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Do You Think that Food Preservatives Nitrate and Nitrite Cause Public Health Hazards

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ABSTRACT

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

Keywords: Cured Meat; Nitrites; Natural Alternatives; Health Concerns

Abbreviations: NO: Nitric Oxide; IARC: International Agency for Research on Cancer; ADI: Acceptable Daily Intake; JECFA: Joint Expert Committee of the Food and the Agriculture Organization; WHO: World Health Organization; WCRF: World Cancer Research Fund; AICR: American Institute for Cancer Research; Mb: Myoglobin

Introduction

Meat curing is an ancient method of the food preservation that is still widely used today. The addition of the nitrite/nitrate salt, common salt (NaCl), and spices to the fresh meat in varying degrees of comminution and at various processing phases Prior to the invention of food refrigeration, the 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 the salt preservation methods as early as 3000 B.C. Among the various additives used in the meat curing, the nitrite salt is very significant. The 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 the dye manufacturing and the food preservation. The Nitrites in various meat products types are significant preservatives and impede the growth of several unwanted micro-organisms. The Nitrite is added to the cured meat at levels less than 150 ppm to prevent the development of microbiological organisms like the *Clostridium botulinum* bacteria, which causes the food poisoning. The main reasons for using the nitrite as a preservative in the meat are: To inhibit the *Clostridium botulinum* bacteria from spreading and secreting their toxins that cause the food poisoning. To provide the necessary bright red color in the meat products like the sausage, the ham, the salami, etc. To give the cured meats the characteristic texture and the aroma. The nitrite inhibits the oxidation of the lipids in the meat products and so prevents the rancidity (off flavor) [1-6].

Since the middle of the 1980s, research has been revealed that the nitrite is a major chemical with the substantial actions on the human health. The Vegetables are a great source of dietary nitrates, and they have been proven to be an important source of the endogenous nitrite as well as the nitric oxide (NO) in the human body. Nitric ox-

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ide (NO), produced through enzymatic synthesis, regulates the blood pressure, wound healing, immunological response and the neurological processes in the human body. New study has demonstrated that NO (nitric oxide) regulates blood circulation in the cardiac tissues and perhaps in other body tissues. The regular nitric oxide and nitrite production may help to prevent cardiovascular diseases like the hypertension, atherosclerosis, and stroke. The High nitrite concentrations, on the other hand, are extremely dangerous for infants since they can develop an infant's methemoglobinemia. The cancer-causing nitrosamines are formed when the nitrite reacts with the secondary or tertiary amines. The International Agency for Research on Cancer (IARC) stated the processed meat as carcinogenic by evaluating sufficient epidemiological data.

The IARC reported that the ingested nitrite from the processed meat can lead to colorectal cancer in the human. Due to the harmful effects, many countries in the world have severely restricted their use on processed food products types. The toxicity of the 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. The Long-term intake of increasing amounts of the red meat, especially the processed meat, is linked to a higher rate of the mortality, colorectal cancer, type-2 diabetes and heart diseases in both male and female, according to the large prospective United States, E.U. cohort studies as well as the meta-analyses of epidemiology. Concerning these items, 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 the Agriculture Organization (JECFA) and the World Health Organization (WHO) that appears to be safe for the healthy newborns, children, and adults [7-12].

The World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) published research in 2007 that found a moderate but the significant link between increasing consumption of the processed meat and a higher risk of the colorectal cancer. The specialists advised limiting red and processed meat consumption. The 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). The proactively in the processing of healthier meat products types rather than anticipating the processed meat consumption to fall [13-18]. Because of the growing concerns regarding the sodium nitrite's long-term adverse effects, their use in the cured meat products types is strictly regulated among most developed countries. The new ideas of all-natural and clean label have raised a demand for healthy and high-quality meat products types. Due to the health hazards, consumers choose natural additives over chemicals in the processed meat. As a result, research on substituting the natural ingredients for the chemical additive nitrite has grown over the years [19-24].

To reduce the risk of nitrosamine formation and mitigate potential human health hazards, researchers are trying to find effective ways in meat curing. The replacement of the nitrite salt with alternative ingredients that have similar properties while posing no health risk. No single alternative that provides the multi-functions of nitrite in meat products types has yet been found. The employment of "hurdle technology" in the meat curing is one proposed solution to this issue where low amounts of the nitrite are mixed with other ingredients. The aim of this present study is to review the role of the nitrite in cured meat products types, the adverse health effects of higher nitrite intake as well as to give an overview of the available knowledge on potential replacements to the nitrite salt in the processed meat either whole or partially [25-30].

Sources of the Nitrite

The Nitrites play a vital role in the biogeochemical cycle of nitrogen in natural water. The Nitrites can be found in soils, waterways, foodstuffs, plants, air (as nitrogen dioxide), and biological samples. In the biological nitrogen cycle, nitrogen is converted to the nitrate by bacteria, which is taken by plants and incorporated into tissues Animals that consume plants utilize nitrate to produce proteins. The animal excrement and the microbial breakdown of the animals and plants after death return nitrate to the environment. The Nitrate or the ammonium ion can be converted to nitrite by the 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 [31-36].

Function of the Nitrite in Cured Meats

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

$$NO_2- \ + H^+ \leftrightarrow \ HNO_2$$

$$2HNO_2 \leftrightarrow N_2O_3 + H_2O$$

$$N_2O_3 \leftrightarrow NO \ + \ NO_2$$

The nitrite reacts with hydrogen ions (H+) of the water to produce the nitrous acid. After that, the nitrous acid progressively decomposes into water molecules (H_2O) and the dinitrogen-trioxide. Then, nitric oxide and the nitrogen dioxide are generated from dinitrogen trioxide (N_2O_3). The major component responsible for nitrite's apparent function in the cured meat products types is nitric oxide. The 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. The myoglobin may react with HNO_2.

The Myoglobin (Fe^{2+}) combines with nitrous acid and forms metmyoglobin (Fe^{3+}) by oxidation. The Metmyoglobin (Fe^{3+}) then reacts with NO to produce NO-metmyoglobin. The NO-metmyoglobin is produced from the reduction of metmyoglobin. 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 [28-30,37-39]. The presence of other additives in cured meats affects the color development. The Antioxidants including erythorbate, ascorbic acid and polyphenols stimulate the production of NO by allowing the $N2O_3$ reduction. The Ascorbic acid reduces Fe3+ to Fe2+ 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. The NaCl, generally added to meat for curing, reacts with HNO_2 to generate nitrosyl chloride, which is more sensitive than $N2O_3$ in terms of the 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 controls nitric oxide formation from the nitrite.

The Nitrous acid (HNO_2) and the 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 [40-45]. A very small quantity of the nitrite is required for the development of the cured color in meats, usually approximately 2–14 ppm. 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 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 regenerationOn the other side, higher levels of sodium nitrite (>600 ppm/kg of meat) and low pH value may lead to the nitrite burn (discoloration) where the meat reveals a green color due to the formation of nitrihemin, a green-brown pigment [46-51].

The Cured Flavour Development

The Flavor is the combination of numerous qualities including the odor, the fragrance, the taste, the texture and the temperature of the meat that influences the perception of the consumer Although it is recognized that the 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 types by suppressing "warmed-over" flavor. The 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. The cured meat has low levels of carbonyl compounds, including 2-heptanone, 3-hexanone, 2-nonenal, and 2-octanal Thus, the nitrite has been demonstrated to simplify the flavor spectrum. The use of the nitrite does not affect the synthesis of specific flavor compounds, but it inhibits the formation of the aldehydes (hexanal), masking the sulfur-containing chemicals that give cured meat its flavor. The Nitrite, on the other hand, has been revealed to cause the production of the Strecker aldehydes. Strecker aldehydes are generated when the amino acids are degraded by dicarbonyl produced through Maillard reactions and these aldehydes are linked to meat flavor formation after adding the nitrite to fermented sausages, the production of Strecker aldehydes increases. This might be due to an increase in carbonyl molecules, which can combine with the amino acids to create Strecker aldehydes due to the pro-oxidant action of the nitrite [52-57].

In the cured meats, less than 1/2 of the overall volatile chemicals, generally found in the 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. The S-nitroso thiol production and disulfide bond breakdown during meat curing is likely to cause increases in sulfur compounds. The antioxidant effect of the nitrite explains why oxidation products, such as hexanal, are reduced in the cured meats. More studies is needed to completely understand the mechanism, reactions and the volatile compounds responsible for the aroma and flavor of cured meat. Sensorial research s reveals that cured meat flavor is not only an outcome of the retardation of lipid oxidation but 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 the nitrite and Nitrite related flavor development [58-63].

The Antioxidant Properties against Lipid and Protein Oxidation

Another notable characteristic of the nitrite is that it can prevent rancidity during storage and the formation of "warmed-over" flavors when meat products types 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. It produces and accumulates chemicals that might endanger consumers' health Oxygen is a significant factor influencing the lipid oxidation in the meat. It interacts with the unsaturated lipids of meat to generate the lipid peroxides which include oxygen absorption as well as double bond reformation the

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production of lipid peroxides ultimately leads to the formation of a variety of chemical components such as the aldehydes, the alcohols and the ketones. The Nitrite acts as an antioxidant by protecting the lipid molecules of meat from oxidation. In the cured meats types, nitrite works as an antioxidant through different mechanisms. The Nitrite serves as a chelating agent of metallic ions (main prooxidants in meats) and it stabilizes the heme, Fe. The nitric oxide, produced from the nitrite, may be readily converted to NO_2 by reacting with oxygen.

The Nitric oxide 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, the lipid radicals are continually oxidized through radical chain reactions. The Nitrite can inhibit the lipid oxidation initiation by reacting with ROS (reactive oxygen species), such as the hydroxyl radicals. The Nitric oxide (NO) can inhibit lipid oxidation by combining with the lipid peroxyl radicals and produce non-radical molecules. The Nitrite has been revealed 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 types [64-68]. The Proteins, in addition to lipids, are oxidized during the preparation of meat. 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 types 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 revealed to have both antioxidant and pro-oxidant properties in meat products types. As evidenced by the decreased generation of carbonyl compounds, sodium nitrite exhibits an antioxidant property towards protein oxidation. The nitrite was 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 [69-74].

The Antimicrobial Effect

The 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 types. The Nitrite has been revealed to impede the reproduction of the *Clostridium botulinum* bacteria. The application of nitrite has been revealed to inhibit the formation of the botulinal toxins from the inoculated *Clostridium botulinum* bacteria in wiener sausages during storage. There are two effects of nitrite found in controlling the growth of *Clostridium botulinum* bacteria. 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 bacteria, which have comparable characteristics to the *Clostridium botulinum* bacteria. The nitrite inhibits the development of the Listeria monocytogenes, Bacillus cereus, Clostridium perfringens and Staphylococcus aureus bacteria in various meat products types. The action of nitrite and inhibitory mechanisms varies with several bacterial species The effectiveness of the antimicrobial activity is dependent on various factors like pH, residual nitrite level, salt concentration, Fe content, reductants presence, storage temperature, etc. At the acidic pH, nitrite hinders the growth of unwanted microorganisms more effectively.

The Nitrite attacks bacteria at numerous sites by blocking metabolic enzymes, restricting oxygen absorption, and breaking the gradient of protons. The nitric oxide binds to the iron and reduces the availability of iron which is required for enzyme activity as well as the 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 the 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 inhibit microbial growth by forming the 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. The antibacterial action of nitrite in Gram-positive anaerobic bacteria has been revealed to be more effective than in the Gram-negative aerobic bacteria. The Most of the nitrite applied to the

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cured meat products types is used to suppress *C. botulinum* bacteria, with only a little amount (about 25 ppm) required for color development. The Suppression of *C. botulinum* bacteria development and toxin generation rises when the nitrite levels rise.

The level of additional nitrite is thought to have a greater influence on inhibiting *C. botulinum* bacteria 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 revealed 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 bacteria 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 bacteria grow slower in the presence of nitrite at levels found in cured meats and poultry products [75-80].

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 types 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. The 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 derived from nitrite. The 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 types.

The quantity of N-nitrosamines in processed meat might be less than the detection limit (one microgram per kilogram) The 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 the 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. The sodium nitrite 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 some types of them cause cancer in different organs. 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), the creatinine and the creatine are present at very low concentrations in the organic meat products types.

The development of nitrosamines in meat products types is a complicated process and it may be influenced by a wide range of factors. The 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. The 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 generated from secondary amines, nitrite and other nitrosating agents. In the 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) [81-86].

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

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

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

$$2HNO_2 \rightarrow N_2O_3 + H_2O$$

$$N_2O_3 \rightarrow NO + NO_2$$

$$NO + M_+ \rightarrow NO_+ + M$$

$$RNH_2\left(Primary\ amine\right) + NO^+ \rightarrow RNH - N = O + H^+ \rightarrow ROH + N_2$$

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

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

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 the 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 revealed the elevated occurrence of the malignant lymphomas. The epidemiological studies found 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 revealed that there is an increased risk of colorectal cancer related to high processed meat intake Excessive nitrite intake can result in tissue poisoning, respiratory center paralysis, and other hypoxia-related symptoms. It can cause suffocation as well as death by decreasing the O_2 carrying capability of hemoglobin in the 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. The Methemoglobinemia, 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. The 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 [87-92]. 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 The Infants under half year of age are the most sensitive to the methemoglobinemia. The disease has been reported in both school-going children and adults. The 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 the methemoglobinemia range from 0.4 mg to over 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 the 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 [93-97].

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

The 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 the nitrite intake. The Consumer's interest is growing in the development of natural alternatives and other preservation methods that are comparatively healthier. The nitrite is broad-spectrum action makes it hard to replace it with a sole antimicrobial agent, a mixture of the 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 the 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 types which contain lower the nitrite levels and the decision of buying new meat products types depend on the function of the nitrite, their application reasons and their outcome Therefore, a successful nitrite reduction in meat products types, along with the addition of several alternatives would provide a variety of benefits for the consumers, including a reduction in cancerogenic substances [98-103].

The Organic Acids and Salts

In the meat industries, the organic acids are used to prevent microbial development, decrease the pH of meat products types, and increase the curing performance of processed meats. The use of the organic acid to the cured meat enhances the color development process while inhibiting the microbiological growth. The 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 [104-108].

High Hydrostatic Pressure (HHP)

Treatment with high pressure (100–800 MPa) is used uniformly to meat products types 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 the pathogenic microorganisms. The use of HHP aids in the inactivation of enzymes for a greater duration of time without the use of synthetic additives. 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 the consumers for the natural and "preservative-free" meat products types while retaining the stable sensory qualities over a longer storage period and ensuring product safety by processing meats using HHP [109-114].

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 types turn grey in color when heated.

The Antibotulinum Factor: nitrite + Fe found in meat which is an essential nutrient for growth and multiplication of Cl. botulinum bacteria, → inhibiting growth of *Cl. botulinum* bacteria 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 the nitrite is not added to brine soln. the product is not considered bacon but considered pickle ham.
- ↓ temperature used → ↓ cost of the final product.

The Disadvantages

Excessive amount → hardness of meat products types.

The Carcinogenic Agent: The 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. The recommended dose of the nitrite is 120 ppm in all meat products types and 50 ppm in canned meat [115-119].

Conclusion

The Nitrite is used as a versatile additive in the meat industry. The Nitrite is liable for the pinkish-red color and the unique flavor of cured meat products types. The Nitrite 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 the *Clostridium botulinum* bacteria. Despite the Nitrite many advantages in the meat curing, the sodium nitrite has been the subject of debate due to the Nitrite probable carcinogenic action 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. The consumers' desire for the organic or nitrite-reduced meat keeps growing. The meat industry is now focusing on finding the efficient ways for minimizing the residual nitrite content in the meat products types and safer nitrite alternatives for the preparation of the organic meat products types.

The nitrite replacements, various plant extracts, the organic acids (lactate, sorbate, etc.) and HHP can be employed efficiently in the processed meats types. Unfortunately, still now no sole alternative for the nitrite has been found that can fulfil all of the nitrite's functions simultaneously. Hurdle technology using reduced levels of the nitrite combined with other additives or processing techniques might have potential in producing the antimicrobial effects against the most prevalent microbial pathogens while improving sensory characteristics. Additional study is required to find a single alternative to the nitrite that can be used to perform the nitrite broad-spectrum activities in a cost-effective way.

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