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**Toxicological Review of Ammonia
Noncancer Inhalation:
Executive Summary**

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EXECUTIVE SUMMARY

Occurrence and Health Effects

Ammonia occurs naturally in air, soil, and water. Ammonia is also produced by humans and other animals as part of normal biological processes.

Ammonia is used as an agricultural fertilizer and in many cleaning products. Exposure to ammonia occurs primarily through breathing air containing ammonia gas, and may also occur via diet, drinking water, or direct skin contact. Measured concentrations of ammonia range from 0.28 to 15 $\mu\text{g}/\text{m}^3$ in ambient outdoor air and from 0.09 to 166 $\mu\text{g}/\text{m}^3$ in indoor air.

Health effects of inhaled ammonia observed at levels exceeding naturally-occurring concentrations are generally limited to the respiratory tract, the site of direct contact with ammonia. Short-term inhalation exposure to high levels of ammonia in humans can cause irritation and serious burns in the mouth, lungs, and eyes. Chronic exposure to airborne ammonia can increase the risk of respiratory irritation, cough, wheezing, tightness in the chest, and impaired lung function in humans. Studies in experimental animals similarly indicate that breathing ammonia at sufficiently high concentrations can result in effects on the respiratory system. Animal studies also suggest that exposure to high levels of ammonia in air may adversely affect other organs, such as the liver, kidney, and spleen.

This assessment presents an evaluation of the noncancer health effects of ammonia by the inhalation route of exposure.

Chemical Properties

Ammonia (NH_3) is a colorless alkaline gas with a pungent odor. In solution, ammonia exists as ammonium hydroxide, a weak base that is only partially ionized in water according to the following equilibrium ([ATSDR, 2004](#)): $\text{NH}_3 + \text{H}_2\text{O} \rightleftharpoons \text{NH}_4^+ + \text{OH}^-$. A decrease in pH results in an increase in the concentration of ammonium ion (NH_4^+) and a decrease in the concentration of the un-ionized form (NH_3). At physiological pH (7.4), this equilibrium favors the formation of NH_4^+ .

Toxicokinetics

Inhaled ammonia is almost completely retained in the upper respiratory tract. Ammonia produced endogenously in the intestines through the use of amino acids as an energy source and by bacterial degradation of nitrogenous compounds from ingested food is largely absorbed. At physiological pH, 98.3% of ammonia is present in the blood as the ammonium ion (NH_4^+). Given its importance in amino acid metabolism, the urea cycle, and acid-base balance, ammonia is homeostatically regulated to remain at low concentrations in the blood. Ammonia is present in fetal circulation and in human breast milk as a source of nonprotein nitrogen. Ammonia production

occurs endogenously by catabolism of amino acids by glutamate dehydrogenase or glutaminase primarily in the liver, renal cortex, and intestines, but also in the brain and heart. Ammonia is metabolized to glutamine via glutamine synthetase in the glutamine cycle or incorporated into urea as part of the urea cycle. The principal means of excretion of ammonia is as urinary urea; lesser amounts are eliminated in the feces, through sweat production, and in expired air.

Effects Other Than Cancer Observed Following Inhalation Exposure

Respiratory effects have been identified as a human health hazard following inhalation exposure to ammonia. This hazard determination is based on findings from multiple epidemiology studies in human populations exposed to ammonia in different settings (workers in industrial, cleaning, and agricultural settings, volunteers exposed for up to 6 hours under controlled conditions, and case reports) and animals (short-term and subchronic studies in several species and across different exposure regimes).

Cross-sectional occupational studies involving chronic exposure to ammonia in industrial settings provide evidence of an increased prevalence of respiratory symptoms ([Rahman et al., 2007](#); [Ballal et al., 1998](#)) and decreased lung function ([Rahman et al., 2007](#); [Ali et al., 2001](#); [Ballal et al., 1998](#); [Bhat and Ramaswamy, 1993](#)). Other studies of exposure to ammonia when used as a disinfectant or cleaning product provide evidence of asthma, asthma symptoms, and impaired pulmonary function, using a variety of study designs ([Casas et al., 2013](#); [Arif and Delclos, 2012](#); [Dumas et al., 2012](#); [Lemiere et al., 2012](#); [Vizcaya et al., 2011](#); [Zock et al., 2007](#); [Medina-Ramón et al., 2006](#); [Medina-Ramón et al., 2005](#)). Further evidence of respiratory effects of ammonia is seen in studies of pulmonary function in an agricultural setting, specifically in studies that accounted for effects of co-exposures to other agents such as endotoxin and dust ([Donham et al., 2000](#); [Reynolds et al., 1996](#); [Donham et al., 1995](#); [Preller et al., 1995](#); [Heederik et al., 1990](#)) and in one study that did not control for co-exposures ([Loftus et al., 2015](#)). Despite the variation in population characteristics, level and pattern of exposure, and potential confounders across these three settings of epidemiology studies, respiratory effects were consistently observed in these studies. Further, but more limited, support for the respiratory system as a target of ammonia toxicity comes from controlled human exposure studies of ammonia inhalation and case reports of injury in humans with inhalation exposure to ammonia. Additionally, respiratory effects were observed in several animal species following short-term and subchronic inhalation exposures to ammonia.

Overall, there are suggestions in experimental animals that ammonia exposure may be associated with effects on organs distal from the portal of entry, but there is inadequate information to draw conclusions about the liver, kidney, spleen, or heart as sensitive targets of ammonia toxicity.

Inhalation Reference Concentration (RfC) for Effects Other Than Cancer

Table ES-1. Summary of reference concentration (RfC) derivation

Critical effect	Point of departure ^a	UF	Chronic RfC
Decreased lung function and respiratory symptoms Occupational epidemiology studies Holness et al. (1989) , supported by Rahman et al. (2007) , Ballal et al. (1998) , and Ali et al. (2001)	NOAEL _{ADJ} : 4.9 mg/m ³	10	0.5 mg/m ³

^aAn estimate of the 95% lower confidence bound of the mean exposure concentration in the high-exposure group of the [Holness et al. \(1989\)](#) study was used as the NOAEL. Because the study involved workplace exposure conditions, the NOAEL of 13.6 mg/m³ was adjusted for continuous exposure based on the ratio of VE_ho (human occupational default minute volume of 10 m³ breathed during an 8-hour workday) to VE_h (human ambient default minute volume of 20 m³ breathed during the entire day) and an exposure of 5 days out of 7 days.

NOAEL = no-observed-adverse-effect level; UF = uncertainty factor

The study of ammonia exposure in workers in a soda ash plant by [Holness et al. \(1989\)](#), with support from three studies in urea fertilizer plants by [Rahman et al. \(2007\)](#), [Ballal et al. \(1998\)](#), and [Ali et al. \(2001\)](#), was identified as the principal study for RfC derivation. Respiratory effects, characterized as increased respiratory symptoms based on self-report (including cough, wheezing, and other asthma-related symptoms) and decreased lung function in workers exposed to ammonia, were selected as the critical effect. [Rahman et al. \(2007\)](#) observed an increased prevalence of respiratory symptoms and decreased lung function in workers exposed in a plant with a mean ammonia concentration of 18.5 mg/m³, but not in workers in a second plant exposed to a mean concentration of 4.9 mg/m³. [Ballal et al. \(1998\)](#) observed an increased prevalence of respiratory symptoms among workers in one factory with exposures ranging from 2 to 27.1 mg/m³,¹ but no increase in another factory with exposures ranging from 0.02 to 7 mg/m³. A companion study by [Ali et al. \(2001\)](#) also observed decreased lung function among workers exposed to higher cumulative ammonia levels (>50 mg/m³-years), with an approximate 5–7% decrease in FVC% predicted and FEV₁% predicted (see definition of spirometry measures in Section 1.2.1). [Holness et al. \(1989\)](#), who investigated a plant with exposures generally lower than other studies, found no differences in the prevalence of respiratory symptoms or lung function between workers (mean exposure 6.5 mg/m³) and the control group, and no differences when stratified by exposure level (highest exposure group, >8.8 mg/m³).

These four studies addressed smoking by a variety of methods (e.g., adjustment for smoking, exclusion of smokers, stratification of the results by smoking status). Two of the

¹This concentration range does not include exposures in the urea store (number of employees = 6; range of ammonia concentrations = 90–130.4 mg/m³) because employees in this area were required to wear full protective clothing, thus minimizing potential exposure.

studies—[Rahman et al. \(2007\)](#) and [Holness et al. \(1989\)](#)—addressed other potential confounders as appropriate. In particular, a high level of control of exposures in the facility studied by [Holness et al. \(1989\)](#) was reported, suggesting a low potential for co-exposures. As discussed in more detail in the Literature Search Strategy | Study Selection and Evaluation section, confounding by other workplace exposures, although a potential concern, was unlikely to be a major limitation of these studies.

Considerations in selecting the principal study for RfC derivation include the higher confidence placed in the measures of ammonia exposure in [Holness et al. \(1989\)](#), evaluation of both respiratory symptoms and lung function parameters in this study, and the fact that the estimate of the no-observed-adverse-effect level (NOAEL) for respiratory effects of 13.6 mg/m³ from [Holness et al. \(1989\)](#) was the highest of the studies with adequate exposure-response information. The synthesis of findings from the full body of evidence demonstrates that there is a relationship between ammonia exposure and respiratory effects. Although [Holness et al. \(1989\)](#) do not report associations between ammonia exposure and respiratory effects, it is included in the body of epidemiologic studies of industrial settings because it is informative of the levels above which ammonia causes effects. Other epidemiology studies include those with higher workplace ammonia concentrations associated with respiratory effects (i.e., higher concentrations relative to those reported by [Holness et al. \(1989\)](#)) and for which lowest-observed-adverse-effect levels (LOAELs) could be identified. The [Holness et al. \(1989\)](#) study is identified as the principal study for RfC derivation based on the quality of the exposure data and other factors, as stated above.

In summary, the study of ammonia exposure in workers in a soda ash plant by [Holness et al. \(1989\)](#) was identified as the principal study for RfC derivation, with support from [Rahman et al. \(2007\)](#), [Ballal et al. \(1998\)](#), and [Ali et al. \(2001\)](#), and respiratory effects were identified as the critical effect. The NOAEL, represented by an estimate of the 95% lower confidence bound of the mean exposure concentration in the high-exposure group from the [Holness et al. \(1989\)](#) study, or 13.6 mg/m³, was used as the point of departure (POD) for RfC derivation. The NOAEL adjusted to continuous exposure (NOAEL_{ADJ}) was 4.9 mg/m³.

An RfC of 0.5 (rounded) mg/m³ was calculated by dividing the POD (adjusted for continuous exposure, i.e., NOAEL_{ADJ}) by a composite uncertainty factor (UF) of 10 to account for potentially susceptible individuals in the absence of data evaluating variability of response to inhaled ammonia in the human population.

Confidence in the Chronic Inhalation RfC

Study – medium

Database – medium

RfC – medium

Consistent with Environmental Protection Agency (EPA) *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* ([U.S. EPA, 1994](#)), the overall confidence in the RfC is medium and reflects medium confidence in the principal study (adequate design, conduct, and reporting of the principal study; limited by small sample size and identification of a NOAEL only) and medium confidence in the database, which includes occupational, cleaner, agricultural, and human exposure studies and studies in animals that are mostly of subchronic duration. There are no studies of developmental toxicity, and studies of reproductive and other systemic endpoints are limited; however, the likelihood of reproductive, developmental, and other systemic effects at the RfC is considered small because it is well documented that ammonia is endogenously produced in humans and animals, and any changes in blood ammonia levels at the POD would be small relative to normal blood ammonia levels. Further, EPA is not aware of any mechanisms by which ammonia can exert effects at the point of contact (i.e., respiratory system) that could directly or indirectly impact tissues or organs distal to the point of contact.

Susceptible Populations and Lifestages

Studies of the toxicity of ammonia in children that would support an evaluation of childhood susceptibility are limited. [Casas et al. \(2013\)](#) and [Loftus et al. \(2015\)](#) reported evidence of an association between ammonia exposure and decrements in lung function in children; however, these studies did not report information that would allow a comparison of children and adults.

A limited number of studies provides inconsistent evidence of greater respiratory sensitivity to ammonia exposure in asthmatics ([Loftus et al., 2015](#); [Petrova et al., 2008](#); [Sigurdarson et al., 2004](#); [Preller et al., 1995](#)). [Loftus et al. \(2015\)](#) reported no increase in asthma symptoms and medication use in asthmatic children living near animal feeding operations; however, ammonia exposure was associated with lower FEV₁.

Hyperammonemia is a condition of elevated levels of circulating ammonia that can occur in individuals with severe diseases of the liver or kidney or with hereditary urea [CO(NH₂)₂] cycle disorders. These elevated ammonia levels can predispose an individual to encephalopathy due to the ability of ammonia to cross the blood-brain barrier; these effects are especially marked in newborn infants. Thus, individuals with disease conditions that lead to hyperammonemia may be more susceptible to the effects of ammonia from external sources, but there are no studies that specifically support this susceptibility.

Key Issues Addressed in This Assessment

Comparison of Exhaled Ammonia to the RfC

Ammonia is generated endogenously in multiple organs and plays central roles in nitrogen balance and acid-base homeostasis ([Weiner et al., 2014](#); [Weiner and Verlander, 2013](#)). Given its

important metabolic role, free ammonia is homeostatically regulated to remain at low concentrations in blood ([Souba, 1987](#)). Elimination of ammonia occurs primarily in urine and exhaled breath. Consideration was given to the presence of ammonia in exhaled air because the range of ammonia concentrations in exhaled breath (0.009–2 mg/m³) overlaps the ammonia RfC (0.5 mg/m³).

In general, higher and more variable ammonia concentrations (0.03–2 mg/m³) are reported in human breath exhaled from the mouth or oral cavity ([Schmidt et al., 2013](#); [Smith et al., 2008](#); [Španěl et al., 2007a, b](#); [Turner et al., 2006](#); [Diskin et al., 2003](#); [Smith et al., 1999](#); [Norwood et al., 1992](#); [Larson et al., 1977](#)). Ammonia concentrations measured in breath derived from oral breathing largely reflect the production of ammonia via bacterial degradation of food protein in the oral cavity or gastrointestinal tract, and can be influenced by diet, oral hygiene, age, and saliva pH. In contrast, concentrations of ammonia in breath exhaled from the nose and trachea of humans (0.0092–0.1 mg/m³) are lower than those in air exhaled from the mouth ([Schmidt et al., 2013](#); [Smith et al., 2008](#); [Larson et al., 1977](#)), and are generally lower than the RfC by a factor of five or more. Concentrations in breath exhaled from the nose appear to better represent levels at the alveolar interface of the lung and are more relevant to understanding systemic levels of ammonia than breath exhaled from the mouth ([Schmidt et al., 2013](#); [Smith et al., 2008](#)); however, concentrations in breath from neither the mouth nor the nose can be used to predict blood ammonia concentration or previous exposure to environmental (ambient) concentrations of ammonia (see Appendix C, Section C.1.4).

Regardless of the source of expired ammonia (mouth or nose), the level of ammonia in breath, even at concentrations that exceed the RfC, does not necessarily raise questions about the appropriateness of the RfC. The exhalation of ammonia is a clearance mechanism for a product of metabolism that is otherwise toxic in the body at sufficiently high concentrations. Thus, ammonia concentrations in exhaled breath may be higher than inhaled concentrations. However, the presence of ammonia in exhaled breath is not considered an uncertainty in the RfC.

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