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Nitrosamine in meat and meat products: a review

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ABSTRACT

Nitrosamines (Nams) have been demonstrated to possess carcinogenic properties in certain animal species, suggesting a potential link between the consumption of this compound and the development of cancer in humans. Multiple reports have highlighted the presence of nitrosamine contamination in various food groups, particularly meat and meat products. Consequently, the presence of nitrosamines in meat products has raised significant concerns. This study aims to examine the levels of nitrosamines in meat and meat products, explore the mechanisms underlying their formation in these foods, and identify potential strategies for reducing this compound in food. To achieve this objective, scholarly articles about the keywords Nitrosamine, Exposure, Meat and Meat Products, and Mechanism of Formation were retrieved from academic databases such as PubMed, Web of Science, and Scopus, among others. The formation of nitrosamines (Nams) can be influenced by several factors including nitrosating agents, pH levels, the presence or accessibility of nitrite and nitrosable amines, and oxidative status. Moreover, the rate at which Nams form can be impacted by reducing these factors. Additionally, processed meat products may contain natural components and additives that interact with these factors to either hinder or facilitate the formation of Nams. Given the increasing consumption of sausages in daily diets, evaluating the levels of nitrosamines in meat products can serve as a quality measure for assessing nutritional value and the effectiveness of processing and thermal treatments.

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1. Introduction

Meat and its derived products constitute a significant component of the human diet, offering essential nutrients such as protein, vitamins, and minerals (1). Nitrates and nitrites have various applications in the meat industry, such as enhancing color stability, and flavor improvement, providing antioxidant properties, inhibiting spoilage and pathogenic microorganisms like *Clostridium botulinum*, and delaying lipid oxidation-induced rancidity. Consequently, these compounds extend the shelf life and prevent spoilage of meat products (2).

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When nitrite decomposes, it produces nitro acid which can react with second-type amines to form nitrosamines (Nams). These Nams can then be converted into hydroalkyl compounds. The hydroxyalkyl carbonium ions generated from these compounds can cause alkylation and DNA mutation, ultimately resulting in carcinogenesis (3). The formation of Nams in meat products is contingent upon the cooking method, cooking temperature and duration, residual and added nitrite concentrations, the presence of precursors and catalysts and inhibitors, preprocessing procedures, the smoking process, and storage conditions (4). The level of Nams formation in meat products is positively correlated with the amount of sodium nitrite concentration added, so the formation of nitrosamine is directly related to the square of the concentration of sodium nitrite in the product. Therefore, a significant reduction in Nams production can be achieved by decreasing the quantity of sodium nitrite utilized (5). It is known that ascorbic acid and alpha-tocopherol can inhibit nitrosation reactions, and these compounds are commonly used in food processing. Moreover, it has been scientifically established that subjecting food to suitable doses of radiation is a secure method for decreasing the levels of nitrosamines. (6). The International Agency for Research on Cancer (IARC) classifies N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), N-nitrosodibutylamine (NDBA), N-nitrosopiperidine (NPIP) and N nitrosopyrrolidine (NPYR) as potential carcinogenic compounds for humans. The classification of NDBA, NPIP, and NPYR compounds falls under Group B2, which indicates a probability of being carcinogenic, while NDMA and NDEA are classified as Group A2 (High Probability carcinogenic) compounds (7,8). In 2005, the United States Department of Agriculture (USDA) implemented a regulation setting the maximum allowable total volatile N-Nitrosoamines (Nams) content in meat products at 10 µg/kg. Additionally, Chinese authorities have established an upper limit of 3 µg/kg for NDMA levels in meat products (9). Establishing the nitrosamine content of meat products is crucial, given the considerable toxicity and carcinogenic effects of these compounds, as well as the high and increasing sausage intake in the nation. Assessing the concentration of Nams in meat products can be used as a metric to evaluate the nutritional quality and to gauge the quality of various processing and thermal procedures (10) this research aims to examine the quantity of nitrosamine present in meat and its related products, the mechanism of formation of nitrosamine, health effects of nitrosamines and prevent nitrosamine contamination in these foods.

2. Materials and Methods

The fitting studies were explored in PubMed, Web of Science, and Scopus, from 2000 to 2023. The used keywords for the search were: (Nitrosamine) AND (Meats OR Meat products) AND (nitrosamine contamination).

3. Mechanism of formation

When secondary amines react with N_2O_3, Nams are produced. This chemical reaction results in the formation of Nams through the interaction between N_2O_3 and secondary amines. The creation of Nams in meat is an intricate process and a variety of compounds can affect nitrosation reactions. The potential precursors of Nams can be derived from various sources such as primary, secondary, and tertiary amines, nitrate, nitrite, amides, proteins, peptides, amino acids, or their precursors. These precursors can undergo microbial activity and be transformed into Nams precursors. Microorganisms could potentially contribute to the formation of Nams through the reduction of nitrates to nitrites, and the process of breaking down proteins into their constituent amines and amino acids (1,2). Secondary amines, including dimethylamine, function as primary precursors of Nams and arise from the degradation of proteins. Additionally, the acidification process of fermentation may catalyze the generation of Nams (3). The process of generating nitrosating agents in fried meat involves a crucial stage wherein nitric oxide (NO) undergoes oxidation to yield higher nitrogen oxides, which then leads to the formation of a nitrosating agent. While the precise structure of this agent remains unknown, the observed substance is hypothesized to be a byproduct of the reaction between nitrite and lipids found within the meat. The available evidence indicates that the agent in question may originate from either N_2O_3 which is produced when nitrite in meat is heated or NO radicals that result from the dissociation of N_2O_3 at elevated temperatures (4). The reaction of nitro acid, generated from the decomposition of nitrite, with secondary amines yields Nams. Subsequent conversion of Nams into unstable hydroalkyl compounds leads to the formation of active hydroxyalkyl carbonium ions, which can cause DNA alkylation and mobility, potentially resulting in the development of cancer (2). Below are the chemical reactions responsible for the formation of nitrosamines in cured meat systems (3):

$$NaNO_2 + H^+ \rightarrow Na^+ + HNO_2$$

$$HNO_2 + H^+ \rightarrow NO^+ + H_2O$$

$$2HNO_2 \rightarrow N_2O_3 + H_2O$$

$$N_2O_3 \rightarrow NO + NO_2$$

$$NO + M^+ \rightarrow NO^+ + M$$

$$RNH_2 \text{ (Primary amine)} + NO^+ \rightarrow RNH\text{-}N = O + H^+ \rightarrow ROH + N_2$$

$$R_2NH \text{ (Secondary amine)} + NO^+ \rightarrow R_2N\text{-}N = O + H^+$$

$$R_3N \text{ (Tertiary amine)} + NO^+ \rightarrow \text{no nitrosamine formation}$$

4. Type of foods containing the chemical hazard of nitrosamine

Nams are found in the environment and various foods such as seafood, canned foods, beer, and meat products. Nitrite and nitrate are frequently employed in the food industry as additives for cured meats. Their properties, which include preservation, antibacterial action, flavor enhancement, and color stabilization, make them a popular choice for processed meat and cheese.(4). Generally, Nams are synthesized through the nitrosation of a secondary amine by a nitrosating agent. Within food items, the primary sources of nitrosyl donors are sodium nitrite, which is utilized in curing, and gaseous nitrogen oxides, which are emitted from smoking.

Table 1 provides a summary of the levels of Nams found in various meat products. In 2005, the United States Department of Agriculture mandated a limit of 10 μg/kg for total volatile Nams in meat products. Similarly, Chinese authorities established a threshold of 3 μg/kg for NDMA in meat products (5). The data presented in Table 1 indicates that certain types of meat products exhibit elevated concentrations of Nams.

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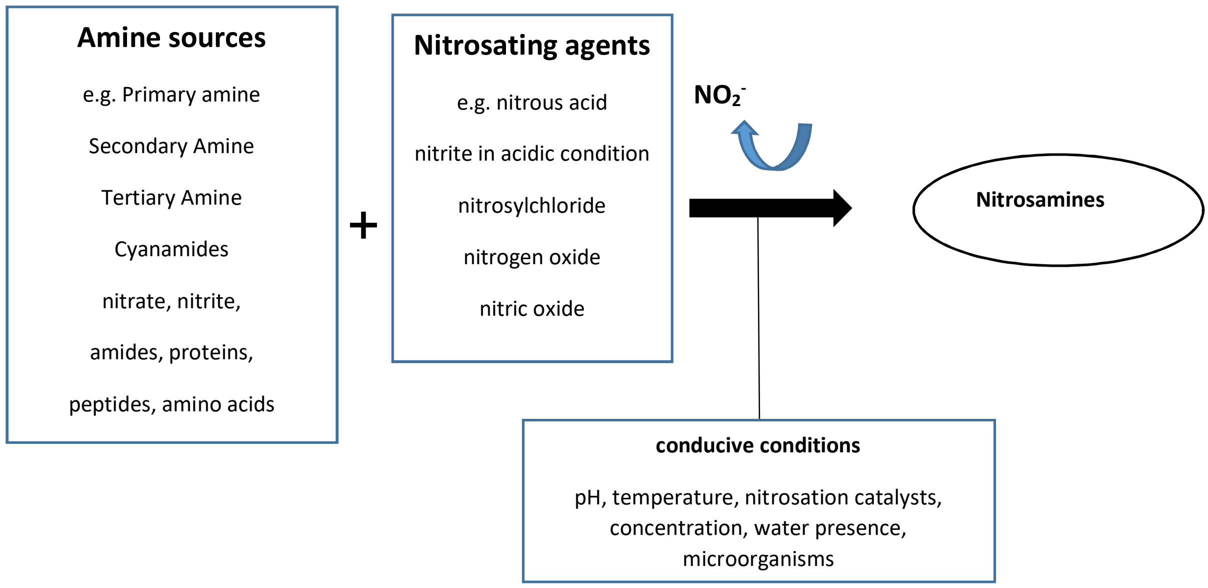

Figure 1. Mechanism of nitrosamine formation

Table1. Summary of Nams levels in types of meat products

Food	Mean content	Marker	Detection method	Reference
Sausages	2.6 µg/kg	NPIP	LC-MS/MS	(6)
Smoked sausage	1.01 µg /kg	NDMA	GC/MS	(7)
HAM	3.73 µg /kg			
Beef Steak	15.84 µg/kg	Nams	GC/MS	(8)
Burger patty	20.44 µg/kg			
Hot dog	2.1 ng/g	NDMA	GC–CI-MS	(9)
Bacon	1.4 ng/g			
canned fish	8.20 µg/kg	Nams	GC-TEA	(10)
meat	0.55 µg/kg			
Chicken salami 90 %	6.57 ng/ g	NPIP	GC–MS	(11)
Frankfurt sausage 40 %	3.79 ng/ g			
Doner Kebab	16.63 µg/kg	The sum of six Nams	GC/GC	(12)
Meat products	5 µg/kg	Nams	GC/MS	(13)
Smoked beef	4227.492 µg/kg	NTCA	LC-MS/MS	(14)
Sucuk	0.31 µg/kg	NDMA	GC-MS	(15)
	5.61 µg/kg	NPYP		
	118.23 µg/ kg	NPIP		

NPIP: N-nitrosopiperidine _ NDMA: N-nitrosodimethylamine_ Nams: N-Nitrosoamines
NTCA: N-Nitrosothiazolidine 4-carboxylic acid_ NPYP: 1-Nitrosopyrrolidine

5. Factors that influence the levels of nitrosamines

The concentration of nitrite and amine groups in a mixture plays a crucial role in determining the rate of Nams formation. Alongside these factors, the presence of nitrosating agents, pH levels, oxidative status, and availability of nitrosable amines can also affect the formation rate of Nams. Additionally, several natural components and supplemental substances present in processed meat may interact with nitrite, nitrosating agents, or amines to either inhibit or promote Nams formation. Overall, numerous factors can impact the level of nitrosamines found in food products.

The antioxidant content in animal feed can influence the antioxidant levels in the resulting meat. For instance, a feed with high antioxidant content may lead to meat with increased oxidative capacity. The pH of meat is subject to variation based on an animal's stress level. The formation of Nams may be influenced by certain variables, however, their impact is limited in comparison to ingredients and/or additives that are directly included in the meat. Notably, it is simpler to regulate these effects when utilizing ingredients and additives (7).

The intricate chemistry of nitrite renders it susceptible to influence from various factors that impact the formation of Nams. These factors comprise antioxidants, sodium chloride, sugars, and polyphosphates. The role of sugar in Nams formation is contingent upon the type of sugar utilized, the product it is incorporated into, and other accompanying ingredients or additives. (16-18). The influence of sugars and polyphosphates on the pH of meat has been noted to potentially impact certain observed effects. Specifically, the creation of Nams in the lipid phase of meat has been proposed to be facilitated by this pH alteration. Additionally, polyphosphates may be significant in interacting with the formation of Nams, which is contingent upon lipids. (7,19). When antioxidants like ascorbate are present, it has been consistently observed that nitrite-preserved meats show a decrease in Nams levels. Conversely, they show an increase in the formation of nitrosylhaem (20,21). Also, the present studies illustrate that the inclusion of sodium chloride in nitrite-preserved meat has the potential to decrease the formation of Nams (22,23). Several studies have demonstrated a possible relationship between the concentration of sodium chloride and its effects, the observed effect appears to vary in intensity based on the concentration of the substance. (20), however, other studies have shown that there is only a minor effect when a concentration of sodium chloride is above 1.5% (24). There is evidence that black pepper and paprika are highly effective in increasing the levels of NPIP and NPYR (7).

Research has demonstrated the crucial role of heat application in altering Nams levels in processed meat. Particularly, frying and baking significantly influence the levels of NDMA and NPYR during processing. (25,26). The application of heat treatment expedites several meat processes, such as nitrosation. This procedure can trigger the liberation of nitrogen oxide or other nitrosating agents that are linked to lipids, which may ultimately lead to the development of Nams (27). Several researchers have proposed that decarboxylation of NVNA, NSAR, and NPRO during frying may lead to the generation of NDMA and NPYR. Additionally, it seems that smoking promotes the

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formation of NTCA and other NVNAs resulting from the condensation of aldehydes and cysteines (28,29).

6. The health effects of nitrosamines

Several epidemiological studies have demonstrated a correlation between the consumption of red and processed meat and an elevated likelihood of developing certain forms of cancer, specifically colorectal cancer (30), stomach (31), and pancreatic cancer (32), as well as cardiovascular disease and other causes of death (33). Studies showed stronger associations with processed meat than red meat consumption. Based on the estimates provided by Rohrmann et al. (2013), consumption of over 20 grams of processed meat per day is associated with an increase in the mortality rate within the population (33).

It is noteworthy that Nams are considered pro-carcinogens, requiring metabolic activation to function as carcinogens. This activation process is facilitated by enzymes belonging to the cytochrome P450 family. Hydroxylation of the carbon atom located at the α position of the nitroso group is a pivotal process in this reaction. Upon hydroxylation, N-nitrosopiperidine (NPIP) generates a highly unstable species that decomposes into three ions, namely diazonium, oxonium, and diazohydroxide. The electrophilic intermediates have the potential to form adducts with DNA. Consequently, Nams hydroxylation-generated electrophilic intermediates can bind to DNA and cause either transcription or incorrect repair, initiating cellular processes. As a result, initiated cells may proliferate uncontrollably and eventually lead to preneoplastic cells becoming neoplastic and causing cancer (34). Of all the groups of carcinogens, Nams are among the simplest structurally. Despite their simplicity, these chemicals are powerful carcinogens in many species and organ systems. There is a huge variation in the carcinogenic potential of Nams. Various Nams have exhibited varying levels of efficacy in inhibiting α-carbon and/or fitting into the active site of the oxidative enzyme. (35). The International Agency for Research on Cancer (IARC) has classified N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) as belonging to the group of substances that are "probably carcinogenic to humans". Conversely, N-nitrosodibutylamine (NDBA), NPIP, and NPYR are classified as belonging to the group of substances that are "possibly carcinogenic to humans". (26).

7. Prevent nitrosamine contamination in food

The synthesis of Nams in processed meat is affected by a multitude of factors such as the cooking technique, residual and added nitrite concentration, levels of nitrosamine precursors, slice thickness, the presence of ascorbate or α-tocopherol, preprocessing conditions, moisture content, the presence of nitrosation catalysts and inhibitors and potentially the smoking process (36). Food irradiation is a common practice permitted in numerous countries to improve food shelf life and technological features. A recent study discovered that irradiation was successful in minimizing volatile Nams in an aqueous model system. Additionally, it was noted that the simulated stomach conditions did not lead to the generation of nitrosamine reformation from the degradation byproducts (37). A study investigated the impact of irradiation on dried ham that had undergone two months of sun-drying. The ham was exposed to a dose of 5 kg Gy, the study demonstrated a significant reduction in nitrite residues, ranging from 26% to 70%, following an 11-month storage period (38).

Also, Ascorbate has been identified as an effective inhibitor of nitrosamine formation and is frequently involved in The process of nitrite reduction and the consequent production of nitrosamine. Various studies have shown that the addition of sodium chloride or sodium ascorbate to meat is a common practice that reduces the level of nitrosamine contamination compared to meat without additives (39). The increase in the formation of Nams depends on the time and temperature of frying meat and meat products. Because at high temperatures, Nams form adducts with unsaturated fats, the decomposition of certain substances at elevated temperatures leads to the liberation of nitrogen oxides, which in turn react with free amines present in the environment, leading to their nitrosation (40). In their study, Li, Wang, Xu, and Zhou (2012) stated that frying increased the formation of NDMA in dried raw sausage. However, boiling and microwaves do not affect nitrosamine formation. Also, a study conducted on fermented raw sausage has demonstrated that the cooking temperature of 180°C has a notable impact on the development of NDMA (41). Yurchenko & Molder conducted an experiment wherein mutton was subjected to temperatures ranging from 50 to 250°C. Based on the findings, it can be concluded that the production of NAs was observed to escalate with an increase in both time and temperature. This trend was particularly evident within the temperature range of 60-100°C. Furthermore, the formation of NAs remained stable after reaching a certain level (7) but Honikel asserted that the generation of NAs does not occur at the onset of heat treatment; rather, it is only possible when the temperature surpasses 130°C (42).

The impact of processing temperature appears to be stronger than that of processing time, while the influence of the latter seems to be less significant. Additionally, it has been observed that among the diverse methods of processing, the act of deep-frying, produces a higher frequency of potential hazards. This is perhaps attributed to the elevated concentration of oil in this particular processing environment (43,44).

Table 2. Inhibitory strategy during processing

Process	strategy
Precursors of nitrosamines	1. Replacing the function of nitrite 2. Choosing appropriate raw meat
Processing condition	1. Lower temperature 2. Avoid direct heating
Exogenous additives	Vitamins, Phenols, spices, Quinones
Degradation	1. Biodegradation 2. Irradiation degradation

8. Conclusion

The ingestion of processed meat and the prolonged build-up of its compounds in the human body may pose a potential health hazard attributable to Nams. This review examined the mechanism of formation of names in foods and studies that measured the level of Names in food products. Meat and meat products had the highest amount of nitrosamine. Also, factors can affect nitrosamine formation such as cooking temperature and duration, additives, and storage conditions. Ultimately, various tactics were addressed with the intent of reducing the presence of nitrosamine in food products. Additional research is necessary to

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identify a more efficacious approach for eliminating nitrosamine from food items.

Conflict of interest

The authors declare that they have no conflict of interest.

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