

# A Scientific Review of Sodium Nitrite and Nitrate: Impact on Human Health and Living Organisms

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[www.sjmars.com](http://www.sjmars.com) || Vol. 4 No. 5 (2025): October Issue

Date of Submission: 27-09-2025

Date of Acceptance: 04-10-2025

Date of Publication: 26-10-2025

## ABSTRACT

Sodium nitrate is an inorganic compound characterized by a white crystalline appearance and high aqueous solubility. Sodium nitrate and nitrite are widely used in numerous industries, notably in food additives, processed meats, fertilizers in agriculture, and pharmaceuticals. While their crucial roles in prolonging shelf life and preventing bacterial growth, their effects on people and other organisms' health led to serious worries. About 80-85% of the nitrate that humans consume comes from their diet, primarily from vegetables as well as drinking water nitrate. Despite sodium nitrate and nitrite being necessary for many bodily processes, excessive exposure to them has been scientifically attributed to harmful effects on health, especially in the reproductive system, respiratory system, liver, and kidneys. This review attempts to present an analysis of sodium nitrite and nitrate's impact on different systems in the bodies of organisms, supported by scientific research and literature. In an attempt to minimize health risks of sodium nitrate, individuals should reduce sodium nitrate intake by opting for fresh, unprocessed foods and carefully reading food labels. Regular monitoring and enforcement of sodium nitrate regulations in food and agricultural products are crucial for public health protection and mitigation strategies to reduce its ecological footprint.

**Keywords-** sodium nitrat, infertility female, fetal defects, liver, kidney failure.

## I. INTRODUCTION

Nowadays, the increasing use of food additives, including sodium nitrite, has led to increased exposure to these additives and preservatives. The LD50 of sodium nitrite is 180 mg/kg in rats and 71 mg/kg in humans, indicating that a person weighing 65 kg would require at least 4.615 g to die. Excessive nitrogen fertilizers in crops cause plants to resist absorption, resulting in nitrogen accumulation in the soil, primarily in the form of nitrates [1,2]. Furthermore, nitrate is abundant in the surrounding ecosystem and diets, particularly in vegetation, which is also released into nature as fertilizers and found in many human organs. Its plasma levels range from twenty to forty  $\mu\text{mol/L}$ , with high quantities in the heart, liver, and muscle [3,4,5]. The human body gets its nitrate from both internal and external sources. The internal source of nitrate is the oxidation of nitric oxide. The external source of nitrate is primarily sourced from food, with different types of vegetables accounting for over 80 percent of the external nitrate [6]. Nitrate, taken by digestion, then enters the bloodstream and mixes with endogenous nitrate. Salivary glands absorb twenty-five percent of plasma nitrate, resulting in elevated amounts. The intestinal bacteria turn nitrate to nitrite and other nitrogen, such as N-nitrosamine (Figure1) [7]. N-nitrosamines can cause cancer, and nitrite or nitric oxide can oxidize hemoglobin in erythrocytes, leading to health issues as it is unable to attach or carry oxygen [8]. Nitrites were prohibited from foods in the 1970s because they may produce nitrosamines, which are carcinogenic [9]. Sodium nitrite ( $\text{NaNO}_2$ ), an easily dissolved in water, white-yellow substance, has numerous uses in food, antibiotics, pharmaceuticals, corrosion inhibitors, and cyanide poisoning treatment [10,11]. It is a preservative

used only 0.6% (coded “E250”) in meat goods to limit bacteria from growing, stop deterioration, and enhance their flavor. International regulation safeguards the safety of people and the preservation of food due to its dose-related toxic effects [12,13,14]. Sodium nitrate and nitrite exposure poses health hazards due to their oxidative, inflammatory, and apoptosis properties, affecting various body organs over prolonged periods.

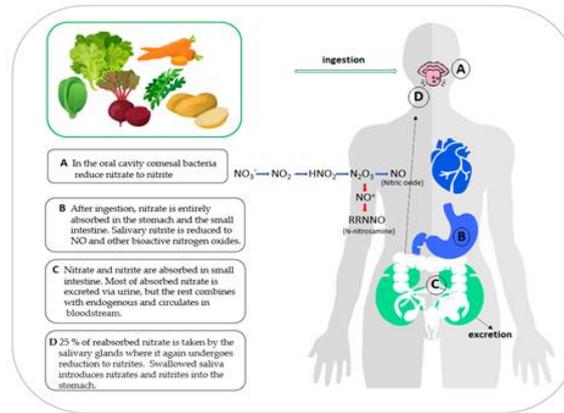


Figure 1. The movement of nitrate and nitrite via the enterosalivary system [7].

## II. SODIUM NITRATE'S IMPACT ON PEOPLE'S HEALTH AND ORGANISMS

Many body organs can suffer tissue loss and inflammation as a result of continuous intake of sodium nitrite in the diet [15,16].

### 2.1 The reproductive system:

Research indicates that the rise in sodium nitrite concentration adversely affects both the reproductive systems of humans and animals. AL-Youssef & Al-Gayyar [17] researched the safety hazard on testicular tissue linked with food containing sodium nitrites and evaluated the cytokine balance and apoptosis. The European Economic Community recommends that water for drinking have an allowed level of 50 mg/L of nitrate [18]. According to [19], the environmental sodium nitrites may affect steroid production, such as testosterone and genital development in vertebrates. In numerous ground and surface water systems (springs in Florida), anthropogenic nitrate contamination has risen dramatically, which may indicate lifelong reproductive alterations in mosquitofish exposed to high nitrate concentrations [20]. The focus of the study was to avoid male reproductive damage caused by sodium nitrite, which could result in infertility [21].

In females, the interaction of dose and response contributes to the adverse impact of nitrate on development and reproduction, including spontaneous abortions, intrauterine growth limitation, reproductive toxicity, stillbirth, elevated risk of subfecundity, infertility, and different birth defects [22, 23]. Mention Greenlee *et al.* [24]; the exposures to nitrite may raise parental risk of infertility and complications of pregnancy, such as spontaneous abortion, preterm birth, and fetal defects. Scientific data has proven that nitrate, nitrite, and nitrous compounds can pass the placenta and harm the fetus in pregnancy [25]. Pregnant women exposed to drinking water containing nitrate (0.1-5.5 mg nitrogen/liter) and nitrite (0.01-0.03 mg nitrogen/liter) during the 27th week of pregnancy encountered 286 cases of spontaneous abortion and 1391 cases of live births with a lower risk of spontaneous abortion [26]. Research on female animals has indicated that adverse effects of nitrates on pregnancy with permeability of the placenta and its associated complications [27]. Consumption of excessive nitrate in water for drinking may raise the hazards of preterm birth and some congenital disorders [28]. According to Laven *et al.* [29], feeding pregnant cattle grasses with elevated nitrate levels had an impact on the fetal growth and rates of survival. Despite amounts below regulated limitations, nitrate exposure in household tap water may raise the incidence of small-for-gestational-age [30] (Table 1).

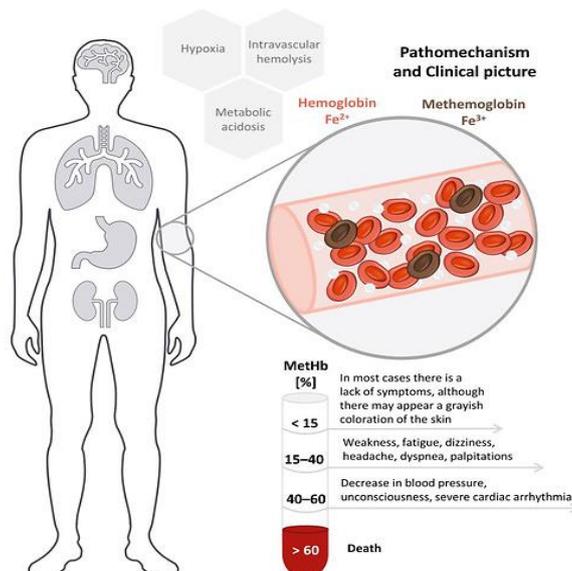
Table 1. Animal research exhibits the impacts of sodium nitrite on the reproductive device.

Number of animals / Gender	Type of animal	Dosage Concentration	Method of give dose/ Study duration	Major effects	Reference
40 male	adult Sprague Dawley rats	80 mg kg <sup>-1</sup>	oral gavage/ daily for 12 weeks	The testis weight increases with a decline in sperm count and a rise in the amount of oxidative stress indicators and inflammatory cytokines in the testicular tissue.	[17]

18 male	Sprague–Dawley rats	distilled water with 50 mg/L	Orally/ 4 weeks	The testicles became large with testosterone concentrations that were significantly reduced	[19]
59 male	adult mosquitofish <i>G. holbrooki</i>	0.2 to 5.1 mg/L	Period between May 18 and June 3, 2003	Raise testicular weight, increase adjusted gonopodium length, and decrease the total number of sperm	[20]
25 male	Adult wistar rats	100 mg/kg bw	Orally/ 52 days	Reduced sperm motility, decreased concentration of testosterone, elevated sperm abnormalities, and altered histology of testis seminiferous tubules	[21]
40 to 80 of each sex	mice	184 and 1840 ppm	27 months	fewer litters of offspring	[23]
20-25 embryos	mouse	low-dose exposures 1X	incubated 96 hour	raised the proportion of apoptosis (cell death)	[24]
48 female	Holstein cows, 20 and 57 days pregnant	3 kg-8Kg/hours/day normal nitrate nitrogen, 3 kg-8Kg/hours/day high nitrate nitrogen	one-week, feeding pregnant cattle grasses	ovulation, fertilization and/or the early embryo	[29]

**2.2 The Respiratory system:**

Sodium nitrite is a powerful oxidant that produces methemoglobin [31]. Normally, hemoglobin is a protein that includes four subunits attached to heme groups by binding  $Fe^{2+}/Fe^{3+}$  ions. Heme typically transports oxygen molecules for tissue release by binding ferrous iron ( $Fe^{2+}$ ) [32,33]. Occasionally, such as through the effect of sodium nitrite, the conversion of the hemoglobin ferrous ion from the second to the third ( $Fe^{3+}$ ) leads to hypotension and loss of its ability to bind oxygen and hypoxia (figure 2) [34]. According to Gupta *et al.* [35], consuming large amounts of nitrates and nitrites in water for drinking due to the body's nitrate metabolism causes alveolar damage, a mismatch between ventilation and perfusion, and abnormal alteration in bronchi and lung tissue, which may be the cause of children's high death rates. Long-term exposure and deep inhalation of excessive nitrite fertilizers in agriculture lead to pneumonia [36].



**Figure 2. The graphic visualization of nitrite overdose and pathological picture [34].**

The nitrites in the food converted to nitric oxide (NO), which is quickly reduced to peroxynitrite by oxygen that leads to animals experiencing respiratory discomfort and pleural hemorrhage [37,38]. Nitric oxide may generate within the

lung and cause damage to pulmonary cells. Therefore, the researcher Gow *et al.* [39] studied the physiological and pathological relationship between nitric oxide and peroxy nitrite at levels of the molecular and cellular by using bovine lung artery endothelium cells and rat type II epithelium cells. In another study, nitric oxide caused vasodilation and bronchodilation as well as showed that NO metabolite concentrations rose with asthma severity in the tracheobronchial secretions and contributed to airway inflammation [40,41]. When exposed to sodium nitrite in a large dose or chronic period, it causes significant side effects on a variety of body organs, including lung damage and fibrosis in rats [42] (Table 2).

**Table 2. Research exhibits the impact of sodium nitrite on the respiratory systems.**

Number of animals / Gender	Type of organism	Dosage Concentration	Method of give dose/ Study duration	Major effects	Reference
randomly selected 88 children	Human	26, 45, 95, 222, and 459 mg NO(3) ion/L	drinking water from five villages in Rajasthan state, India	methemoglobinemia, hypoxia, overabundance of oxygen and free radicals of nitric oxide, and maybe alterations in alveoli and pulmonary circulation.	[35]
5 X 10 <sup>6</sup> cells from calf and male rats cells	bovine pulmonary artery endothelium cells and rat type II epithelium cells	0.01–2.5 μM/min	2-18 hours	mitochondrial membrane depolarization, DNA fragmentation, and loss of cellular viability	[39]
30 male	adult albino rats	80 mg/kg	Orally/daily for 3 months	pulmonary morphological changes, pulmonary toxicity and fibrosis lung	[42]

**2.3 The Urinary system:**

The kidneys are vital for filtering blood and excreting waste materials, like nitrates. Chronic exposure to high sodium nitrate levels due to renal toxicity and damage to the urinary system, necessitating their limited or low-dose usage. Thus, Atef *et al.* investigated the effects of feeding birds a meal high in sodium nitrate and sodium nitrite on kidney physiology and function [43]. According to Zaidi [44], revealed Renal hypoxia has an evident role in kidney function, causing acute and chronic kidney disease, which leads to acute renal failure. Another study demonstrated damages of sodium nitrate on the kidney tissue of mice by causing cell degeneration and an increase in the distribution of fiber connective tissue in glomeruli and among renal tubules [45]. (Table 3).

**Table 3. Studies demonstrate both sodium nitrite and nitrate affect the urinary systems.**

Number of animals / Gender	Type of organism	Dosage Concentration		Method of give dose/ Study duration	Major effects	Reference
		sodium nitrate	sodium nitrite			
45 male	Cockerels (Balady)	(4.2 g/kg)	(1.7 g/kg)	4 weeks	Raise urea concentrations in serum and consider the etiology of kidney diseases	[43]
8 male	Adult albino rats	—	(75 mg/kg)	subcutaneous injection/ one hour	necrotic alterations in the proximal convoluted tubules and glomeruli	[44]
70 male	albino rats	(1mg/kg)	—	Orally/ 30 days- stop taking dose for a month	The renal tubules' lumen dilates, containing more fibrous connective tissue and some deteriorated cells. The glomerular and peritubular capillary dilatation and congestion.	[45]

**2.4 Liver function:**

The liver serves as a crucial organ for the detoxification of hazardous substances such as nitrates. Excessive intake of sodium nitrate has been associated with hepatic toxicity. Researchers were observed rabbits feeding on nitrate-fertilized lettuce for 12 weeks could cause significant liver damage, characterized by severe hepatocyte necrosis. These structural alterations suggest impaired liver function and potential progression to liver diseases [46,47].

### III. CONCLUSIONS

Although sodium nitrite and nitrate serve useful functions in various industries, their overexposure poses serious negative health effects, especially for the reproductive system, respiratory system, liver, and kidneys. Balancing its benefits with potential hazards requires informed regulatory policies, public awareness campaigns, and continuous research to develop safer substitutes and mitigation techniques.

#### **Funding:**

This review is self-funded.

#### **Conflicts of Interest:**

Non- conflicts of Interest.

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