2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO AMMONIA IN THE UNITED STATES

Ammonia is a natural compound, as well as a manufactured compound. In nature, most ammonia probably comes from decomposing animal excreta, with the decay of organic materials from plants, dead animals, and the like also contributing significant amounts. It is also exhaled by animals. Production of fixed nitrogen (NH_3) by plants and microorganisms is estimated at 90–130 metric tons annually. Manufacture of ammonia within the United States was 9.5 million metric tons in 2001, which is down from 16.6 million metric tons in 1999. Commercially produced ammonia is used primarily as fertilizer, with plastics, synthetic fibers and resins, explosives, and other uses accounting for most of the remainder.

Ammonia is released to the atmosphere by natural processes such as the decay of organic matter and animal excreta, or by volcanic eruptions. It can also be released to the atmosphere by anthropogenic activities such as fertilizer use; spillage or leakage from storage or production facilities; or by loss from waste water effluents. Releases to water are usually due to effluent from sewage treatment plants or industrial processes, or runoff from fertilized fields or livestock areas. Soils usually obtain ammonia from natural or synthetic fertilizer application, animal excreta, decaying organic matter, or natural fixation from the atmosphere.

In the atmosphere, ammonia can react with acidic substances in the air to produce ammonium aerosols, which can undergo dry or wet deposition. The best estimate of the half-life of atmospheric ammonia is a few days. In water, ammonia can volatilize to the atmosphere, be removed by microbial processes, or adsorb to sediment and suspended organic material. In soil, ammonia can volatilize to the atmosphere, adsorb to soil, undergo microbial transformation to nitrate or nitrite anions, or be taken up by plants.

For the general population, the most likely source of exposure to elevated levels of ammonia is from the use of household cleaners containing ammonia or ammonium salts. People who live near farms, who visit farms during the application of fertilizer, or who live near cattle feedlots, poultry confinement buildings, or other areas where animal populations are concentrated can also be exposed to ammonia. Populations that live or work near a hazardous waste site that contains ammonia or ammonium salts could be exposed to above-average levels of ammonia in soil, water, or air; however, the half-life of ammonia in nature is

probably very short. Ammonia has been identified in at least 135 of 1,613 National Priority List (NPL) hazardous waste sites.

2.2 SUMMARY OF HEALTH EFFECTS

The most important injurious effects of ammonia on humans are due to its irritative and corrosive properties. Exposures to ammonia as a gas cause chemical burns of the respiratory tract, skin, and eyes. Ammonia dissolves in the water present in skin, mucous membranes, and eyes and becomes ammonium hydroxide, which is a highly ionized weak base that causes necrosis of the tissues. Specifically, ammonium hydroxide causes saponification of cell membrane lipids resulting in cell disruption and death. Additionally, it breaks down cell structural proteins, extracts water from the cells, and initiates an inflammatory response, which further damages the surrounding tissues. Contact with liquid ammonia (not ammonium salts) results in cryogenic injury in addition to the alkali burns. Airway blockage and respiratory insufficiency may be lethal outcomes of exposure to anhydrous ammonia vapors or concentrated aerosols. Ingestion of concentrated ammonium solutions may produce severe burns and hemorrhage of the upper gastrointestinal tract. Survival of the initial insult may be compromised by infections, scarring, and other complications that may develop days or weeks following inhalation or ingestion. Effects that have been observed in humans exposed to ammonia as a gas and ammonium salt aerosols have also been observed in animals. Hepatic and renal effects have also been reported in animals and humans; however, ammonia does not appear to be a primary liver or kidney toxicant.

Increased systemic ammonia/ammonium salts/ion, or hyperammonemia, is generally not seen following inhalation or dermal exposure, but can result from ingestion and from certain disease states such as cirrhosis of the liver, acute liver failure, and congenital deficiencies of any of the urea cycle enzymes . Ammonia is also produced endogenously in the gastrointestinal tract, pancreas, and kidney and is metabolized predominantly via the urea cycle in the liver. It is excreted primarily as urea and urinary ammonium compounds through the kidneys. Liver disease can result in decreased metabolism of ammonia with resultant increased levels of ammonia in the bloodstream and in the brain, which can produce neurological effects such as seizures and coma. The most likely and significant effects of ammonia are discussed below.

Respiratory Effects. Ammonia is an upper respiratory irritant in humans. Exposures to levels exceeding 50 ppm result in immediate irritation to the nose and throat; however, tolerance appears to develop with repeated exposure. Exposure to an air concentration of 250 ppm is bearable for most persons for 30–60 minutes. Acute exposure to higher levels (500 ppm) have been shown to increase respiratory minute volume. Accidental exposures to concentrated aerosols of ammonium salts or high concentrations of ammonia gas have resulted in nasopharyngeal and tracheal burns, airway obstruction and respiratory distress, and bronchiolar and alveolar edema. Chronic occupational exposure to low levels of airborne ammonia (<25 ppm) had little effect on pulmonary function or odor sensitivity in workers at some factories, but studies of farmers exposed to ammonia and other pollutants in livestock buildings indicated an association between exposure to pollutants, including ammonia, and an increase in respiratory symptoms (such as bronchial reactivity/hyperresponsiveness, inflammation, cough, wheezing, or shortness of breath) and/or a decrease in lung function parameters. The contribution of ammonia to these respiratory symptoms is unclear.

Dermal Effects. Skin is extremely sensitive to airborne ammonia or ammonia dissolved in water. The topical damage caused by ammonia is probably due mainly to its reactivity and irritation properties. Its high water solubility allows it to dissolve in moisture on these surfaces, react with fatty substances, be absorbed into deeper layers, and inflict extensive damage. Reports of skin damage in humans are numerous, but good quantitative data are lacking. The severity of the damage is proportional to the concentration and duration of exposure; flushing with water immediately after contact alleviates or prevents effects.

Dermal exposures to liquid ammonia or concentrated solutions and/or ammonia gas are frequently occupationally related and produce cutaneous burns, blisters, and lesions of varying degrees of severity . Burns can be severe enough to require skin grafting, and loss of the epidermal layer increases body fluid loss and incidence of infection. While most ammonia exposures are occupational, household products containing ammonia can also cause dermal injury. Several cases of young children (2–3 years old) who bit into ammonia pellets/capsules and sustained oral and esophageal lesions have been reported in the literature.

Very limited animal data regarding dermal effects of exposure to ammonia support the findings in humans.

Ocular Effects. Reported ocular effects in humans following ammonia gas exposure increase in severity with dose and duration. Good quantitative data are lacking, but symptoms progress as follows: inflamed eyes, lacrimation, swelling of the eyelids, hyperemic conjunctiva, blurred vision, possible transient blindness, corneal abrasions, and sustained corneal damage. Ammonia is slightly irritating to human eyes in a brief exposure at concentrations of 100 ppm, and immediately irritating to the eyes and throat at 698 ppm. Exposure to an air concentration of 250 ppm is bearable for most persons for 30–60 minutes.

Limited animal data regarding ocular effects of exposure to ammonia support the findings in humans. .

Neurological Effects. Neurological effects in humans following inhalation and dermal exposure to ammonia are usually limited to blurred vision, but more severe exposures can result in diffuse nonspecific encephalopathy, muscle weakness, decreased deep tendon reflexes, and loss of consciousness . However, hyperammonemia in humans can result from certain disease states such as cirrhosis of the liver, acute liver failure, and congenital deficiencies of any of the urea cycle enzymes, which may cause encephalopathy. Cerebral edema and herniation and intracranial hypertension have been noted in animal models of hyperammonemia. The mechanism of ammonia-induced encephalopathies has not been definitively elucidated. It is thought to involve the alteration of glutamate metabolism in the brain with resultant increased activation of N-methyl-D-aspartate (NMDA) receptors, which causes decreased protein kinase C-mediated phosphorylation of Na^+/K^+ ATPase, increased activity of Na^+/K^+ ATPase, and depletion of ATP. Additional evidence of altered energy levels include changes in some TCA cycle-associated components including acetoacetate, and NAD^+/NADH ratio, 2-oxoglutarate, and 3-hydroxybutarate. This reduced ATP level may be involved in ammonia-induced coma and death . A disruption in neurotransmission has also been suggested by alteration of brain tubulin, which is an essential component of the axonal transport system.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

- An MRL of 1.7 ppm has been derived for acute-duration inhalation exposure (14 days or less) to ammonia.

This MRL is based on a lowest-observed-adverse-effect level (LOAEL) of 50 ppm for mild irritation to the eyes, nose, and throat in humans exposed to ammonia as a gas for 2 hours (Verberk et al. 1977). The measurements for irritation were subjective and were reported by the subjects as no sensation (0), just perceptible (1), distinctly perceptible (2), nuisance (3), offensive (4), or unbearable (5); no statistical analysis was performed. Pulmonary function parameters were not statistically significantly different from pre-exposure values. The LOAEL was divided by an uncertainty factor of 30 (10 for variation in sensitivity among humans and 3 for use of a minimal LOAEL). A study of piggerie workers exposed to a mean level of 7.9 ppm ammonia measured pulmonary function change over a workshift; a small but borderline significant decrease in pulmonary function was noted (Heederik et al. 1990). This was not used as a basis for MRL derivation because the workers were also exposed to other potential respiratory toxicants (dust and endotoxins). The MRL is supported by other observations of respiratory effects associated with acute- and intermediate-duration exposure including transient irritation of the nose and throat of humans exposed to 100 ppm (Ferguson et al. 1977); nasal discharge in rats at 376 ppm (Coon et al. 1970); nasal lesions in rats at 150 ppm (Broderson et al. 1976); and nasal inflammation and lesions in rats at 500 ppm (Richard et al. 1978a).

No intermediate inhalation MRL for ammonia has been derived because adequate data were not available concerning the effects of ammonia for this route and duration of exposure. Humans exposed to 100 ppm ammonia vapors 6 hours/day, 5 days/week for 6 weeks experienced transient nasal and throat irritation (Ferguson et al. 1977). This study was not adequate for MRL derivation because the study description was contradictory between the text and tables, especially regarding the length of daily exposure. Rats exposed continuously to up to 179.1 ppm and guinea pigs, rabbits, dogs, and monkeys exposed to 56.4 ppm ammonia for 114 days had no clinical or histopathological respiratory effects; exposure to 369.4 ppm caused mild nasal discharge in 25% of exposed rats (Coon et al. 1970). Exposures of rats or guinea pigs to >640 ppm ammonia resulted in significant lethality as well as other signs of toxicity (Coon et al. 1970). No clinical or gross abnormalities were seen in rats, guinea pigs, rabbits, dogs, or monkeys exposed intermittently to up to 218.6 ppm (52 ppm adjusted to continuous exposure) for 6 weeks and only mild nonspecific inflammatory changes were noted in the lungs of rats and guinea pigs exposed to up to 1,085.7 ppm (254.4 ppm adjusted to continuous exposure) (Coon et al. 1970). No weight loss, conjunctivitis, or respiratory disease was seen in guinea pigs exposed to 90 ppm ammonia for 3 weeks; however, there was a decreased immune response at this level (Targowski et al. 1984). Guinea pigs exposed to 170 ppm ammonia for 6 hours/day 5 days/week for 18 weeks had no histopathological changes in the lungs, heart, or gastrointestinal tract, but increased hemosiderin in the spleen and hepatic and renal congestion were seen (Weatherby 1952); no effects were seen at 12 weeks of exposure. Only

one exposure level was tested in this study and other studies have not supported these findings. Adrenaline levels in urine, 17-oxycorticosteroids in the urine, and 11-oxycorticosteroid levels in blood were increased in humans exposed to 3.0 ppm ammonia for 37 days (Kalandarov et al. 1984). Exposure to 7.2 ppm for 17 days also increased adrenaline levels in urine and 17-oxycorticosteroids in the urine, and increased free, but not total, 11-oxycorticosteroid levels in blood (Kalandarov et al. 1984). No clinical or histological data were provided for this or other end points and no supporting data are available in the literature. No histopathological changes in the lungs were noted in rats exposed to 500 ppm ammonia for 8 weeks (Richard et al. 1978a).

- An MRL of 0.3 ppm has been derived for chronic-duration inhalation exposure (365 days or more) to ammonia.

This MRL is based on a NOAEL of 12.5 ppm for sense of smell, prevalence of respiratory symptoms (cough, bronchitis, wheeze, dyspnea, and others), eye and throat irritation, and lung function parameters (FVC, FEV_1, FEV_1/FVC, FEF_{50}, and FEF_{75}) in humans exposed for an average of 15 years in a soda ash plant (Holness et al. 1989); no LOAEL was determined. The NOAEL was adjusted for intermittent exposure and divided by an uncertainty factor of 10 (10 for variation in sensitivity among humans). The study authors calculated a time-weighted average (TWA) exposure level for the entire cohort of 9.2±1.4 ppm, but divided the cohort into groups of individuals that were exposed to low (<6.25 ppm), medium (6.25–12.5 ppm), and high (>12.5 ppm) ammonia levels. The MRL is supported by other observations of respiratory effects associated with chronic-duration exposure. A cross-sectional study of male workers at two fertilizer factories in Saudi Arabia showed that exposure to $25.4 ppm ammonia was significantly related to cough, phlegm, wheezing, dyspnea, and asthma (Ballal et al. 1998). However, continuous exposure levels for workers could not be calculated because the number of days worked per week was not provided by the study authors. An association was found between exposure to pollutants, including ammonia, in livestock confinement buildings and an increase in respiratory symptoms (such as bronchial reactivity/hyperresponsiveness, inflammation, cough, wheezing, or shortness of breath) and/or a decrease in lung function (such as forced expiratory volume in the first second [$FEV_{1.0}$], maximum expiratory flow rates [MEF_{50} and MEF_{75}], and maximal mid-expiratory flow rate [MMEF]) in farmers exposed to ammonia levels of 2.3–20.7 ppm (Choudat et al. 1994; Cormier et al. 2000; Donham et al. 1995, 2000; Heederik et al. 1990; Reynolds et al. 1996; Vogelzang et al. 1997, 2000). The farmers were also exposed to other possible respiratory toxins, such as dust, endotoxins, NO_2, and plant materials (hay dust).

Oral MRLs

No acute oral MRL was derived for ammonia. The only human acute oral studies available were case reports with no exposure levels (Klein et al. 1985; Klendshoj and Rejent 1966; Lopez et al. 1988). Animal studies were limited to a food intake study (Noda and Chikamori 1976), single-exposure studies with no effect, serious effects, or unsupported effects (Benyajati and Goldstein 1975; Koenig and Koenig 1949), a gavage study that lacked study details (Boyd and Seymour 1946), and a 6-day drinking water study with effects at high levels (Barzel 1975). Rats exposed to 3,102 mg NH_4^+/kg/day in the diet and drinking water for 7 days had statistically significantly reduced body weight gain (64% less) compared to a control group that consumed only 22 mg NH_4^+/kg/day (Boyano-Adánez et al. 1996). Food intake was also decreased. The reduction in body weight gain remained significant 8 days after cessation of exposure. It is impossible to tell where the actual NOAEL is from this study.

- An MRL of 0.3 mg NH_4/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to ammonia.

This MRL is based on a NOAEL of 39.5 mg/kg/day for weight loss in rats exposed to ammonium sulfamate in drinking water 6 days/week for 90 days (Gupta et al. 1979). The NOAEL was adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for variation in sensitivity among humans and 10 for extrapolation of animal data to humans). Body weights were 16% lower in treated adults than in controls at 90 days. Food intake was also decreased and water intake increased, but without statistical significance. Decreased body weight or body weight gain has also been seen in rats exposed orally to 991 mg/kg/day for 330 days (Barzel and Jowsey 1969) and to 960 mg/kg/day for 5 days (Noda and Chikamori 1976). Animals exposed to ammonia gas via inhalation have also had decreased body weight or reduced weight gain (Diekman et al. 1993; Drummond et al. 1980; Gustin et al. 1994; Richard et al. 1978a; Stombaugh et al. 1969).

No chronic oral MRL was derived for ammonia due to absence of data for this duration.