APPENDIX A6.1.3.25 AMMONIA - FACTSHEET

	HPHC	BoExp assessed by PMI
IUPAC name	Azane (IUPAC)	NA
Usual abbreviation		
Other names	Ammonia	
CAS number	7664-41-7	
Formula and molecular weight	NH_3 MW: 17.03	

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Main characteristics

Chemical class	Inorganic compound
HPHC lists	FDA-93 [1]; FDA-18 [2]; HC [3, 4]; PMI-58; WHO-39 [5]
Source in cigarettes	Amount in mainstream smoke (3R4F): 11.1 µg (ISO); not measured (HCI) [6] Smoke phase: gas/vapor phase [7] Presence in tobacco / pyrosynthesis (T°): present in uncombusted tobacco / Pyrolysis of a U.S. blended tobacco on its own generates ammonia in two main temperature regions, i.e., 200–450 and 450–700 °C [8]. Precursors in of ammonia in smoke are amino acids, pigments and proteins in tobacco. Ammonia is also formed by reduction of nitrate [9]. Ammonia (or its precursors) in tobacco or smoke lead to lower smoke yields of aldehydes (in particular formaldehyde) [9].
Other sources [10]	Ammonia is naturally produced and used by all mammals in their normal metabolism. Most of this ammonia is produced by organs and tissues, but some is produced by bacteria living inside the intestines. 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 and dead animals also contributing significant amounts. It is also exhaled by animals. 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. Exposure to ammonia in the environment is most likely to occur by breathing in ammonia that has been released into the air. Outdoors, exposure to high levels of ammonia in air occurs from leaks and spills at production plants and storage facilities, and from pipelines, tank trucks, railcars, ships, and barges that transport ammonia. Higher levels of ammonia in air may occur when fertilizer with ammonia or ammonium compounds is applied to farm fields. Indoors, exposure may occur while using household products that contain ammonia. Some of these products are ammonia-cleaning solutions, window cleaners, floor waxes, and smelling salts.
Toxicity class (FDA) [1]	RT
Toxicity – CA	-

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Toxicity – RT [10]	Ammonia is an upper respiratory irritant in humans. 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 causes 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, at high doses, 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.
Toxicity – CT [10]	Acute exposure to highly concentrated aerosols of ammonium compounds may cause elevated pulse and blood pressure, bradycardia, and cardiac arrest in humans.
Toxicity – RDT	-
Toxicity – AD	-
Toxicity - others	Skin is extremely sensitive to airborne ammonia or ammonia dissolved in water [10]. The topical damage caused by ammonia is probably due mainly to its reactivity and irritation properties. Ammonia can be irritating for the eyes. The primary effects of ammonia in humans are due to its corrosive and irritative properties. All available toxicity data can be found on the Website Aggregated Computational Toxicology Resource (ACToR) [11].

ADME properties

Absorption [10, 12] - Although it has not been extensively studied, dermal absorption of ammonia does not occur to a great extent; thus systemic effects from skin and eye exposure to ammonia are not quantitatively important. Most of the inhaled ammonia is retained in the upper respiratory tract and is subsequently eliminated in expired air. Almost all of the ammonia produced endogenously in the intestinal tract is absorbed. Exogenous ammonia is also readily absorbed in the intestinal tract. As the ammonia concentration increases, the ability of the upper respiratory tract to retain ammonia is saturated, and a larger percentage is absorbed into the blood stream. Ammonia that reaches the circulation is widely distributed to all body compartments although substantial first pass metabolism occurs in the liver where it is transformed into urea and glutamine. Ammonia or ammonium ion reaching the tissues is taken up by glutamic acid, which participates in transamination and other reactions. The principal means of excretion of ammonia that reaches the circulation in mammals is as urinary urea; minimal amounts are excreted in the feces and in expired air.

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Nasal and pharyngeal irritation, but not tracheal irritation, suggests that ammonia is retained in the upper respiratory tract. Unchanged levels of blood-urea-nitrogen, non-protein nitrogen, urinary-urea, and urinary-ammonia are evidence of low absorption into the blood. Exposure to common occupational limits of ammonia in air (25 ppm) with 30% retention (and assuming this quantity is absorbed into the blood stream) would yield an increase in blood ammonium concentration of 0.09 mg/L. This calculated rise is only 10% above fasting levels.

Absorption data from human inhalation exposure suggest that only small amounts of ammonia are absorbed into the systemic circulation. Initial retention of inhaled ammonia in the mucus of the upper respiratory tract may be 80% or more, but after equilibrium is established (within 30 minutes) 70–80% of inspired ammonia is expired in exhaled air. The lack of change in blood nitrogen compounds and urinary-ammonia compounds lends further support to a limited absorption into the systemic circulation.

Available data indicate that ammonia has similar targets of toxicity in humans and animals. Ammonia is most hazardous as a site-of-contact toxicant; therefore, the respiratory system is most vulnerable after inhalation exposure, the gastrointestinal tract is most vulnerable after oral exposure, and the skin and eyes are most vulnerable after dermal/ocular exposure.

Distribution [10, 12] - No quantitative reports of distribution of ammonia from inhalation exposure were found in the available literature. Studies on endogenously produced ammonia, however, indicate that it is distributed to most of the organs and tissues of the body via the blood, where it is used in protein synthesis or as a buffer, and that excess levels would be reduced to normal by urinary excretion, or converted by the liver to glutamine and urea.

Metabolism [10, 12, 13] - 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.

Quantitative data on human metabolism of exogenously introduced ammonia were not located in the available literature. Extensive work has been completed on the metabolism of ammonia and its participation in the glutamine cycle and the urea cycle. Ammonia and ammonium ion are metabolized to urea and glutamine mainly in the liver by the process diagrammed in Figure 1 and Figure 2 [10, 13]. However, it can be rapidly converted to glutamine in the brain and other tissues as well. The nitrogen is released from glutamine within tissue cells and used for protein synthesis as needed. Ingestion of ammonium salts leads to almost complete conversion of ammonium ion into urea in the liver, whereas exposure by other routes may lead to its metabolism in body tissues to glutamine or tissue protein.

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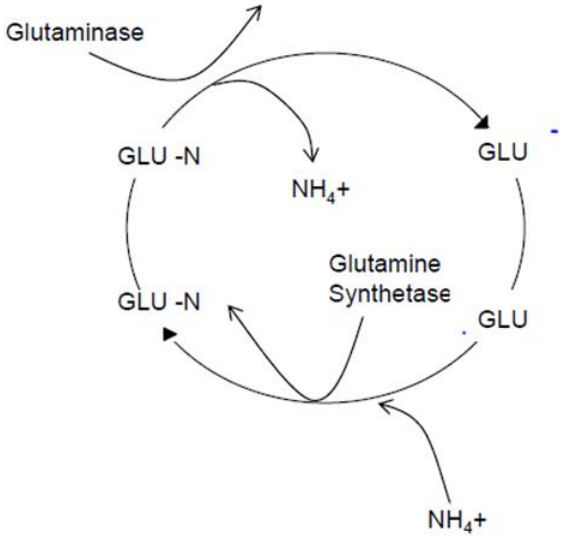


Figure 1 Glutamine cycle (GLU = Glutaminate; GLU-N = Glutamine) [10]

Figure source: Agency for Toxic Substances and Disease Registry.

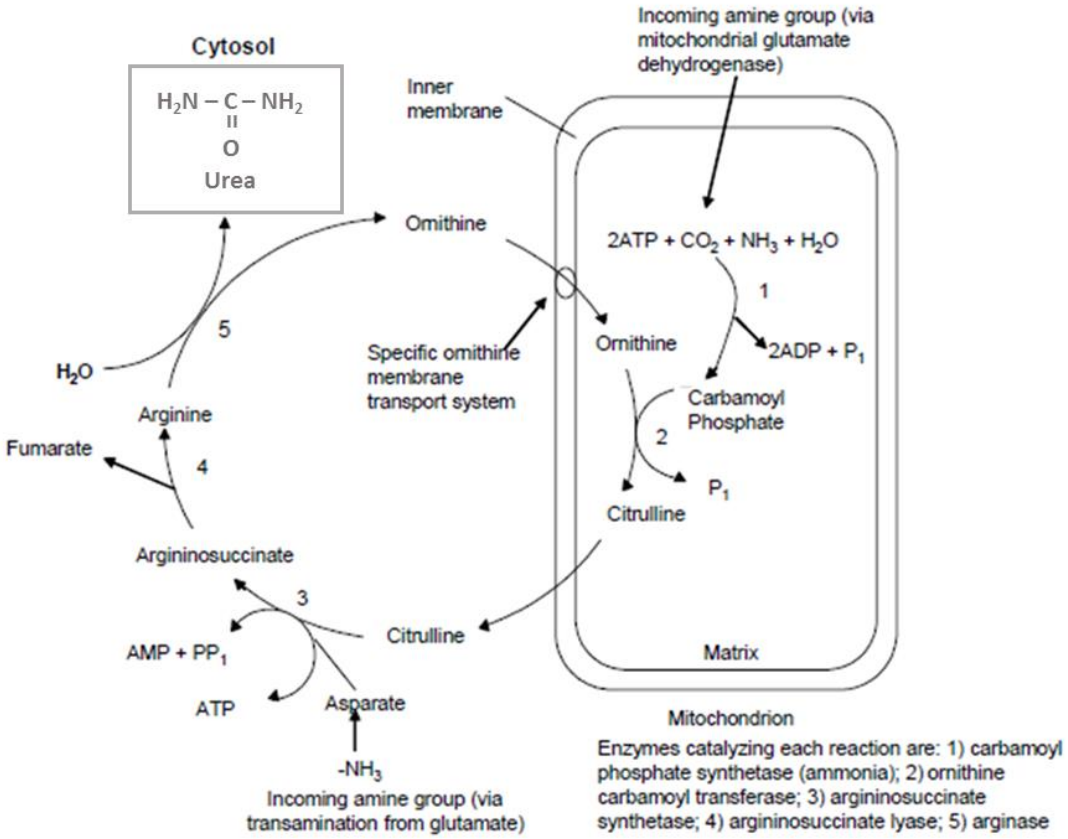


Figure 2 The urea cycle showing the compartmentalization of its steps within liver cells

Figure source: Agency for Toxic Substances and Disease Registry (Modified; chemical formula of urea corrected)

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Excretion [10, 12] - Data regarding excretion are limited, but it is known that ammonia inhaled at low levels is excreted primarily unchanged in the expired breath. No information regarding excretion after dermal exposure was located. Ammonia absorbed from the gastrointestinal tract is excreted primarily in the urine as urea and other urinary nitrogen compounds, but also as urea in feces, and as components of sweat, even though quantitative data are lacking. Toxic levels do not develop as a result of chronic inhalation exposure because the body has multiple effective mechanisms for detoxifying and excreting it. Data regarding the pharmacokinetic mechanisms of ammonia were not located in the available literature.

Limited human and animal data are available for toxicokinetics; however, these data indicate that humans and animals are probably very similar regarding the toxicokinetic disposition of ammonia. Furthermore, it is reasonable to expect, especially given the biochemical importance of ammonia, that humans and animals would handle this compound similarly. The use of the ^{13}N-Ammonia as a positron emitting radiopharmaceutical for diagnostic purposes indicates that half-life of injected ammonia is short, i.e., less than 3 minutes [14, 15].

Exposure levels in smokers and non-smokers

Tests that measure ammonia/ammonium ion in blood and urine are available, however, they would probably not tell whether there has been exposure to ammonia because it is normally found in the body [10]. Levels of ammonia in the blood from healthy humans range from 0.7 to 2 mg/L.

There are no known specific biomarkers of exposure for ammonia in humans or animals. Furthermore, no evidence for alterations in clinical indices of body ammonia or nitrogen levels after exposure to exogenous ammonia has been reported. It does not seem useful at this time to develop biomarkers of exposure for ammonia because after exposure to low levels, ammonia is either rapidly cleared from the body or metabolized to compounds found endogenously at appreciable levels. Exposure to high concentrations is immediately and overtly toxic, which eliminates the need for a more subtle biomarker.

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List of abbreviations

3R4F	Kentucky 3R4F reference research cigarette [16]
ACToR	Aggregated Computational Toxicology Resource
AD	Addictive
ADME	Absorption and Distribution, Metabolism, and Excretion
CA	Carcinogen
CAS number	Chemical Abstracts Service number
CT	Cardiovascular toxicant
FDA	Food and Drug Administration
HC	Health Canada
HCI	Health Canada Intense regime [17]
HPHC	Harmful and Potentially Harmful Constituents
IARC	International Agency for Research on Cancer
ISO	International Organization for Standardization smoking regime [18]
IUPAC	International Union of Pure and Applied Chemistry
MW	Molecular weight
NA	Not applicable
PMI	Philip Morris International
RDT	Reproductive or developmental toxicant
RT	Respiratory toxicant
WHO	World Health Organization

References

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