WINSOME PUBLISHING
Dietary Nourishment and Food Processing Techniques ISSN: 3064-7061

Review Article Open Access

Additives Extend the Food Shelf Life by Addition of Preservatives Nitrate, and Nitrite to Food

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Received date: September 30, 2024; **Accepted date:** October 11, 2024; **Published date:** October 16, 2024
Citation: Fahim Aziz Eldin Shaltout, Additives Extend the Food Shelf Life by Addition of Preservatives Nitrate, and Nitrite to Food, **Dietary Nourishment and Food Processing Techniques**, vol 1(3). DOI: 10.9567/3064-7061/WSJ.83

Abstract

Nitrite is one of the most widely used curing ingredients in meat industries. Nitrites have numerous useful applications in cured meats and a vital component in giving cured meats their unique characteristics, such as their pink color and savory flavor. Nitrites are used to suppress the oxidation of lipid and protein in meat products and to limit the growth of pathogenic microorganisms such as Clostridium botulinum. Synthetic nitrite is frequently utilized for curing due to its low expenses and easier applications to meat. However, it is linked to the production of nitrosamines, which has raised several health concerns among consumers regarding its usage in meat products. Consumer desire for healthier meat products prepared with natural nitrite sources has increased due to a rising awareness regarding the application of synthetic nitrites. However, it is important to understand the various activities of nitrite in meat curing for developing novel substitutes of nitrites. This review emphasizes on the effects of nitrite usage in meat and highlights the role of nitrite in the production of carcinogenic nitrosamines as well as possible nitrite substitutes from natural resources explored also.

Introduction

Meat curing is an ancient method of food preservation that is still widely used today. It refers to adding nitrite/nitrate salt, common salt **(NaCl),** and spices to fresh meat in varying degrees of comminution and at various processing phases Prior to the invention of refrigeration, meat was preserved using methods discovered to be efficient in controlling deterioration after slaughter and extending the food supply during times of shortage. Despite being lost in time, the curing process is thought to be evolved from salt preservation methods as early as 3000 B.C.

Among the various additives used in meat curing, nitrite salt is very significant. Nitrite is a major intermediary throughout the biological N-cycle present in soil and water surface. It's a versatile chemical with a wide range of uses, including dye manufacturing and food preservation. Nitrites in various meat products are significant preservatives and impede the growth of several unwanted micro-organisms. Nitrite is added to cured meat at levels less than 150 ppm to prevent the development of microbiological organisms like *Clostridium botulinum*, which causes food poisoning The main reasons for using nitrite as a preservative in meat are: To inhibit the *Clostridium botulinum* from spreading and secreting toxins that cause food toxicity. to provide the necessary bright red color in meat products like sausage, ham, salami, etc. To give cured meats their characteristic texture and aroma. In addition, nitrite also inhibits the oxidation of lipids in meat products and thus prevents rancidity **(off flavor)** (1,2,3,4,5 and 6).

Since the middle of the 1980s, research has shown that nitrite is a major chemical with substantial impacts on human health. Vegetables are a great source of dietary nitrates, and they have been proven to be an important source of endogenous nitrite as well as nitric oxide **(NO)** in the human body. Nitric oxide **(NO),** produced through enzymatic synthesis, regulates blood pressure, wound healing, immunological response and neurological processes in the human body. New research has demonstrated that NO **(nitric oxide)** regulates blood circulation in cardiac tissues and perhaps in other body tissues. Furthermore, regular nitric oxide and nitrite production may help to prevent cardiovascular diseases like hypertension, atherosclerosis, and stroke.

High nitrite concentrations, on the other hand, are extremely dangerous for infants since they can develop an infant's methemoglobinemia. Furthermore, cancer-causing nitrosamines are formed when nitrite reacts with secondary or tertiary amines. Recently, the International Agency for Research on Cancer **(IARC)** stated processed meat as carcinogenic by evaluating sufficient epidemiological data. IARC also reported that ingested nitrite from processed meat can lead to colorectal cancer in human. Because of these harmful effects, many countries have severely restricted their use on processed food products. The toxicity of nitrite is ten times that of nitrate. For humans, the fatal oral dosage is 80 to 800 mg nitrate per Kg body weight and just 33 to 250 mg nitrite per Kg body weight. Long-term intake of increasing amounts of red meat, especially processed meat, is linked to a higher rate of mortality, colorectal cancer, type-2 diabetes and heart diseases in both male and female, according to large prospective United States, E.U. cohort studies as well as meta-analyses of epidemiology. Concerning these issues, an acceptable daily intake **(ADI)** of 0.07 mg nitrite per kg of body weight was set by the Joint Expert Committee of the Food and Agriculture Organization **(JECFA)** and the World Health Organization **(WHO)** that appears to be safe for healthy newborns, children, and adults (7,8,9,10,11 and 12).

The World Cancer Research Fund **(WCRF)** and the American Institute for Cancer Research **(AICR)** published research in 2007 that found a moderate but significant link between increasing consumption of processed meat and a higher risk of colorectal cancer. As a result, specialists advised limiting red and processed meat consumption. Anywise, eating less meat alone may not result in a significant reduction in carcinogenic effects and it may be associated with several disadvantages, including the loss of nutritive value, especially iron **(Fe).** So, it will be wise to invest proactively in the processing of healthier meat products rather than anticipating processed meat consumption to fall (13,14,15,16,17 and 18).

Because of growing concerns regarding sodium nitrite's long-term adverse effects, their use in cured meat products is strictly regulated among most developed countries. Parallel to this, the new ideas of all-natural and clean label have raised a demand for healthy and high-quality meat products. Due to health hazards, consumers choose natural additives over chemicals in processed meat. As a result, research on substituting natural ingredients for the chemical additive nitrite has grown over the years (19,20,21,22,23 and 24). To reduce the risk of nitrosamine formation and mitigate potential human health hazards, researchers are trying to find effective ways in meat curing. One such method is the replacement of nitrite salt with alternative ingredients that have similar properties while posing no health risk . However, no single alternative that provides the multi-functions of nitrite in meat products has yet been found. The employment of "hurdle technology" in meat curing is one proposed solution to this issue where low amounts of nitrite are mixed with other ingredients. The aim of this present work is to review the role of nitrite in cured meat products, the adverse health effects of higher nitrite intake as well as to give an overview of the available data on potential replacements to nitrite salt in processed meat either whole or partially (25,26,27,28,29 and 30).

Sources of Nitrite

Nitrites play a vital role in the biogeochemical cycle of nitrogen in natural water. They can be found in soils , waterways , foodstuffs , plants , air (as nitrogen dioxide) , and biological samples.

In the biological nitrogen cycle, nitrogen is converted to nitrate by bacteria, which is taken by plants and incorporated into tissues Animals that consume plants utilize nitrate to produce proteins. Animal excrement and microbial breakdown of animals and plants after death return nitrate to the environment. Nitrate or the ammonium ion can be converted to nitrite by micro-organisms; this reaction occurs in the environment, digestive tracts of humans and other animals. Once bacteria in the environment convert nitrate to nitrite and subsequently convert the nitrite to nitrogen, the cycle is completed (40,41,42,43,44 and 45).

Function of Nitrite in Cured Meats

Cured Color Development

Meat color is highly variable and is influenced by a variety of factors. When nitrite is introduced to meat, it is converted to nitric oxide **(NO)** via the reactions listed below

$$NO_2^- + H^+ \leftrightarrow HNO_2$$
$$2HNO_2 \leftrightarrow N_2O_3 + H_2O$$
$$N_2O_3 \leftrightarrow NO + NO_2$$

Here, nitrite reacts with hydrogen ions **(H^+)** of water to produce nitrous acid. After that, nitrous acid progressively decomposes into water molecules **(H_2O)** and dinitrogen-trioxide**.** Then, nitric oxide and nitrogen dioxide are generated from dinitrogen trioxide **(N_2O_3).** The major component responsible for nitrite's apparent function in cured meat products is nitric oxide.

Nitric oxide combines with the iron of both myoglobin **(Fe^{2+})** and metmyoglobin **(Fe^{3+})** to produce a cured pink color in meat Myoglobin is the sarcoplasmic protein responsible for the red color in meat, and metmyoglobin (**brown in color)** is the oxidized form of myoglobin **(Mb).** NO-myoglobin is formed when nitric oxide **(NO)** reacts with myoglobin **(Fe^{2+}).** The bright red nitrosyl-myoglobin complex provides the foundation for the distinct color of cured meat This complex is extremely unstable, and it turns into a stable, eye-catching reddish-pink pigment **(nitroso-hemochrome)** during heat treatment

Furthermore, myoglobin may react with HNO_2. Myoglobin **(Fe^{2+})** combines with nitrous acid and forms metmyoglobin **(Fe^{3+})** by oxidation. Metmyoglobin **(Fe^{3+})** then reacts with NO to produce NO-metmyoglobin. NO-metmyoglobin is also produced from the reduction of metmyoglobin. As a result, the meat becomes brown in color. NO-metmyoglobin can be converted to NO-myoglobin by a reductant, causing the formation of the cured color **(pink)** again when heated (28,29,30,31,32 and 33).

The presence of other additives in cured meats also affects the color development. Antioxidants including erythorbate, ascorbic acid and polyphenols stimulate the production of NO by allowing the N_2O_3 reduction. Ascorbic acid reduces Fe^{3+} to Fe^{2+} effectively and enhances the reduction process of NO-metmyoglobin. Thus, antioxidants with reducing activity aids in the cured meat color development by raising NO production and lowering NO-metmyoglobin levels. NaCl, generally added to meat for curing, reacts with HNO_2 to generate nitrosyl chloride, which is more sensitive than N_2O_3 in terms of generating nitric oxide **(NO)** and initiating the formation of NO-myoglobin.

The rate of nitrosyl myoglobin production has been found to increase with increased salt concentration. The sensory panelists rated the bacon with a high sodium chloride level as having more redness. The pH also controls nitric oxide formation from nitrite. Nitrous acid **(HNO_2)** and nitrite reactivity increase as pH decreases. The rate of nitric oxide **(NO)** formation is doubled when the pH is slightly reduced by 0.2–0.3 units (34, 35,36,37,38 and 39).

Basically, a very small quantity of nitrite is required for the development of the cured color in meats, usually approximately 2–14 ppm However, the level of residual nitrite in cured meats gradually decrease owing to oxidation during storage time. As a result, the meat starts to lose its cured color and become faded. Color loss also occurs when meat is exposed to air and light, while the presence of adequate residual nitrite as well as reducing chemicals delay this process Usually, 10–15 ppm of residual nitrite is recommended, which can act like a reservoir for the cured meat color regeneration. On the other side, higher levels of sodium nitrite **(>600 ppm/kg of meat)** and low pH value may lead to nitrite burn (discoloration) where meat shows a green color due to the formation of nitrihemin, a green-brown pigment (46,47,48,49,50 and 51).

Cured Flavour Development

Flavor is the combination of numerous qualities including odor, fragrance, taste, texture and temperature of meat that influences the perception of the consumer Although it is generally recognized that nitrite influences the meat flavor, the reactions responsible for this thing are not completely understood.

The antioxidant activity of nitrite against lipid oxidation is assumed to be one of the methods which might alter the flavor of meat products by suppressing “warmed-over” flavor. Aldehydes such as pentanal, hexanal, etc., which are the products of lipid oxidation, are suppressed in cured meat when lipid oxidation is inhibited by nitrite Uncured meat has considerably greater levels of hexanal than cured meat. Furthermore, cured meat has low levels of carbonyl compounds, including 2-heptanone, 3-hexanone, 2-nonenal, and 2-octanal Thus, nitrite has been demonstrated to simplify the flavor spectrum. The use of nitrite does not affect the synthesis of specific flavor compounds, but it inhibits the formation of aldehydes **(hexanal),** masking the sulfur-containing chemicals that give cured meat its flavor. Nitrite, on the other hand, has been shown to cause the production of Strecker aldehydes. Strecker aldehydes are generated when amino acids are degraded by dicarbonyl produced through Maillard reactions and these aldehydes are linked to meat flavor formation After adding nitrite to fermented sausages, the production of Strecker aldehydes increases. This might be due to an increase in carbonyl molecules, which can combine with amino acids to create Strecker aldehydes due to the pro-oxidant action of nitrite (52,53,54,55,56 and 57).

In cured meats, less than $^1/_2$ of the overall volatile chemicals, generally found in uncured meats have been detected and much of the variation is considered to be related to the partial production of the by-products of lipid oxidation. Alcohols and phenolic compounds may go through nitration reactions, which may have an effect on volatile chemicals. S-nitroso thiol production and disulfide bond breakdown during meat curing is likely to cause increases in sulfur compounds. The antioxidant effect of nitrite explains why oxidation products, such as hexanal, are reduced in cured meats. More research is needed to completely understand the mechanism, reactions and the volatile compounds responsible for the aroma and flavor of cured meat

Sensorial research shows that cured meat flavor is not only an outcome of the retardation of lipid oxidation but also a blending of complex cured aromas/flavors in collaboration with the scarcity of rancid flavors. In this manner, it can be said that cured meat flavor is the combination of two things, Lipid oxidation suppression by nitrite and Nitrite related flavor development (58,59,60,61,62 and 63).

Antioxidant Properties against Lipid and Protein Oxidation

Another notable characteristic of nitrite is that it can prevent rancidity during storage and the formation of “warmed-over” flavors when meat products are heated The oxidation process affects lipids, proteins as well as pigments of meat and causes changes in hue, flavor, texture, and nutritive value During cold storage, lipid oxidation produces off-flavors which are typically characterized as rancid and enhances the discoloration of food Moreover, it produces and accumulates chemicals that might endanger consumers' health Oxygen is a significant factor influencing lipid oxidation in meat. It interacts with the unsaturated lipids of meat to generate lipid peroxides which include oxygen absorption as well as double bond reformation The production of lipid peroxides ultimately leads to the formation of a variety of chemical components such as aldehydes, alcohols and ketones.

Nitrite acts as an antioxidant by protecting the lipid molecules of meat from oxidation. In cured meats, nitrite works as an antioxidant through different mechanisms. Nitrite serves as a chelating agent of metallic ions (main prooxidants in meats) and it also stabilizes the heme Fe. Furthermore, nitric oxide, produced from nitrite, may be readily converted to NO_2 by reacting with oxygen. Nitric oxide also reacts with radicals of lipid to break the oxidation chain reactions. Lipid oxidation may be started in a variety of ways and once initiated, grows exponentially due to free radical interactions. Once they are generated in the starting phase, lipid radicals are continually oxidized through radical chain reactions. Nitrite can inhibit lipid oxidation initiation by reacting with ROS **(reactive oxygen species),** such as hydroxyl radicals. Nitric oxide **(NO)** can also inhibit lipid oxidation by combining with lipid peroxyl radicals and produce non-radical molecules. Nitrite has been shown to have an antioxidant property at concentrations as low as 40 mg per kg A reduction of about 65% in lipid oxidation has been reported when 50 ppm sodium nitrite was added to the meat products (64,65,66,67 and 68).

Proteins, in addition to lipids, are oxidized during the preparation of meat. Moreover, the antioxidant action of nitrite in the inhibition of protein oxidation is yet unknown. As the protein oxidation mechanism is similar to the mechanism of lipid oxidation, it is believed that nitrite might hinder protein oxidation. The quantity of peroxide value, sulfhydryl, carbonyl groups and thiobarbituric acid-reactive compounds **(TBARS)** produced during meat processing are commonly used to assess meat oxidation The application of sodium nitrite to meat products results in a considerably lower TBARS value than that of controls **(without sodium nitrite),** but no influence on the carbonyl compound concentration, used to evaluate protein oxidation Sodium nitrite has been shown to have both antioxidant and pro-oxidant properties in meat products. As evidenced by the decreased generation of carbonyl compounds, sodium nitrite exhibits an antioxidant property towards protein oxidation. However, nitrite was also discovered to possess a pro-oxidant effect on protein oxidation by lowering the total sulfhydryl concentration and increasing disulfide bond formation in cooked sausage proteins. By absorbing oxygen from sensitive molecules or producing reactive nitrogen species, nitrite can serve as a pro-oxidant Protein oxidation causes a variety of physicochemical as well as nutritional changes in meat proteins along with a reduction in amino acid bioavailability, difference in composition of amino acids, decline in protein solubility, reduction in protein digestibility and lack of proteolytic activity All these changes can be minimized by the antioxidant activity of nitrite. Therefore, it can be said that nitrite plays a great role as an antioxidant by inhibiting lipid and protein oxidation and thus it can prevent meat quality deterioration (69,70,71,72,73 and 74).

Antimicrobial Effect

Nitrite has been found to be very effective as a bacteriostatic and bactericidal agent in inhibiting or regulating the development of bacteria to various degrees in meat products. Nitrite has been shown to impede the reproduction of *Clostridium botulinum*. The application of nitrite has been shown to inhibit the formation of botulinal toxins from inoculated *Clostridium botulinum* in wiener sausages during storage. There are two effects of nitrite found in controlling the growth of *Clostridium botulinum*. The first effect is inhibiting vegetative cells developing from surviving spores. The second effect is the prevention of vegetative cell division During meat preservation, nitrite lowers the amount of *Clostridium sporogenes*, which have comparable characteristics to *Clostridium botulinum*. In addition, numerous studies have found that nitrite inhibits the development of *Listeria monocytogenes*, *Bacillus cereus*, *Clostridium perfringens* and *Staphylococcus aureus* in various meat products The impact of nitrite and inhibitory mechanisms varies with several bacterial species The effectiveness of antimicrobial activity is dependent on various factors like pH, residual nitrite level, salt concentration, Fe content, reductants presence, storage temperature, etc. At acidic pH, nitrite hinders the growth of unwanted microorganisms more effectively.

Nitrite attacks bacteria at numerous sites by blocking metabolic enzymes, restricting oxygen absorption, and breaking the gradient of protons. Furthermore, nitric oxide binds to iron and reduces the availability of iron which is required for enzyme activity as well as bacterial metabolic activity and development Because of the strong reactivity of Fe and nitrite, heme ion centers of enzymes and Fe-sulfur complexes are the major target of nitrite. The antibacterial activity of nitrite may be due to the peroxynitrite **(ONOO)** formation and nitric oxide formation from nitrite Acid catalysis may cause oxymyoglobin to be autoxidized, generating superoxide radicals. The interaction of nitric oxide with superoxide radicals as well as the reaction of nitrite with hydrogen peroxide can produce peroxynitrite. Under physiological environments, peroxynitrite and peroxynitrous acid **(ONOOH)** stay in equilibrium. These two compounds are strong oxidants as well as nitrating agents They penetrate the bacterial cells by passive anionic diffusion and disrupt the microorganisms by causing protein and lipid oxidation or by damaging DNA Nitric oxide **(NO)** can also inhibit microbial growth by forming protein-bound dinitrosyl iron complexes when it reacts with iron-sulfur proteins, which are engaged in critical physiological activities including energy metabolism & DNA synthesis Various kinds of microorganisms have various metabolic pathways and antioxidant defense strategies, and certain microorganisms are found to be resistant to the oxidative stress of peroxynitrite and peroxynitrous acid Furthermore, the antibacterial action of nitrite in Gram-positive anaerobic bacteria has been shown to be more effective than in Gram-negative aerobic bacteria.

Most of the nitrite applied to cured meat products is used to suppress *C. botulinum*, with only a little amount **(about 25 ppm)** required for color development. Suppression of *C. botulinum* development and toxin generation rises when nitrite levels rise. The level of additional nitrite is thought to have a greater influence on inhibiting *C. botulinum* than that of the residual nitrite during storage, implying that the production of antimicrobial compounds as a consequence of nitrite-related reactions might be noteworthy. The growth of starter cultures and bacteriocin production have been shown to be inhibited when the nitrite concentration was 100 ppm in sausage **(fermented using *Lactococcus lactis*).** An estimation predicts that when the nitrite content in sausage fermented with *Lactococcus lactis* reached 100 ppm, the development of starter cultures and bacteriocin synthesis were suppressed Several other estimates suggest that pathogens including *Listeria monocytogenes*, *Staphylococcus aureus*, *Bacillus cereus* and *E. coli* grow slower in the presence of nitrite at levels found in cured meats and poultry products (75,76,77,78,79 and 80).

Health Concerns Associated with Nitrite in Meat

Despite all of sodium nitrite's benefits, its use in meat has been a bone of contention. Due to nitrite's high chemical reactivity, it can combine with a variety of components in meat systems. The heat used throughout the thermal treatment of cured meat products increases its reactivity. Particularly, nitrite ions are highly reactive when the pH is lower than 7; it may react with a variety of meat components, including amino acids, sulfhydryl, amines, phenolic compounds, ascorbic acid and myoglobin. Nitrite can play a role as a nitrosating agent and form various nitroso compounds Other nitrosating agents include nitrous acid and nitric oxide which are also derived from nitrite. Nitrous acid participates in the processes that result in the formation of endogenous N-nitroso compounds **(NOCs).** NO, on the other hand, maybe a generator of nitrates and nitrites, which circulate in the body of human Generally, N-nitroso compounds are classified into six types: non-volatile N-nitrosamines, volatile N-nitrosamines, N-nitrosated heterocyclic carboxylic products, N-nitrosamides, Amadori compounds and N-nitrosated glycosylamines The majority of volatile nitrosamines are categorized in group 2B, which means they are potentially carcinogenic to the human body The number of nitrosamines in processed meat products varies depending on the type of meat product. The quantity of N-nitrosamines in processed meat might be less than the detection limit **(one microgram per kilogram)** Furthermore, NOCs are formed when food is cooked at high temperatures or when cured meat is processed. Recent epidemiologic studies have indicated nitrate, nitrite and N-nitroso compounds as a potential risk for cancer Among the various nitroso compounds, N-nitroso dimethylamine is thought to be potentially more carcinogenic to the human body. Although nitrite is known to be associated with general health implications, no evidence has been found to support the connection between cancer risk and processed meats consumption Only high exposure to nitrites from various sources has been attributed to the elevated risk of health problems

As sodium nitrite can be a predecessor of nitrosamines, its usage in meat curing has gathered public concern. It is currently considered that the amount of nitrite added and the production of N-nitrosamines have a positive relationship but the relationship is not linear The majority of N-nitrosamines are organ-specific, implying that only certain types of them cause cancer in certain organs Furthermore, they exhibit teratogenic effects too. There are about 300 variety of nitrosamines and almost all of them **(97%)** have been demonstrated to be teratogenic in experimental animals Amines, in the form of free amino acids (proline, hydroxyproline), creatinine and creatine are present at very low concentrations in organic meat products.

The development of nitrosamines in meat products is a complicated process and it may be influenced by a wide range of factors. Nitrite, nitrate, primary and secondary amines, amides, peptides, proteins and various amino acids are the initial compounds for N.A. synthesis in meats and these are converted into N.A. **(nitrosamines)** precursors by microbial activity. Microorganisms may contribute to the formation of N.A.s by converting nitrates to nitrites and degrading proteins to amino acids and amines N-nitrosamines can develop in meat throughout the production processes, during home cooking and in the digestive tract after ingestion They are mostly generated from secondary amines, nitrite and other nitrosating agents. In cured meats, residual nitrite may combine with amines and free amino acids and yield nitrosamines under specific conditions, such as the existence of secondary amines, low pH, product temperature >130 °C and the NO_2 availability to react During the grilling or frying of cured meats, nitrosamines may occur in little amounts and are expected to cause cancer in the human body **(even with the little exposure over prolonged time)** (81,82,83,84,85 and 86).

The chemical reactions that result in the developments of nitrosamines in cured meat systems are noted below:

$$NaNO_2 + H^+ \rightarrow Na^+ + HNO_2$$
$$HNO_2 + H^+ \rightarrow NO^+ + H_2O$$
$$2HNO_2 \rightarrow N_2O_3 + H_2O$$
$$N_2O_3 \rightarrow NO + NO_2$$
$$NO + M^+ \rightarrow NO^+ + M$$
$$RNH_2 \text{ (Primary amine)} + NO^+ \rightarrow RNH\text{-}N = O + H^+ \rightarrow ROH + N_2$$
$$R_2NH \text{ (Secondary amine)} + NO^+ \rightarrow R_2N\text{-}N = O + H^+$$
$$R_3N \text{ (Tertiary amine)} + NO^+ \rightarrow \text{no nitrosamine formation.}$$

These chemical reactions exhibit the same process leading to the formation of nitric oxide and nitrous acid. As a result, the same consequences can lead to the nitrite reduction and favors the production of nitrosamine. Among the primary, secondary and tertiary amines, the secondary amines generate more persistent nitrosamines. In addition, the mixture of secondary amines and nitrite cause lung adenomas in mice. An investigation into mice treated with 0.5% sodium nitrite and 0.85% butyl urea showed the elevated occurrence of malignant lymphomas. Numerous epidemiological studies have found a link between nitrosamines **(N.A.s)** and various type of cancer risk In 2006, a working group of IARC **(International Agency for Research on Cancer)** stated that "ingested nitrite under certain conditions resulting in endogenous nitrosation is presumably carcinogenic to human body" An epidemiological study conducted in 2008 showed that there is an increased risk of colorectal cancer related to high processed meat intake Excessive nitrite intake can also result in tissue poisoning, respiratory center paralysis, and other hypoxia-related symptoms. In extreme cases, it can cause suffocation as well as death by decreasing the O_2 carrying capability of hemoglobin in human blood High nitrite consumption can impair iodine metabolism and decrease iodine absorption by the thyroid, which can result in the enlargement of the thyroid gland. Methemoglobinemia, also known as blue baby syndrome", is another health concern of high nitrite intake. It develops when nitrate is converted to reactive nitrite by reducing bacteria in the saliva or digestive system of humans. The blue baby syndrome is named after the blue color of a newborn's skin when their blood nitrite levels are high. As a result, methemoglobinemia is often known as "blue baby syndrome," and it is a life-threatening disease. When nitrite enters the bloodstream, it causes the hemoglobin **(the protein that transports oxygen in the bloodstream to the body's tissues)** to be oxidized to methemoglobin (87,88,89,90,91 and 92). This reaction produces methemoglobin which is responsible for the reduced oxygen supply to body tissues, causing the skin to become blue and possibly causing asphyxia. In the initial stages of methemoglobinemia, the blue color can be observed in the nose, lips, and ears and in extreme cases it can affect the peripheral tissues Infants under six months of age are the most sensitive to methemoglobinemia. Meanwhile, this disease has been reported in both school-going children and adults. Furthermore, decreased tissue oxygenation can have a variety of negative consequences for the children, involving coma and eventually death. The toxic amounts of nitrites responsible for methemoglobinemia range from 0.4 mg to more than 200 mg per kg of body weight. The nitrite ion limit for newborns is up to 3 ppm The U.S. Environmental Protection Agency reported contradictory evidence over the relationship between higher nitrite intake and the elevated incidence of cancer in children and adults. In certain studies, it has been found that a high intake of nitrite can lead to the elevated occurrence of leukemia, nasopharyngeal and brain tumors in some children (93,94,95,96 and 97).

Potential Alternatives to Nitrite in Processed Meat and Their Effect on Color, Flavor, Antimicrobial and Antioxidant Properties.

As nitrite is involved in the production of nitrosamines, meat industries are recently focusing on new strategies to substitute traditional $NaNO_2$ in cured meat with the aim of minimizing nitrite intake. Consumer's interest is also growing in the development of natural alternatives and other preservation methods that are comparatively healthier. Although nitrite's broad-spectrum action makes it hard to replace it with a sole antimicrobial agent, a mixture of nitrite and other antimicrobial agents might become effective Nevertheless, any improvements in terms of consumption safety should be made without compromising the distinctive features of the organic and natural processed meats, and this must be linked to the consumer's desire to purchase such foods. It is possible that a replacement for nitrite might be found and new products may be developed, but it is questionable if this might be good enough to entice people to buy. Consumers prefer meat products which contain lower nitrite levels and the decision of buying new meat products depend on the function of nitrite, their application reasons and their outcome Therefore, a successful nitrite reduction in meat products, along with the addition of several alternatives would provide a variety of benefits for the consumers, including a reduction in cancerogenic substances (98,99,100,101,102 and 103).

Organic Acids and Salts:

In meat industries, organic acids are used to prevent microbial development, decrease the p^H of meat products, and increase the curing performance of processed meats The use of organic acid to cured meat enhances the color development process while inhibiting microbiological growth. Lactate, sorbate, acetate, and benzoate are some important organic acids that have been widely used as food additives for many years. The rationale for employing organic acids is that they have the potential to lower pH to a level that prevents bacteria from proliferating (104,105,106,107 and 108)

High Hydrostatic Pressure (HHP):

Treatment with high pressure **(100–800 MPa)** is used uniformly to meat products at moderate temperature **(less than 45 °C)** as an anti-microbial process with the purpose of extending the shelf life of that product. HHP increases the meat product's shelf life by reducing the growth of pathogenic microorganisms The use of HHP also aids in the inactivation of enzymes for a greater duration of time without the use of synthetic additives. However, in order to ensure food safety and to increase the shelf life, proper application of pressure and temperature has to be set in accordance with the product's characteristics Meat processors can now satisfy the growing demand of consumers for natural and "preservative-free" meat products while retaining the stable sensory qualities over a longer storage period and ensuring product safety by processing meats using HHP (109,110,111,112,113 and 114).

Salt petre (Na nitrite or Na nitrate):

Advantages:

Color stabilizer:

Nitrate (by nitrate reducing m.o) → Nitrite (in the absence of light and oxygen) → Nitric oxide + H_2O

Nitric oxide + Myoglobin (Mb) → Nitric oxide metmyoglobin (NOMMb) → Nitric oxide myoglobin (NOMb) (unstable) by acidity or cooking → Nitric oxide haemochromagen (stable pickling pink attractive colour). **Without nitrite** meat products turn grey in color when heated.

Antibotulinum factor: nitrite + Fe found in meat which is an essential nutrient for growth and multiplication of Cl. botulinum, → inhibiting growth of Cl. botulinum and delaying the production of botulinal toxins.

Antioxidant: retard development of oxidative rancidity, off-odors and off-flavors during storage. Inhibit development of warmed-over flavor (WOF).

It preserves the flavor of spices and smoke.

It acts as flavoring agent in bacon production, (bacon is salted, cured, smoked, and canned hindquarter of pigs). If nitrite is not added to brine soln. the product is not considered bacon but considered pickle ham.

↓ temperature used → ↓ cost of the final product.

Disadvantages:

Excessive amount → hardness of meat products.

Carcinogenic agent:

Nitrite (in the presence of light and oxygen) → Nitrous acid + dimethylamine → (by cooking and high temperature of frying) nitrosamine (carcinogenic). This problem may be reduced by adding:

a- 550 ppm Na ascorbate + 120 ppm Na nitrite.

b- K sorbate c- ∞ tochopherol.

It is prohibited to be used in canned baby meat. Recommended dose of nitrite is 120 ppm in all meat products and 50 ppm in canned meat (115, 116, 117, 118, and 119).

Conclusion:

Nitrite is used as a versatile additive in the meat industry. It is liable for the pinkish-red color and unique flavor of cured meat products. It also acts as an antioxidant that prevents the development of a warmed-over flavor as well as a bacteriostatic effect that prevents the formation of botulinum toxins from Clostridium botulinum. Despite its many advantages in meat curing, sodium nitrite has been the subject of debate due to its probable carcinogenic impact on humans, according to various research. Ingesting too much nitrite can induce methemoglobinemia in children and raise the risk of developing colorectal cancer in adults. On the other hand, consumers' desire for organic or nitrite-reduced meat keeps growing. As a result, the meat industry is now focusing on finding efficient ways for minimizing residual nitrite content in meat products and safer nitrite alternatives for the preparation of organic meat products. As nitrite replacements, various plant extracts, organic acids (lactate, sorbate, etc.) and HHP can be employed efficiently in processed meats. Unfortunately, still no sole alternative for nitrite has been found that can fulfil all of nitrite's functions simultaneously. Hurdle technology using reduced levels of nitrite combined with other additives or processing techniques might have potential in producing the antimicrobial effects against the most prevalent microbial pathogens while also improving sensory characteristics. However, additional research is required to find a single alternative to nitrite that can be used to perform the nitrite broad-spectrum activities in a cost-effective way.

Conflicts of Interest:

The author declare no conflicts of interest.

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