolein *in vivo*. Though similar inhalation effects have been observed in rats and humans (Cassee et al. 1996; Weber-Tschopp et al. 1977) at comparable levels, the animal species that serves as the best model for extrapolating results to humans remains unknown. Additional studies comparing the toxicokinetic properties of acrolein in several animal species would be useful for identifying potential species differences.

***Priority Recommendation*:** The identified data needs to assess the toxicokinetics of acrolein following inhalation, oral, and dermal exposure are not considered priority. Additional inhalation toxicokinetics studies would be useful because inhalation is the main route of acrolein exposure

for populations surrounding hazardous waste sites, but are not considered priority because sufficient data are available indicating that the main effects of exposure are due to direct effects of unabsorbed acrolein at the point of contact (i.e., the respiratory tract). Studies by the oral and dermal routes are not priority for reasons similar to inhalation exposure, i.e., because the main targets of toxicity are the tissues in direct contact with unabsorbed acrolein at the site of exposure (the gastrointestinal tract, eyes, and skin). Additionally, oral and dermal exposures are not primary routes for populations near hazardous waste sites.

2. Level III Data Needs

a. Epidemiologic Studies

***Purpose*:** To evaluate the extant epidemiologic database and to propose the conduct of additional studies that may lead to cause- and effect- findings. The ATSDR Division of Health Studies will be informed of all candidate substances.

***Finding*:** A data need has been identified. No epidemiological studies of acrolein are available. The only information concerning effects of acrolein in humans comes from observations of nasal, eye, and skin irritation in two acute inhalation studies involving volunteers (Sim and Pattle 1957; Weber-Tschopp et al. 1977) and several case reports of acute accidental inhalation and dermal exposure to apparent high levels of acrolein (Bauer et al. 1977; Champeix et al. 1966; Gosselin et al. 1979; Lacroix et al. 1976; Mahut et al. 1993; Schöning 1966). Nasal irritation was the most sensitive effect of inhalation exposure, and the LOAEL for this effect in volunteers (Weber-Tschopp et al. 1977) serves as the basis for the acute inhalation MRL. Epidemiological studies of exposed workers could add to and clarify the existing database on acrolein-induced human health effects (e.g., by providing information on effects of long term inhalation exposure to tolerable concentrations), but identification of a suitable exposed group in the general population would probably be difficult. The general population is exposed to acrolein primarily through the inhalation of air, but the main source of general inhalation exposure is indoor air containing cigarette smoke. Ingesting food containing acrolein is another route of exposure because acrolein is formed in food as the result of the ripening of fruit, fermentation, and from the overheating of fats. However, due to a lack of monitoring data for acrolein in food and water, there is no information on the relative importance of each source of oral exposure. Populations residing near waste disposal sites might be subject to higher than average levels of acrolein in air since acrolein

is volatile, but exposure to acrolein in drinking water is not expected to be a problem for these populations due to the volatilization of acrolein from soils and of the retention or degradation of acrolein in soils. However, data for acrolein exposures of residents living near hazardous waste sites through inhalation or drinking water ingestion are not available.

Priority Recommendation: The identified data need to conduct epidemiologic studies on acrolein is not considered priority. Acrolein has been identified in a relatively small number of NPL hazardous waste sites in the United States (at least 31 of 1,662 sites) (HazDat 2005). Studies of populations living near sites contaminated with acrolein are likely to be confounded by exposure to other chemicals. Epidemiologic studies should be undertaken if either worker or general populations with appropriate exposures can be identified, but acrolein toxicity should be further investigated in experimental animals before conducting epidemiologic studies. In particular, inhalation studies in animals should be designed to identify thresholds of toxicity for respiratory and systemic effects of chronic exposure.

b. Mechanism of Toxic Action

***Purpose*:** To evaluate the mechanism of acrolein-induced toxicity to define target organs and future mitigation activities.

***Finding*:** A data need has been identified. Respiratory tract, eye, and gastrointestinal irritation are sensitive effects of acrolein in both humans and animals. Acrolein is a highly reactive compound that binds rapidly and essentially irreversibly to the sulfhydryl groups occurring in many cellular molecules, including most proteins (Beauchamp et al. 1985). Acrolein can bind to structural and biological messenger compounds to produce direct cytotoxic effects or secondary effects from interrupted cell signaling pathways. It is hypothesized that rapid binding of acrolein to neural receptors in the corneal and nasal mucosa may result in rapid depolarization of the associated neurons to produce ocular and nasal irritation (Alarie 1973). Acrolein also binds rapidly to glutathione, resulting in reduced cellular protection against oxygen radical toxicity as well as generation of a propionaldehyde that was shown to produce oxygen and possibly hydroxide radicals via cytosolic aldehyde dehydrogenase (Adams and Klaidman 1993; Arumugam et al. 1999). Depletion of glutathione and other available cellular thiol sources might also permit the movement of acrolein at high concentrations past the initial tissue point of contact (Beauchamp et al. 1985). Data were not found that correlated gastrointestinal lesions with

glutathione content and peroxidative status (Arumugam et al. 1999), but the appearance of endothelial metaplasia in multiple species of animals following oral exposures suggests that gastrointestinal and respiratory toxicity could occur by the same mechanism of action. Although information is available on the general mechanisms of toxicity for the main irritant effects of acrolein in humans and animals, detailed mechanisms for effects of systemically absorbed acrolein, such as reproductive and developmental toxicity, need to be elucidated.

***Priority Recommendation*:** The identified data need is not considered priority. It is reasonably well established that the irritant effects of acrolein in humans and animals have common mechanisms of action of cellular thiol reactivity and glutathione depletion. Although research is needed to elucidate mechanisms of non-irritant effects of acrolein, this research is not given priority because the preponderance of available evidence indicates that the main effects of inhalation, oral, and dermal exposure are due to irritation at the site of contact.

c. Biomarkers

***Purpose*:** To evaluate the need to develop additional biomarkers of exposure and effect for purposes of future medical surveillance that can lead to early detection and treatment.

***Finding*:** A data need has been identified. No reliable information is available on biomarkers that could be used to identify or quantify exposure to acrolein. Acrolein is a metabolite of the drug cyclophosphamide, and a product of the conjugation of acrolein with glutathione, 3-hydroxypropylmercapturic acid, was identified in the urine of people receiving cyclophosphamide (Kaye and Young 1974). The same metabolite was identified in the urine of rats administered acrolein subcutaneously, suggesting that urinary levels of 3-hydroxypropyl-mercapturic acid could be used to identify exposure to acrolein in humans (Alarcon 1976). The formation of acrolein-albumin adducts in blood is another measure of the presence of absorbed acrolein, but changes in levels of this biomarker in blood and urine have not been correlated with exposures to acrolein (Li et al. 2004). Also, use of the aforementioned biomarkers would be complicated by their formation as a consequence of the normal endogenous production of acrolein. Further identification of acrolein metabolites in the urine or adducts in the blood and their correlation with levels of exposure would be useful. No studies were located regarding biomarkers that could be used to characterize toxic effects caused by acrolein, indicating that

there is also a need for studies correlating levels of acrolein or its metabolites with effects in target tissues.

***Priority Recommendation*:** The identified data need is not considered priority. Although there are no reliable biomarkers of exposure and no biomarkers of effects for acrolein, the development of biomarkers is not a priority, because respiratory tract and ocular irritation are useful indicators for exposure to acrolein by inhalation, the main route of exposure for populations surrounding hazardous waste sites.

d. Clinical Methods for Mitigating Toxicity

***Purpose*:** To determine whether any efforts are currently under way to mitigate the effects of exposure to acrolein.

***Finding*:** A data need has not been identified. There are no specific established methods of treatment for reducing the absorption of acrolein. However, because acrolein is a point-of-contact irritant (Bouley et al. 1975; Buckley et al. 1984; Costa et al. 1986; Feron et al. 1978; Kutzman et al. 1981, 1984, 1985; Lyon et al. 1970; Schöning 1966; Weber Tschopps et al. 1977), measures to dilute the concentration at the pulmonary, gastrointestinal, or dermal tissue surfaces are likely to mitigate the main effects of exposure. Emergency treatment for acrolein inhalation exposure includes ventilation and oxygenation. Gastric lavage or nasogastric suction may be administered if life-threatening amounts of acrolein are ingested (HSDB 2005). Acrolein is not believed to accumulate in the body. With the exception of gastric lavage and nasogastric suction, there is no available information regarding procedures for reducing the body burden of acrolein.

Priority Recommendation: A data need has not been identified. Acrolein is known to react rapidly with thiol groups in every type of tissue (Beauchamp 1985), and human and animal studies and case reports suggest that point-of-contact toxicity dominates the onset of adverse health effects. For this reason, simple dilution of acrolein at the point of tissue contact is likely to provide the best protection against acrolein-induced injury and obviate the need for additional data concerning the reduction of toxic effects.

e. Children's Susceptibility

***Purpose*:** To determine whether adequate data exist to identify potential health effects from exposures to acrolein during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation.

***Finding*:** A data need to conduct additional studies relevant to children's susceptibility via inhalation, oral, and dermal exposure has been identified. No information was located on the toxicity of acrolein in children. Although the available animal data suggest that the developing organism may be susceptible to acrolein toxicity, developmental toxicity was observed at doses that were generally maternally toxic (King 1982; Parent et al. 1991, 1993). Studies are needed to determine if children have an increased sensitivity to acrolein, particularly for respiratory effects of inhalation in children with pre-existing conditions such as asthma and reactive airway dysfunction. No data are available on potential toxicokinetic differences between adults and children or on whether acrolein is stored in maternal tissues and could be mobilized during pregnancy and lactation. Toxicokinetic studies examining how aging can influence absorption, distribution, metabolism, and excretion of acrolein would be useful in assessing children's susceptibility to acrolein.

Priority Recommendation: The identified data need to conduct additional studies on children's susceptibility via inhalation exposure is not considered priority. There are no human anecdotal reports of toxic effects in children following acrolein exposure, and there are no current data available to suggest that children may be more susceptible than adults to acrolein-induced adverse health effects. Also, as discussed in the "Developmental Toxicity" section, the available data indicated that developmental toxicity was observed at maternally toxic doses only. Additional studies on mechanisms of action and toxicokinetics of acrolein in immature and adult animals need to be conducted and evaluated before assigning priority to the identified data need. Studies by the oral and dermal routes are not considered priority because these are not primary routes of exposure for populations near hazardous waste sites.

IV. Summary: Prioritization of Data Needs for Acrolein

A. Exposure

Application of the hierarchy of research priorities presented in the Decision Guide begins with the evaluation of available analytical methods for acrolein and proceeds through assessing the need for epidemiologic studies. As stated previously, much information is available on acrolein, though some of the studies are very old. This does not mean that data derived from older studies are not adequate. ATSDR agrees with the National Research Council in that it is not appropriate to judge the quality of past and future studies solely by the standards of today.

Building a sound basic data foundation for higher level environmental research via the Decision Guide requires the determination of human exposure levels and media-specific data on acrolein. Although a lot of information is available, a need to evaluate existing data on concentrations of acrolein in contaminated environmental media at hazardous waste sites has been identified.

Furthermore, a need to collect data on levels of acrolein in body tissues and fluids for populations living near hazardous waste sites has been identified. This information is necessary to establish a database that can be used to assess the need to conduct follow-up human health studies of adult and children populations exposed to acrolein.

One effort is now under way at ATSDR that will examine the extant data at the 31 NPL sites at which acrolein has been found. When complete, this database will include maximum concentrations of acrolein in on-site and off-site media, and an indication of relevant routes of exposure. This database will be developed and evaluated before the need to collect additional media-specific data is assigned priority. This database will not, however, supply information on the levels of acrolein (or its metabolites) in the tissues of adults and children living near hazardous waste sites or other exposed populations such as workers.

Thus, on the basis of the findings given in Section II and above, ATSDR is recommending the initiation of research or studies to fill the following exposure priority data needs (Table 3):

- Evaluation of existing data on concentrations of acrolein in contaminated environmental media at hazardous waste sites

- Exposure levels in humans living near hazardous waste sites
- Exposure levels of children

B. Toxicity

The toxicity of acrolein has been studied in animals by inhalation, oral, and dermal exposure. For all exposure routes, the primary target of toxicity is the site of tissue contact, as shown by irritation to the respiratory tract, gastrointestinal tract, eyes, and skin. Systemic effects occurred in some of the inhalation and oral studies, but were essentially minor, not clearly toxicologically significant, and/or occurred at exposure levels similar to or higher than those causing respiratory or gastrointestinal irritation. In the only chronic inhalation study in animals, respiratory toxicity (epithelial hyperplasia) was observed in rats that were exposed to 8 ppm of acrolein for 1 hour/day, 7 days/week for 18 months (Le Bouffant et al. 1980). Use of this study for chronic inhalation MRL derivation is precluded by the short daily exposure period and single exposure level. Therefore, additional inhalation studies are needed to identify sensitive targets and establish dose-response relationships for chronic-duration exposure.

This nonhuman research need is justified because of the widespread domestic and environmental contamination of acrolein, and the possibility that significant past exposures have affected many people.

Thus, on the basis of the findings given in Section II and above, ATSDR recommends the initiation of research or studies to fill the following toxicity priority data need (Table 3):

- Dose-response data for chronic-duration via inhalation exposure

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Table 1. Exposure Data Needs

Exposure	Level I	Level II	Level III
Analytical	Methods for parent compound in REM*	Methods for degradation products in REM*	
	Methods for parent compound in blood or urine	Methods for parent compound/metabolites/biomarkers	
	Structure-Activity relationships (SAR)		
Physical Chemical Properties	Water solubility		
	Volatility/vapor pressure		
	K_{ow}		
	Henry's law		Registries of exposed persons
Exposure Levels	Production volume; Use; Release/ disposal (may be used in lieu of monitoring data)	Monitoring in REM*	Human dosimetry studies
		Monitoring for human exposure (personal sampling, biomarkers of exposure, tissue levels)	Epidemiology
			Disease registries
		Exposures of children	
Environmental Fate	Aerobic/anaerobic Biodegradation in H_2O Oxidation Hydrolysis Aerosolization Photoreactivity Volatilization Soil adsorption/desorption	Small field plot studies	
		Monitoring for products in REM*	
Bioavailability		Food chain bioaccumulation	
		Availability from REM* (analytical or toxicity) emphasize *in vivo*	

*REM = Relevant Environmental Media

Table 2. Toxicity Data Needs

Toxicity	Level I	Level II	Level III
Single dose exposure	Single dose disposition Skin/eye irritation Acute toxicity		
Repeated dose exposure	14-Day by relevant route 90-Day subchronic	Comparative toxicokinetics*	
Chronic exposure	Structure-activity relationships (SAR)	1-Year chronic 2-Year bioassay	Epidemiology*
Genotoxicity*	Ames Micronucleus	Additional genotoxicity studies*	Mechanism of toxic action*
Endocrine disruption	*In vivo* & *in vitro* screen	2-Generation reproductive study	
Reproductive toxicity	Extended reproworkup in subchronic	2-Generation or continuous breeding	Biomarkers*
			Clinical methods for mitigating toxicity*
Developmental toxicity*	Short term *in vivo* screen*	2-Species developmental*	Children's susceptibility**
Immunotoxicity	Use subchronic results	Immunotox battery	
Neurotoxicity	Neuropath in subchronic	Neurotox battery	
Sensitization	Dermal sensitization		
Carcinogenicity	Use muta & subchronic results	2-Year bioassay	

*Useful data for examining children's susceptibility issues

**Data needed for addressing children's susceptibility issues include genotoxicity (Level II), developmental toxicity (Levels I and II), epidemiology, mechanism of toxic action, biomarkers, and clinical methods for mitigating toxicity (Level III)

Table 3. ATSDR Substance-Specific Applied Research Program for Acrolein

	EXPOSURE		
	Level I	Level II	Level III
Analytical			
Physical Chemical Properties			
Exposure Levels		*EXP LEVELS IN ENV MEDIA*	Potential candidate for exposure registry
		EXP LEVELS IN HUMANS	
		EXP LEVELS IN CHILDREN	
Environmental Fate	persistence in soil and groundwater		
Bioavailability		availability from ambient air, drinking water, food, and fermented beverages	
	TOXICITY		
	Level I	Level II	Level III
Acute	inhal, oral, dermal		
Repeated	inhal, oral, dermal	toxicokinetics	
Chronic		*INHAL*, oral, dermal	epidemiology
Genotoxicity		*in vivo*	mechanisms
Endocrine disruption	endocrine histopath, dermal		
Reproductive toxicity		inhalation, dermal	biomarkers
Developmental toxicity		inhal, dermal	
Children's susceptibility			Inhal, oral, dermal
Immunotoxicity		inhal oral, dermal	
Neurotoxicity		inhal oral, dermal	
Carcinogenicity		inhal, oral, dermal	

UPPER CASE: Priority data needs identified for acrolein