

# Health Effects of Ammonia

*Extreme overexposure to ammonia can cause irreversible pulmonary damage. There, however, is no credible evidence that inhaling a small amount of ammonia leads to chronic lung impairment.*

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In the recent past, ammonia has been the focus of several regulatory agencies' activities. The OSHA (Occupational Safety and Health Administration) changed its workplace exposure limit to a 35 ppm (part per million) STEL (short term exposure limit). The ACGIH (American Conference of Governmental Industrial Hygienists) set a TLV (threshold limit value) for ammonia at 25 ppm as a TWA (time-weighted average). Many States have or are in the process of setting an AAC (acceptable ambient concentrations) for ammonia. Ammonia is currently on the SARA 313 list (Superfund Amendments and Reauthorization Act), prompting the ATSDR (Agency for Toxic Substance and Disease Registry) to prepare a toxicological profile for

ammonia. The DOT (Department of Transportation) revoked its proposal to reclassify anhydrous ammonia as a poison, and retained the non-flammable gas classification and required an inhalation hazard warning on domestic shipments. Finally, the EPA (Environmental Protection Agency) is currently attempting to set an RfD (risk reference dose, - defined as an estimate of the daily exposure to the human population that likely is to be without an appreciable risk of deleterious effect during a lifetime) for ammonia. Each of these areas of regulation has a profound impact on several industries. It is extremely important that any standards set act to both protect human health and retain the necessary production of ammonia.

The purpose of this report is to present an overview of the health effects of ammonia. The focus is on the effects following inhalation

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exposure, however, other routes of exposure are included in order to provide information regarding potential effects and insight into mechanisms of ammonia toxicity. Information regarding physical and chemical properties, sources, and estimates of human exposure is included to provide context and perspective.

#### BACKGROUND INFORMATION

Ammonia (CAS No. 7664-41-7) has the empirical and molecular formula  $\text{NH}_3$ . It is a colorless gas at room temperature with a sharp and repellant odor and a molecular weight of 17.03. Ammonia is very soluble in water (34% at 20 degrees C) and has a high vapor pressure (8.7 atm at 20 degrees C) and a low vapor density (0.6 g/L).

Ammonia is one of the most widely used industrial chemicals. With a production volume of 16.2 million tons in 1987, it is ranked fourth in the U.S. after sulfuric acid, nitrogen, and ethylene (1). The total annual capacity of ammonia production in the U.S. for 1988 was 19.1 million tons (2) and the ammonia output during the 1987-88 fertilizer year was 16.4 million tons (3).

Most of the ammonia produced in the United States goes into fertilizers (80%). Of the total domestic ammonia output that goes into fertilizer applications, 40% is used directly and the rest is converted to various nitrogen-containing fertilizers, mainly diammonium phosphate and urea (4). In addition to fertilizer usages, ammonia is used in explosives production, manufacturing of metals, petroleum refining, pulp and paper, food and beverage, refrigeration, textile industries, and other chemical production processes.

Ammonia is released into the atmosphere by agricultural, waste-disposal, and industrial activities. In the U.S., industrial emissions from ammonia and fertilizer production, petroleum refineries, coke ovens, and sodium carbonate manufacture, and loss of anhydrous ammonia during distribution, handling, and application have been estimated at 840,000

tons/year for 1980 (5). The largest anthropogenic sources of ammonia emissions result from livestock waste management practices, including beef cattle feedlots and cropland spreading (6). Ammonia is released into the aquatic environment from a variety of natural and man-made sources.

#### ESTIMATES OF HUMAN EXPOSURE

Levels of ammonia in the human body are the result of both exogenous (internal) production which occurs during normal metabolic processes. External exposure accounts for a daily intake of approximately 20 mg/day, while the body produces approximately 17 g/day. Occupational exposure can account for an additional 300 mg/day (7).

The general population is exposed to ammonia through inhalation, ingestion, and dermal exposure. The normal ammonia intake in food is at least 10 times greater than all other exposure sources combined, even for urban smokers (8). Typical urban areas have environmental ammonia levels of approximately 0.03 ppm. Intake via inhalation in non-urban areas has been estimated to be between 0.08 and 0.1 mg/day. Intake of ammonia can reach 0.4 mg/day in urban areas. Ammonia is also inhaled during smoking. Approximately .042 mg ammonia is inhaled from smoking one cigarette (9).

Ammonia and ammonium compounds are present in small quantities in drinking water and food. The average human intake from drinking water has been estimated to be 1 mg/day in urban areas and less than 0.4 mg/day in non-urban areas. Ammonia in food is present principally through the use of ammonium salts as stabilizers, leavening agents, and other food additives; the ammonia intake from these sources has been estimated to be 18 mg/day (10).

There is little ocular or dermal exposure to ammonia under normal conditions, although these pathways of exposure may occur under accidental conditions.

## METABOLISM AND PHARMACOKINETICS

Before beginning the discussion of the metabolism and pharmacokinetics of ammonia, it is necessary to define the relevant terms. Exogenous refers to exposure from the external environment, for example, breathing a gas. Endogenous exposure refers to exposure from within the body, for example, the body's exposure to blood. The distribution of a chemical is the way a chemical migrates to different areas in the body. Absorption of a chemical is the process by which a chemical gets into the bloodstream. Metabolism or biotransformation refers to the sum of the processes by which a foreign chemical is subjected to chemical change by living organisms. Excretion is the mechanism by which the body eliminates a chemical. Pharmacokinetics is the study of drugs or chemicals within the body, that is, their absorption, distribution via the blood, metabolism, and excretion.

Ammonia is a unique industrial chemical in that it is produced and utilized endogenously, that is, internally in all mammalian species. It is produced in the body via catabolism or breakdown of proteins in the liver, kidney, and stomach. It is also produced in the body from amino acids, which are the building blocks of protein, in the liver by a process called gluconeogenesis (11). In addition, bacteria in the intestine break down urea and other nitrogenous compounds to form ammonia. About 17 grams (1 mole) of ammonia are produced per day. Four grams of ammonia are absorbed daily into the circulation following its production from urea and protein catabolism in the stomach (12).

Exposure to ammonia also occurs by the exogenous route, that is, from outside of the body. The principle exogenous route of human exposure to ammonia in the industrial setting is by inhalation. Since ammonia is very water soluble at low concentrations, very little inhaled ammonia may reach or be absorbed by the lung. Rather, it may be absorbed in the mucous of the upper respiratory tract and swallowed. Experiments show that concen-

trations as high as 543 ppm ammonia would be absorbed primarily in the nasal passages then swallowed (13). It has been estimated by the World Health Organization that inhalation exposure to low concentrations of ammonia (25 ppm) would result in an increase in blood-ammonia concentration only 10% greater than normal levels (14). Taken together, this information suggests that an inhalation exposure to ammonia below 500 ppm will not result in a significant increase in blood ammonia concentration.

Ammonia is normally distributed throughout the body, so that any analysis of distribution of ammonia received from outside the body must take into account endogenous pools of ammonia and ammonium ion. The distribution is dependent to some extent on the pH because the unionized form diffuses rather freely among the various compartments of the body. The ammonium ion diffuses less readily and is therefore restricted to locations in the body where it is generated.

The distribution of ammonia received from outside sources depends on the route of exposure. Ammonia which is inhaled or swallowed enters the gastrointestinal tract then is transported to the liver where it enters the urea cycle and glutamine pathway (15). Excess ammonia present in the blood supply is detoxified by the skeletal muscle.

Humans have a number of metabolic pathways for the detoxification and removal of ammonia. The two principal pathways for ammonia are conversion into urea or glutamine. These processes occupy a central role in the regulation of systemic acid-base balance. The integrated metabolism of ammonia in the liver, kidney and skeletal muscle is an important part of this process. Figure 1 represents a schematic of the relationship between the metabolic pathways of the liver and the kidney. In the liver, excess amino acids can be converted into glucose, ammonium and bicarbonate ion. During acidosis, that is, when the body is in an acidic state, urea synthesis accompanied by a net gluta-

mine uptake by the liver (16). The liver is the only organ that converts ammonia to urea, all of the ammonia formed in the gastrointestinal tract is transported to the liver by the hepatic portal circulation.

In man, the maximal rate of urea synthesis is about 4 moles per 24 hours (17). Therefore, man has a large capacity for handling excess ammonia. Although the liver detoxifies ammonia present in the blood supply.

Ammonia is eliminated in exhaled air and in the urine under normal conditions (18, 19, 20).

#### HEALTH EFFECTS OF AMMONIA

In determining the health effects of any chemical, it is important to distinguish between an exposure and an effect. Chronic, subchronic, and acute exposures refer to the length of time of the chemical exposure. Chronic and acute effects refer to the persistence of the health effect.

In order to evaluate how inhalation of potentially toxic chemicals may affect human health, several endpoints can be examined. Some of the endpoints examined in experiments attempting to assess ammonia toxicity include changes in various blood, liver, and kidney enzyme activities or levels, pathological changes in various organs, physical impairment of lung function, changes in cilia beating in the trachea, effects on nerve conduction and enhancement of bacterial lung infections. Other health effects that can be examined are carcinogenicity, mutagenicity or damage to the genetic material of cells, and damage to the reproductive system or developing fetus. This section reviews the major findings from several chronic, subchronic and acute exposure studies conducted in humans and animals. The studies evaluated were drawn from published scientific literature.

#### Chronic Exposure

Analysis of the present available chronic exposure data for both human and animal studies provide no sub-

stantial evidence that ammonia is carcinogenic (21). In epidemiology studies (studies which examine the effect of chemical on defined human populations) no causal relationship could be demonstrated between exposure to ammonia and a decrease in lung functions (ability to inhale and exhale efficiently). It is concluded that due to its chemical properties and interactions within the respiratory tract, ammonia does not have the potential to cause chronic damage from long term, low level exposure.

#### Subchronic Exposure

A summary of the low-level ammonia subchronic studies appears in Figure 2. Contained in this table are the LOEL's (lowest observable effect levels) which represent the lowest concentrations reported to cause effects in various animals, and the NOEL's (no observable effect levels) which represent the exposure concentration at which no effects were observed. The most significant study in the NOEL table, that is, well conducted and scientifically sound, is that of Coon et al (22). Rats, guinea pigs, rabbits, dogs and monkeys exposed to ammonia at a concentration of 57 ppm for 114 days exhibited no histopathological changes and no signs of toxicity.

In determining a LOEL for ammonia, several studies were examined which reported effects such as decreased ability to fight bacterial infections, lung congestion, accumulation of fluid in the lungs, and a decrease in weight gain. However, upon further analysis of these studies, it was found that they had major flaws and therefore the findings were not substantiated. The lowest reported substantial LOEL occurred at 100 ppm at which pigs that were exposed to ammonia for 6 weeks experienced conjunctival irritation and thickening of the tracheal epithelium (23).

In considering all of the available studies, the weight of evidence supports the establishment of an animal subchronic NOEL at about 50 ppm, that is, it would appear that ammonia levels below 50 ppm are unlikely to

result in any adverse systemic effects. There are some reports of effects at lower levels, but the quality of the studies is generally poor. When these studies are eliminated, the remaining data showing effects at lower levels were judged insufficient to warrant establishing a lower animal subchronic NOEL, particularly when the metabolism data are taken into consideration.

#### Acute Exposure

Ammonia gas and liquid are irritants to the eyes, respiratory tract and skin. Due to the alkaline nature of ammonia, prolonged contact of concentrated ammonia with biological tissue can result in a corrosive effect. The biological effects of ammonia in humans after acute exposures are closely related to air concentrations, that is, effects from acute exposure are concentration dependent.

The range of odor thresholds for ammonia is approximately 5-50 ppm. 25 ppm is the ACGIH TLV, that is, the average exposure permitted in the workplace during an 8 hour day. OSHA recommends a 15 minute short term exposure limit of 35 ppm. Between 100 ppm and 400 ppm are the amounts of ammonia most often reported to be irritating to the eyes and throat. 500 ppm is the OSHA defined exposure concentration causing no escape impairing symptoms or irreversible effects. 1000 ppm causes eye, nose and throat irritation along with chest tightness. 1700-2500 ppm results in coughing, bronchospasm, and chest pain along with severe eye irritation and tearing. 2500-5000 ppm ammonia causes shortness of breath, airway spasms, increased fluid in the lungs and chest pain. 5000-10,000 ppm is potentially fatal. These levels can cause chemical bronchitis, fluid accumulation in the lungs, and direct chemical burns of the skin. Permanent pulmonary damage has not been associated with acute ammonia exposures unless exposure concentrations are at near lethal levels (24).

Chronic respiratory dysfunction

has occurred in humans following high level acute ammonia exposure, as would occur in a spill situation, however, this appears to be secondary to subsequent infections rather than the ammonia burn alone. Following uncomplicated ammonia exposure, late effects such as scar-related pulmonary obstruction are rare.

Mutagenicity. The purpose of mutagenicity studies is to determine if a chemical can effect the DNA or genetic material of a cell. It is hypothesized that cancer can occur through an alteration of DNA, therefore, mutagenicity is usually used as a screening test for potential carcinogens.

Two studies have reported mutagenic effects of ammonia (25), however, evaluation of those studies indicated the results are of questionable validity. An in vitro study in bacteria was flawed by low bacterial survival at mutagenic effect levels (26). The authors also suggest that altered bacterial genetics may have been related to general deleterious chemical effects on cell metabolism and not specific gene loci. The second study, published in the Russian literature (27), does not meet requirements of acceptability for a study with statistical significance and compliance with established scientific principles. Therefore, there is no credible evidence of ammonia mutagenicity (28).

Reproduction, Embryotoxicity, and Teratogenicity. There have not been any formal studies based on current protocols to address the effects of ammonia on reproduction or the developing fetus. Work investigating the effects of ammonia at concentrations of 0 - 78 ppm for 8 weeks in hen houses on the egg-laying performance of reared poultry led to no systematic conclusions (29). Oral exposure of ammonium chloride in drinking water to mice reduced the incidence of cleft palate formation in the offspring (30). Based on the existing metabolism evidence, it does not appear that studies addressing teratogenicity of ammonia are necessary.

## CONCLUSIONS

Ammonia is a normal constituent in all mammalian species. It is produced internally and used in the synthesis of essential components as nucleoside bases and amino acids. Excess amounts of ammonia are exhaled in the gaseous state. The normal blood level of ammonia in humans is about 1.0 mg/liter and is similar to other mammalian species. Approximately 17 grams of ammonia are produced per day; 4 grams of which are absorbed into the circulation. That which is not utilized by intermediate metabolism from dietary sources can readily be excreted. The urea cycle, which is mainly responsible for clearing excess ammonia from the body fluids under normal conditions, is operating at about 10% of capacity. It has been calculated that continuous exposures to 25 ppm results in only a 10% increase in blood levels of ammonia. This amount is well within the variable levels found in human blood (0.8 - 1.74 mg/liter). Much of the human data available describes acute exposures resulting from accidents and is not useful in establishing low ambient safe levels of ammonia.

The average total intake of ammonia per day from air and water and food is about 20 mg, which is about 0.5% of the total amount of ammonia produced daily by intestinal bacteria. If the exposure to ammonia via inhalation is increased by 25 ppm, there would be a 2.8% increase in daily dose of ammonia over internal and external exposure. The weight of evidence from several experiments and species supports the establishment of a NOEL at around 50 ppm. That is, it would appear that ammonia levels below 50 ppm are unlikely to result in any adverse effects. There are some reports of effects at lower levels, but the quality of the studies is generally poor. When these studies are disregarded, the remaining data showing effects at lower levels were judged insignificant to warrant establishing a lower NOEL, particularly when the metabolic data are taken into account. Ammonia levels in the air ranging

between 4 ppm and 45 ppm are generally recognized as a perceptible level. The Institution of Chemical Engineers has stated that the odor threshold is around 5 ppm (31) and continuous exposures at this level are likely to have virtually no toxic effect.

Ammonia at levels above approximately 100 ppm are irritating to the eyes, respiratory tract and skin. The biological effects of ammonia in humans after acute exposures are closely related to air concentrations.

Based on the weight of evidence, ammonia levels in the air below 50 ppm for extended periods of time are unlikely to result in any adverse systemic effects in human or other mammalian species.

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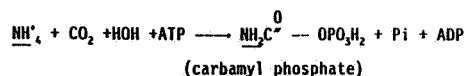
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REMOVAL OF AMMONIA VIA THE UREA CYCLE IN THE LIVER

$\text{NH}_4^+$  (ammonium ion) from blood enters the liver where it is transformed into carbamyl phosphate

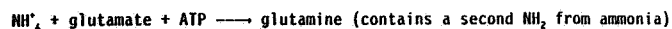
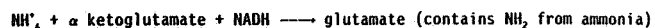


Carbamyl phosphate enters urea cycle and forms urea ( $\text{NH}_2\text{C}^{\text{O}}\text{NH}_2$ ) where it is transported via circulation to the kidneys and excreted in the urine

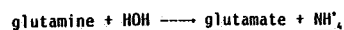
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REMOVAL OF AMMONIA FROM OTHER BODY TISSUES

$\text{NH}_4^+$  (ammonium ion) absorbed or formed in tissues is converted into glutamate.



Glutamine as the carrier for ammonia enters circulation and is transported to the kidney where the following reaction occurs:



where the  $\text{NH}_4^+$  ammonium ion is excreted in the urine.

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**Figure 1. Removal of ammonia via the urea cycle in the liver.**



NOEL				
Species	Inhalation Exposure	Length of Exposure		Reference
Rat	4 ppm	4 months; 35 hr/week	No change in ability to fight bacterial nasal infection	Mikhailuts et al. (1979) <sup>a</sup>
Guinea Pig	50 ppm	3 weeks	No effect on mitogenic response of blood lymphocytes to infection	Targowski et al. (1984)
Rats	181 ppm	90 days	No histopathological changes No signs of toxicity	Coon et al. (1970)
Rat, guinea pig, rabbit, dog, monkey	57 ppm	114 days	No histopathological changes No signs of toxicity	Coon et al. (1970)
Pig	61 ppm	5 weeks	No gross pathological changes	Stombaugh et al. (1969)
Pigs	50 ppm	71 days	No decrease in weight gain	Curtis et al. (1975)
Rats	30-90 ppm	50-60 days	No effect on weight gain	Stolpe and Sedlag (1976)
LOEL				
Species	Inhalation Exposure	Length of Exposure	Endpoint	Reference
Rat	9 ppm	4 months; 35 hr/week	Noticeable decrease in ability to combat bacterial infections	Mikhailuts et al. (1979) <sup>a</sup>
Chicken	20 ppm	greater than 6 weeks	Hyperemia, lung congestion and hemorrhaging, edema	Anderson et al. (1964) <sup>b</sup>
Mouse, guinea pig	20 ppm	greater than 6 weeks	Lung edema, congestion hemorrhaging (slight for guinea pig)	Anderson et al. (1964) <sup>c</sup>
Chicken (young)	25 ppm	4 weeks	Decrease in weight gain	Reece et al. (1981) <sup>b</sup>
Rat	29 ppm	12 weeks	Inhibition of brain cholinesterase activity (effect reversible)	Saifutdinov (1966) <sup>d</sup>
Rat	43 ppm	2 months	Increased unconditional pain reflex; no biochemical or pathomorphological changes observed	Prokop'eva and Yushkov (1975)
Pig (young)	50 ppm	4 weeks	Decrease in growth (12%)	Drummond et al. (1980)
Pig	100 ppm	6 weeks	Conjunctival irritation; thickening of tracheal epithelium	Doig and Willoughby (1971)
Rat	102 ppm	5 hr/day for 8.6 weeks	Loss of tracheal cilia	Dahmann and Reid (1967)
Rat	102 ppm plus inhalation of carbon particles	5 hr/day for 8.6 weeks	Enhanced tracheal damage	Dahmann and Reid (1967)
Rat	109 ppm	28 days	Enhanced infectivity to <u>M. pulmonis</u>	Schoeb et al. (1982) <sup>e</sup>
Rat	150 ppm	75 days	Pathological changes in the nasal passages	Broderson et al. (1976)

<sup>a</sup> Animals were exposed to 800x10<sup>8</sup> pathogenic Staphylococcus (No. 209) three times during the experiment. The level of pathogens were abnormally high in order to maximize the response in the experiment.

<sup>b</sup> Chickens are uteroecic animals and may not be an appropriate model to extrapolate to humans.

<sup>c</sup> Only two guinea pigs and four mice were used per exposure time.

<sup>d</sup> There was insufficient information in the English translation to evaluate the experimental protocol. The study also reported an increase at the 3 ppm exposure level in the time necessary for blood to reduce methylene blue (which disappeared after cessation of exposure). The reduction of methylene blue is unlikely to be of any physiological significance.

<sup>e</sup> These animals were infected with either 1x10<sup>4</sup> to 4x10<sup>4</sup> or 4x10<sup>8</sup> to 8x10<sup>8</sup> colony-forming units of Mycoplasma pulmonis. These pathogenic levels of exposure could not normally be encountered in the environment.

Figure 2. Summary of pertinent no observable effects (NOEL) and lowest observable effect levels (LOEL) responses following ammonia inhalation exposures.