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Safety Study of Dietary Nitrate in Humans: Carcinogenicity and Thyroid Function

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Abstract:

The nutritional nitrate is widespread in the human diet. The conventional approaches primarily view it as having possible health hazards, particularly in the formation of nitrosamines and cancer vulnerability. During the last twenty years, a body of evidence has slowly accumulated that demonstrates the beneficial effect of the nitrate to nitrite to nitric oxide pathway in the cardiovascular health. This route controls blood pressure and improves exercise performance making nitrate a dual-function molecule that has advantages and has the potential to be toxic. The other major challenge in the field today is the absence of an all-inclusive risk-assessment framework. This framework must consider dose-response relations, exposure, and individual variation and the general dietary setup. Safe levels have not been defined in regard to people at risk like those with renal failure or those within thyroid disease susceptibility. Future studies should be able to define the extent and pathways of action of nitrate at two critical toxicological endpoints. The carcinogenicity and thyroid perturbation are these endpoints, and research must be conducted on modulatory responses of dietary habits and antioxidants. The current paper is a systematic review of the nitrate carcinogenicity, the mechanisms that may cause this carcinogenicity, and the influence on thyroid functioning. It is a summary of the available information to inform safety evaluation and health instructions of dietary nitrate.

Keywords: dietary nitrate; carcinogenicity; thyroid function.

1. Introduction

Dietary nitrate is ubiquitously present in human daily diets, particularly in leafy green vegetables, drinking water, and processed meats. Traditional perspectives have generally regarded it primarily as a substance with potential health risks, especially in association with the formation of nitrosamines and cancer susceptibility. Nevertheless, over the past two decades, research has revealed the central role of the nitrate-nitrite-nitric oxide pathway in human physiology. As an important exogenous source of nitric ox-

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ide, dietary nitrate has demonstrated definitive benefits in maintaining cardiovascular health, regulating blood pressure, and enhancing exercise performance. Thus, nitrate serves both as an indispensable precursor of signaling molecules for sustaining vital activities and a compound that may be converted into carcinogens or interfere with endocrine function under certain conditions, which constitutes the contradiction and focus of current research on the functions and safety of nitrate.

Vascular endothelial dysfunction and insufficient nitric oxide production constitute the core pathological mechanisms underlying the development and progression of hypertension. In the human body, nitrite acts as an important reservoir of nitric oxide, which can rapidly release nitric oxide through enzymatic reduction reactions under pathological conditions. Nitric oxide is a crucial vasodilator factor and signaling molecule that precisely participates in the relaxation of vascular smooth muscle and the dynamic regulation of blood pressure. Based on the discovery of this beneficial effect, dietary nitrate has even been explored as an adjuvant to improve exercise capacity. Currently, numerous preclinical studies have confirmed that supplementation with an appropriate amount of nitrite can enhance vascular elasticity in hypertensive model animals. Dietary nitrate ingested by humans (e.g., leafy green vegetables such as spinach and lettuce, and root vegetables such as beets and celery) must be converted into nitrite by the reduction of nitrate-reducing bacteria such as Lactobacillus and Streptococcus in the oral cavity[1].

However, long-term research has demonstrated that dietary nitrate exhibits potential toxicity. For instance, studies have found that in low-salinity aquaculture water, nitrite shows strong toxicity, with median lethal concentrations (LC_{50}) of 15.96 mg/L and 5.25 mg/L for Litopenaeus vannamei at 24 h and 96 h, respectively, which can induce elevated activities of superoxide dismutase (SOD) in hemolymph and glutathione peroxidase (GSH-Px) in hepatopancreas [2]. In addition, the 24 h and 96 h LC_{50} values of nitrite for smolts of Atlantic salmon (Salmo salar) are 46.636 mg/L and 8.744 mg/L, respectively [3]. These findings indicate that nitrate possesses certain physiological toxicity. Particularly under specific conditions (e.g., co-ingestion with amine or amide compounds, or presence of specific microbial flora), it may lead to the endogenous formation of N-nitroso compounds. Such compounds have been explicitly classified as Group 1 carcinogens by the International Agency for Research on Cancer (IARC). Long-term intake of these compounds can increase the risk of gastric cancer by 33%, colorectal cancer by 36%, and esophageal cancer by 38%, with the risk being even higher in populations with gastrointestinal mucosal damage.

In addition, high concentrations of nitrate and nitrite intake may competitively inhibit thyroid iodine uptake, thereby potentially interfering with thyroid hormone synthesis and impairing thyroid function. At present, there is a lack of a comprehensive risk assessment framework for balancing the functions and toxicity of nitrate based on dose-effect relationships, exposure sources, individual differences and overall dietary context. For specific populations, such as individuals with renal insufficiency or populations susceptible to thyroid diseases, their safety thresholds also need to be further clarified [4]. Therefore, conducting a systematic safety assessment of dietary nitrate, especially sorting out existing evidence, clarifying the association strength and underlying mechanisms regarding the two key toxicological endpoints of carcinogenicity and thyroid function impact, holds important scientific significance and public health value. This review aims to systematically summarize the latest research advances, so as to achieve a more comprehensive understanding of the effects of dietary nitrate on human health.

2. Carcinogenicity of Nitrate

Nitrate ingested through daily diets is not directly carcinogenic in itself, and it has an extremely wide distribution range. For example, it exists naturally in fresh vegetables (the nitrate content of leafy vegetables such as spinach and lettuce can reach 1000–3000 mg/kg, while that of root vegetables such as beets and celery is 500–1500 mg/kg) as well as pickled foods like pickled vegetables and salted vegetables (the nitrate content of pickled vegetables is usually 1/3–1/2 of that of fresh vegetables). To extend shelf life, maintain the pink color and tender taste of meat, nitrate is often artificially added as a food additive in processed meats (the addition level in ham and sausages is generally 50–150 mg/kg). Drinking water may also contain a small amount of nitrate, most of which originates from groundwater infiltration after agricultural fertilization; the nitrate content in well water in rural areas may reach 10–50 mg/L. However, as long as it meets the national drinking water standards ($\leqq$ 50 mg/L), it generally does not cause direct harm to health. After entering the oral cavity and gastrointestinal tract, such nitrate is converted into nitrite under the action of bacteria. If it encounters amines and amides in food, it will further form N-nitroso compounds with definite carcinogenic risks, which constitutes the core reason for the association between nitrate and cancer [4].

Multiple population-based studies and pooled analyses across different regions support the aforementioned conclusion. A 2023 meta-analysis by Malik et al., which encompassed 12 global prospective cohort studies, re-

vealed that populations with high nitrite intake had a 33% (95% confidence interval [CI]: 1.02–1.73), 38% (95% CI: 1.01–1.89), and 36% (95% CI: 1.18–1.58) higher risk of developing gastric cancer, esophageal cancer, and colorectal cancer, respectively, compared with those with the lowest intake. This study included over 500,000 participants with a mean follow-up duration of 8.5 years, lending high credibility to the data [5]. A more detailed systematic study conducted by Kassim et al. in 2022, which covered 13 cancer types (including gastric cancer, bladder cancer, thyroid cancer, lung cancer, and liver cancer), indicated that nitrite intake was significantly associated with an elevated risk of bladder cancer and gastric cancer. In contrast, excessive nitrate intake increased the likelihood of thyroid cancer [6].

Table 1: Studies on the association between dietary nitrate intake and risks of different cancers

Reseach Type	Study Population / Size	Key Findings	Ref.
Meta-analysis	12 global prospective cohort studies, over 500,000 participants, mean follow-up duration of 8.5 years	Populations with high nitrite intake had a 33% increased risk of gastric cancer, 38% increased risk of esophageal cancer, and 36% increased risk of colorectal cancer	[6]
Systematic Review/ Meta-analysis	Relevant studies covering 13 cancer types	Nitrite intake was significantly associated with elevated risks of bladder cancer and gastric cancer; excessive nitrate intake increased the risk of thyroid cancer	[3]
Cohort Study	74,941 women, follow-up for 11 years	The risk of thyroid cancer in the high nitrite intake group was 2.05 times that in the low intake group, and nitrite derived from processed meats showed a more significant association with this risk	[1]
Cohort Analysis	Licensed pesticide applicators and their spouses	Individuals who frequently consumed processed meats had a 45% increased risk of end-stage renal disease, which could indirectly increase the risk of urinary system tumors by 30%, forming a health hazard chain of "nitrate intake - kidney disease - tumor"	[10]

Long-term follow-up studies on specific populations have further corroborated this viewpoint. The Shanghai Women's Health Study conducted an 11-year continuous follow-up of 74,941 women. The results showed that the risk of thyroid cancer among the population with the highest nitrite intake (daily intake $\geqq$ 2.1 mg) was 2.05 times that of the population with the lowest intake (daily intake $\leqq$ 0.8 mg) (95% confidence interval: 1.20–3.51). Moreover, the nitrite derived from processed meats such as ham, sausages, and cured meat was more significantly associated with this elevated risk—nitrate is usually added in relatively high doses to such processed meats, and processes like high-temperature cooking and curing during production may promote nitrosation reactions, thereby further increasing the carcinogenic risk [7]. Another cohort analysis based on the Agricultural Health Study found that individuals who frequently consumed processed meats ($\geq$ 3 times per week) had a 45% higher risk of developing severe kidney disease compared with those who rarely ate them. Severe kidney disease can alter the internal metabolic environment and reduce toxin excretion efficiency, which in turn indirectly increases the risk of urinary system tumors by 30%, forming a health hazard cascade of "nitrate intake–kidney disease–tumor".

Nevertheless, the carcinogenicity of nitrate is not absolute but regulated by multiple factors. Currently, there is no clear evidence indicating an association between plant-derived nitrate and cancer, which may be related to the synergistic effect of antioxidant components such as polyphenols, vitamin C, and vitamin E contained in plants—polyphenols can inhibit the nitrate-reducing activity of intestinal bacteria, while vitamin C, acting as a reducing agent, can directly react with nitrite to generate nitric oxide, thereby reducing nitrosamine formation. In contrast, nitrite derived from meat, especially processed meat, has a more significant association with renal cell carcinoma, due to the high amine content in meat and the substantial loss of antioxidant substances during processing. In addition, the overall impact of dietary patterns cannot be ignored [8]. For example, high-fiber diets can promote intestinal peristalsis and reduce the residence time of nitrosamines in the intestinal tract. When regular dietary fiber intake is combined with nitrate intake, the cancer risk can be further reduced. These factors have collectively led to the absence of a significant association between nitrate and cancer in some studies, with the core reason being that the

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study subjects maintained a more balanced dietary pattern and sufficient intake of nutrients such as vitamin C and dietary fiber, which to a certain extent offset the potential risks of nitrate [9].

3. Nitrate Impacts on Thyroid Function.

It is not only the carcinogenicity of nitrate that has raised the possibility of serious health consequences, and its ability to disrupt the function of the endocrine system, notably the operation of thyroid function, has also drawn significant interest. The production of thyroid hormones requires the absorption of iodine and the nitrate can potentially disrupt this mechanism by competing with the sodium-iodide symporter [10]. Nevertheless, there has been a mixed clinical evidence on the effects of dietary nitrate as a matter of fact, which can be dependent on the study design, dose and duration of exposure as well as features of the study population.

One week of randomized, double-blind, cross over, placebo controlled study was done on 13 healthy adults by administration of nitrate-rich beetroot juice (about 8.12 mmol/day) daily. These findings indicated that plasma concentrations of triiodothyronine, thyroxine, nitrate, nitrite or urinary concentration of iodine did not show any statistically significant difference before and after one week of intervention when compared to the controls with placebo juice containing nitrates [10]. This paper indicates that dietary nitrate supplementation as a one-week study may not be enough to cause clinically significant shifts in thyroid functioning or iodine metabolism in healthy people. However, the limitations of the study were also given, including the absence of measuring thyroid-stimulating hormone levels and the briefness of the supplementation, and the impact of continuous exposure is still not explained [10].

Nonetheless, investigations with extensive population observational data using high population volumes indicate that the exposure to nitrates could be linked to changes in the levels of thyroid hormones under particular circumstances. An observational study based on data of U. S. National Health and Nutrition Examination Surveys of 2001-2002 and 2007-2008, was aimed at showing the relationship between perchlorate concentrations, thiocyanate and free thyroxine serum in the urine. It was observed that the level of urinary nitrates was a strong predictor across serum free thyroxine in nonpregnant women, and the relationship had been observed in both subgroups with urinary iodine concentration below and above 100 μg/L. Conversely there was no significant relationship between urinary nitrate and serum free thyroxine in men or even pregnant women. The correlation between the markers of thyroid function and nitrate among non-pregnant women was again supported in a meta-analysis of the study. These findings indicate that the possible effects of nitrate on the thyroid could be more population heterogeneous, and non-pregnant women could be a rather sensitive group. Another point that was highlighted in this research is that the possible cumulative health risks of co-exposure to chemicals with similar mechanisms of action (i.e. the inhibition of sodiumiodide symporter) amid nitrate and thiocyanate need to be considered when determining the health hazards of substances like perchlorate.

Combined, short-term dietary nitrate exposures do not seemingly result in any major disruption of thyroid functionality in normal adults, which is somewhat reassuring on the safety of moderate nitrate vegetable intake. Nevertheless, the possible consequences of low-level and long-term exposure to nitrates on the thyroid activity of some subpopulations (e.g., the non-pregnant women), especially when combined with other sodium-iodide sympathetic inhibitors, is a concern. There remains a need of extended length of intervention by studies in future taking on bigger populations to thoroughly examine the thyroid safety of extensive dietary consumption of nitrate.

4. Conclusions

This paper carefully examined the existing literature of the duality of dietary nitrate in human health and took an important step towards bridging the critical gap in its safety risk assessment system. The key findings are as follows: first, it was able to define the main cardiovascular health issues of nitrate as a precursor of nitric oxide in the so-called oral-circulatory pathway initiating the functional level of its physiology; second, with regard to carcinogenicity, the study was able to demonstrate that nitrate per se is not a carcinogen, but that the metabolites of N-nitroso compounds are correlated with the risk of a number of gastrointestinal cancers, and that the risk is again greatly modulated by dietary. The study was able to demonstrate that nitrate per se is not a carcinogen, but that the metabolites of N-nitroso compounds are correlated with the risk of some number of gastrointestinal cancers, and that the risk is again greatly modulated by dietary. The general direction will incorporate deeply into the concept of precision nutrition, apply multi-omics technologies to define the characteristics of individual differences at the metabolic, microbiome, and genetic level to achieve the goal of stratifying risk, encourage innovation in food processing technologies to come up with new additives or processing methods that prevent the formation of nitrosamines, and

rely on real-world big data and dynamic monitoring of the biomarkers to build an overall intelligent risk assessment model that includes the entire dietary history, life cycle, and co-exposure history will drive the transformation of the public health guidelines.

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