

Ammonia

Toxicological overview

Key Points

Kinetics and metabolism

- Ammonia dissolves in moisture in the air and on tissue or mucous membranes to form ammonium hydroxide, a strong base
- Ammonium is produced in the intestines by bacteria and is efficiently absorbed from the gastrointestinal tract
- Dermal or ocular absorptions are considered not to contribute significantly to systemic ammonium following exposure
- Ammonia is readily metabolised in the liver to urea or glutamine
- Ammonia is excreted primarily in the urine as urea

Health effects of acute exposure

- Ammonia and ammonia solutions are irritant and corrosive and may be harmful by all routes of exposure
- Acute oral exposure rapidly results in pain, excessive salivation and burns to the mouth, throat and oesophagus
- Acute inhalation may initially cause upper respiratory tract irritation. Substantial exposures can cause burns in the oral cavity, nasopharynx, larynx and trachea, together with airway obstruction, respiratory distress and bronchiolar and alveolar oedema
- Ammonia or ammonia solutions are corrosive in contact with tissue, and splashes to the eye may result in serious injury

Health effects of chronic exposure

- Effects following chronic oral exposure have not been defined in humans. Experiments in animals suggest osteoporosis, occurring secondary to chronic metabolic acidosis
- Chronic inhalation has been associated with increased cough, phlegm, wheeze and asthma
- Ammonia is considered not to be a human carcinogen
- Ammonia is considered not to be a human reproductive or developmental toxicant

Toxicological Overview

Summary of Health Effects

Ammonia and ammonium hydroxide are corrosive and can rapidly penetrate the eye and may cause permanent injury. Therefore, splashes in the eye should be considered an ophthalmic emergency.

Dermal exposure to ammonia or its solutions may result in irritation and, depending on the concentration, alkali burns. Pressurised ammonia (as a liquefied gas) may also cause cryogenic burns following skin or eye contact.

Ingestion of ammonia solutions (ammonium hydroxide) causes rapid onset of signs and symptoms including pain in the mouth, throat and chest, excessive salivation and extensive alkali burns to the aerodigestive tract. Chronic oral exposure to ammonia has not been characterised in humans. Limited animal data have shown that osteoporosis secondary to chronic metabolic acidosis may occur.

Inhalation of ammonia causes rapid onset of signs and its toxic effects are mediated through its irritant and corrosive properties. Features include irritation to the nose, throat and respiratory tract. Increased lacrimation, coughing, an increased respiratory rate as well as respiratory distress may occur. Substantial exposures can cause burns of all depths in the oral cavity, nasopharynx, larynx and trachea, together with airway obstruction and bronchiolar and alveolar oedema. Exposure to a massive concentration of ammonia gas may be fatal within minutes. There are limited data on the chronic effects of ammonia in exposed populations. In one study, an association was noted between exposure to ammonia and cough, phlegm, wheezing, dyspnoea and asthma; with a concomitant reduction in lung function.

Ammonia has no structural alerts for DNA reactivity, and is not mutagenic.

Ammonia has not been classified as a human carcinogen. Ammonia is not considered to be an animal carcinogen, ingestion by rats of ammonia as ammonium hydroxide for 2 years did not result in an increase in cancers.

It is unlikely that exposure to environmental levels of ammonia would result in reproductive or developmental toxicity. Data from animal studies show that foetal toxicity or embryotoxicity may occur but secondary to maternal toxicity after very high exposures.

Kinetics and Metabolism

Ammonia is extremely soluble in water and dissolves in the mucus fluid covering the mucous lining of the respiratory system to produce ammonium hydroxide, a strong base. Following a short term inhalation exposure, ammonia is almost entirely retained in the upper nasal mucosa [1]. Inhalation of high concentrations of ammonia may exceed the capacity of this mechanism leading to systemic absorption through the lungs.

Although ammonia rapidly enters the eye, systemic absorption is considered not to be quantitatively significant [1]. The toxicity findings after acute skin exposure to ammonia suggest that systemic absorption is not significant by this route either [2].

Ammonia is absorbed readily through mucous membranes and the intestinal tract but not through the skin [3]. It also rapidly penetrates the eye but as a route of systemic absorption, this is likely to be quantitatively insignificant.

Absorbed ammonia is well distributed throughout body compartments and reacts with hydrogen ions, depending on the pH of the compartment to produce ammonium ions [3]. The ammonium ion is less mobile due to its charged nature [1].

Ammonium ion is endogenously produced in the gut from the bacterial breakdown of nitrogenous constituents of food. Almost all of this endogenous ammonium (approximately 99% of the 4 g produced daily) is absorbed by passive diffusion from the intestinal tract before entering the hepatic portal vein [2].

In the liver, ammonium ions are extensively metabolised to urea and glutamine. Consequently, levels of ammonia that reach the circulation are low [2]. Clearly, hepatic insufficiency could affect ammonium ion metabolism.

Ammonia reaching the circulation is principally excreted by humans as urinary urea [2], excretion of absorbed ammonia in exhaled breath and faeces is not significant [3]. Small amounts of ammonia are excreted via the urine; the average daily excretion for human beings is approximately 2-3 µg, about 0.01 % of the total body burden. Small amounts of unabsorbed ammonia may also be excreted from the gastrointestinal tract in the faeces [2].

Sources and Route of Human Exposure

Apart from endogenously produced ammonia and ammonium, the major route of exposure to ammonia is by inhalation. Ammonia is released from a number of natural processes, and low levels are present in ambient air.

In Europe, agriculture is the largest source of ammonia [4], where it is liberated from manure spread on land and from livestock housing. In the UK, total ammonia emissions have been estimated at around 320,000 tonnes per year. Emissions from cattle, pig and poultry farming alone account for around 66% of this total [4] with volatilisation of some fertilisers (such as ammonium carbonate) accounting for a further 9% of total emissions. Local concentrations may therefore be elevated where organic waste matter is concentrated, such as in intensive farming environments for cattle and pig farming and chickens [4]. Non agricultural sources include sewage sludge, pets, industrial and combustion processes and petrol vehicles fitted with catalytic converters [4]. Ammonia is also produced in the human gut by bacteria.

Ammonia is used either directly or indirectly in many industrial processes and as such exposure may occur in a range of industrial settings, some of which are described above.

Ammonia is transported in bulk as a pressurised gas and spills or leaks after accidents are another potential source of exposure.

Domestically, exposure may occur from certain cleaning agents and dyes. Reaction of cleaning products may cause liberation of ammonia gas.

Ammonia gas is not persistent and rapidly reacts in the environment to ammonium compounds. This means that the hazards associated with the pure chemical rapidly decrease after release.

Health Effects of Acute / Single Exposure

Human Data

Inhalation

The clinical manifestations of acute ammonia exposure are usually immediate in presentation and its toxic effects are mediated through its irritant and corrosive properties.

Ammonia is an upper-respiratory tract irritant and inhalation will rapidly cause irritation to the nose, throat and respiratory tract. Increased lacrimation, coughing, an increased respiratory rate as well as respiratory distress may occur [1]. The retention of ammonia in the nasal mucosa may protect against some lung effects at low concentrations.

Substantial exposures to concentrated aerosols of ammonium hydroxide, elevated levels of ammonia gas or anhydrous ammonia fumes, can cause burns of all depths in the oral cavity, nasopharynx, larynx and trachea, together with airway obstruction, respiratory distress and pulmonary oedema [2, 5, 6].

Exposure to a massive concentration of ammonia gas may be fatal within minutes and asphyxiation may occur after exposure in poorly ventilated or enclosed spaces. Findings in fatal cases include extensive oedema, full thickness burns to the entire respiratory tract, purulent bronchitis and greatly distended lungs [2, 5, 7]. Bronchial walls may also be stripped of their epithelial lining [7, 8].

Lower levels of ammonia exposure that do not result in upper-airway obstruction may cause significant alkali burns throughout the tracheo-bronchial tree [5].

Systemic effects following acute exposures to high concentrations of ammonia include an elevated pulse and blood pressure, bradycardia, cardiac arrest, cyanosis and hemorrhagic necrosis of the liver [2].

The primary features after ammonia exposure are summarised in Table 1.

Table 1. Summary of toxic effects following acute exposure to ammonia by inhalation [2, 9].

Dose		Signs and Symptoms
mg m ⁻³	ppm	
35	50	Irritation to eyes, nose and throat (2 h exposure)
70	100	Rapid eye and respiratory tract irritation
174	250	Tolerable by most persons (30-60 min exposure)
488	700	Immediately irritating to eyes and throat
>1045	>1500	Pulmonary oedema, coughing, laryngospasm
1740-3134	2500-4500	Fatal (30 min)
3480-6965	5000-10000	Rapidly fatal due to airway obstruction

Values in mg m⁻³ are approximate calculations from ppm, where mg m⁻³ = ppm x gram molecular weight/24.45 (molar volume of air at standard temperature and pressure)

Ammonia has a pungent and characteristic odour of drying urine which is discernible at around 35 mg m⁻³ (50 ppm) [1, 2]. However, ammonia causes olfactory fatigue (adaptation)

making its presence difficult to detect when exposure is prolonged. Odour, therefore, is not to be considered as a reliable indicator of exposure, or the extent of an exposure.

Ingestion

Ingestion of ammonia solutions (ammonium hydroxide) causes rapid onset of signs and symptoms including pain in the mouth, throat and chest, excessive salivation and extensive alkali burns to the aerodigestive tract. Though there is little quantitative data, these features have been noted in one case involving ingestion (with a suicidal intent) of as little as 20-25 mL of 6% household ammonia solution [10].

Paediatric exposures to ammonia capsules (used as “smelling salts”) or small volumes of ammonia solutions may cause the child to be drooling and irritable, dysphagic and with ulcerative lesions to the buccal cavity and first degree burns to the tongue or aerodigestive tract [11-13]. Complete recovery was, however, noted in all these cases of oral paediatric poisoning.

Adult fatalities have occurred from deliberate ingestion of ammonium solutions. In one case, ingestion of an unspecified volume of 3% ammonium ion resulted in aspiration pneumonia and laryngeal and epiglottic oedema and a friable and erythematous oesophagus with severe corrosive injury. The individual died several days later from acute respiratory distress syndrome and renal failure. In another case, after the ingestion of an unspecified amount of 2.4% ammonium ion solution, findings at autopsy included haemorrhagic oesophagus, stomach and duodenum [2].

Ocular / dermal exposure

Ammonia and ammonium hydroxide rapidly penetrate the eye and can be highly damaging and may cause permanent injury: therefore, splashes in the eye should be considered an ophthalmic emergency [14].

Effects may range from increased lacrimation, conjunctivitis, palpebral oedema, photophobia, blepharospasm, through to corneal ulceration, corneal opacification, iritis, anterior and posterior synechia formation, retinal atrophy, glaucoma, cataract formation and blindness [15]. Irritation arising from low atmospheric concentrations of $>20 \text{ mg m}^{-3}$ ($>29 \text{ ppm}$) is considered to be readily reversible when exposure ceases [1].

Anhydrous ammonia gas stored under pressure as a compressed liquid expands rapidly on liberation, resulting in vaporisation and a large endothermic reaction. The result may be evaporative freezing of any tissue in contact with the ammonia [16]. Ammonia readily forms ammonium hydroxide on contact with moisture in the air and skin and the resultant hydroxide saponifies lipids of the epidermal fats and cell membranes [9]. The resultant liquifactive necrosis may appear pale and without charring or blistering [3] and may cause an increased depth of injury. The combination of both cryogenic effects with an alkali burn can produce serious injuries.

Individuals with extensive burns to the eyes and skin are likely to have obstruction of the airway [5].

Delayed effects following an acute exposure

Inhalation exposures to low concentrations for a short period, from which an individual recovers quickly on removal to fresh air, are unlikely to result in delayed or long term adverse health effects.

Substantial inhalation exposures to ammonia may cause long-term health effects, including persistent airway obstruction, cough, exertional dyspnoea, bronchiolitis obliterans and bronchiectasis, which for some cases may persist for many years [2, 5, 8, 9]. Dysphonia may persist for many months as a result of burns to the aerodigestive tract [5, 7].

Scarring to body tissue can be pronounced following burns from ammonia exposure [9].

Health Effects of Chronic / Repeated Exposure

Human Data

Inhalation

Minor respiratory effects have been associated with chronic inhalation exposure to low levels of ammonia in some studies.

A study in a fertiliser factory considered both workers and administrative staff. It was found that workers exposed to levels above 18 mg m^{-3} (26 ppm) had significantly higher relative risks for cough, phlegm, wheezing, dyspnoea and asthma than those exposed to levels below 18 mg m^{-3} . Within the exposed group, FEV₁% predicted and FEV₁%/FVC% were significantly lower in symptomatic than asymptomatic individuals [17]. Whilst a small study, with high levels of smoking in the controls as a possible confounder, it suggests that chronic exposures to ammonia may impact respiratory function. Similar findings have been noted in a study conducted at a series of factories producing fertiliser chemicals, with decreased performance in respiratory function tests of exposed workers when compared with controls. Data from the ammonia plants show a small statistically significant decrease in FVC₁ and a substantial decrease in PEF_R/min. No significant decrease in FVC was noted and the specificity of these studies for an effect by ammonia alone was, however, limited as no concentrations were presented [18].

Acclimatisation to the irritant effects of ammonia at concentrations up to 70 mg m^{-3} (100 ppm) has been demonstrated after repeated exposure for 6h a day for 5 days each week over a 6 week period [19]. No further interpretation was possible due to the limited design of this study.

In another study, occupational exposures of around 12 years to low concentrations of airborne ammonia 6 mg m^{-3} (9 ppm) had no significant effect on pulmonary function in a group of workers at a factory making sodium bicarbonate [20].

Ingestion

There are no human data on which to assess the effects of chronic excessive ammonia intake.

Ammonium may be ingested in both food and water, however as ammonium is readily metabolised to products of low toxicity (such as urea and glutamate) within the body; it is unlikely that chronic exposures to low levels will have a significant adverse health effect.

Genotoxicity

There is limited data in humans on the genotoxicity of ammonia. One small study in humans examining the exposure to ammonia at a fertiliser factory noted an increase in chromosomal aberrations, sister chromatid exchanges and increased mitotic index [21]. There was a weak association reported between increased length of exposure and increased frequency of chromosomal aberrations and sister chromatid exchange. No detail was given as to how well the exposed and control group were matched for age, smoking habits etc. Furthermore, it appears that gaps were included in the cytogenetic analysis. Given these limitations and the

small size of this study, the low levels of ambient ammonia and the likely exposure to other chemicals no conclusions can be drawn regarding the mutagenicity of ammonia.

There is no other *in-vivo* human data on which to assess the genotoxicity of ammonia and there is conflicting evidence between this study and *in-vitro* studies. However, ammonia has no structural alerts for DNA damage and when the *in-vitro* data is considered, ammonia can be considered as not having significant mutagenic potential.

Carcinogenicity

There is insufficient evidence to classify ammonia as a carcinogen in humans and it has not been classified by the IARC.

Reproductive and developmental toxicity

No data were located on the possible developmental effects of ammonia. It is, however, unlikely that exposure to ammonia would result in reproductive or developmental toxicity in the absence of maternal toxicity.

Animal and In-Vitro Data

Inhalation

Inhalation exposure of several animal species to ammonia has been conducted. In some series of studies [22], repeated exposures (8 h/5 days a week for 30 days) to ammonia (155 mg m⁻³/223 ppm) produced no adverse clinical signs effects in rats, guinea pigs, rabbits, dogs and monkeys. The group sizes of higher order animals were, however, small (2 or 3). After continuous exposure to 40 mg m⁻³ (58ppm) ammonia for 114 days, there were no adverse clinical observations noted and findings at necropsy were normal. Histological examination revealed lipid filled macrophages in the lungs of 2/2 dogs, 1/3 monkeys and 1/15 rats; these findings were considered to be of uncertain toxicological significance. No lung alterations were seen in the remaining experimental or control animals [22].

A limited study in pigs compared low atmospheric exposures to ammonia of approximately 5 mg m⁻³ (7 ppm) with moderate exposures of approximately 35 ppm/24 mg m⁻³. Mean daily body weight was reduced in the moderate exposure group in the first 2 weeks of exposure, which resulted in small animals at slaughter after 6 weeks of exposure [23].

Ingestion

There is limited data available on the effects of chronic oral exposure to ammonia (as ammonium hydroxide).

In one study, rabbits were given ammonium hydroxide (100 mg kg⁻¹ bodyweight) as a 0.5-1% solution by oral gavage for up to 17 months. The key findings from this study included an initial fall in blood pressure, followed by an increase above the baseline and enlarged adrenal glands [1].

Long term exposure of rats, rabbits and dogs to ammonium salts such as ammonium chloride can cause metabolic acidosis. This acidosis occurs from H⁺ ions released during conversion to urea and may produce a range of non-specific effects on cardiovascular, pulmonary (including increased ventilation), gastrointestinal and musculoskeletal functions [2]. Osteoporosis has been noted, arising from the mobilisation of bone mineral to spare bicarbonate. However, these are considered to be secondary to prolonged metabolic acidosis [1].

Genotoxicity

Ammonia gas was negative in the Ames tests for *S. typhimurium* sp. TA98, TA100, TA1535, TA1537 and TA1538 in both activated and non-activated systems. Concentrations in the range 500-25000 ppm were employed. Tests conducted in *E. Coli* WRP uvrA were also negative [24].

Positive effects were noted in a separate reverse mutation study test in *E. Coli* sp but only at treatments of NH₃ that caused severe toxicity [1].

There is very limited *in-vivo* mammalian data on the effects of ammonia. One study with mice (single intraperitoneal dose of ammonium at dose of 12, 25 or 50 mg kg⁻¹) reported dose dependent increases in the frequencies of micronuclei when compared to controls [21]. Few details were given (not stated if ammonia was given as a gas or a solution) and no conclusions can be drawn.

It is considered from the battery of Ames tests (all negative) that ammonia does not have any significant mutagenic properties.

Neither ammonia nor its metabolites has any structural alerts for DNA reactivity. In view of this and the negative *in vitro* data it is concluded that ammonia does not have any significant mutagenic properties.

Carcinogenicity

Ammonia is considered not to be a carcinogen in animals.

The carcinogenic potential of ammonia gas has not been considered by the IARC. Mice dosed orally with 193 mg ammonia kg⁻¹ day⁻¹ as ammonium hydroxide in drinking water for 2 years did not result in a carcinogenic effects or increase the spontaneous incidence of breast cancer in the C3H female mice used in the study [2].

Reproductive and developmental toxicity

There is little data on the reproductive or developmental toxicity of ammonia. However, ammonia is not considered to be a developmental toxin.

Several studies have investigated the effects of ammonium ion on development using embryo culture techniques [25, 26]. There was a relationship between concentration of ammonium in the culture medium and the incidence of abnormalities or toxicity to the blastocyst [25, 26]. The relevance of this to an *in-vivo* model or indeed to humans is doubtful; as high concentrations of ammonia are unlikely to reach the foetus *in-vivo* due to its rapid and extensive metabolism.

A study in female pigs compared low exposures, (around 7 ppm ammonia/ca 5 mg m⁻³) and moderate exposure (around 35 ppm/ca 24 mg m⁻³). The female pigs were continuously exposed from 6 weeks prior to breeding until day 30 of gestation. The time of onset of puberty or number of live foetuses or size of foetus (foetal length) was not affected [23].

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This document will be reviewed not later than 3 years or sooner if substantive evidence becomes available.