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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 to 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 loss from waste water effluents. The average global ammonia concentration in the atmosphere ranges from 0.3 to 6 ppb, with concentrations sometimes higher in the vicinity of agricultural or industrial areas. For example, near industrial sources or manure heaps in Germany, ammonia concentrations ranged from 10.3 to 89 ppb. Concentrations may be orders of magnitude higher near some types of livestock areas, such as pigpens, where local atmospheric concentrations have been reported to be as high as 47 ppm.

Elevated concentrations of ammonia in water are usually due to effluent discharges from sewage treatment plants or industrial processes, or runoff from fertilized fields or livestock areas. Ammonia concentrations can therefore vary widely in aquatic environments, with concentrations being lower in bodies of water that are unimpacted by residential, industrial, or farming effluents, compared to those that are impacted (where concentrations can be orders of magnitude higher). In unimpacted waterways, ammonia concentrations have been reported to range from 8.5 to 43 ppb, whereas in impacted waterways, concentrations as high as 16 ppm have been reported.

Soils usually obtain additional ammonia from natural or synthetic fertilizer application, animal excreta, decaying organic matter, or natural fixation from the atmosphere. Soils have been reported to have background concentrations of ammonia ranging from 1 to 5 ppm. Immediately following application of

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fertilizer or manure, however, ammonia concentrations can rise to 2–3,000 ppm, with levels dropping after 5 days to 2–850 ppm. These high ammonia concentrations are usually limited to the upper few centimeters of topsoil.

In the atmosphere, ammonia can react with acidic substances in the air to produce ammonium aerosols, which can be subject to 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 particles, 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. Local atmospheric concentrations in these agricultural settings have been reported to range from 280 to 88,000 ppb.

There is also the possibility for exposure to ammonia via water and food ingestion. If untreated surface water is ingested, the average uptake would be 0.36 mg/day (assuming an ammonia concentration in untreated water of 0.18 mg/L and a consumption rate of 2 L/day). For most sources of drinking water, however, adsorption, nitrification, and the conversion of ammonia to chloramines upon chlorination will result in negligible levels of ammonia in most drinking water supplies. Food ingestion can also lead to an exposure to ammonia, primarily due to the use of various ammonium salts as food stabilizers; the estimated exposure from these food additives is 18 mg/day.

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 in similar concentrations as those in agricultural settings. While these exposures may occur, the half-life of ammonia in nature is probably very short. Ammonia has been identified in at least 137 of 1,647 National Priority List (NPL) hazardous waste sites.

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2.2 SUMMARY OF HEALTH EFFECTS

Ammonia is an essential mammalian metabolite for DNA, RNA, and protein synthesis and is necessary for maintaining acid-base balance. Ammonia is produced and used endogenously in all mammalian species. It has been estimated that up to 17 grams of ammonia are produced in humans daily. Of these 17 grams, approximately 4 grams are produced in the gut by intestinal bacteria, where it enters the portal circulation and is metabolized rapidly in the liver to urea. Ammonia is excreted primarily as urea and urinary ammonium compounds through the kidneys. Levels of ammonia in the blood from healthy humans range from 0.7 to 2 mg/L.

The most important injurious effects of exposure to excessive amounts of ammonia on humans are due to its irritative and corrosive properties. Exposures to ammonia 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 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 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. 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, and eventually death. In chronic liver failure, arterial ammonia concentrations may reach approximately 3.6 mg/L, whereas arterial ammonia in acute liver failure may rise as high as 8 mg/L. The most likely and significant effects of exposure to elevated levels of ammonia are discussed below.

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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. Ammonia vapor readily dissolves in the moisture present on the skin, eyes, oropharynx and lungs forming ammonium hydroxide which dissociates to yield hydroxyl ions. 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. Unlike acid burns, which cause a coagulation necrosis, ammonia causes alkali burns, resulting in liquification of the tissue and deeper penetrations. 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.

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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 increased 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.

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Neurological Effects. Neurological effects in humans following inhalation or dermal exposure to ammonia are usually limited to blurred vision, most likely due to direct contact, but more severe exposures, which result in significant elevation of blood ammonia levels (hyperammonemia), can result in diffuse nonspecific encephalopathy, muscle weakness, decreased deep tendon reflexes, and loss of consciousness. 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; hyperammonemia may lead to encephalopathy. Some have suggested that ammonia may be involved in the generation of the symptomatology and progression of Alzheimer's disease as a result of pathological ammonia metabolism in the brain. 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 includes 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.

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2.3 MINIMAL RISK LEVELS*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). In that study, a group of 16 subjects were tested, 8 of them (experts) knew the effects of ammonia from the literature, but had no personal contact, whereas the remaining 8 subjects (non-experts) were students from a non-science faculty and were not familiar with ammonia or experiments in laboratory situations. All members of a group were exposed on the same day to one of the concentrations tested (50, 80, 110, or 140 ppm). The testing was repeated with a 1-week interval. Immediately before and after exposure, vital capacity, forced expiratory volume, and forced inspiratory volume were measured. During exposure, each subject recorded subjective feelings every 15 minutes as no sensation (0), just perceptible (1), distinctly perceptible (2), nuisance (3), offensive (4), or unbearable (5). No statistical analysis was performed and there was no group exposed to air only. Results of the pulmonary function tests after exposure were not statistically significantly different from pre-exposure values. For the non-experts, there was a clear increase in the number of reported symptoms for smell, eye irritation, throat irritation, cough, and general discomfort as the exposure concentration increased. The latter was not as clear for the experts. It should also be mentioned that the subjective responses appeared more pronounced in the non-expert group than in the expert group. The LOAEL was divided by an uncertainty factor of 30 (10 to protect sensitive individuals and 3 for the 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 study was not used as a basis for MRL derivation because the workers were also exposed to other potential respiratory toxicants (dust and endotoxins). Although the Verberk et al. (1977) study has limitations (no statistical analysis, subjective end points, no control group), it demonstrates that concentrations of 50 ppm ammonia produce minimal discomfort in healthy members of the general population and therefore, should be avoided. A more detailed discussion of additional information supporting the findings of Verberk et al. (1977) is presented in Appendix A.

No intermediate-duration inhalation MRL was derived for ammonia. The only available intermediate-duration inhalation study in humans is that of Ferguson et al. (1977). In that study, a group of 6 healthy

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volunteers, not previously accustomed to working in an ammonia environment, were exposed 5 days/week to 25 ppm (2 hours/day), 50 ppm (4 hours/day), or 100 ppm (6 hours/day) of ammonia, or to 50 ppm of ammonia 6 hours/day for 6 weeks. End points monitored included subjective and objective measures of eye and throat irritation as well as pulse rate, respiration rate, pulmonary function (FVC, FEV), assessment of neurological function (reflex, balance, and coordination), and body weight. The exposure protocol consisted of a pre-exposure evaluation by a physician, 3 hours of exposure (this conflicts with exposure data on table 2 of the study and mentioned above), a mid-point physician's observation, lunch break, 3 additional hours of exposure, and a third physician's observation 30 minutes after exposure ceased. The conjunctiva and mucosa of the nose and throat were examined by a physician before and after each daily exposure and the degree of irritation noted was described as mild, moderate, or marked. Exposure to ammonia had no significant effect on the measures of respiratory function or in the neurological tests conducted. The results of the evaluations of irritation conducted by the physician showed no significant differences between the exposure groups, including the 0 ppm exposure group (pre-exposure). All subjects experienced some watering of the eyes and a sensation of dryness in the nose and throat, and there was one observation of definite redness in the mucosa of the nose after a 6-hour exposure to 100 ppm during which time, there was an excursion to 200 ppm ammonia. No redness was observed in this subject the following morning. Throughout the study, the physician observed 6 cases of eye irritation, 20 of nose irritation, and 9 of throat irritation, and most cases appeared to have occurred the first week of the study during exposure to 50 ppm. It is difficult to determine in this study a no-observed-adverse-effect level (NOAEL) or LOAEL for irritation due to the different exposure durations experienced by the subjects. In general, studies in animals have used higher exposure concentrations and the overall quality of the studies is less than desirable. For ammonia, a corrosive irritant gas that affects the portal of entry and produces irritation of eyes and respiratory tract, use of human data should be preferred over animal studies.

- An MRL of 0.1 ppm has been derived for chronic-duration inhalation exposure (365 days or more) to ammonia.

This MRL supersedes the previous chronic inhalation MRL of 0.3 ppm derived in the 2002 draft for public comment version of this profile. The MRL is based on a NOAEL of 9.2 ppm for sense of smell, prevalence of respiratory symptoms (cough, bronchitis, wheeze, dyspnea, and others), eye and throat irritation, and lung function parameters (FVC, FEV₁, FEV₁/FVC, FEF₅₀, and FEF₇₅) in humans exposed for an average of 12.2 years in a soda ash plant (Holness et al. 1989); no LOAEL was determined. The cohort consisted of 52 workers and 35 controls. The subjects were assessed on two workdays: on the first workday of their workweek and on the last workday of their workweek. Spirometry was performed at the

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beginning and end of each work shift, so that each worker had four tests done. To determine the exposure levels, exposed and control workers were sampled over one work shift; the average sample collection period was 8.4 hours. All of the participants in the study were males. Analysis of the results showed no significant differences in the prevalence of reported symptoms, but the exposed workers reported that exposure in the plant aggravated some of their reported symptoms (cough, wheeze, nasal complaints, eye irritation, and throat discomfort). Odor threshold was not affected by exposure to ammonia and there were no significant differences in baseline lung functions between exposed and control subjects. Analysis of each worker separately showed no significant relationship between the level of ammonia exposure and changes in lung function. Also, when the workers were divided 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, no significant association was found between reporting of symptoms, decline in baseline function, or increasing decline in function over the work shift and exposure to ammonia. Furthermore, no association was evident between increasing years of exposure and decreasing lung function. However, the power of the indices of both level and length of exposure is low because only eight workers were in areas with relatively high ammonia exposure. The MRL was calculated by adjusting the mean TWA exposure concentration of 9.2 ppm for continuous exposure (8/24 hours x 5/7 days) and dividing by an uncertainty factor of 10 to protect sensitive individuals. A modifying factor of 3 was added for the lack of reproductive and developmental studies.

Oral MRLs

No oral MRLs were derived for ammonia because of two main reasons. In the first place, the overall quality and/or usefulness of the oral database is limited. 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 NH₄⁺/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 NH₄⁺/kg/day (Boyano-Adánez et al. 1996). Such a high dose of ammonium (as acetate) is equivalent to a 70 kg human ingesting approximately 1.4 lb of ammonium acetate daily. No human studies or reports of intermediate-duration oral exposure to ammonia were located. Intermediate-duration animal studies have reported decreases in body weight gain in rats exposed via drinking water (Gupta et al. 1979) or diet (Boyano-Adánez et al. 1996). It should be

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mentioned that Gupta et al. (1979) administered ammonium sulfamate to the rats. Ammonium sulfamate is an herbicide whose herbicide properties reside in the sulfamate portion of the salt and for which there is little toxicity information in the open literature. The EPA (IRIS 2004) has derived an oral RfD for the sulfamate moiety based on the results of Gupta et al. (1979). Following gavage administration of ammonium salts, bone, blood pressure, adrenal gland, and renal effects have been observed in early studies, generally inadequate by current standards (Bodansky et al. 1932; Fazekas 1939; Seegal 1927). No chronic-duration oral data were located.

An additional reason not to derive oral MRLs for ammonia is because of the role played by the anion of the salt administered. Briefly, in many animal studies, the animals were administered ammonium chloride. Ammonium chloride is commonly used to induce metabolic acidosis in experimental animals. The acidosis is due to the formation of hydrogen ions from the metabolism of ammonium ions to urea. WHO (1986) notes that the ingestion of ammonium chloride in doses around 500–1,000 mg/kg/day for 1–8 days (longer treatment would worsen the condition) has induced metabolic acidosis in mice, guinea pigs, rats, rabbits, and dogs. Metabolic acidosis can result in a variety of nonspecific changes in neurological, cardiovascular, pulmonary, gastrointestinal, and musculoskeletal function, as well as in changes in hematological and clinical chemistry parameters. Acidosis following the administration of ammonium chloride is due to the formation of hydrogen chloride and although it will occur with any ammonium salt, the degree of acidosis (and associated consequences) will be determined by the ability of the kidneys to excrete the specific anion. DeSousa et al. (1974) showed that administration of hydrochloric acid to dogs induced a significantly greater decrease in plasma bicarbonate than administration of equivalent quantities of H⁺ as nitric or sulfuric acid. This means that it would be inappropriate to extrapolate findings obtained with ammonium chloride (or any ammonium salt) to equivalent amounts of ammonium, but derived from a different salt.

Finally, as discussed by WHO (1986), the amount of excess ammonia (over and above the amount normally produced in the body) that can be safely ingested and assimilated is difficult to define. However, data from human and animals suggest that that amount may be substantial based on the existence of various efficient ways by which the body can dispose of ammonia.