

A review of the biological toxicity effects of Ammonia exposure

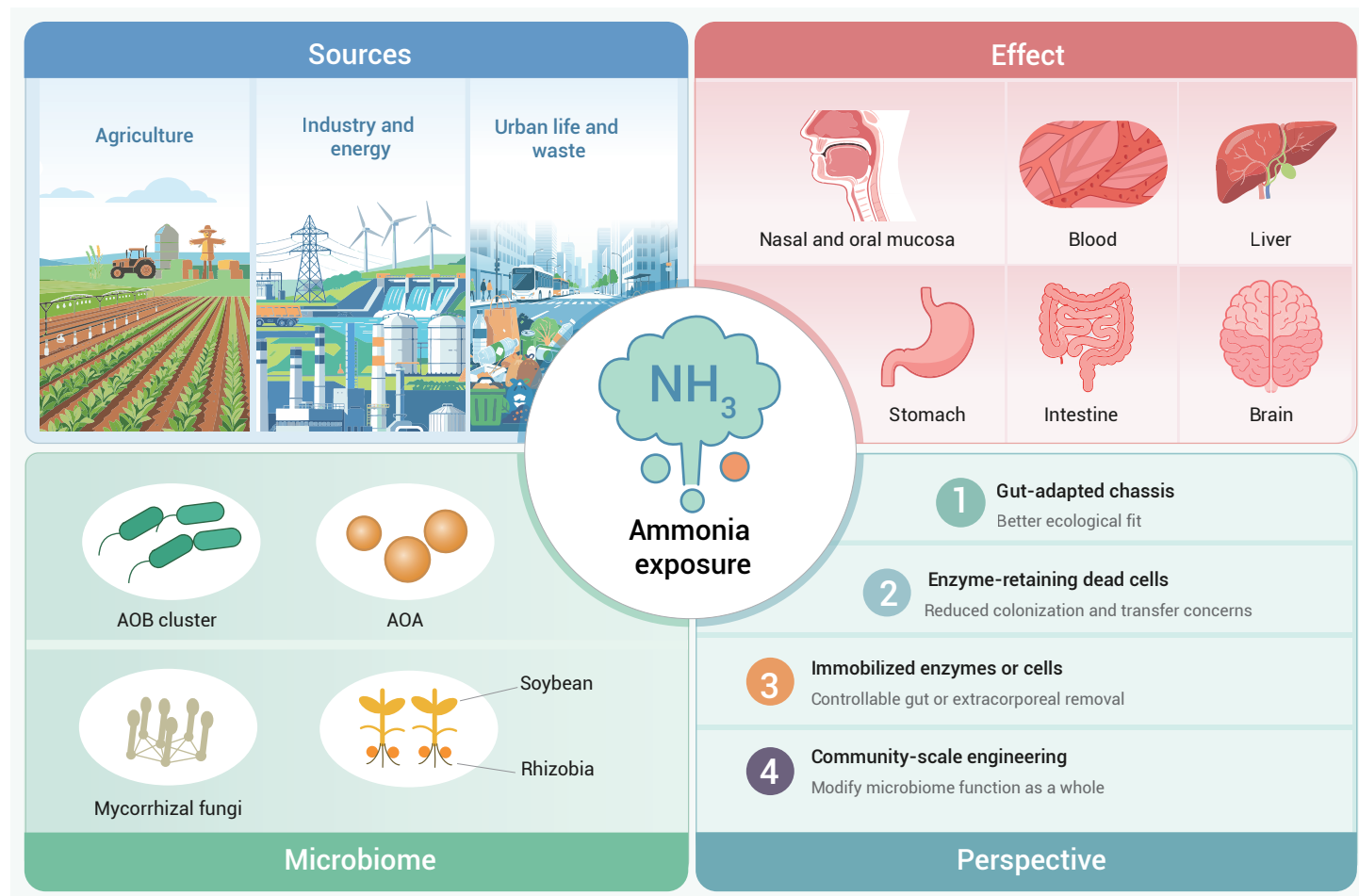
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- The sources of ammonia exposure in the environment were discussed.
- The direct and indirect toxicity of ammonia exposure to human health was emphasized.
- The metabolism of endogenous ammonia in the human body and the role of intestinal microbiota were also presented.
- The development of ammonia-oxidizing bacteria and broader and more flexible engineering strategies was further explored and envisioned.

A review of the biological toxicity effects of Ammonia exposure

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Ammonia exposure is a significant environmental concern, as it can enter the human body through multiple exposure routes, including the atmosphere, water sources, and the food chain, posing a multidimensional threat to public health. This review first describes the sources of ammonia exposure and its direct and long-term effects on human health, including respiratory diseases, the risk of gastrointestinal cancer, and liver toxicity from water eutrophication. Physiologically, the urea cycle in the liver and intestinal microorganisms mainly converts ammonia into relatively non-toxic compounds. However, when liver function is impaired, elevated blood ammonia can induce hyperammonemia, accompanied by intestinal microbiota imbalance. Existing treatments, such as drugs and dialysis, are limited by long cycles and high costs. In recent years, fecal microbiota transplantation based on engineered bacteria has shown potential therapeutic promise. Finally, we discuss the ammonia metabolism mechanisms and key enzyme systems of autotrophic and heterotrophic ammonia-oxidizing bacteria, and then talk about using these genes for therapeutic intervention. This review first elaborates on the effects of ammonia exposure on various aspects of the human body, then discuss the physiological aspects of intestinal microbiota disorder caused by elevated blood ammonia under impaired liver function.

INTRODUCTION

Ammonia exposure has become an increasingly serious environmental and public health issue. Ammonia or ammonium ions enter the environment through agricultural, industrial and urban activities and reach the human body through the atmosphere, water sources and the food chain. In the body, ammonia is usually detoxified through the urea cycle in the liver. However, when liver function is impaired, it can lead to hyperammonemia, accompanied by intestinal microbiota imbalance and multi-organ damage. The current treatment methods for hyperammonemia. However, it is limited by factors such as the long treatment period, high cost, and the limited research on the types and components of microorganisms in microbial treatment. In recent years, the strategy based on fecal microbiota transplantation has attracted attention as a potential preventive or therapeutic option, but there are still some limitations.

This review first summarizes the sources of ammonia exposure and its effects on health through literature. Then this review elaborates on the metabolic process of ammonia in the body under normal circumstances. The focus of the review is on the changes in the intestinal microbiota when liver metabolism stops, leading to the onset of hyperammonemia. Finally, based on the exploration of the chemical reaction mechanism of ammonia-oxidizing bacteria and the current limitations in the prevention or treatment of hyperammonemia, four emerging treatment strategies are proposed. These provide new ideas and strategies for the prevention and treatment of hyperammonemia and related diseases.

AMMONIA EXPOSURE AND ITS EFFECTS ON THE ENVIRONMENT

Ammonia exposure refers to the excessive accumulation of reactive nitrogen compounds, mainly ammonia (NH₃) and its ionic form, ammonium (NH₄⁺), in environmental media (mainly the atmosphere, water, and soil), beyond the environment's self-purification capacity. As a result, it threatens ecosystems and human health.¹ It comes from both endogenous and exogenous sources. Endogenous sources include protein breakdown and intestinal metabolism. Exogenous sources come from agriculture, industry, and urban

activities.

Among these, exogenous ammonia exposure is of particular concern due to its direct link to anthropogenic drivers and widespread environmental contamination. No single source explains this exposure. Instead, ammonia exposure is linked to agricultural modernization, industrialization, and urbanization. These emissions move through biogeochemical cycles and affect the atmosphere, soil, and water (Figure 1).

Agriculture is a major source.² Synthetic ammonia fertilizers have been widely used to meet food demand. It has been a major driver of ammonia exposure.³ Livestock and poultry farming also produces large amounts of ammonia-containing waste. Ammonia in manure and urine decomposes easily and releases ammonia during storage and processing. Agricultural sources, including fertilizer use and aquaculture, account for 80%-90% of global anthropogenic ammonia emissions.⁴ China, India, the United States, and Europe are major hotspots.⁵

Industry and energy production are another source. Chemical plants, especially fertilizer plants, pharmaceutical plants, and petroleum refining facilities, may release ammonia. In addition, during fossil-fuel combustion, especially coal consumption, nitrogen impurities in fuels and nitrogen gas in air form nitrogen oxides (NO_x) at high temperature. The sulfur dioxide (SO₂) and NO_x emitted in industry combine with the NH₃ emitted in agriculture to form ammonium sulfate, ammonium hydrogen sulfate and ammonium nitrate. These three compounds are typically important chemical components of fine particulate matter. When the aerodynamic diameter of these particles is less than 2.5 μm, they are included in PM_{2.5}.⁶⁻⁸

Third, the contribution of urban life and transportation should not be underestimated. If some diesel vehicles use low-quality urea, ammonia may be released into the environment.^{9,10} Urbanization also increases waste, such as household garbage and sewage. If this waste is not properly managed, ammonia may also enter the environment.

Some NH₄⁺ in soil can be converted into reactive nitrogen compounds through microbial nitrification. These compounds move into water through leaching and runoff during rainfall or irrigation. In water, these compounds drive eutrophication. Algae can absorb them directly, which promotes rapid growth and can trigger algal blooms or red tides.¹¹

EFFECTS OF AMMONIA EXPOSURE ON HUMANS

The effects of ammonia exposure on humans are all-round, multi-pathway, and latent, forming a complete threat chain from the environment to health. In this section, the effects are divided into two parts. The first is the direct toxicity of ammonia itself. The second is the indirect toxicity of reactive nitrogen products. These two parts follow different pathways, but they are closely related.

Direct toxicity of ammonia

Ammonia can irritate mucosal surfaces (eyes, respiratory tract) after exposure. People with long-term exposure to ammonia near farms or industrial areas may suffer direct mucosal damage.¹² In addition, ammonia exposure in some mammals increases the relative abundance of Proteobacteria in the nasal mucosa. Changes in Proteobacteria in the colon are consistent with those in the nasal mucosa.¹³ Under normal circumstances, the body can metabolize ammonia, but impaired hepatic metabolism can lead to hyperammonemia. The nervous system and kidneys are also affected to some extent.^{14,15}

PM_{2.5} can trigger or worsen respiratory diseases such as asthma, bronchi-

Ammonia exposure and its negative effects on the human body

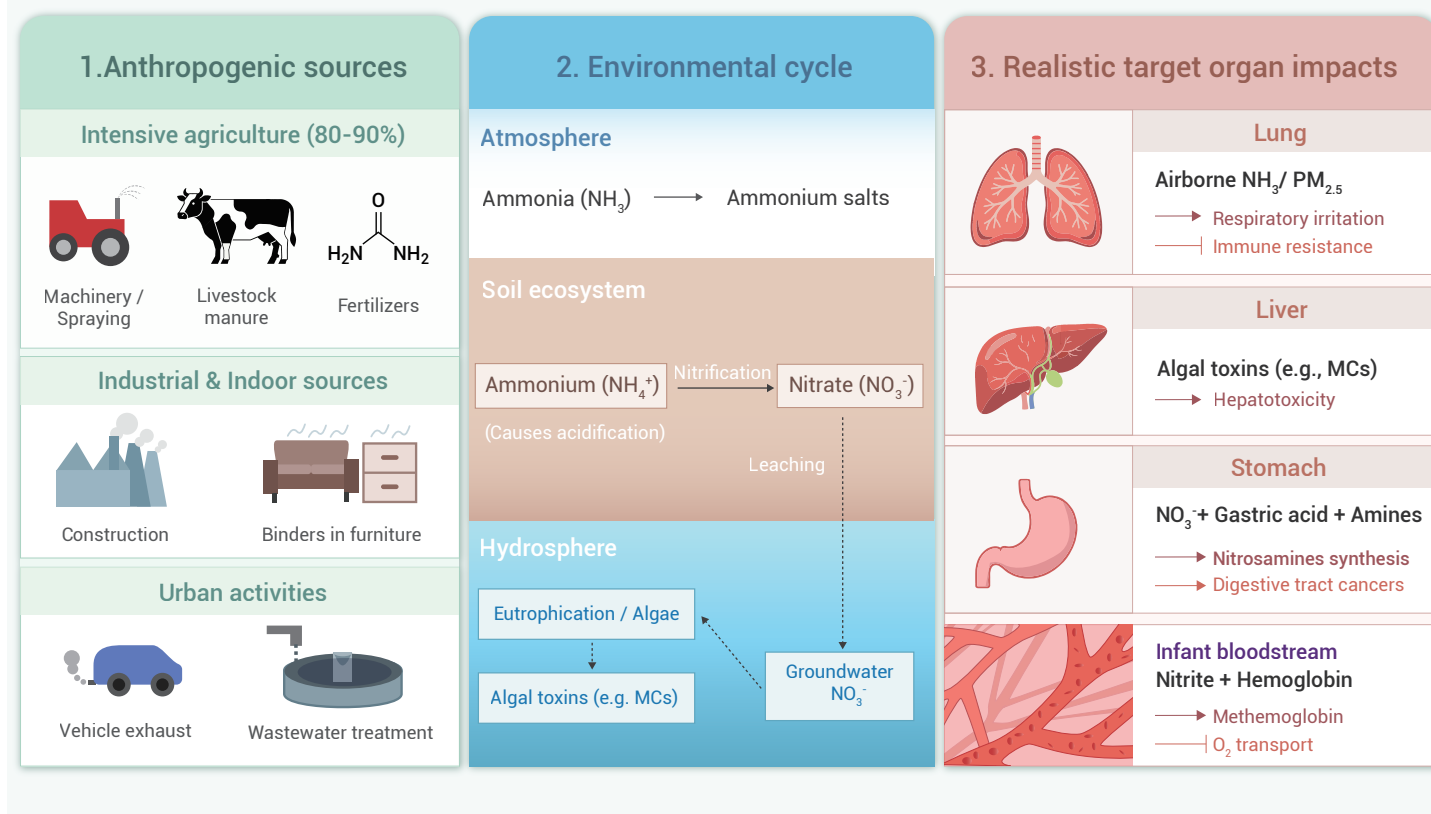


Figure 1. Ammonia exposure and its negative effects on the human body

tis, and chronic obstructive pulmonary disease. They can also increase cardiovascular morbidity and mortality. Many epidemiological studies have clearly associated $\text{PM}_{2.5}$ concentration with the risk of human diseases.¹⁰

Table 1 also lists database-based literatures on the impact of ammonia exposure on the population. The literatures suggest that ammonia (or $\text{PM}_{2.5}$) exposure significantly affects public health.

Indirect toxicity via reactive nitrogen transformation products

Nitrate ions (NO_3^-) and nitrite ions (NO_2^-) are extremely harmful to human health. Excess $\text{NH}_3/\text{NH}_4^+$ in the soil was converted to NO_3^- by nitrification. NO_3^- is highly soluble in water and penetrates the ground with rainfall or irrigation, polluting drinking water sources.¹⁹ Excess NO_3^- in drinking water can be reduced to NO_2^- in the human body, especially in the gastrointestinal tract of infants. NO_2^- can combine with hemoglobin to form methemoglobin, which loses its oxygen-carrying ability and can cause fatal blue baby syndrome. The World Health Organization has already set strict standards for NO_3^- concentrations in drinking water. More worrying, NO_3^- and NO_2^- can combine with amine substances to form strong carcinogens, namely nitrosamines, in the presence of gastric acid and other substances. Long-term intake of NO_3^- and NO_2^- significantly increases the risk of gastric cancer, esophageal cancer, and other digestive tract cancers. At the same time, crops, especially leafy vegetables, actively absorb NO_3^- from the soil and concentrate it in edible tissues.²⁰ Toxins (such as microcystin) produced by some algae in eutrophic water can enter the human body through drinking water or aquatic products (fish and shellfish), causing serious liver damage.²¹

Addressing ammonia exposure cannot rely on a single technology or end-point governance; it must drive systemic change. First, ensure proper monitoring. Safety matters most. This includes monitoring ammonia in the air, as well as the sealing performance of storage devices containing ammonia gas or liquid. In case of a leak, evacuate the crowd promptly to a safe area. Secondly, use acid or spray-like water for neutralization or absorption. In case

someone accidentally comes into contact with it, they must receive immediate first aid and be rushed to the hospital as soon as possible. Taken together, the public health implications of ammonia exposure are substantial.

THE WAY AMMONIA IS METABOLIZED IN LIVING ORGANISMS

When people are exposed to ammonia and its compounds without adequate protection, they may inhale ammonia. This can cause organ damage. Normally, ammonia enters the bloodstream through the alveolar wall. Most of ammonia enters the liver, where it is converted to urea and excreted through the urea cycle (Figure 2).²²

Some intestinal bacteria can convert ammonia into other compounds. *Segatella copri* (Bacteroides) contains an ammonia assimilation gene *asnA*. This gene can alleviate the deterioration of chronic kidney disease caused by ammonia accumulation.²³ *Lactobacillus plantarum* WCFS1 can combine ammonia with branched-chain amino acids. *Lactobacillus plantarum* WCFS1 lowers the ammonia concentration in the brain and may reduce the occurrence of hepatic encephalopathy.²⁴ *Cetobacterium somerae* *ceto* (CSC) (Proteobacteria) promotes ammonia detoxification to urea by generating arginyl succinate.²⁵

HYPERAMMONEMIA AND CHANGES IN INTESTINAL MICROBIOTA AFTER TREATMENT

The liver detoxifies ammonia, reducing its concentration to the organism's normal range. If liver function is severely damaged, the urea cycle cannot work properly. Blood ammonia then rises and affects the whole body. This is a key feature of hyperammonemia (HA). Patients with hepatic encephalopathy (HE) have impaired cognitive and motor function. HA is one of the main factors in HE (Figure 3).¹⁵

After hyperammonemia develops, the microbiome changes. In patients with cirrhosis, glutaminase activity increases and leads to higher intestinal

Table 1. Literature on the effects of ammonia exposure on the population

Article	Year	Conclusion
Exploring the association between air pollution and urogenital congenital anomalies: a global ecological analysis. ¹⁶	2025	Many air pollutants, especially SO ₂ , NH ₃ and NO _x , are positively associated with the global burden of genitourinary congenital anomalies (UCAs). The effect of SO ₂ was more consistent in men and women.
The health burden of air pollution in the UK: a modelling study using updated exposure-risk associations. ¹⁷	2023	PM _{2.5} , an important precursor of ammonia that enters the atmosphere and becomes ammonium salts, is more harmful to British adults than previously reported. The unregulated agricultural sector, in particular, can significantly increase public health benefits.
Response of global particulate-matter-related mortality to Changes in Local Precursor Emissions. ¹⁸	2015	Outdoor fine particulate matter (PM _{2.5}) is responsible for more than 5% of premature deaths globally.

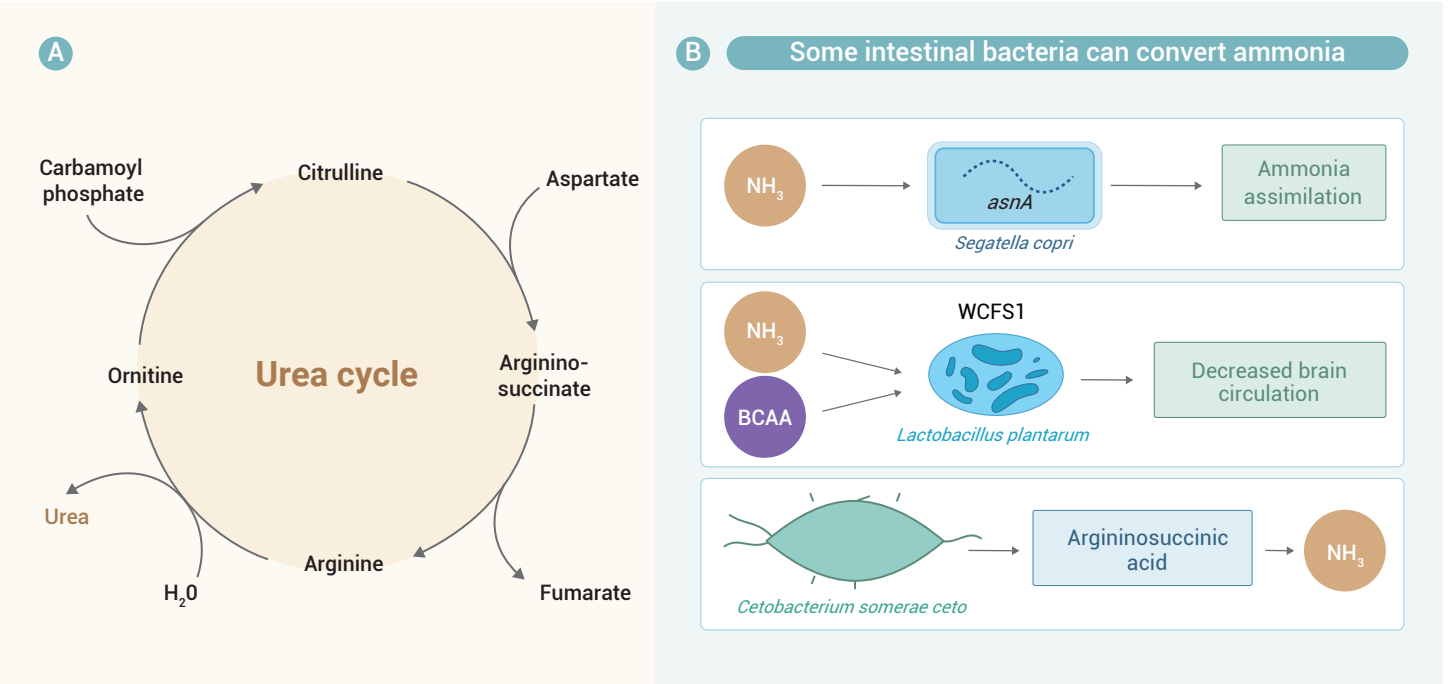


Figure 2. The way ammonia is metabolized in living organisms (A)Urea cycle. (B) Some intestinal bacteria can convert ammonia into other compounds.

ammonia levels.²⁶ Some studies have found that the abundance of *Enterobacteriaceae*, *Streptococcaceae*, and *Enterococcaceae* increased, and the abundance of *Lactobacillus* decreased in the intestinal microbiota of mice with chronic hyperammonemia.²⁷ The oral system also contains these bacteria in patients with chronic kidney disease (CKD) (HA is one of the main factors of CKD). Some of these bacteria have drug resistance.¹⁴

Currently, treatment of hepatic encephalopathy is divided into two categories: surgical treatment and drug treatment. Firstly is surgical treatment. Liver transplantation and hemodialysis are basic surgical methods, but they can only temporarily relieve hyperammonemia symptoms. These treatments are expensive and do not change the intestinal microbiota.²⁸ Studies have shown that the abundance of *Phocaeicola vulgatus* in the intestine is significantly increased in cirrhotic patients undergoing transjugular intrahepatic portosystemic shunt (TIPS). The enrichment of this bacterium is strongly positively correlated with increased blood ammonia levels and postoperative HE. Its mechanism of action is related to down-regulation of urea cycle function or reduced ammonia metabolism in the host.²⁹ Secondly is medication. Rifaximin can maintain and functionally modulate the overall composition and diversity of the gut microbiota. It may reduce the abundance of harmful bacteria such as *Klebsiella*, *Streptococcus*, and *Clostridium*, and it may increase the abundance of probiotics such as *Bifidobacterium* and *Bacteroides*.³⁰ However, some patients have developed severe diarrhea after taking rifaximin.³¹ Lactulose is also a pharmacologic treatment. It promotes intestinal proliferation of *Lactobacillus acidophilus* and improves the relative abundance of each bacterial group in the gut of patients with hyperammonemia.³² However, overuse of lactulose can lead to complications such as dehydration, aspiration, hypernatremia, and perianal skin irritation.³³ In addition,

Lactobacillus helveticus NS8 supplementation ameliorated cognitive decline and anxiety behavior.³⁴ However, the research on probiotic types and compositions remains limited, and validation studies are lacking, even though the probiotics used in research are expensive. Other medications can also be used for treatment, including sodium benzoate, carbamic acid, arginine, etc.³⁵⁻³⁷ However, researchers have rarely studied the effects of these three drugs on gut microbiota before and after treatment. Among them, sodium benzoate, when used as a food additive, has been studied for its effects on the gut microbiota but showed minimal effect on the gut microbiome, even at a 10-fold dose that is higher than the accepted daily intake limit.³⁸

In short, there are many treatments for hyperammonemia, but the long treatment time and high cost still make many patients complain. Therefore, developing a new treatment method is urgent.

LITERATURES ON AMMONIA-OXIDIZING BACTERIA

Beyond the microbiota changes described above, ammonia exposure also affects agricultural ecosystems. In agricultural fields, excessive nitrogen fertilizer can affect not only plants but also the annelids living in the soil. Some plants and crops can convert ammonia into other substances through the GS-GOGAT cycle pathway.³⁹ Some leafy vegetables contain NO₃⁻. When humans consume them without boiling, these compounds may be transformed into strong carcinogens, such as nitrosamines. This creates a direct threat to human health.⁴⁰ Therefore, leafy vegetables are usually boiled at high temperature before consumption. In addition, high concentrations of ammonia are directly toxic to earthworms. This is especially true after the application of immature organic fertilizers or excessive urea. For example, urea concentrations in soil above 1500 mg/kg can cause 100% death of *E.*

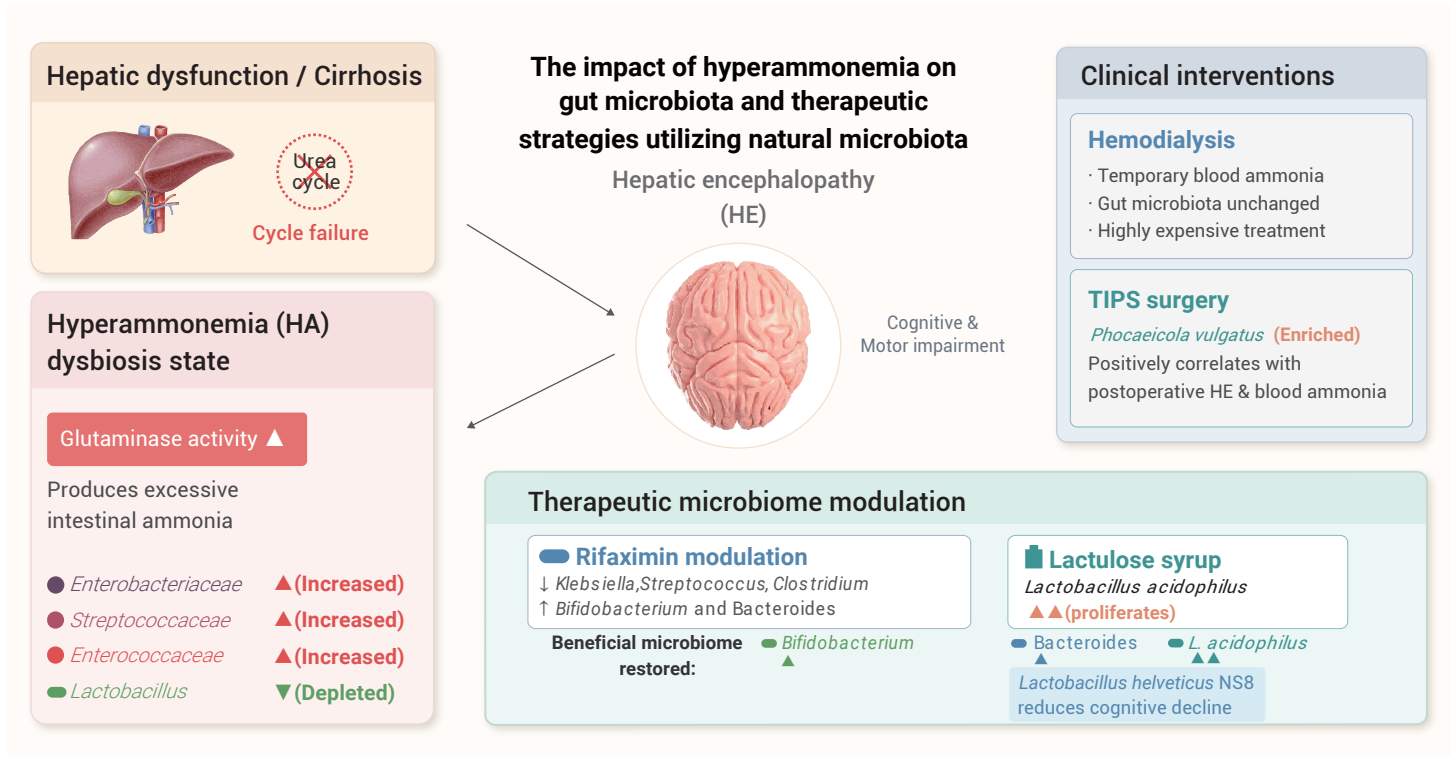


Figure 3. The effect of hyperammonemia on intestinal microbiome and therapeutic strategies of microbiome modulation

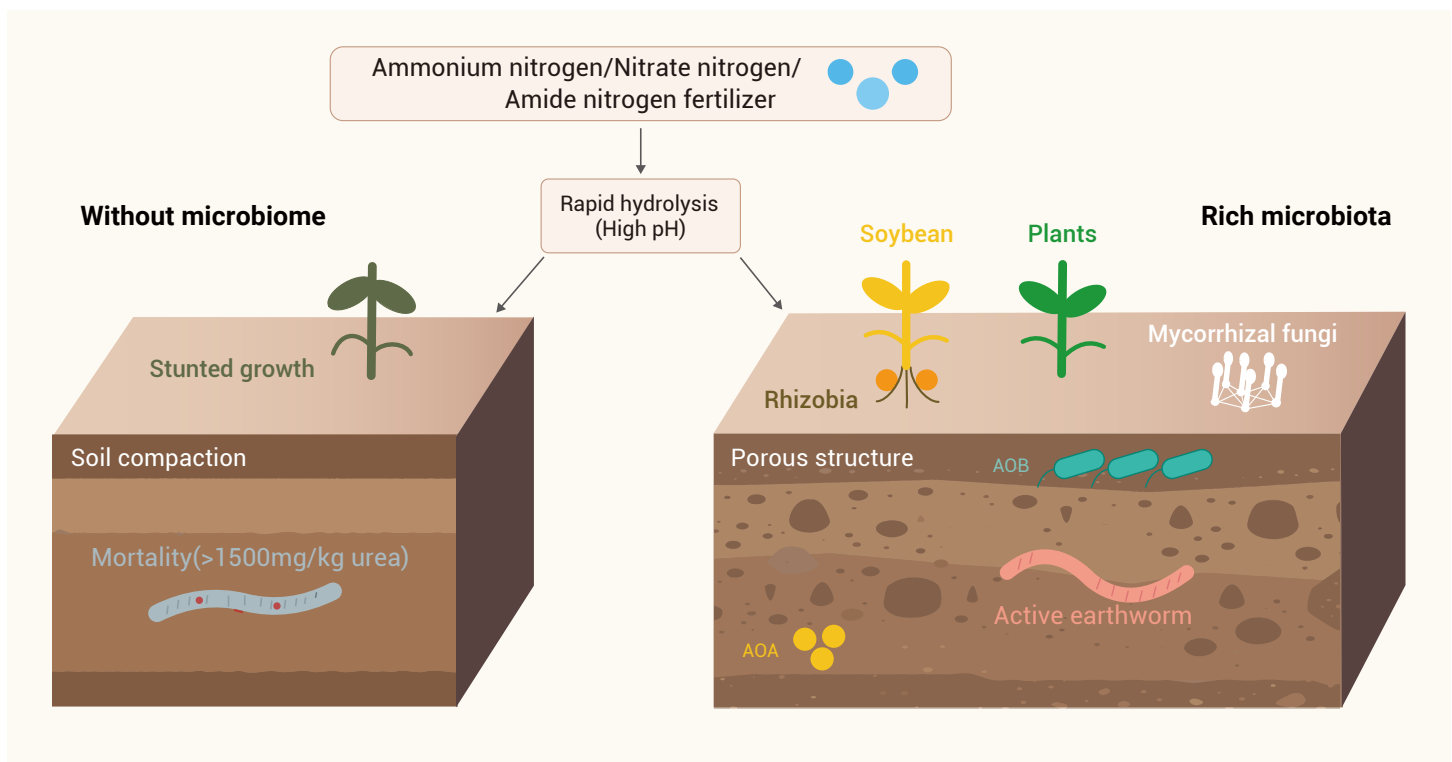


Figure 4. Effects of Ammonia exposure on soil and earthworms

euginae earthworms.⁴¹ Urea toxicity to earthworms may result from NH_3 penetrating cell membranes and disrupting earthworm homeostasis, leading to death. At the same time, when crops are planted, earthworms can promote the transfer of ^{15}N -labeled urea from soil to lettuce. This can promote plant growth (Figure 4).⁴²

After the application of organic nitrogen fertilizers, the abundance of genes related to nitrification (*amo*) and denitrification (*narG*, *nirS*, *nirK*, *nosZ*) increases.⁴³ Among them, *amo* is derived from autotrophic AOB, and some

heterotrophic AOB contain denitrification genes.

Autotrophic AOB

Autotrophic AOB are chemoautotrophic microorganisms that are widely distributed in soil, freshwater, marine, and artificial ecosystems. They play an important role in the nitrogen cycle.⁴⁴ These microorganisms can use ammonia as an energy source by catalyzing ammonia monooxygenase (AMO) and hydroxylamine oxidoreductase (HAO) under aerobic conditions. AMO and

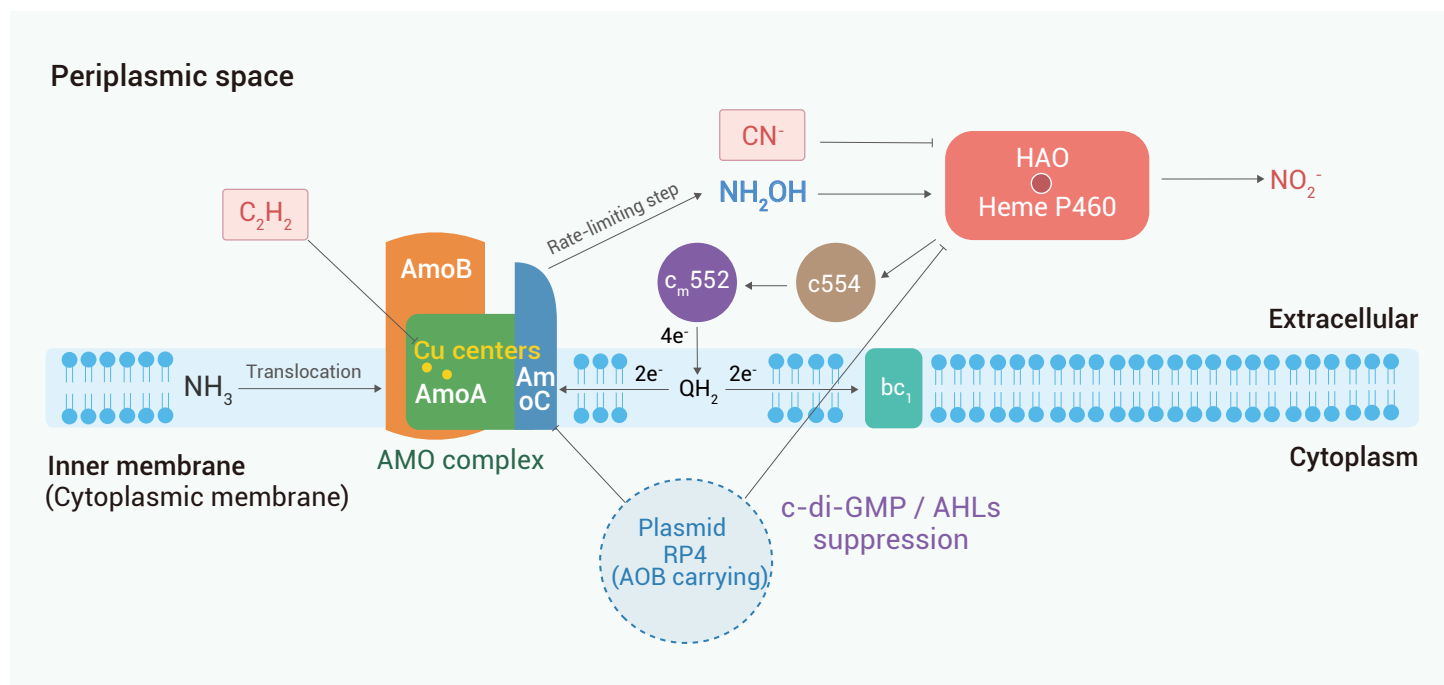


Figure 5. Model of electron flow in *N. europaea*

HAO act together to oxidize NH_4^+ to NO_2^- . Based on classic literature and supplemented by existing literature, we obtained the mechanism diagram (Figure 5).^{45,46}

AMO is a membrane-bound metalloenzyme. Copper in its active center is an essential cofactor.⁴⁷ The enzyme is built from three subunits, AmoA, AmoB, and AmoC.^{48,49} AmoA forms the catalytic core and contains binuclear copper centers (CuA and CuB) that are involved in ammonia activation.⁵⁰ AmoB and AmoC help maintain enzyme stability and function.^{44,51} AMO catalyzes the rate-limiting oxidation of NH_3 to hydroxylamine (NH_2OH) and is sensitive to inhibitors such as acetylene.⁵²

HAO oxidizes NH_2OH to NO_2^- in the periplasmic space.⁵³ The electrons released in this step help support AMO activity.⁴⁴ HAO can be inhibited by cyanide, which has a high affinity for heme P460.^{53,54}

Cytochrome c554 is a core electron carrier in AOB.⁵⁵ It receives electrons from HAO and transfers them to membrane tetraheme cytochrome (c_m552).^{56,57} Half of the electrons pass rapidly and precisely delivered by dihydroquinone (QH_2) to the cytochrome bc_1 complex located in the inner membrane of the cell.⁵⁸ In addition, the other half of the electrons are required to continuously supply the electrons needed for the ammonia-oxidation reaction catalyzed by AMO.

Current studies have confirmed that inhibiting both AMO and HAO inhibits the ammonia-oxidation function of AOB. In this study, the RP4 plasmid was transferred from an *Escherichia coli* donor strain to *Nitrosomonas europaea* ATCC 25978 in a conjugation model. The transfer of RP4 significantly inhibited ammonia oxidation in AOB and suppressed the expression of ammonia-oxidation genes, including *amoA*, *amoC*, and *hao*.⁵⁹ Furthermore, the RP4 plasmid could inhibit AMO and HAO by inhibiting cyclic di-guanylate (c-di-GMP) and acyl-homoserine lactones (AHLs).⁶⁰

A series of key physicochemical factors strictly restrict the growth and metabolism of autotrophic ammonia. These bacteria grow slowly, and the logarithmic phase may not appear until days or even weeks after inoculation.^{61,62} This is mainly due to the relatively low energy obtained from the oxidation of NH_3 to NO_2^- and the use of most energy for carbon dioxide (CO_2) fixation and the Calvin cycle.⁶³ For example, *Nitrosomonas europaea* has an optimum pH of 8 and an optimum temperature of 25°C. Its growth is still sensitive to culture conditions.⁶⁴ A higher inoculation density can improve culture success.⁶⁵

Heterotrophic AOB

Heterotrophic AOB have gained attention for their potential in wastewater

treatment. Heterotrophic AOB usually convert ammonia in the presence of organic matter through multiple enzymatic systems, and some strains can even directly oxidize ammonia to nitrogen. The direct ammonia-oxidizing pathway was first proposed: this process directly converts NH_4^+ to nitrogen (N_2) without producing NO_3^- and NO_2^- . This process no longer depends on AMO and HAO, but on specific genes in the Heterotrophic AOB.⁶⁶ For example, *Alcaligenes ammonioxydans* sp. nov. strain HO-1 responds via a specific gene cluster, *Dnf*, with *DnfR* as part of the cluster and acting as a major regulator. *DnfABC* plays a role in converting NH_4^+ to N_2 .^{67,68} However, the NH_4^+ reaction yields NH_2OH more slowly. Another strain with a similar reaction, *Zobellella taiwanensis* DN-7, was recently found to convert NH_4^+ to N_2 using acetone and acetoxime as intermediates, and three genes were identified to facilitate the reaction.^{69,70} An earlier study successfully cloned the heterotrophic nitrifying gene from the heterotrophic bacterium *Paracoccus denitrificans* and achieved active expression of its *amo* gene in heterologous hosts.⁷¹ Based on classic literature and recent experimental studies on new reaction mechanisms of heterotrophic AOB, we integrated an existing mechanism diagram (Figure 6).⁶⁶⁻⁶⁸

In addition, Heterotrophic AOB are more widely studied and more widely distributed than Autotrophic AOB. Future research is envisaged to construct and search for a strain that can summarize the characteristics of most Heterotrophic AOB.

PERSPECTIVE

Most current research on hyperammonemia has mostly focused on hyperammonemia caused by endogenous metabolic disorders. By contrast, exogenous ammonia exposure has received much less attention. Biological interventions targeting exogenous ammonia exposure route remain limited. Existing studies have shown that the intestinal microbiota and engineered bacteria can reduce endogenous ammonia levels and alleviate hyperammonemia. Further optimization of engineered bacteria may provide a more effective strategy for treating or preventing both endogenous hyperammonemia and hyperammonemia caused by exogenous ammonia exposure.

At present, research on bioengineered bacteria mainly focuses on the isolation of individual strains, the cultivation of single strains, and fecal microbiota transplantation.⁷²⁻⁷⁹ These approaches are quite common, but they remain limited. Future studies may therefore need broader and more flexible engineering strategies. Several future strategies are worth considering. First, the host chassis could be switched from a single laboratory strain to a gut-adapted species with better ecological fit. Second, dead bacteria that retain

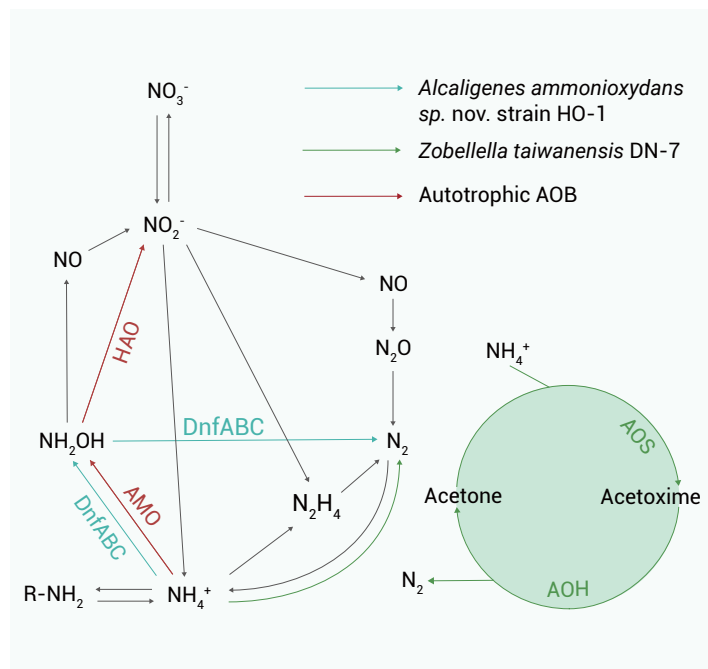


Figure 6. An overview of microbe-driven N_2 transformation in nature (Heterotrophic AOB)

functional enzymes could serve as safer catalytic vehicles. They may reduce concerns about colonization and gene transfer. Third, immobilized enzymes or immobilized cells could provide a controllable way to remove ammonia in the gut or in extracorporeal systems. Fourth, broader microbiome engineering may be possible through gene-editing-based strategies that modify the intestinal community as a whole rather than one strain at a time. Because gut-derived microbes are already adapted to the low-oxygen intestinal environment, they may be especially suitable for such strategies. This theoretical basis for this idea is that the microbiota originates in the gut and does not trigger an intestinal immune response or functional expression in the gut's hypoxic environment. Overall, these ideas suggest broad and profound potential for microbiota-based strategies in the prevention and treatment of hyperammonemia.

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AUTHOR CONTRIBUTIONS

M.-Y. M. and Y.-Z. G. wrote and revised the manuscript. Z. Z., Y. Z., H. Z., Y.-Z. G. supervised the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.