2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ACROLEIN IN THE UNITED STATES

Acrolein is a reactive aldehyde primarily used as an intermediate in chemical manufacturing and as a biocide. It is used in the synthesis of many organic chemicals, as a biocide in agricultural and industrial water supply systems, in the manufacture of methionine (an animal feed supplement), as a warning agent (due to its pungent odor) in methyl chloride refrigerant, and as a component of chemical weapons. Acrolein can be formed in burning tobacco, wood, plastics, gasoline and diesel fuel, paraffin wax, and in the heating of animal and vegetable fats and oils at high temperatures. It is also found naturally in the body in very small amounts.

Because acrolein is formed naturally in the body as a product of lipid oxidation and the metabolism of α-hydroxyamino acids, the general population is endogenously exposed to small amounts of acrolein. However, the general population is not likely to receive high exposures of acrolein. Individuals likely to receive the highest exposures include smokers and those inhaling second-hand smoke, persons in close proximity to sources of wood and plastic smoke, including those in the forest products and firefighting communities, and populations living or working in areas of dense automotive traffic. The predominant route of environmental exposure would be inhalation of smoke or automotive exhaust. No significant acrolein exposure is expected from ingestion of drinking water or from dermal contact during bathing or showering.

Acrolein is expected to volatilize rapidly from surface water and soil. Degradation in water, soil, and air occur quickly. Thus, environmental persistence is not expected. When applied to surface water as an herbicide, acrolein may persist for up to 6 days. It has been detected in 32 of 1,684 National Priority List (NPL) sites. It has not been found as a contaminant in drinking water. Acrolein has been detected in very low levels in rainwater in Los Angeles, California, a high-smog area. Average acrolein concentrations measured at various monitoring stations ranging from 0.5 to 3.186 ppbv (parts acrolein per billion parts of air by volume). The concentrations of acrolein in indoor air range from <0.02 to 12 ppb in residential homes. Acrolein concentrations are found to be typically higher in indoor air when comparing paired indoor/outdoor samples taken at a site. A burned cigarette has been measured to generate 0.06–0.22 mg of acrolein, which may result in a variable and significant inhaled concentration for the smoker or by stander by increasing the concentration of acrolein in the air of a typical room by 0.4–2 ppb.

With the exception of smoking, children and adults are expected to be exposed to acrolein by the same routes of exposure. Like adults, however, children may be exposed to unknown levels of acrolein from inhaling second-hand tobacco smoke. Since acrolein is volatile, ineffectively transported in soil, and nonpersistent in the environment, children's dermal exposure from soil contact or ingestion is not likely to differ from adults.

See Chapter 6 for detailed information regarding concentrations of acrolein found in environmental media.

2.2 SUMMARY OF HEALTH EFFECTS

Acrolein can exert toxic effects following inhalation, oral, and dermal exposures. It is a potent irritant to the mucous membranes. At high concentrations, it can also cause irritation to skin. As such, its toxicity is exerted at the point of contact with tissues. Signs and symptoms resulting from inhalation exposure to airborne acrolein may include irritation of the nose, throat and lungs, pulmonary edema, lung hemorrhage, and death. The nasal tissues appear to be the most sensitive target of inhalation exposure, with onset of noticeable irritation occurring in seconds (0.3 ppm). Higher airborne concentrations of acrolein (2–5 ppm) result in increasingly severe manifestations of irritation over the entire respiratory tract. Oral acrolein exposure may result in gastrointestinal discomfort, vomiting, and stomach ulceration and/or hemorrhage. The stomach epithelium appears to be the most sensitive target for oral exposure (0.75 mg/kg). Higher concentrations of ingested acrolein have primarily resulted in increasingly severe irritation effects in the stomach (2 mg/kg and higher). Dermal exposure to acrolein vapors or liquids may cause stinging of the eyes, lacrimation, and reddening, ulceration, or necrosis of the skin (10% acrolein solution). The eye appears to be the most sensitive target for dermal exposure (0.3 ppm in air). Histological changes in respiratory and gastrointestinal epithelium have been observed from both inhalation and oral exposures, respectively. Changes in body and organ weights, hematology, and serum biochemistry have been observed in animals. Developmental effects, such as skeletal malformations and reduced weight of offspring, occurred at exposure levels resulting in maternal mortality. Developmental effects were not observed independent of frank maternal toxicity. Some of these effects are believed to be secondary effects of gastrointestinal and/or respiratory tract irritation (i.e., loss of appetite and weight loss due to gastrointestinal irritation). Similar effects appear to result from similar exposure levels across durations of inhalation exposures. *In vitro* studies have shown acrolein to be weakly mutagenic, capable of interfering with DNA repair mechanisms. The evidence for the carcinogenicity of acrolein is weak, with a significant tumor incidence found in a single animal drinking water study. Pathology samples

from this study were re-evaluated by an independent pathology working group and tumor incidence was determined to be not significantly different than historical controls. A later well-designed cancer bioassay in rats orally-gavaged at lower doses failed to detect significant increases in cancer incidence. The Department of Health and Human Services (DHHS) has not classified acrolein as to its carcinogenicity. The International Agency for Research on Cancer (IARC) has determined that acrolein is not classifiable as to carcinogenicity in humans. The EPA has stated that the potential carcinogenicity of acrolein cannot be determined based on an inadequate database.

The following sections discuss significant effects resulting from exposure to acrolein in greater detail: eye irritation, respiratory, and gastrointestinal.

Eye Irritation. Acrolein vapor or liquid causes adverse ocular effects through simple point-of-contact irritation. At low airborne levels (0.3 ppm), ocular irritation is perceived as rapid-onset mild to moderate stinging of the eyes accompanied by increased blinking. Lacrimation occurs at higher levels (0.81 ppm), with an increase in severity of irritant sting. At low levels of vapor exposure, humans appear to adapt to ocular irritation, as volunteers exposed to a constant level of acrolein vapors for 60 minutes reported increasing irritation of the eyes up to 40 minutes, but reported no further increase in discomfort thereafter. Dogs and monkeys appear to be more sensitive than rodents to acrolein, as evidenced by lacrimation and blinking or closing of the eyes during intermediate-duration exposures to 3.7 ppm; however, no observable ocular changes were reported in guinea pigs and rats exposed for the same duration. It is not known at what exposure level acrolein liquid or vapor causes structural damage to the eye, as no histological evaluation of the eye following acrolein exposure has been conducted.

Respiratory Effects. Acrolein may affect the entire respiratory tract, from the nasal epithelium to the alveolar spaces. The variety and severity of effects and depth of the respiratory tract to which effects extend increases as exposure level increases. Nasal irritation appears to be the most sensitive respiratory effect, based on reported irritation in humans and animals and cellular changes observed in animals. Rapid onset of nose and throat irritation and a reduction in breathing rate (believed to be a protective measure triggered by nose irritation) was reported by volunteers acutely exposed to low levels (0.3 ppm); mild nasal epithelial dysplasia, necrosis, and focal basal cell metaplasia have been reported in rats at similar concentrations (0.25 ppm). Respiratory irritation was observed in animals as evidenced by decreased respiratory rates in mice and rats exposed to 1–3 ppm. Higher acute inhalation exposure levels (2–5 ppm) have resulted in more severe effects in animals, including epithelial hyperplasia, inflammation, and moderate to severe histological alterations of the nasal, tracheal, and bronchial epithelium, bronchial

epithelial destruction, pulmonary edema, and lung hemorrhage have been seen in mice, rats, and guinea pigs. Four human case reports of massive acute acrolein inhalation exposures, either occupationally or from heated cooking fats, list similar effects, including high fever, dyspnea, coughing, foamy expectoration, cyanosis, pulmonary edema, and death (concentrations unknown). Fatal pulmonary edema may develop many hours after a high, acute exposure. Observed effects following intermediate- and chronic-duration exposures to acrolein (1–3 ppm) include histological alterations and inflammation across the entire respiratory tract of rats, monkeys, guinea pigs, dogs, rabbits, and hamsters. Respiratory effects seem to be similar in type of effect and severity across species and exposure duration.

Gastrointestinal Effects. The irritation of gastrointestinal mucosa appears to be the primary effect of oral exposure to acrolein. Human data for oral exposures are not available. The clinical signs of gastrointestinal effects in animals are similar and dose-related across species and acute and intermediate exposures, although possible adaptation to irritating effects may occur during chronic exposures. Effects of increasing severity include vomiting, epithelial hyperplasia, ulceration, hemorrhage, and edema of the stomach mucosa. There are little data for low-level (<2 mg/kg/day) acute doses. Acute and intermediate exposure effects of high doses (4–25 mg/kg) in mice, rats, and rabbits include severe mucosal inflammation ulceration, focal hemorrhage, and edema. Effects from low, intermediate-duration doses of 2.5 mg/kg/day in mice and female rats resulted in forestomach squamous epithelial hyperplasia. Conversely, chronic dosing levels of 2–4.5 mg/kg/day produced no significant gross or histopathological effects in rats, mice, or dogs. The reported differences in gastrointestinal sensitivity are not well understood; however, study differences in dose volumes may play a role. Dogs chronically given acrolein doses by capsule as low as 0.5 mg/kg/day vomited significantly through the first 4 weeks of exposure, but appeared to adapt as vomiting incidence was reduced thereafter. Data are not available to determine if an adaptive effect for chronic oral exposures would be observed at higher dose levels.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for acrolein. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for

acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

- An MRL of 0.003 ppm has been derived for acute-duration inhalation exposure (14 days or less) to acrolein.

Studies in both humans and animals have reported acute effects of airborne acrolein. Observed effects include nasal irritation, discomfort, and reduction in respiratory rate in humans (Weber-Tschopp et al. 1977), reduction in respiratory rate in mice (Buckley et al. 1984; Kane and Alarie 1977) and rats (Cassee et al. 1996), histological changes in nasal epithelium of rats and mice (Cassee et al. 1996; Nielsen et al. 1984; Steinhagen and Barrow 1984), and reduction in bactericidal activity (as reflected by macrophagic clearance of *Klebsiella pneumoniae* bacteria) in mice (Aranyi et al. 1986). More severe observed effects include high fever, dyspnea, coughing, foamy expectoration, cyanosis, tracheal and alveolar epithelial destruction, pulmonary edema, lung hemorrhage, and possible death 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 Mackenzie 1978; Murphy et al. 1964; Skog 1950).

A reduction in bactericidal activity in rat lungs was observed at 0.1 ppm (Aranyi et al. 1986), the lowest lowest-observed-adverse-effect level (LOAEL) identified, and at 3 ppm (Astry and Jakab 1983). The biological significance of this finding is unclear. Irritation of the nasal epithelium of rats exposed to 0.25 ppm resulted in mild disarrangement and necrosis of nasal epithelium (Cassee et al. 1996). Animals in the same study exposed to 0.67 ppm exhibited focal basal cell metaplasia, reduced epithelial glutathione reductase activity, cellular disarrangement, necrosis, and cell proliferation of the nasal respiratory epithelium. Mice and rats exhibited decreased respiratory rates following exposures of 1–3 ppm (Kane and Alarie 1977; Nielsen et al. 1984; Steinhagen and Barrow 1984). Severe irritation and

lung hemorrhage were observed in rats exposed to 130 ppm (Skog 1950). Death occurred in rats exposed to acrolein levels ranging from 130 to 327 ppm for 30 and 10 minutes, respectively (Catilina et al. 1966; Skog 1950).

Nasal irritation in humans has been observed at levels similar to those seen in animals. Weber-Tschopp et al. (1977) exposed volunteers for 40 minutes to gradually increasing levels of acrolein vapors. At the end of 15 minutes, exposure levels were approximately 0.26 ppm. Volunteers scored irritancy as "a little" or "medium", which was statistically different from controls. However, the changing concentrations of acrolein made it difficult to fix the duration or level of exposure that was actually responsible for the onset of significant irritation. In another test reported in Weber-Tschopp et al. (1977), volunteers exposed to 0.3 ppm acrolein for 60 minutes scored nose and throat irritation as "a little irritating" by 40 minutes into the exposure. A decrease in respiratory rate was also observed. This test, with a fixed exposure level and duration, was used as the basis for an acute duration inhalation MRL, providing a LOAEL of 0.3 ppm.

An acute duration inhalation MRL of 0.003 ppm was derived using the LOAEL of 0.3 ppm for nasal and throat irritation and decreased respiratory rate in humans. The LOAEL of 0.3 ppm was divided by an uncertainty factor of 100 (10 for using a LOAEL and 10 for human variability).

While Aranyi et al. (1986) reported a LOAEL of 0.1 ppm for reduced bactericidal activity in rats, the toxicological significance of this finding is unclear. Cassee et al. (1996) reported a LOAEL of 0.25 ppm, which was very similar to the human LOAEL of 0.3 ppm. This being the case, the human-derived data were deemed preferable for the basis of the MRL, eliminating the introduction of uncertainty from inter-species extrapolation.

- An MRL of 0.00004 ppm has been derived for intermediate-duration inhalation exposure (15–364 days) to acrolein.

No data were available for intermediate-duration exposure of humans to acrolein. Exposures to airborne 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, rabbits, guinea pigs, and monkeys (Costa et al. 1986; Feron et al. 1978; Kutzman et al. 1984, 1985; Lyon et al. 1970). Effects in the deeper respiratory tract became more severe at the 3–5 ppm exposure levels. Effects included tracheal epithelial metaplasia in hamsters (Feron et al. 1978), epithelial dysplasia in rats (Leach et al. 1987), squamous lung epithelial metaplasia in rats (Kutzman et al. 1985), tracheal metaplasia

and bronchial necrosis in rats (Feron et al. 1978; Kutzman et al. 1985), pulmonary edema in rats (Costa et al. 1986), and lung hemorrhage in monkeys (Lyon et al. 1970).

The most sensitive effect for intermediate-duration inhalation appears to be nasal epithelial metaplasia and bronchial inflammation. These effects were observed in rats at 0.4 ppm (Feron et al. 1978; Kutzman et al. 1984). Lung inflammation was seen in monkeys and guinea pigs at 0.7 ppm (Lyon et al. 1970). At 1–1.4 ppm, bronchiolar, lung, and liver inflammation were observed in guinea pigs, hamsters, and rats (Feron et al. 1978; Kutzman et al. 1985; Lyon et al. 1970). At 1.4–1.8 ppm, lung and tracheal hyperplasia was seen in rats and monkeys (Costa et al. 1986; Lyon et al. 1970). Lung hemorrhage and decreased weight gain occurred in monkeys at 3.7 ppm (Lyon et al. 1970). Increased brain weight, tracheal squamous metaplasia, bronchial necrosis, and lung edema were observed in rats at 4 ppm (Costa et al. 1986; Kutzman et al. 1985). Monkeys and rats died at 3.7–4 ppm (Kutzman et al. 1985; Lyon et al. 1970).

The intermediate-duration inhalation MRL was based on the lowest identified LOAEL of 0.4 ppm for nasal metaplasia in rats (Feron et al. 1978). This study compared the effects of a 13-week exposure of rats, rabbits, and hamsters for 6 hours/day, 5 days/week to 0.4, 1.4, and 4.0 ppm acrolein. The rat appeared to be the most sensitive species in the study, exhibiting more severe histological changes across the respiratory tract than the other species. Though bronchiolar inflammation was also observed in rats at 0.4 ppm (Feron et al. 1978), structural changes in the nasal epithelium appear to be a more sensitive effect, as such changes have been observed in lower, acute inhalation exposures of rats (Cassee et al. 1996). Structural changes to lung cells have not been observed in rats below 1.4 ppm (Costa et al. 1986). For these reasons, the LOAEL of 0.4 ppm for nasal metaplasia in rats was chosen as the most sensitive end point for the derivation of an intermediate-duration inhalation MRL.

The intermediate-duration inhalation MRL of 0.00004 ppm was derived by dividing the human equivalent LOAEL ($LOAEL_{HEC}$) of 0.012 ppm by 300 (10 for using a LOAEL, 3 for species extrapolation using dosimetric adjustment, and 10 for human variability). The duration-adjusted LOAEL ($LOAEL_{ADJ}$) was calculated as follows:

$LOAEL_{ADJ}$ = 0.4 ppm x 6 hours/24 hours x 5 days / 7 days = 0.071 ppm

Dosimetric adjustments for species differences for a category 1 gas in rats and humans (EPA 1994b) resulted in a regional gas dose ratio for the extrathoracic region ($RGDR_{ET}$) of 0.17. The $LOAEL_{ADJ}$ was multiplied by the $RGDR_{ET}$ to derive the $LOAEL_{HEC}$ of 0.012 ppm as follows:

$LOAEL_{HEC} = LOAEL_{ADJ} \times RGDR = 0.071 \times 0.17 = 0.012$ ppm

No chronic-duration MRL for inhalation of acrolein was derived due to an inadequate database. An 18-month study with rats (Le Bouffant et al. 1980) reported epithelial hyperplasia. However, the study involved a 1-hour exposure to a very high concentration (8 ppm) of acrolein in which acrolein-treated animals were compared histologically to animals exposed daily to cigarette smoke rather than controls. The study is unclear as to whether this effect was attributable to the animals' exposure to acrolein or cigarette smoke.

Oral MRLs

No human oral exposure data for any exposure duration were available. Oral exposure studies in rabbits (Parent et al. 1993) and rats (Sakata et al. 1989) exposed to 4 and 25 mg/kg/day, respectively, reported severe stomach ulceration and edema, and death. Pregnant rabbits given 2 mg/kg/day by gavage exhibited a transient decrease in body weight which rebounded completely in 3 days (Parent et al. 1993). The lowest acute LOAEL identified was capsule dosing of 0.5 mg/kg/day in dogs, which resulted in vomiting shortly after dosing for the first 4 weeks of a chronic study (Parent et al. 1992b). This effect was transient and may have been impacted by the capsule sub-route of administration. Further, statistical significance of the vomiting incidence was not determined. Since a higher no-observed-adverse-effect level (NOAEL) of 1.25 mg/kg/day was identified in a well-conducted intermediate-duration oral gavage study (NTP 2006), no acute-duration MRL for ingestion of acrolein was derived.

- An MRL of 0.004 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to acrolein.

No studies were located for intermediate-duration oral exposure to acrolein in humans. The limited number of animal studies identified for this exposure duration reported similar effects on the gastrointestinal and respiratory mucosa from oral and inhalation exposures, respectively. Forestomach squamous epithelial hyperplasia was seen in rats and mice given 2.5 mg/kg/day by gavage (NTP 2006). Forestomach and glandular stomach hyperplasia, ulcers, and glandular stomach hemorrhage were observed in rats given 3 mg/kg/day (Parent et al. 1992c). Stomach ulceration and hemorrhage was

observed in rats given 5.4–10 mg/kg/day (King 1984; NTP 2006). Labored breathing and increased mortality were seen in rats given 6 mg/kg/day (Parent et al. 1992c). Stomach hemorrhage was observed in rats and mice given 10 and 20 mg/kg/day, respectively, while stomach necrosis was observed in mice given 20 mg/kg/day (NTP 2006).

The 14-week gavage toxicity study in rats and mice (NTP 2006) served as the basis for deriving an intermediate-duration oral MRL. In this study, rats were administered 0.75, 1.25, 2.5, 5, and 10 mg/kg/day by gavage for 14 weeks, while mice were given 1.25, 2.5, 5, 10, and 20 mg/kg/day for the same duration. Glandular stomach lesions were observed in male and female mice gavaged with 20 mg/kg/day. Glandular stomach lesions were observed in rats given 10 mg/kg/day. Forestomach squamous epithelial hyperplasia was observed in male and female rats gavaged with 5 and 2.5 mg/kg/day, respectively, and in male and female mice gavaged with 2.5 mg/kg/day. No significant effect was observed in male or female mice or female rats given 1.25 mg/kg/day or in male rats given 2.5 mg/kg/day. Although humans do not have a forestomach, this study provides an example of gastrointestinal mucus membrane irritation. Similar irritative effects are expected in humans. This effect represented the highest identified NOAEL associated with the lowest LOAEL in a well-designed study and served as the basis for the intermediate oral MRL.

The intermediate-duration oral MRL of 0.004 mg/kg/day was derived by dividing the 95% lower confidence limit on the benchmark dose for 10% extra risk ($BMDL_{10}$) of 0.36 mg/kg/day for forestomach squamous epithelial hyperplasia in mice by a factor of 100 (10 for species extrapolation and 10 for human variability).

No chronic-duration oral MRL was derived for acrolein due to an inadequate database. Chronic gavage studies in which rats were dosed with up to 2.5 mg/kg/day for 24 months (Parent et al. 1992a), mice were gavage dosed with up to 4.5 mg/kg/day for 18 months (Parent et al. 1991a), and dogs were gavage dosed with up to 2 mg/kg/day for 12 months (Parent et al. 1992b) all failed to produce significant gross or histopathological changes as have been observed in other studies of the same species at lower dose levels (NTP 2006). One possible explanation for discrepancies in effects observed by Parent et al. (1991a, 1992a, 1992b) and NTP (2006) is the use of a thickening agent in the dosing vehicle of the NTP (2006) study, which may have increased the gastrointestinal residence time compared to doses in the Parent et al. (1991a, 1992a, 1992b) studies, which administered acrolein in a deionized water vehicle. Body weight decreases were significant in male mice and rats (Parent et al. 1991a, 1992c); however, the magnitude of body weight change could not be determined since variation between treatment groups was not reported.

The Parent et al. (1992b) rat study also reported significantly depressed serum creatinine phosphokinase levels. However, the significance of this finding is unknown. Decreased survival (increased mortality) was observed in rats and mice dosed with 0.5 and 4.5 mg/kg/day, respectively (Parent et al. 1991a, 1992a), but no explanation for the mortality was given.