



# 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
- systemic absorption following dermal or ocular exposure is not considered significant
- 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

- irritant, corrosive and may be harmful by all routes of exposure
- acute inhalation may initially cause upper respiratory tract irritation
- oral exposure results in pain, excessive salivation and burns to the aerodigestive tract
- substantial exposures can cause oral cavity, nasopharynx, larynx and trachea burns, with airway obstruction, respiratory distress and bronchiolar and alveolar oedema
- 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
- animal studies suggest osteoporosis secondary to chronic metabolic acidosis may occur
- chronic inhalation is associated with increased cough, phlegm, wheeze and asthma

## 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 solution (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. In severe cases perforation of the stomach or oesophagus may occur, which can result in complications such as cardiac injury, mediastinitis and pneumonitis. Aspiration of ammonia following ingestion may also lead to respiratory complications. Chronic oral exposure to ammonia has not been characterised in humans. Limited animal data has 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.

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.

## 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 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].

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].

Ammonia is endogenously produced in the gut from the bacterial breakdown of nitrogenous constituents of food; estimates of production range from 10 mg a day in the duodenum to 3 g a day in the colon [4]. In healthy adults the physiological ammonium level in blood is typically below 35  $\mu\text{mol/L}$  (approximately 0.67 mg/L) [5].

In the liver, ammonium ions are extensively metabolised to urea and glutamine. Consequently, levels of ammonia that reach the circulation are low [2]. The metabolites may be either excreted as urea or used in the synthesis of amino acids and other biomolecules [5]. Ammonia produced in peripheral tissues is not transported to the liver but metabolised into glutamine and alanine [4]. In individuals with deficiencies in ammonia metabolism or urea excretion (eg enzyme deficiencies, or severe renal or hepatic impairment) toxic ammonia levels may be reached within the body [5].

Ammonia reaching the circulation is principally excreted by humans as urinary urea, excretion of absorbed ammonia in exhaled breath and faeces is not significant [2, 3]. Small amounts of ammonia are excreted in urine; the average daily excretion for humans is approximately 2–3  $\mu\text{g}$ , about 0.01% of the total body burden. Small amounts of unabsorbed ammonia may also be excreted from the gastrointestinal tract in faeces [2].

## Sources and Route of Human Exposure

Apart from endogenously produced ammonia, the most common route of exposure to ammonia is inhalation [6].

Ammonia in the environment originates from both anthropogenic and natural sources. In 2013 agriculture contributed 81.7% of UK ammonia emissions [7]. The total emissions for the UK in 2013 were estimated at 271,000 tonnes, having fallen 22.7% from 1980 [7]. Local concentrations may be elevated where organic waste matter is concentrated, such as in intensive farming environments for cattle, pig and chickens [8]. Non-agricultural sources include sewage sludge, pets, industrial and combustion processes, and petrol vehicles fitted with catalytic converters [8].

High levels of ammonia are naturally present in certain foods – eg in vegetables levels can range from 4,000–15,000 mg/kg; however, higher levels have been reported [5]. In dairy products ammonia may form as a result of processing – eg cheese ripening, sterilisation and acidification – in some food products it may be added artificially [5].

Ammonia is used either directly or indirectly in many industrial processes. It is transported in bulk as a pressurised gas. Exposure to ammonia may occur in industrial settings or following an accidental spill or leak during transport.

Domestically, exposure may occur from certain cleaning agents and dyes.

Ammonia gas is not persistent and rapidly reacts in the environment to form ammonium compounds.

In light of the levels of ammonia produced endogenously and the ability to detoxify ammonia, environmental exposure is not considered to represent a risk to human health [5]. For vulnerable groups, endogenous ammonia still represents a more relevant exposure source than that from environmental sources [5]. The World Health Organization (WHO) does not consider exposure from ammonia in drinking water to be of immediate health relevance [9].

## Health Effects of Acute/Single Exposure

### Human data

#### General toxicity

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

#### Inhalation

After inhalation of ammonia the damage to the respiratory tract depends on the concentration, pH, length of exposure and depth of inhalation [6].

Inhalation of ammonia will rapidly cause irritation to the nose, throat and respiratory tract. Increased lacrimation, coughing and increased respiratory rate as well as respiratory distress may occur [1]. Ammonia is water soluble and is therefore absorbed by the mucosa of the upper respiratory tract, this protects the lungs from exposure to low concentrations of ammonia [1].

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, 10, 11].

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, 10, 12]. Bronchial walls may also be stripped of their epithelial lining [12, 13].

Lower levels of ammonia exposure that do not result in upper airway obstruction may cause significant alkali burns throughout the tracheobronchial tree [10].

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

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

Ammonia has a pungent and characteristic odour of drying urine which is discernible at around  $35 \text{ mg/m}^3$  (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.

**Table 1: Summary of toxic effects following acute exposure to ammonia by inhalation**

Exposure		Signs and symptoms
mg/m <sup>3</sup>	ppm	
35	50	Irritation to eyes, nose and throat (2 hours' exposure)
70	100	Rapid eye and respiratory tract irritation
174	250	Tolerable by most people (30–60 minutes' exposure)
488	700	Immediately irritating to eyes and throat
>1,045	>1,500	Pulmonary oedema, coughing, laryngospasm
1,740–3,134	2,500–4,500	Fatal (30 minutes' exposure)
3,480–6,965	5,000–10,000	Rapidly fatal due to airway obstruction, may also cause skin damage

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

**References**  
[2, 14]

## 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. Although 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 [15]. In more severe cases perforation of the stomach or oesophagus may occur soon after ingestion, perforation may also follow ulceration with complications including cardiac injury, mediastinitis and pneumonitis [6].

In severe cases haemorrhagic or hypovolemic shock and airway obstruction from laryngeal or epiglottic oedema may occur [6]. Aspiration following ingestion may result in stridor and respiratory complications such as pneumonitis, pulmonary oedema, acute respiratory distress syndrome (ARDS) and pulmonary necrosis [6].

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 [16-18].

Adult fatalities have occurred from deliberate ingestion of ammonia 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 [2]. The individual died several days later from ARDS and renal failure. In another case, after the ingestion of an unspecified amount of ammonium hydroxide

solution (2.4% ammonium ion), findings at post-mortem included haemorrhagic oesophagus, stomach and duodenum [2].

### Dermal/ocular exposure

Splashes of ammonia into the eye may cause serious and potentially irreversible damage [6]. Effects may range from increased lacrimation, conjunctivitis, palpebral oedema, photophobia and blepharospasm, through to corneal ulceration, corneal opacification, iritis, anterior and posterior synechia formation, retinal atrophy, glaucoma, cataract formation and blindness [19]. 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 [20]. 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 [14]. The resultant liquifactive necrosis may appear pale and without charring or blistering and may cause an increased depth of injury [3]. Initially alkali burns may be painless, which could lead to a delay in treatment. Effects may develop over several hours and can be difficult to assess as a result of rapid skin discolouration [6]. The combination of both cryogenic effects and alkali burn can produce serious injuries. Skin damage may occur after exposure to ammonia gas at concentrations of approximately  $7,634 \text{ mg/m}^3$  (10,000 ppm) [6].

Individuals with extensive burns to the eyes and skin are likely to have obstruction of the airway [10].

### Delayed effects following 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.

In severe cases pulmonary oedema, breathlessness, wheezing, hypoxia and cyanosis may take 36 hours to develop after the initial inhalation exposure [6].

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, 10, 13, 14]. Dysphonia may persist for many months as a result of burns to the aerodigestive tract [10, 12].

Ingestion of ammonia may lead to the development of strictures between 2 weeks and 2 months after exposure, though may not be clinically apparent for years [6]. Ammonia ingestion may lead to a pyloric stenosis with a small, scarred, immobile stomach [6].

Scarring to body tissue can be pronounced following burns from ammonia exposure [14].

## Health Effects of Chronic/Repeated Exposure

### Human data

#### Inhalation

There is limited data on the effects of chronic inhalation of ammonia. Inhaled ammonia is retained by the mucosal membranes of the upper respiratory tract, therefore effects on the lower respiratory tract are less common [21]. However, there are a few case reports of interstitial lung disease associated with chronic low level exposure to ammonia [22]. Occupational studies have reported an increase in prevalence of acute and chronic respiratory symptoms and a decline in respiratory function in fertiliser factory workers exposed to ammonia [21-24].

Acclimatisation to the irritant effects of ammonia at concentrations up to 70 mg/m<sup>3</sup> (100 ppm) has been demonstrated after repeated exposure for 6 hours a day for 5 days each week over a 6-week period [25]. No further interpretation was possible due to the limited design of this study.

Chronic inhalation of ammonia may result in optic neuropathy [6].

#### Ingestion

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

Ammonia may be ingested in both food and water; however, as ammonia 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 [26]. There was a weak association reported between increased length of exposure and increased frequency of chromosomal aberrations and sister chromatid exchanges. 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 taken into account, 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 International Agency for Research on Cancer (IARC).

## Reproductive and developmental toxicity

There is no published data available on the potential effects of exposure to ammonia on reproductive function or human pregnancy [27]. A healthy adult with normal liver function and sufficient dietary arginine would be expected to be able to metabolise ammonia. Therefore, exposure to low levels of ammonia in the environment would not be expected to result in damage to the fetus [27].

The UK Teratology Information Service (UKTIS) followed up 24 cases of women exposed to ammonia during pregnancy [27]. Exposures ranged from acute to 20 weeks [27]. The rate of major congenital malformations was found to be higher than the background; however, owing to the small sample size and resultant wide confidence intervals, this finding may be due to chance [27].

## Animal and in-vitro data

### Inhalation

Inhalation exposure of several animal species to ammonia has been conducted. Repeated exposures (8 hours a day for 5 days a week for 30 days) to 155 mg/m<sup>3</sup> (233 ppm) ammonia produced no adverse clinical effects in rats, guinea pigs, rabbits, dogs and monkeys [28]. The group sizes of higher order animals were, however, small (2 or 3). After continuous exposure to 40 mg/m<sup>3</sup> (58 ppm) ammonia for 114 days, there were no adverse clinical observations noted and findings at post-mortem 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 [28].

A limited study in pigs compared low atmospheric exposures to ammonia of approximately 5 mg/m<sup>3</sup> (7 ppm) with moderate exposures of approximately 24 mg/m<sup>3</sup> (35 ppm). 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 [29].

### 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 bw) 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<sup>+</sup> 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 *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 in both activated and non-activated systems. Concentrations in the range 714–35,700 mg/m<sup>3</sup> (500–25,000 ppm) were employed. Tests conducted in *Escherichia coli* WRP uvrA were also negative [30].

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

There is very limited in-vivo mammalian data on the effects of ammonia. One study with mice (a single intraperitoneal dose of ammonia at 12, 25 or 50 mg/kg) reported dose-dependent increases in the frequencies of micronuclei when compared to controls [26]. Few details were given (it was not stated if ammonia was given as a gas or a solution) and no conclusions can be drawn.

Neither ammonia nor its metabolites have 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 IARC. Administering a daily oral dose to mice of 193 mg/kg bw of ammonia as ammonium hydroxide in drinking water for 2 years did not result in 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 [31, 32]. There was a relationship between the concentration of ammonium in the culture medium and the incidence of abnormalities or toxicity to the blastocyst [31, 32]. 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 fetus in-vivo due to its rapid and extensive metabolism.

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