

# ***Sodium Nitrite in Processed Meat and Poultry Meats: A Review of Curing and Examining the Risk/Benefit of Its Use***

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# *Sodium Nitrite in Processed Meat and Poultry Meats: A Review of Curing and Examining the Risk/Benefit of Its Use*

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## **Introduction**

Meat and poultry curing is one of the oldest forms of food preservation still in use today. Before the advent of refrigeration, fish and meat were preserved by methods found effective to control spoilage after animal harvest and to extend food supplies during times of scarcity. Although lost in antiquity, the curing process for meats is believed to have derived from preservation methods with salt as early as 3,000 B.C. (Romans et al., 2001). Over time, the realization that salt contaminated with saltpeter (potassium nitrate) was responsible for curing, would unknowingly provide the basis for the beginnings of unraveling the mystery of curing.

With the development of refrigeration and food packaging technologies, the original purpose of curing highly perishable foods for preservation purposes has been widely replaced with creating convenience and variety for consumers (Pegg, 2004). The meat and poultry industry has greatly benefited from the use of sodium nitrite by allowing for the production of products with improved food safety and an extended shelf-life with excellent storage stability (Pegg and Shahidi, 2000). In fact, many of today's processed meat products that are most enjoyed by

consumers contain sodium nitrite. Sodium nitrite allows for the existence of meat and poultry products with unique colors, textures, and flavors which cannot be recreated by any other ingredient (Sebranek, 1979).

The use of sodium nitrite for curing, however, has not been without controversy. Due to a strong debate in the 1970s surrounding certain nitroso compounds with potential to yield carcinogenic nitrosamines, the use of nitrite for curing was nearly banned (Cassens, 1990, 1997a). As a result, several steps were taken by both industry and government to significantly reduce the risk of nitrosamine formation and alleviate potential human health concerns. Since that time, health concerns involving risks related to cancer and leukemia, believed to be directly related to the consumption of nitrite cured meat and poultry products, have periodically resurfaced. Each of these occurrences has been addressed scientifically reassuring the public of the safety of nitrite usage in cured meats.

Research conducted since the mid-1980s has suggested that nitrite is a significant molecule important for human health. New scientific discoveries are now providing a better understanding of the profound and important roles nitrite plays in normal body functions. Dietary nitrates from vegetable consumption, for example, have been shown to serve as significant sources for the endogenous production of nitrite and nitric oxide in the human body. As a product of enzymatic synthesis in humans, nitric oxide controls blood pressure, immune response, wound repair, and neurological functions (Hunault et al., 2009). Recent research has clearly shown that nitric oxide can be produced directly from nitrite and is involved in controlling blood flow in cardiac muscle and potentially other tissues (Bryan et al., 2007; Bryan and Hord, 2010). Further, the normal production of nitric oxide and nitrite may prevent various types of cardiovascular disease including hypertension, atherosclerosis, and stroke (Bryan et al., 2007; Hunault et al., 2009).

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## Product-Related Benefits of Curing with Nitrite

Nitrite is considered an essential curing ingredient responsible for 'fixing' the characteristic color associated with cured meats, creating a unique flavor profile that is distinguishable from products not containing nitrite, providing control of the oxidation of lipids, and serving as an effective antimicrobial by itself or synergistically with other ingredients (Sebranek and Fox, 1985; Townsend and Olson, 1987; Pegg, 2004). Nitrate, also considered a curing ingredient, is only effective in the same manner as nitrite if first reduced to nitrite. This reduction can be accomplished by either naturally present bacteria on the meat or by the addition of bacteria possessing nitrate reductase activity (Gray et al., 1981; Sebranek and Bacus, 2007). Although used very little today, nitrate is still included in products, such as dry sausages and dry-cured hams, where an extended maturing process necessitates a long term reservoir of nitrite. More recently, nitrate reduction is a common mode of action for indirect curing of "Natural" and "Organic" processed meats made specifically to simulate the typical curing process. For the remainder of this review, we will consider nitrite (and not nitrate) the true curing ingredient.

Tracing back to the origins of curing, the exact discovery of saltpeter (potassium nitrate) may never be known but is generally accepted to be associated with the inadvertent contamination of salt used for the sole purpose of meat preservation centuries ago. As the use of preservation practices resulting in meat with a 'fixed' red color and a unique flavor increased, the practice of treating meat with salt, saltpeter, and smoke became more commonplace (Pegg and Shahidi, 2000). Late in the 19th century and early in the 20th century, classical discoveries about meat curing were made by pioneering scientists E. Polenske, J. Haldane, K. Kisskalt, R. Hoagland, and K. B. Lehman. These scientists were able to create the foundational understanding of curing ingredients in that nitrite, and not nitrate, was responsible for meat curing (Cassens, 1990).

From the time of discovering nitrate and nitrite, maximizing the benefits these unique ingredients offer while adding them at sufficient levels to still achieve the functional benefits of adding them to meat and poultry products have both changed and stayed the same over time. Upon the discovery of curing compounds, sausage and cured meat products that were once heavily spiced and cured for preservation reasons were slowly being refined to meet flavor characteristics that were deemed desirable by consumers (Cervený, 1980). Unknowingly, these compounds allowed for the emergence of early ready-to-eat type meat products. By using significantly less salt and/or other preservation methods due to the introduction and incorporation of nitrate or nitrite, meat and poultry products began to move from a state of unsatisfactory quality and poor shelf-life to improved quality and longer shelf life. As meat curing has evolved, it has changed from an inexact art to a sophisticated science. Decades

of research have been performed to better understand the quality and safety improvement observations that were made centuries ago. Due to the complexity of curing and curing related reactions, this research continues today. Nitrite is considered a fascinating, remarkable, irreplaceable, and yet not clearly understood ingredient which imparts distinctive properties common to all, and yet only, cured meat products. Also of interest are the clear benefits of using nitrite from both a microbiological as well as a qualitative standpoint.

### Quality Impact from Curing

**Color.** The fixation of a desirable red color, shaded pink, is the most obvious effect from nitrite addition and is often considered an extremely important attribute for consumer acceptance (Cornforth and Jayasingh, 2004). Interestingly, very little nitrite is needed to induce a cured color. It has been reported that as little as 2 to 14 parts per million (ppm), depending on species, is necessary to induce a cured color. However, significantly higher levels are required to prevent rapid fading and non-uniform curing while also maintaining cured color throughout an extended shelf life (Sebranek and Bacus, 2007). Investigating the consumer acceptance of hams manufactured with varying levels of nitrite (0, 25, 75, and 125 ppm), DuBose et al. (1981) reported that no significant ( $P > 0.05$ ) differences existed for color among the 25, 75, and 125 ppm nitrite containing samples while all were found different ( $P < 0.05$ ) than the sample containing 0 ppm nitrite. A similar study conducted by Hustad et al. (1973) reported the only differences found between wieners having varying levels of nitrite (0, 50, 100, 150, 200, and 300 ppm) were when comparisons were made to the 0 ppm added nitrite treatment. Sebranek et al. (1977) investigating the consumer acceptance of frankfurters cured with varying levels (0, 26, 52, and 156 ppm) of nitrite found frankfurters containing 156 ppm nitrite to be more acceptable ( $P < 0.05$ ) for color, flavor, and overall acceptability than all other nitrite concentrations. The researchers concluded that nitrite concentration was of critical importance for consumer acceptance of products possessing cured meat characteristics. The aforementioned research are examples of the extensive research studies that supported that minimum levels between 25 and 50 ppm of nitrite were likely sufficient for acceptable cured meat color in most meat and poultry products. However, higher levels would be necessary to achieve and maintain acceptable cured meat color, especially during a long product shelf-life period.

When nitrite is added to meat systems, it reacts with or binds to a number of chemical components such as protein (Cassens, 1997b). Much of the nitrite added during the product manufacturing is either depleted through a series of reactions or physically lost during certain manufacturing steps. Typically, between 10 and 20 percent of the originally added nitrite normally remains after the manufacturing process and those levels

continue to decline during storage (Pérez-Rodríguez et al., 1996; Cassens, 1997b). These levels of nitrite, referred to as residual nitrite, slowly decline over the storage life of cured meat products until they are often nondetectable (Skjelkvåle and Tjaberg, 1974; Eakes and Blumer, 1975; Honikel, 2004). To maintain a cured meat color throughout extended shelf-life, it is generally accepted that a small amount (10–15 ppm) of residual nitrite is needed to serve as a reservoir for the re-generation of cured meat pigment lost from oxidation and light-induced fading (Houser et al., 2005). Color chemistry has been one of the most studied and well understood aspects of nitrite usage and a number of investigations exploring detailed cured meat color chemistry reactions have been reviewed owing to the depth of our current understanding (Sebranek and Fox, 1985; Townsend and Olson, 1987; Pegg and Shahidi, 2000; Sebranek, 2009). The complexity of these reactions, however, underscores what is still not yet known about nitrite chemistry. Many factors contribute to the impressive complexity of this pale yellow crystalline substance. It is well accepted that the production of nitric oxide from nitrite is a required step for cured color. The highly reactive ion, nitrite, itself does not fix the pigment causing cured meat color. Rather, it forms nitrosylating agents by several different mechanisms which then have the ability to transfer nitric oxide that subsequently reacts with myoglobin to produce cured meat color. Further, several significant factors affect the many nitrite curing reactions including meat system pH, the amount of reductants present, temperature, and time (Sebranek, 2009).

**Flavor.** Cured meat flavor associated with nitrite was first described by Brooks et al. (1940) comparing pork cured in brines containing different levels of nitrate and nitrite. The role nitrite has on meat flavor is a complex stimulus involving properties such as aroma/odor, texture, taste, and temperature (Gray et al., 1981). Nitrite chemistry and the associated reactions likely play a role in imparting the unique flavor resulting from the addition of nitrite; however, the specific compounds involved have eluded scientists and are still not yet known. Cured meat flavor continues to be one of the least understood aspects of nitrite curing and can be described as ‘at best obscure’ (MacDonald et al., 1980b). Although clear differences exist between the cured and uncured versions of the same product (e.g., cured ham vs. fresh ham), little is known about what, specifically, is responsible for these differences. A proposed reason for cured flavor differences between products containing nitrite and those without is due to the nitrite-related suppression of oxidation products; thus controlling rancid flavor compound development (Shahidi, 1998). However, other commonly used antioxidants do not show this same effect. A comparison of salami with and without nitrite by Skjelkvåle and Tjaberg (1974) reported no sensory differences existed between nitrite and non-nitrite containing fermented sausages until after 3 months of storage when the nitrite containing sausage was scored

higher. This research supports the fat oxidation impact of nitrite on cured flavor. Noel et al. (1990), investigating the flavor of cured vs. uncured fermented dry sausages, also found a significant flavor improvement when nitrite was included in the product formulation. Although the reason for the flavor differences was not understood, the authors concluded their results illustrated the extremely important role sodium nitrite plays for specific flavor notes found in cured meats.

In sensory studies, consumer panelists were able to differentiate between samples manufactured with different levels of nitrite (10 or 20 vs. 156 or 200 ppm) (Gray et al., 1981). Examining the importance of nitrite for the development of cured ham aroma and flavor, MacDonald et al. (1980b) found a greater ( $P < 0.05$ ) cured meat flavor in ham containing nitrite compared to ham only containing salt. In addition, nitrite levels as low as 50 ppm was found to be sufficient to induce meat flavor differences as identified by consumer sensory evaluations. Acceptable cured flavor development at lower levels was supported in work by Brown et al. (1974) who found that flavor scores from consumer sensory panelists were not different ( $P > 0.05$ ) between samples containing 91 or 182 ppm of nitrite. Noel et al. (1990), concluded nitrite plays an extremely important role in the development of specific flavor notes as supported by sensory analysis. Cho and Bratzler (1970) demonstrated that cured flavor could be distinguished ( $P < 0.05$ ) in pork longissimus dorsi containing nitrite over those without nitrite using a consumer triangle sensory test. Dethmers and Rock (1975) stated the addition of nitrite above 50 ppm in thuringer sausage reduced off-flavor development and improved the flavor quality, whereas treatments with no added nitrite were considered to be the most rancid and had the poorest flavor quality ( $P < 0.05$ ). Investigating the role of nitrite addition in ham, Froehlich et al. (1983) reported a significant ( $P < 0.05$ ) improvement in trained sensory cured meat flavor intensity scores as ingoing nitrite levels increased from 0, 50, and 100 ppm.

As illustrated, much research has been conducted to better understand the impact that nitrite has on the unique flavor development and characteristics of cured meats. While it is relatively easy to determine consumer acceptance between products with no, extremely low, and normal amounts of nitrite for cooked ham from pork (Froehlich et al., 1983), the chemical identity of cured flavor still remains unknown. Several studies have investigated flavor compounds that may be unique to cured meats with limited success (Ramarathnam et al., 1991a,b, 1993a,b; Shahidi, 1998; Olesen et al., 2004). Through this extensive work, hundreds of compounds have been thus far identified including hydrocarbons, alcohols, ketones, furans, pyrazines, and sulfur- and nitrogen containing heterocycles. Pegg and Shahidi (2000) identified an astonishing 135 volatile compounds in nitrite-cured ham. Although a few of these compounds



may play a role in cured flavor, no definitive confirmation of this currently exists.

Sensory research suggests that cured flavor is not solely a result of retarding lipid oxidation but a combination of a complex cured aroma and flavor in cooperation with a lack of rancid flavors. It is thus possible that a combined effect from the suppression of lipid oxidation by nitrite and the development of nitrite-related flavor, through yet unknown reactions, is responsible for the development of cured meat flavor. If nitrite does form volatile flavor compounds, this premise would suggest an unknown mechanism of nitrite or nitric oxide reactions may exist.

**Lipid Oxidation.** One of the most noteworthy properties of nitrite is its ability to effectively delay the development of oxidative rancidity. This prevention occurs even in the presence of salt, which is a strong oxidant. Lipid oxidation is considered to be a major reason for the deterioration of quality in meat and poultry products which often results in the development of rancidity and subsequent warmed over flavors (Yun et al., 1987; Vasavada and Cornforth, 2005). The rate and degree of lipid oxidation is related to the levels of unsaturated fats present as well as temperature, time, oxygen exposure, the removal of oxygen, and the addition of antioxidants and/or reducing agents (Shahidi, 1998).

The antioxidant effect of nitrite is likely due to the same mechanisms responsible for cured color development involving reactions with heme proteins and metal ions, chelating of free radicals by nitric oxide, and the formation of nitroso- and nitrosyl compounds having antioxidant properties (Sebranek, 2009). The antioxidant effect of nitrite has been well documented (Townsend and Olson, 1987; Pearson and Gillett, 1996; Pegg and Shahidi, 2000; Honikel, 2004). Nitrite has been shown to inhibit warmed over flavor development at relatively low levels. Sato and Hegarty (1971) reported significant inhibition of warmed over flavor development at a 50 ppm nitrite level with complete inhibition at a 220 ppm level. Investigating the effect of nitrite on lipid oxidation in various muscle systems, Morrissey and Tichivangana (1985) reported as little as 20 ppm nitrite was sufficient to significantly ( $P < 0.01$ ) inhibit oxidation of lipid in fish, chicken, pork, and beef systems. These researchers also reported that 50 ppm ingoing nitrite provided a significant ( $P < 0.001$ ) reduction whereas a 200 ppm ingoing level caused a 12-fold reduction in thiobarbituric acid (TBA) values for chicken, pork, and beef suggesting complete inhibition occurred. Fooladi et al. (1979) reported a protective effect against warmed over flavor in cooked, nitrite containing (156 ppm) beef, pork, and chicken compared to samples not containing nitrite. MacDonald et al. (1980a) studied the antioxidant behavior of different levels of nitrite (50, 200, and 500 ppm), butylated hydroxytoluene (BHT) and citric acid, and showed a significant reduction in TBA values when treated with any level of nitrite when compared to a non-nitrite treatment. Of particular interest was the observation that neither BHT nor citric acid was

as effective in controlling lipid oxidation when compared to the lowest concentration (50 ppm) of ingoing nitrite. In studying the feasibility of replacing nitrite with sorbate in mortadella, Al-Shuibi and Al-Abdullah (2002) also showed that antioxidant effect of nitrite is present at low levels (40 ppm). Because nitrite is highly effective as an antioxidant, the United States Department of Agriculture (USDA), prohibits the use of synthetic antioxidants in a majority of products already containing nitrite. One exception to this ruling is for dry and semidry sausages where long, slow drying conditions during product manufacture would necessitate additional fat oxidation protection.

### **Safety Impact from Curing**

Another important function of nitrite is the role it plays as a bacteriostatic and bacteriocidal agent. Although not well understood, nitrite has been shown to have varying degrees of effectiveness on either preventing or controlling the growth of certain bacteria. A recent risk-benefit review of nitrite included a discussion of the antibacterial benefits of nitrite in cured meat products (Milkowski et al., 2010). Generally considered to be more effective against gram-positive bacteria, nitrite has been shown to contribute in controlling growth of pathogenic bacteria. Bauermann (1979) concluded in a study comparing the coliform levels in poultry products with and without nitrite that sodium nitrite does provide improved bacterial shelf-life. Bang et al. (2007) also reported a nitrite-coliform control phenomenon when nitrite was present. Buchanan and Solberg (1972) found a bacteriostatic action of nitrite on *Staphylococcus aureus* and suggested their results provided evidence that *S. aureus* may be effectively controlled with 200 ppm of nitrite. However, other researchers have reported conflicting results as Bayne and Michener (1975) reported no effect on the control of *Staphylococcus*, *Salmonella*, or naturally occurring spoilage bacteria present in frankfurters whether or not nitrite was included.

The inhibitory mechanism which results in the effects nitrite has on some bacteria likely differs among bacterial species (Tompkin, 2005). For example, nitrite is not generally considered to be effective for controlling gram-negative enteric pathogens such as *Salmonella* and *Escherichia coli* (Tompkin, 2005). Even though the specific inhibitory mechanisms of nitrite are not well known, its effectiveness as an antimicrobial is dependent on several factors including residual nitrite level, pH, salt concentration, reductants present, iron content, and others (Tompkin, 2005). As an example, nitrite inhibits bacteria more effectively at low pH (Roberts, 1975; Allaker et al., 2001). Further, the means of antimicrobial action of nitrite is likely attributed to reactions associated with the generation of nitric oxide or nitrous acid. The tolerance of nitric oxide by bacteria varies from acting as a metabolite for some to being toxic for others (Møller and Skibsted, 2002). The presence of nitrous acid has also been suggested to contribute to the antibacterial impact

of nitrite. Therefore, it is likely that nitrite reactions related to the development of cured meat color are related to and important for the antimicrobial properties attributed to nitrite

Before 2000, *Clostridium botulinum* was the most widely recognized bacteria associated with the antimicrobial impact from nitrite addition. The properties of curing with nitrite that also make it an effective antibotulinal compound are dependent on interactions of nitrite with several other factors. Those factors include salt, pH, heat treatment, spore level, ingoing nitrite level during manufacture, and residual nitrite levels in the meat (Roberts and Gibson, 1986). The nature of the competing flora, available iron in the product, and other present additives such as ascorbate, erythorbate, phosphate are other additional factors (Roberts and Gibson, 1986). The antibotulinal effects of nitrite on *C. botulinum* in thermally processed meat product systems takes place at two different stages in the life cycle of the microorganism. The first *C. botulinum* controlling effect of nitrite is the inhibition of vegetative cells emerging from surviving spores. The second controlling effect is preventing cell division in any vegetative cells that do emerge from surviving spores (Pierson and Smooth, 1982).

Less nitrite is needed to provide for color development than to control bacteria (Roberts, 1975). The main portion of nitrite added to cured meats is for *C. botulinum* control whereas only a small portion (roughly 25 ppm or less) is needed for color development (Sofos et al., 1979a). However, as nitrite levels increase, control of *C. botulinum* growth and toxin production also increases (Sofos et al., 1979a). The level of ingoing nitrite is believed to have more impact than the residual level during storage in providing inhibitory control of *C. botulinum* which suggests the formation of antibacterial compounds as a result of nitrite related reactions may be significant (Hustad et al., 1973).

Over the last 20 years, a greater appreciation for the contribution nitrite has in protecting from other food-borne pathogens has developed. Models developed to predict bacterial growth of pathogens such as *Listeria monocytogenes*, show improved effectiveness of antimicrobials like sodium lactate and sodium diacetate in the presence of nitrite (Schlyter et al., 1993; Duffy et al., 1994; Buchanan et al., 1997; McClure et al., 1997; Seman et al., 2002; Gill and Holley, 2003; Legan et al., 2004; USDA, 2006) These estimations predict that growth rates of pathogens such as *L. monocytogenes*, *E. coli* O157:H7, *S. aureus*, and *Bacillus cereus* are reduced in the presence of nitrite at levels used in cured meat and poultry products (Milkowski et al., 2010).

The complete understanding of the chemistry of nitrite related to cured meat color and flavor, retarding of fat oxidation, and antimicrobial action still remains elusive. After decades of research, only a partial understanding of the mechanisms related to the unique nitrite-related properties exist. It is clear that this highly reactive compound, having the capacity to act as an oxidizing,

reducing, or nitrosating agent and with the ability of being converted to a number of active compounds including nitric oxide, nitrous acid and nitrate, is an important and yet irreplaceable ingredient.

## Nitrate and Nitrite Use in Foods

The use of nitrites to preserve and cure meats evolved centuries ago (Cassens, 1995). Before the discovery of refrigeration, fish and meat were preserved by methods effective for controlling spoilage well past animal harvesting and immediate consumption or to also extend food supplies for a significant period of time. Drying to decrease water activity, smoking, salting, marinating, or pickling foods were commonly used methods of preservation (Pegg and Shahidi, 2000). Modern day curing technologies can still be directly related to early salting procedures.

The exact historical origin of meat curing is unknown but is believed to have been discovered by accident. It is understood and well accepted that impurities in natural salt led to the discovery of modern day meat curing (Pierson and Smooth, 1982; Townsend and Olson, 1987; Pearson and Gillett, 1996). The history of meat processing refers to several accounts of the contamination of salt with saltpeter (potassium nitrate) resulting in a stable red color in the meat (Cassens, 1990). It is unclear whether the saltpeter-cured characteristics were deemed desirable before the 10th century, but during and after the 10th century, the Romans were intentionally adding saltpeter to meat to obtain the desired red color and distinctive flavor. It was not until the 19th century that several scientific investigations to better understand the curing process were prompted by a discovery that pure salt (sodium chloride) did not produce a "cured color" (Pierson and Smooth, 1982).

In the early 1900s, the benefits of meat curing were recognized by the meat industry resulting in broader use of the practice. But with increased use, unsatisfactory and irregular curing was commonplace and was likely associated with the use of both nitrite and nitrate together. Recognizing the potential of "unfit" or unwholesome foods being produced if excessively high levels of nitrate and/or nitrite were used, the USDA Bureau of Animal Industry swiftly facilitated a series of experiments to better understand the formulation level/safety relationship (Binkerd and Kolari, 1975). From these experiments, the following conclusions were made:

- 1) From one-fourth to 1 oz. of sodium nitrite is sufficient to fix the color in 100 lb, the exact quantity depending on the meat to be cured and process to be employed;
- 2) Meats cured with sodium nitrite need contain no more nitrites than meats cured with nitrates, and are free from the unconverted nitrates regularly present in nitrate-cured meats;

- 3) "A shortening of the customary curing period may be obtained by the use of nitrite."

Early US regulatory discussion on the use of nitrate from saltpeter can be found in the regulation 18 Bureau of Animal Industry Order 218. With these conclusions, the first USDA regulations defining the regulatory allowance for nitrate and nitrite use in meat products were established in 1925 permitting no more than 200 ppm ingoing levels of nitrate, nitrite, or combinations thereof. Further research and findings regarding a better understanding of the curing capacity of nitrate, the early concern about nitrosamine formation, and the impact of reductants and acidulants, or so called "cure accelerators" resulted in a re-clarification of curing regulations in 1970 that still exist today (Cassens, 1990). Table 1 illustrates the maximum ingoing allowable limits for various curing agents and curing methods for cured meat products.

The exception to the general limits for curing ingredients is bacon as immersion cured and massaged/pumped bacon (skin off) must have an ingoing level of 120 ppm nitrite while dry-cured is limited to 200 ppm nitrite. Nitrate is not permitted in bacon so that actual concentrations of nitrite can be controlled more precisely. Further, bacon is required to also have either 550 ppm ingoing sodium erythorbate or sodium ascorbate, regardless of curing method, to inhibit the potential for nitrosamine formation during frying (USDA, 2009).

The change from nitrate to nitrite use by the meat industry was not a fast one (Binkerd and Kolari, 1975). In 1930, over 54% of packers were using nitrate compared to only 17% using nitrite. A survey of nitrate and nitrite levels in 1936 reported samples obtained at retail outlets contained an average of 3 to 86 ppm nitrite but alarmingly levels of 160 to 3,900 ppm nitrate. In 1937, a similar survey reported an average of 16 to 102 ppm nitrite and 210 to 3,000 ppm nitrate. From the period of 1970 to 1974, a marked decline in the amount of nitrate being used by the meat industry was found and likely due to the following:

- 1) A better understanding of meat curing and meat curing chemistry;

- 2) Advances in meat processing including the use of cure accelerators such as sodium or potassium ascorbate and erythorbate, or their acid form;
- 3) Regulatory changes for curing ingredients an processing including no longer allowing the use of nitrate in bacon; and
- 4) A growing consumer concern about the potential negative impacts of consuming nitrite/nitrate containing meat products underlined by the discovery of possible nitrosamine formation.

Detected in certain products where high heat greater than 130°C is employed, such as during the frying of bacon, specific nitrosamines, such as nitrosopyrrolidine, formation can occur. Nitrosamine formation was first identified in 1971 and has periodically resurfaced as a potentially significant risk to human health. The formation of nitrosamines can take place only under special conditions where secondary amines are present, nitrite is available to react, and necessary pH and temperatures exist. If significant levels of residual nitrite are present in products where high heat (>130°C) cooking methods are used, the ability for nitrosamine formation does exist.

Because of this fact and the growing concerns and controversy over nitrite usage, a series of proposed regulations were submitted, reviewed and acted upon in the interest of avoiding a complete ban on nitrite. Proposed nitrite regulations in 1975, centered on nitrosamine formation in bacon and resulted in the reduction of ingoing nitrite in bacon from 200 ppm to 125 ppm and a mandatory ingoing addition of 550 ppm sodium ascorbate or erythorbate. Additional petitions to this proposed rule resulted in a 1978 published final rule requiring the use of 120 ppm ingoing nitrite (or equivalent potassium nitrite of 148), 550 ppm ingoing sodium ascorbate or erythorbate, and the banning of nitrate addition during bacon processing. The rule also included the establishment of a nitrosamine monitoring and regulatory control program. Within one year of the newly developed monitoring program and with the cooperation of industry and government, nearly all bacon manufactured was confirmed free of nitrosamines. Today, a thorough scientific understanding of nitrosamine formation, specific regulatory control, and more stringent plant production practices have essentially eliminated all nitrosamine concerns in meat and poultry products.

**Table 1.** Maximum ingoing allowable levels for curing ingredients in meat and poultry in the United States<sup>1</sup>

Curing agent	Curing method			
	Immersion cured (ppm)	Massaged or pumped (ppm)	Comminuted (ppm)	Dry cured (ppm)
Sodium nitrite	200	200	156	625
Potassium nitrite	200	200	156	625
Sodium nitrate	700	700	1,718	2,187
Potassium nitrate	700	700	1,718	2,187

<sup>1</sup>Limits are based on total formulation/brine weight for immersion cured, massaged, or pumped and green weight for comminuted or dry cured products (USDA, 1995).

## Concerns Associated with Nitrate and Nitrite

Nitrate and nitrite has been a topic of debate for several decades now. Reviewing the history and timeline of the "nitrite dilemma" reveals a long, controversial, heated, and confusion filled period of time. A critical report in the long-lasting nitrite debate was a 1970 paper by Lijinsky and Epstein (1970) titled "Nitrosamines as Environmental Carcinogens" published in *Nature*, which showed that nitrosamines were potent and specific carcinogenic



compounds. Further, the authors concluded the most appropriate means to address the problem was to eliminate one or the other nitrosamine precursors (nitrite and secondary amines). Since all cured meats were viewed as containing both precursors, consumption of cured meat was considered a potential public health hazard. Then, in 1978, news began to leak out to the press about a study nearing completion, with findings suggesting that nitrite, itself, was a carcinogen. The study conducted by Dr. Paul Newberne from the Massachusetts Institute of Technology (MIT), investigating cancer contraction of the lymphatic system in rats, became the centerpiece of heated debates including the USDA, FDA (Food and Drug Administration), media, the meat industry, scientists, and many others (Newberne, 1979). Ultimately, a number of discrepancies found in the study would bring into question the validity of the findings ultimately deemphasizing some of the more sensitive accusations. A specially formed National Academy of Sciences (NAS) committee was created to comprehensively review the available literature including consultations with many experts and organizations. This extensive review resulted in two reports by NAS entitled “The Health Effects of Nitrate, Nitrite, and N-Nitroso Compounds” and “Alternatives to the Current Use of Nitrite in Foods” issued in 1981 and 1982, respectively (NAS, 1981, 1982). Because of these two exhaustive reports, the concerns of nitrite usage were addressed resulting in significant diffusion of the heightened debate and ultimately avoiding a total ban on nitrite as a food additive.

The 1982 National Academy of Sciences report also called for a more thorough evaluation of nitrite in cancer bioassays and thus it was nominated by FDA for study in the National Toxicology Program (NTP). This study was completed in the 1990s and the results were peer reviewed by a panel at a meeting held on May 18, 2000. The review panel concluded that there was no evidence for nitrite induced carcinogenicity in any major tissues of male and female rats and male mice. There was only equivocal evidence for carcinogenicity in the forestomach of female mice (NTP, 2001). This “gold standard” of cancer bioassays was, at the time, the definitive statement of safety for nitrite as an ingredient.

In 1998, the state of California proposed classification of nitrite as a developmental and reproductive toxicant (DART) under their “Proposition 65” law (Safe Drinking Water and Toxic Enforcement Act). In the process, the California Office of Environmental Health Hazard Assessment (OEHHA) staff produced a Hazard Identification Document to support the proposal (Campbell, 2000). The consequence of listing nitrite as DART would have resulted in a requirement to place warning labels on all cured meat products. However, at a public hearing on June 2, 2000, the state’s review committee of independent technical experts voted eight to one against this listing. A California Appeals court ruling in 2009 affirmed federal labeling regulation as preempt any potential California

requirements for Federally inspected meat products. That decision was appealed to the California Supreme Court, which declined to hear the case thereby ending the matter in favor of Federal preemption. The NTP and Proposition 65 reviews of nitrite safety in the context of nitrite benefits have been summarized by Archer (2002).

In 2006, another review of the carcinogenicity of nitrite and nitrate was conducted by a working group convened by the International Agency for Research on Cancer (IARC); a part of the United Nations sponsored World Health Organization headquartered in Lyon, France (WHO, 2006a,b), and the results of this review were published in a summary monograph in 2010 (IARC, 2010). During an eight day period in the summer of 2006 the working group composed of epidemiologists, toxicologists, and cancer researchers reviewed the literature and made a decision based on IARC guidelines on classifying nitrate and nitrite for their potential as human carcinogens. Their final conclusion was as follows:

Ingested nitrate or nitrite under conditions that result in endogenous nitrosation is *probably carcinogenic to humans* (Group 2A) (Grosse et al., 2006).

When carefully examined, this conclusion is very narrow in scope. Under certain conditions, ingested amines and amides can be nitrosated to form carcinogenic nitrosamines and nitrosamides. However, one must question the practical application to any type of public policy or regulatory activity. Because nitrite is also readily formed via metabolism and in saliva, swallowing one’s own saliva in combination with any food could be considered a potentially carcinogenic event. Thus, the biological common sense of this classification is open to question (Milkowski et al., 2010).

Despite the published conclusions of the NAS, NTP and Proposition 65 reviews, concerns regarding the safety of nitrate and nitrite use still periodically emerge including those of chemical toxicity, formation of carcinogens, and reproductive and developmental toxicity. In the 1990s, for example, a series of epidemiological studies reported consumption of cured meats was related to brain cancer and childhood leukemia (Peters et al., 1994; Preston-Martin and Lijinsky, 1994; Sarasua and Savitz, 1994; Preston-Martin et al., 1996). As information involving sensitive topics surrounding human health surfaces, media normally and commonly formulate opinionated pieces, often with incomplete explanations of scientific merit. One such example of this was a Washington Post news piece by Maugh (1994) who reported that “Children who eat more than 12 hot dogs per month have nine times the normal risk of development leukemia” and was based on the epidemiological paper “Processed meats and risk of childhood leukemia” written by Peters et al. (1994). Also in 2008, an epidemiological study concluded that “excessive risk” for colorectal cancer exists, attributed to several proposed pathways related to consumption of processed meats (Santarelli et al., 2008). Many epidemiologists



who report associations regarding cured, processed meat and poultry consumption and health risks do not recognize or consider the new findings, knowledge, and understanding surrounding nitrite as a natural metabolite in physiology and its benefits to food safety. The growing number of studies incorporating epidemiological studies have allowed for more interpretation, and at times extrapolation, by media and consumer groups allowing for growing confusion and inaccurate interpretation of the science.

The relationship between diet and cancer continues to be studied by researchers and headlined in the media. Several reports have asserted that red meat and/or processed meat consumption have been associated with higher rates of certain types of cancer. A 2007 report from the World Cancer Research Fund (WCRF), a confederation of cancer research and treatment advocacy groups including the American Institute for Cancer Research (AICR), represented a major global initiative to link diet to cancer (WCRF, 2007). This WCRF report—*Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective*—was released in November 2007. The report included 10 broad recommendations for cancer prevention regarding diet, lifestyle, and exercise. Specifically, the report made a recommendation to limit red meat consumption to no more than 18 oz (cooked) per week and eliminate processed meat consumption entirely. A subsequent February 2009 Policy Report was issued to seek international public policy changes to promote their opinions on how dietary changes could reduce cancer incidence (WCRF, 2007). The conclusions and recommendations made by WCRF were largely based on weak epidemiological associations and have been challenged by researchers both associated and independent of the meat and poultry industry (Boyle et al., 2008; Truswell, 2009; Alexander and Cushing, 2009; Alexander et al., 2009, 2010a,b; Ferguson, 2010; Huffman and Bryan, 2010; Navia et al., 2010). Numerous factual errors in the WCRF analysis of meat consumption and cancer risk have been acknowledged, however, the organization has maintained that their recommendations are unchanged. The intense debate will continue.

## Biology of Nitric Oxides

### ***Nitrite and Nitrate as Part of the Nitrogen Oxide Metabolic Cycle***

One of the basic approaches in the study of the biochemical and metabolic properties of nitrite in the 1970s and 1980s was to measure consumption and excretion of nitrite and nitrate. The results produced an anomaly. Excretion always seemed to exceed consumption (Tannenbaum et al., 1979; Green et al., 1981a,b). This anomaly implied that synthesis of these compounds was occurring in the body and led to a search for the pathways. In 1987, nitric oxide was identified as the transient factor that caused smooth muscle relaxation (Ignarro et al.,

1987; Ignarro, 1999). It was determined that synthesis of nitric oxide occurred from the amino acid arginine as a substrate and that nitric oxide was metabolized into nitrite and nitrate for excretion as a biological control mechanism (Buga et al., 1989; Gold et al., 1989a,b). Since the late 1980s there has been an explosion of research surrounding the biological functions of nitric oxide.

Nitric oxide is a profoundly active molecule, being involved in control of smooth muscle relaxation, neurotransmission, wound healing, immune response, and a host of other biological functions. In 1998, the Nobel Prize for medicine was awarded to researchers for their efforts in the discovery of the basic functions and synthetic pathways of nitric oxide (Smith, 1998). Typical endogenous nitric oxide is produced at about 1 milligram per kilogram of body weight per day in humans (Tricker, 1997). Being a very reactive molecule, it is quickly bound to heme and oxidized to nitrite and nitrate. The nitrate is circulated in the blood and can be excreted in the urine, sweat, or saliva of the individual. A number of reports have suggested that entero-salivary recirculation of nitrogen oxides serves as a biological adaptation to protect mammals from ingestion of pathogens (Dykhuizen et al., 1996, 1998; Duncan et al., 1997). Additionally, emerging evidence indicates that nitrite itself has a biological function as a signaling molecule independent of nitric oxide (Feelisch et al., 2002; Bryan et al., 2005). Curiously, this function involves nitrosyl and s-nitroso heme species—the very same compounds involved in meat curing reactions and the subsequent production of cured meat pigments. Blood pressure control may indeed have circulating nitrite as a component based on studies that show deoxyhemoglobin will reduce nitrite to nitric oxide and cause circulatory vasodilation (Cosby et al., 2003). Deoxymyoglobin has also been shown to act as a nitrite reductase, producing nitric oxide, which participates in regulation of mitochondrial respiration (Shiva et al., 2007). Further, German researchers have proposed classifying nitrite as a “pro-drug” based on its many newly identified physiological functions (Suschek et al., 2006).

At a 2005 symposium at the US National Institutes of Health, researchers highlighted advances in the understanding of nitrite biochemistry, physiology, and therapeutics (Gladwin et al., 2005). The summary from this conference (Gladwin et al., 2005) suggested the following as important areas for continued research:

- “The contribution of NO-dependent and NO-independent signaling in cellular processes regulated by nitrite.
- The mechanisms of cytoprotection afforded by nitrite after ischemia-reperfusion, and the role of endogenous nitrite and diet in modulating these events.
- The role of myoglobin and other heme proteins, xanthine oxidoreductase, and other enzyme

systems in the ‘physiological’ reduction of nitrite to NO in different tissues at different pH or oxygen gradients.

- The potential role for the nitrite-hemoglobin reaction in regulating vascular homeostasis, signaling and hypoxic vasodilation, and the study of potential intermediates in these reactions and mechanisms of NO export from the red cell.”

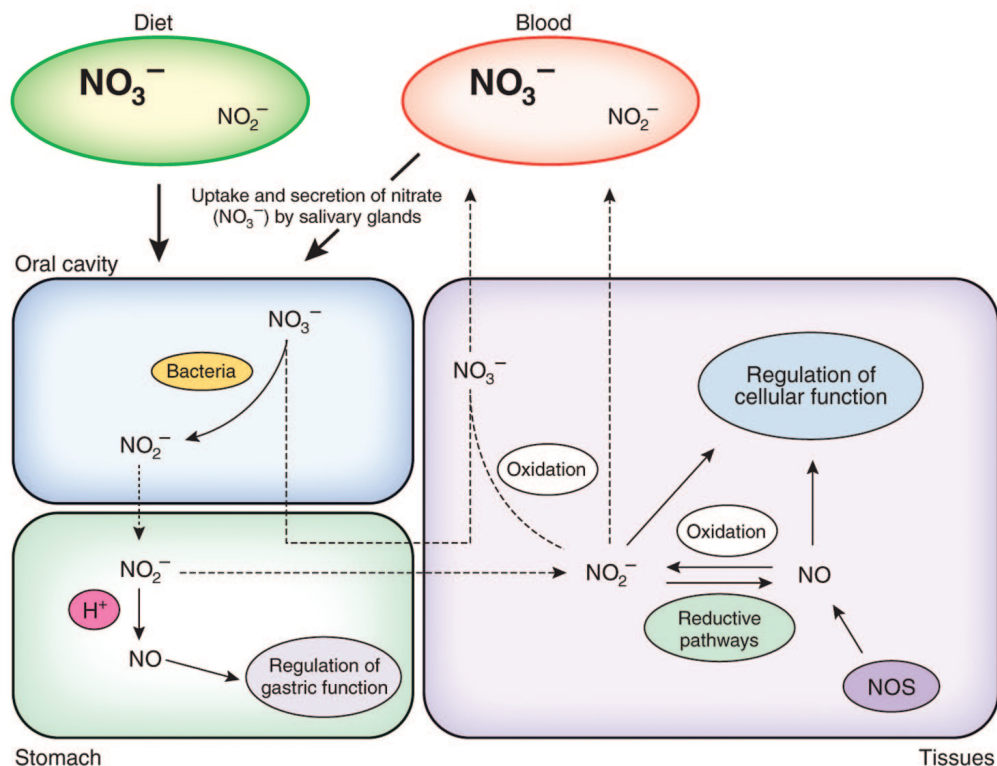
Figure 1 summarizes the interrelationships of nitric oxide, nitrite, and nitrate. Clearly, nitrite is a metabolite and is naturally made in significant quantities. Exogenous nitrite ingestion is small, by comparison, being at a typical residual level of approximately 10 ppm in commercial cured processed meats (Cassens, 1997a,b; Kilic et al., 2001; Keeton et al., 2009).

Given the complex biology of nitrogen oxides, involving endogenous synthesis, metabolic conversions

and recycling via the entero-salivary pathway, estimates of total human exposure are difficult to make. Often they have focused on diet or water as exogenous sources while ignoring the latter. These potential sources for error have been more recently addressed in a few publications. Hord et al. (2009) summarized dietary intake estimates of nitrite and nitrate for the “DASH” (dietary approaches to stop hypertension) diet that included two scenarios for vegetables and fruit consumption. They indicated that a high nitrate intake from these sources could result in as much as 5 mg nitrite ingestion via recycling in the saliva and reduction of nitrate to nitrite by oral bacterial. An overall summary of this exposure was developed by Milkowski (2011) and is shown in Table 2.

### Medical Uses of Nitrogen Oxides

Since the discovery of nitric oxide, numerous therapeutic uses of targeted delivery of nitric oxide in specific tissues have been identified. Newborn infants, both full term and



The human nitrogen cycle. Dietary nitrate is rapidly absorbed into the bloodstream, where it mixes with endogenous nitrate from the NOS/NO pathway. A large portion of nitrate is taken up by the salivary glands, secreted with saliva and reduced to nitrite by symbiotic bacteria in the oral cavity. Salivary-derived nitrite is further reduced to NO and other biologically active nitrogen oxides in the acidic stomach. Remaining nitrite is rapidly absorbed and accumulates in tissues, where it serves to regulate cellular functions via reduction to NO or possibly by direct reactions with protein and lipids. NO and nitrite are ultimately oxidized to nitrate, which again enters the enterosalivary circulation or is excreted in urine.

**Figure 1. The human nitrogen cycle.** Reprinted by permission from Macmillan Publishers Ltd: *Nature Chemical Biology*. M. T. Gladwin, A. N. Schechter, D. B. Kim-Shapiro, R. P. Patel, N. Hogg, S. Shiva, R. O. Cannon, M. Kelm, D. A. Wink, M. G. Espey, E. H. Oldfield, R. M. Pluta, B. A. Freeman, J. R. Lancaster, M. Feelisch, and J. O. Lundberg. 2005. *The emerging biology of the nitrite anion. Nat. Chem. Biol.* 1:308–314, copyright 2005.

**Table 2.** Ranges of nitrate, nitrite and nitric oxide exposure from diet, endogenous synthesis and recycling for adult humans expressed as milligrams per day

Source	Nitrate (mg/kg NO <sub>3</sub> <sup>-</sup> )	Nitrite (mg/kg NO <sub>2</sub> <sup>-</sup> )	Nitric oxide (mg/kg NO)
Diet (excluding cured processed meat) <sup>1</sup>	50–220	0–0.7	—
From 75 g/day cured processed meat intake <sup>2</sup>	1.5–6	0.05–0.6	—
Water <sup>3</sup>	0–132	0–10	—
Saliva <sup>4</sup>	>30–1,000	5.2–8.6	—
Endogenous synthesis <sup>5</sup>	—	—	70

<sup>1</sup>Based on IARC Table 1.8 (IARC, 2010).

<sup>2</sup>Based on Keeton et al. (2009) average values and intake described in White (1975).

<sup>3</sup>Based on none present to US EPA maximum allowed contaminant level for water of 44 ppm and 2.7 L water consumption/day.

<sup>4</sup>Based on data from White (1975) and Hord et al. (2009) and includes both recycling of diet derived nitrate via the enterosalivary route and that from endogenous NO.

<sup>5</sup>Based on 1 mg/kg per day endogenous synthesis for 70 kg adults (Tricker, 1997).

premature, with a variety of pulmonary problems are now treated with nitric oxide gas to relieve respiratory distress (Kinsella and Abman, 2005; Lonnqvist and Jonsson, 2005; Sehgal et al., 2005). Heart medications utilize the delivery of nitric oxide to dilate smooth muscles and improve oxygenation of heart tissue. The long utilized cardiac drug, nitroglycerin, is a nitric oxide delivery vehicle (Clermont et al., 2003; Buch et al., 2004). Nitrite itself has been demonstrated to protect against reperfusion injury in cardiac ischemia (Bryan et al., 2007, 2008; Garg and Bryan, 2009).

Another particularly active area of research involves skin. Psoriasis, acne, and other skin disorders are being treated with nitrite and nitric oxide delivery drugs (Weller et al., 1997, 1998, 2001; Schwentker et al., 2002; Weller, 2003; Seabra et al., 2004). The response of skin tissue to UV light and wound healing are beneficially affected by nitric oxide and nitrite. (Childress and Stechmiller, 2002; Suschek et al., 2003, 2005, 2006; Luo and Chen, 2005; Broughton et al., 2006).

Although it is not widely realized, potassium nitrate is used in many toothpaste formulations. Toothpaste designed for sensitive teeth is formulated with up to five percent potassium nitrate (Manochehr-Pour et al., 1984; Silverman, 1985; Cohen et al., 1994; Orchardson and Gillam, 2000; Poulsen et al., 2001; Tzanova et al., 2005; Wara-aswapati et al., 2005). These products can be purchased at any drugstore.

## A World Without Meat Curing

Curing agents, namely nitrite, provide a number of important and unique cured meat characteristics already discussed. Each important function of nitrite has is

deemed beneficial by different entities (e.g., consumers or manufacturers) and for specific reasons. The color fixing and flavor development properties are considered desirable by consumers and thus manufacturers of cured meats have a great interest in using nitrite as an ingredient for both quality-related and economic reasons. An extended storage time due to the protection of lipids from oxidation can be viewed as a benefit to both manufacturers and consumers as both parties receive quality and economic benefit if product degradation is decreased. A long storage shelf-life provides manufacturers with greater flexibility in warehousing, distribution, and retail display times. A product formulated to maintain quality and safety longer in a consumer's home is considered an important benefit to the consumer and the manufacturer. A cured product with the potential of a longer refrigerated quality shelf life, even after package opening, can allow for maintaining certain quality attributes beyond that of uncured versions and result in less urgency for customers to use or consume the product before it "goes bad."

Since nitrite is an ingredient that has been shown to be an effective antimicrobial with bacteriostatic activity, its usage is clearly a benefit to both industry and consumers. With the relentless approach to ensuring the safety of meat and poultry products, nitrite (in addition to Good Manufacturing Practices and well established intervention strategies) is a powerful tool that the meat and poultry industries can use judiciously to help ensure, on a daily basis, the safest products are reaching their consumers. Although the level of nitrite needed for providing maximum effectiveness against many pathogens is still debated, a great deal of evidence supports that nitrite has an effect on many different bacteria in a variety of different processed meat products. The effect of nitrite in the control of *C. botulinum* is indisputable and well documented serving as a compelling and important reason for widespread meat and poultry industry use. Although rarely considered a concern by consumers, botulism has been completely controlled by nitrite use in cured meat products.

A world without meat curing would present some extraordinary challenges and concerns to both industry and consumers alike. The immediate ramifications would likely be a significant increase in finished product cost, a considerable increase of consumer dissatisfaction, and an increased challenge to control microbial growth. The long-term consequence would be many steps backwards on the already scientifically supported knowledge base surrounding the improved safety, quality, and health effects of nitrite. Throughout the past several decades, substitution of nitrite with alternative ingredients has been extensively studied but has been unsuccessful in identifying a comparable ingredient replacement.

The difficult challenge has been to identify an ingredient that would provide the same product characteristics of nitrite without representing a health hazard. Indeed, much research has identified ingredients such as sorbic acid (Sofos et al., 1979b), short-chain aliphatic and



alkenoic acids and esters (Huhtanen et al., 1985), various organic acids (Miller et al., 1993), and cooked, cured-meat pigment (Shahidi and Pegg, 1992). Several of the aforementioned ingredients have been found only limited effectiveness. Although single ingredient alternatives are usually effective for only replacing one of the important characteristics of nitrite, full replacement has not been successful through numerous scientific investigations, even with combinations of ingredients. In fact, to date, no ingredient has ever been identified that effectively reproduces all the important properties of stabilizing color, producing flavor, preventing fat oxidation, changing texture, and acting as a preservative as effectively as nitrite.

The substantiating importance of meat and poultry curing can be demonstrated by the widespread interest in “natural curing” of natural or organic meat products. Although natural and organic labeling standards ban the addition of any synthetic chemical, including nitrite and nitrate, the importance of curing by the industry coupled with the quality demands from consumers has fostered the development of creative, new, and novel technologies where curing from an indirect approach is commonplace in these categories of products. Because of the high regard for the important properties of cured meats, a majority of natural and organic processed meat products labeled “uncured” are actually quite the opposite. As a result, “naturally cured” products, because of indirect nitrite inclusion, have again provided consumers with variety, convenience, and satisfaction while giving manufacturers improved quality, shelf-life and safety.

### Summary

Curing with nitrite has been used, essentially, for thousands of years to produce safe and nutritious products and to effectively preserve meat. Since the controversies about the safety of nitrite that started in the mid-20th century, much has been learned about nitrite and heme chemistry and the overall metabolism of nitrogen oxides in humans. Curing practices in the meat and poultry industries have been adjusted using the knowledge obtained about nitrosamine risks. The ongoing research focused on the metabolism of nitric oxide, nitrite, and nitrate appears to reaffirm the safety and benefits of current curing practices. The challenge to meat scientists is two-fold. First, is to continually broaden their understanding of curing in the context of human physiology and metabolism of nitrite and to keep current on the medical literature in this area. The second is to effectively educate a broad community of public health scientists, nutritionists, and the general public about the fundamental role of nitrite in biology in order to address their unfounded fears and concerns about adverse health effects from consuming cured meat and poultry products.

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