Nothing affects our health more than what we decide to eat. The role of diet in the prevention and control of morbidity and premature mortality due to noncommunicable diseases has been well established by the vast population-based epidemiological studies carried out during the last decade (World Health Organization, 2003). Numerous epidemiological data have indicated an inverse relationship between dietary intake of fruits and vegetables and incidence of cardiovascular disease as well as cancer. Among the candidates that may account for these cardioprotective and anticancer effects are antioxidants such as polyphenolics, ascorbate, and glutathione. Although antioxidants are generally credited with improving states of oxidative stress, studies that have evaluated the efficacy of supplementation with a high dose of an antioxidant alone, such as vitamin E or vitamin C, have shown no apparent improvement and in some cases a decrease in cardiovascular protection (Yusuf et al., 2000). Yet, when these antioxidants are consumed through the diet in the form of fruits and vegetables, there is a significant degree of protection and in some cases a decrease in cardiovascular protection (Yusuf et al., 2000). Yet, when these antioxidants are consumed through the diet in the form of fruits and vegetables, there is a significant degree of protection.

Emerging physiological data indicate nitrite and nitrate from the diet is reduced to nitric oxide (NO), which may be responsible for these beneficial effects (Lundberg et al., 2006; Hord et al., 2009). To the contrary, there are some epidemiological reports that weakly associate consumption of cured meats with specific cancers (most associations fall below 1.4). In these very weak associations, the studies suggest the nitrite and nitrate content of the cured meats as the culprit responsible for the weak and modest increased risk of cancer. In 1994 the US National Cancer Institute publicly indicated that relative risks values less than 2 were not strong enough to use for public policy pronouncements, so these weak associations should be understood as such. Nitrite is but one of many bioactive components of cured meats, and therefore, it is virtually impossible to establish a firm causal relationship from a very weak association. Yet it is still regarded as a Group 2A probable carcinogen according to the International Agency for Research on Cancer (IARC) under the specific conditions that cause endogenous nitrosation of amines. Ironically though, the overwhelming burden of human exposure to nitrite and nitrate comes from vegetables and not from cured and processed meats (Hord et al., 2009). Understanding that simple fact, the arguments implicating harmful effects of nitrites and nitrates in our food supply are dubious and require reconsideration based on undisputed research showing benefit for the past 15 years.

We must, however, acknowledge and understand the long-held notion that dietary sources of nitrate and nitrite are harms in certain contexts due to their ability to cause methemoglobinemia or perform nitrosation reactions in the stomach to form potentially carcinogenic low molecular weight N-nitrosamines. Although there are case reports for methemoglobinemia from nitrite and nitrate intoxication and at least the biological plausibility of nitrosation reactions, the burden of proof for such cases in the context of nitrite and nitrate at levels found in certain foods is far from being firmly established. In fact, there is very little, if any, evidence on the carcinogenicity directly of nitrite and nitrate despite over 40 years of intense investigation. The confusion and public misconception on nitrite and nitrate stems from the propensity to form N-nitrosamines from nitrite during cooking and ingestion. The emerging and undisputed cardiovascular benefits of nitrite and nitrate necessitate new dialogue with regard to risk–benefit evaluations and highlight the need to define the context for potential health benefits and risk for consumption of nitrite- and nitrate-rich foods.
HISTORY OF NITRITE AND NITRATE IN THE FOOD SUPPLY

It is prudent first to discuss the history of nitrite and nitrate that alarmed the regulatory officials and the general population, which caused these two molecules to be viewed as a menace to our food supply. There is a rich history of nitrite and nitrate use in our food supply. In fact, inorganic nitrite and nitrate have been in use for as long as 5000 years in the preservation of food. However, it was not realized until the 19th century that the mechanism underlying food preservation was actually the conversion of nitrate to nitrite by bacteria (Binkerd and Kolari, 1975). This provided the rationale for the use of nitrite rather than nitrate in the meat preservation industry in the early 1900s. Nitrite in meat greatly delays the development of botulinum toxin, develops cured meat flavor and color, retards development of rancidity during storage, inhibits development of warmed-over flavor, and preserves flavors of spice and smoke (Binkerd and Kolari, 1975). Ascorbic acid, or dehydroascorbate, is also a common meat preservative. It was demonstrated very early on that the chemical basis for the nice red color and appearance of cured meat was the reaction of nitrite with oxyhemoglobin to form S-nitrosohemoglobin (Haldane, 1901). In the early 20th century, meat preservation regulations in the United States for the first time allowed nitrite to be used as a curative salt. Nitrite has since become a common dietary nutrient in those who consume cured meats.

In the 1970s, there arose major public health concern regarding nitrite when there was indication of endogenous formation of N-nitrosamines from nitrite and nitrate and its relevance to human cancer. The first report in the 1950s on the hepatocarcinogenic effects of N-nitrosodimethylamine (Magee and Barnes, 1956) and the suggestion that low molecular weight N-nitrosamines (RNNOs) can be formed following nitrosation of various amines (Druckrey and Preussmann, 1962) ignited an enormous interest in N-nitrosamines and their association with cancer. Direct proof that such nitrosation reactions can occur in foods was provided by Ender et al. (1964), who identified N-nitrosodimethylamine in nitrite-preserved fish, and by Sander and Sief (1969), who demonstrated the in vivo formation of a nitrosamine in the acidic conditions of the human stomach. Because of the potent carcinogenicity of some low molecular weight N-nitrosamines, considerable effort was made to determine the levels of nitrite and nitrate in the external and internal human environment and to assess exposure in order to correlate it with human cancer at specific sites (Bartsch and Montesano, 1984). Since the early 1980s, there have been numerous reports on the association of N-nitrosamines and human cancers (Craddock, 1983; Bartsch and Montesano, 1984), but a causative and specific link between nitrite or nitrate exposure and cancer is still missing (Ward et al., 2005). Furthermore, a two-year study by the National Institutes of Health on the carcinogenicity of nitrite conclusively found that there was no evidence of carcinogenic activity by sodium nitrite in male or female rats or mice (NTP, 2001).

Considering its widespread use, there have been many toxicological studies on acute and chronic exposure to nitrite. The fatal dose of nitrite is in the range of 22 to 23 mg/kg of body weight (Battele-Columbus Laboratories et al., 1972). Lower doses of either nitrite or nitrate have caused acute methemoglobinemia, particularly in infants where a high nitrite or nitrate intake has been associated with blue baby syndrome caused by methemoglobinemia (Comly, 1945; Donohoe, 1949; Lecks, 1950). These negative connotations of nitrite and nitrate have led the government to regulate and restrict the levels in food and drinking water.

In the late 1970s, despite all the fear and paranoia surrounding nitrite exposure, our appreciation and understanding of nitrite and nitrate took a drastic turn. Studies on nitrogen balance in humans and analyses of fecal and ileostomy samples indicated that nitrite and nitrate are formed de novo in the intestine. These early findings by Tannenbaum et al. (1978) significantly altered our conceptions of human exposure to exogenous nitrite and nitrate and represented the original observations that would eventually lead to the discovery of the L-arginine: NO pathway. Prior to these studies, it was thought that steady-state levels of nitrite and nitrate originated solely from the diet and from nitrogen-fixing enteric bacteria. Since this seminal discovery, however, nitrite and nitrate have been recognized as natural molecules produced by normal metabolism in our body. However, epidemiologists are still reporting potential health risks of dietary sources of nitrite and nitrate. A cursory review is presented below.

NUTRITIONAL EPIDEMIOLOGY OF NITRITE AND NITRATE

In the largest study of its kind, the European Prospective Investigation into Cancer and Nutrition (EPIC) found that vegetable and fruit consumption was associated with lower risk of colon cancer (hazard ratio: 0.76; 95% CI: 0.63–0.91; P-value for trend <0.01; van Duijnhoven et al., 2009). This association, as well as the blood pressure lowering effect of the Dietary Approaches to Stop Hypertension (DASH) diet, may be attributable, in part, to nitrates and nitrites in vegetables and fruits (Hord et al., 2009), which can be metabolized to bioactive nitric oxide. Many epidemiologic studies have shown that populations that eat diets high in vegetables and fruits and low in animal fat, meat, and calories have reduced risk of some of the most common cancers and lower risk of cardiovascular disease. Coincidently, fruits and vegetables are enriched with nitrite and nitrate from the soil. The association of nitrates and nitrites in vegetables and fruits with decreased cancer risk is confounded by reported health risks, including methemoglobinemia in infants from drinking excess nitrate and nitrite in water and gastrointestinal cancer in adults, associated with nitrite-mediated nitrosation of low molecular weight amines to produce carcinogenic N-nitrosamines. Consumption of specific food components has
been associated with risk of colorectal cancer. Colorectal cancer is the third leading cause of cancer-related deaths for both males and females in the United States. Dietary factors associated with increased colorectal cancer risks include red meats and processed meats, whereas dietary fiber consumption is associated with decreased risk in low-risk populations. The consumption of red meat and, in particular, processed or preserved or cured meats (i.e., meats treated with nitrite as a food additive, including ham, bacon, hot dogs, and others) has been related to the incidence of colorectal cancer since 1975 in several epidemiological studies, although the risk index was very low and the association weak. A worldwide recommendation for moderation in the consumption of preserved meats, such as sausages, salami, bacon, and ham, was launched by the World Health Organization in 2003 (2002). However, a 2007 report by the World Cancer Research Fund and the American Institute of Cancer Research (WCRF/AICR) presented a recommendation to “avoid processed meats” based on a meta-analysis of a limited number of selected cohort studies showing increased risk of colorectal cancer with increased intake of processed meats. The summary estimate of relative risk was determined to be 1.21 (95% CI = 1.04–1.42) per 50 g of intake/d and was supported by case-control studies. A separate Swedish meta-analysis of 14 cohort studies reported a slightly lower summary hazard ratio estimate of 1.09 (95% CI = 1.05–1.13) per 30 g of intake/d (Larsson and Wolk, 2006). However, these findings must be interpreted cautiously considering that a relative risk ratio of 1.0 indicates no increase in risk and anything less than 2.0 should not be used for public policy recommendations, according to the US National Cancer Institute (Anderson, 1994).

Although estimates of daily nitrate and nitrite intake are reported to vary between 53 and 350 mg/d and between 0 and 20 mg/d, respectively, recent analyses (Hord et al., 2009) indicate these may dramatically underestimate intakes of nitrates from specific fruit and vegetable juices and food supplements. The presence of nitrates and nitrites in these two different food matrices helps explain this conundrum but has not removed the negative stigma arising from the association of health effects of nitrates in processed meats. Studies to establish the carcinogenicity of nitrates and nitrites have been negative. The primary dietary sources of nitrates and nitrites include plants; vegetables and a few fruits; and processed and cured meat, fish, and poultry to which nitrates have been added. Human epidemiological data have not shown increased risk of cancer due to vegetable and fruit sources of nitrate and nitrite.

To explain the disparities reported in the literature on dietary sources of nitrite and nitrate, I would like to summarize the past 10 to 5,000 years of biomedical research on nitrite and nitrate regarding its safety and its efficacy toward a number of disease conditions and then put the collective data in perspective in terms of a risk–benefit evaluation.

**Atmospheric Nitrogen Cycle**

Have you ever wondered why the air we breathe contains 78% nitrogen? The store of nitrogen found in the atmosphere, where it exists as a gas (mainly N₂), plays an important role for all life on earth. Most plants can only take up nitrogen in two solid forms: ammonium ion (NH₄⁺) and the nitrate ion (NO₃⁻). Atmospheric nitrogen must be processed, or fixed, to be used by plants. Some fixation occurs in lightning strikes, but most fixation is performed by free-living or symbiotic bacteria. These bacteria have the nitrogenase enzyme that combines gaseous nitrogen with hydrogen to produce ammonia, which is then further converted by the bacteria to make their own organic compounds. Some nitrogen-fixing bacteria live in the root nodules of plants. Here they form a mutualistic relationship with the plant, producing ammonia in exchange for carbohydrates. Nutrient-poor soils can be planted with legumes to enrich them with nitrogen. Most plants obtain the nitrogen they need as nitrate from the soil. When released, most of the ammonium is chemically altered by a specific type of bacteria (genus *Nitrosomonas*) into nitrite (NO₂⁻). Further modification by another type of bacteria (genus *Nitrobacter*) converts the nitrite to nitrate. All nitrogen obtained by animals can be traced back to the eating of plants at some stage of the food chain. Figure 1 illustrates the atmospheric nitrogen cycle. This essential environmental cycle provides the basis of the nitrite and nitrate in the foods that we eat, particularly plants and vegetables grown in soil.

**NO Generation Without NO Synthase**

In 1994 two groups independently presented evidence for generation of NO in the stomach resulting from the acidic reduction of inorganic nitrite (Benjamin et al., 1994; Lundberg et al., 1994). Benjamin and colleagues demonstrated that the antibacterial effects of acid alone were markedly enhanced by addition of nitrite, which is present in saliva, whereas Lundberg and colleagues measured high levels of NO in expelled air from the stomach in humans. These levels were abolished after pretreatment with a proton pump inhibitor and markedly increased after ingestion of nitrate, showing the importance of both luminal pH and the conversion of nitrate to nitrite for stomach NO generation. These were the first reports of NO synthase-independent formation of NO in vivo. In the classical NO synthase pathway, NO is formed by oxidation of the guanidino nitrogen of L-arginine with molecular oxygen as the electron acceptor (Moncada and Higgs, 1993). This complex reaction is catalyzed by specific heme-containing enzymes, the NO synthases, and the reaction requires several cofactors. The alternative pathway was fundamentally different; instead of L-arginine, it used the simple inorganic anions nitrate (NO₃⁻) and nitrite (NO₂⁻) as substrates in a stepwise reduction process that did not require NO synthase or multiple cofactors. The biochemical pathway and biological effects of nitrate reduction to nitrite and further on to NO in the gastrointestinal tract.
have now been further characterized (Lundberg et al., 2004). Oral commensal bacteria are essential for the first step in the nitrate-nitrite-NO pathway because they are responsible for the reduction of the higher nitrogen oxide nitrate to form nitrite. It was known from the literature that the salivary glands extract nitrate from plasma, but the reason for this active process was not explained. This active process leads to levels of salivary nitrate that are 10- to 20-fold higher than in plasma. Oral facultative anaerobic bacteria residing mainly in the crypts of the tongue then reduce nitrate to nitrite by the action of nitrate reductase enzymes (Spiegelhalder et al., 1976; Duncan et al., 1995). These bacteria use nitrate as an alternative electron acceptor to gain ATP in the absence of oxygen. This highly effective bacterial nitrate reduction results in salivary levels of nitrate that are 1,000-fold higher than those found in plasma (Lundberg and Govoni, 2004). When nitrate-rich saliva meets the acidic gastric juice, nitrite is protonated to form nitrous acid (HNO$_2$), which then decomposes to NO and a variety of other nitrogen oxides (Benjamin et al., 1994; Lundberg et al., 1994). It is now established that oral commensal bacteria are pivotal in gastric NO formation, and gastric NO levels are consistently low in animals reared under completely germ-free conditions (Sobko et al., 2004). If the oral flora is selectively removed by topical treatment with an antibacterial mouthwash, the gastric NO levels decrease drastically (Petersson, 2008).

**Organic Nitrates**

Organic nitrates have been used for treating coronary atherothrombotic disease for over 150 years and offer highly effective relief from acute angina pectoris (Bian and Murad, 2003). Yet the precise biochemical and molecular mechanisms by which organic nitrates are biotransformed to NO remain elusive. Notably, all thiols facilitate nitrovasodilator conversion to nitrite, but only a select few induce concomitant NO formation, supporting the view that organic nitrates may be considered nitrite donors instead of NO donors (Feelisch and Noack, 1987; Feelisch et al., 1988; Thatch et al., 2004). In fact, organic nitrates such as nitroglycerin are able to release about 100 times more nitrite than free NO (Feelisch et al., 1988). As a result, patients have been exposed to high concentrations of nitrite for years without harm, and this, in fact, may explain the cardioprotective properties of therapeutic organic nitrate treatment.

**Nitrite Physiology and Therapeutics**

In 1995, Jay Zweier’s group, then at Johns Hopkins, reported in *Nature Medicine* that sodium nitrite can form nitric oxide in the ischemic heart, thereby providing protection from injury. Since that seminal report, there have been numerous accounts on the biological activity of nitrite as a treatment strategy for ischemic disease, including heart attack and stroke. The production of NO from L-arginine is a complex, complicated 5-electron oxidation reaction requiring numerous cofactors, substrates, and prosthetic groups of which oxygen is requisite. In conditions of ischemia or hypoxia where there is a deficiency in oxygen, NO can no longer be produced from L-arginine. Strategies to provide an alternative source of NO have shown remarkable effects at limiting the amount of injury to a tissue or organ as a result of ischemia followed by reperfusion (I/R) such as during transplantation surgery.
heart attack, or stroke. Nitrite has emerged as the lead candidate for such interventions. The nitrite anion (NO\textsubscript{2}\textsuperscript{−}) has moved to the forefront of NO biology (Gladwin et al., 2005) because nitrite represents a major storage form of NO in tissues (Bryan, 2006). Nitrite, the oxidative breakdown product of NO, has been shown to serve as an acute marker of NO flux and formation (Kleinbongard et al., 2003); therefore, a reduction in NO production results in a decrease in steady-state concentrations of nitrite. Conversely, increased NO production leads to an increase in steady-state nitrite. Nitrite has been shown to increase regional blood flow (Cosby et al., 2003), increasing oxygen delivery to hypoxic tissues. Enhancing nitrite availability through therapeutic intervention by administering bolus nitrite prior to cardiovascular insult has shown remarkable effects in reducing the injury from myocardial infarction, ischemic liver and kidney injury, stroke, and cerebral vasospasm (Webb et al., 2004; Duranski et al., 2005; Lu et al., 2005; Pluta et al., 2005; Jung et al., 2006; Tripathi et al., 2007) in animal models. These first reports on the efficacy of nitrite in cytoprotection have led to numerous clinical trials for the use of nitrite or nitrate in both healthy volunteers and patients with specific cardiovascular complications (www.clinicaltrials.gov). Most recently, nitrite has been shown to precondition the myocardium when given 24 hours prior to ischemic insult due to the modulation of mitochondrial electron transfer (Shiva et al., 2007), as well as augment ischemia-induced angiogenesis and arteriogenesis (Kumar et al., 2008). Nitrite also presents remarkable efficacy in promoting regional blood flow in sickle cell patients (March et al., 2008). Plasma nitrite levels increase in response to exercise in healthy individuals, whereas in aged patients with endothelial dysfunction, there is no increase in nitrite from exercise (Lauer et al., 2008). Nitrite has also been shown to predict exercise capacity in humans (Rassaf et al., 2007), and most recently nitrate has been shown to reduce the oxygen cost during low-intensity exercise and enhance tolerance to high-intensity exercise in humans (Bailey et al., 2009). We now know that nitrite is just as efficacious when given orally at low intensity exercise in humans (Rassaf et al., 2007), reversing hypertension from NOS inhibition (Tsuchiya et al., 2005), protecting from myocardial ischemia-reperfusion injury (Bryan et al., 2007), inhibiting microvascular inflammation, reversing endothelial dysfunction, and reducing levels of C-reactive protein (Stokes et al., 2009). This provides proof of concept that dietary sources of nitrite and nitrate have very important and essential physiological functions.

**Nitrite and Nitrate in Human Breast Milk**

Perhaps the most compelling argument for implication for nitrite and nitrate requirements in the diet comes from breast milk of nursing mothers and the nutritional and immunological benefits to the infant. Breast milk is nature’s most perfect food. Ongoing studies in our lab reveal the presence of high concentrations of nitrite and nitrate in human breast milk, which is consistent with previous reports (Iizuka et al., 1999). Early postpartum breast milk from certain mothers contained the highest nitrite concentration of any food or beverage product tested (Hord Bryan, manuscript under review). Human breast milk contains high concentrations of nitrate and nitrite in the early postpartum period, and the relative concentrations of the two anions change throughout the colostrum to transition milk to mature milk changes—in fact at concentrations much higher than those found in commercial baby formulas. The nitrite consumed by the infant enters the acidic environment of the stomach, leading to the generation of nitric oxide in the gastric lumen. We know of the effects of NO in adult stomachs in terms of gastric mucosal integrity and blood flow from the reduction of nitrate to nitrite to NO. At birth, the gastrointestinal tract of the infant is sterile, and it is rapidly colonized by bacteria originating from the mother and the environment (Fujita and Murono, 1996; Mandar and Mikelsaar, 1996). The first colonizing bacteria are aerobic bacteria, such as staphylococci, enterococci, and enterobacteria (Orrhage and Nord, 1999). Then, anaerobic bacteria, such as *Bacteroides, Bifidobacterium*, and *Clostridium* species, gradually colonize the gastrointestinal tract (Orrhage and Nord, 1999). We now appreciate that the reduction of nitrate to nitrite requires the commensal bacteria that normally reside in our bodies. However, in newborn infants this pathway has not yet developed. Therefore, breast milk, high in nitrate relative to nitrate, overcomes nature’s deficiency early in life. At later stages of development, nitrate becomes the predominant anion when a symbiosis exists with the colonized bacteria. This becomes extremely interesting in terms of levels of nitrite exposure from ingestion based on body weight of an infant (near 1 mg/kg). The Joint Food and Agricultural Organization/World Health Organization has set the acceptable daily intake at 3.7 mg/kg of body weight for the nitrate ion and 0.06 mg/kg of body weight for the nitrite ion (European Food Safety Authority, 2008). Comparing these values you begin to see a discrepancy based on ignorance in terms of regulation of nitrite and nitrate exposure. If there were merits to any of the claims about nitrite and nitrate in promoting carcinogenesis, we would expect a higher incidence of cancer in breast-fed infants compared with formula fed. In fact there is a recognized and huge disparity in the health of breast-fed versus formula-fed babies. Current dogma is that immunoglobulins transferred from mother to baby are responsible for the benefits of breast milk. A strong case can be made for nitrite as an essential molecule in the development and immune function of infants. Nature has devised a perfect system to nourish and foster the growth and development of nursing babies. Nitrite appears to be one of those indispensable nutrients.

**Nitrite and Nitrate Are Naturally Occurring in Almost All Foods**

Nitrite in cured meats does not significantly change the body burden of nitrite. We recently reported the nitrite and nitrate content of a convenience sample of foods,
both meats and vegetables as well as commercially available drinks. We found that most of the exposure to nitrite and nitrate comes from vegetables and not from cured and processed meats. In fact we report that the nitrate content from vegetables may be the mechanism of blood pressure lowering effects of the Dietary Approach to Stop Hypertension (DASH) diet (Hord et al., 2009).

**Nitrite and Nitrate in Traditional Chinese Medicines**

Traditional Chinese Medicine (TCM) has been used for over 5,000 years to treat and prevent certain ailments and diseases. Although TCM has served as a mainstream of medical care throughout Asia for many generations, it is considered an alternative medical system in much of the Western world. Because many of these TCMs are used primarily for cardiovascular indications characterized by NO insufficiency, we hypothesized that some, if not all, of these TCMs have a robust NO bioactivity that may act to restore NO homeostasis. We recently tested a group of convenience samples of TCMs obtained in the United States for endogenous nitrite, nitrate, nitrosation products, and nitrite reductase activity. The results from our study reveal that all of the TCMs tested reveal NO bioactivity through their inherent nitrite and nitrate content and their ability to reduce nitrite to NO. Many of the TCM extracts contain a nitrite reductase activity greater by 1,000 times than that of biological tissues. Repletion of biological nitrite and nitrate by these extracts and providing a natural system for NO generation in both endothelium dependent and independent mechanisms may account for some of the therapeutic effects of TCMs (Tang et al., 2009). Because all of these herbs and TCMs contain relatively high levels of nitrate and some residual nitrite, there is in essence over 5,000 years of phase I safety trials in humans regarding nitrite and nitrate. I am confident any harmful effects would have been recognized long ago if they existed.

**A Call to Change Regulatory Policy**

A report from the National Research Council (NRC, 1981) estimated based on food consumption tables that the average total nitrite and nitrate intake in the US was 0.77 mg and 76 mg, respectively. If we assume our body (70 kg) produces 1.68 mmol of NO per day (based on 1 μmol/kg per hour of NO production), those average daily intakes would equate to 11.1 μmol of nitrite per day and 76 mg of nitrate, which total 894 μmol per day or roughly 1 mmol total nitrite and nitrate per day from diet. This almost matches what our body makes from NO if we assume most of the NO goes to stepwise oxidation to nitrite and nitrate. Therefore, our steady-state levels of nitrite and nitrate, which are routinely used as clinical biomarkers of NO activity, come almost 50% from diet. Moreover, if nitrite were a carcinogen, we would be advised to avoid swallowing because saliva contains 50 to 100 μM nitrite, which can increase to near millimolar levels (McKnight et al., 1997) after a nitrate-rich meal. Assuming 50 μM nitrite in saliva and a daily production of up to 1.5 L per day, the total nitrite exposure from saliva alone is 75 μmol or 5.18 mg. The enterosalivary concentration and circulation of nitrate, and ultimately nitrite, provides an essential pathway for health and host defense. Even more, studies on high-altitude natives of Tibet revealed that increasing nitrite and nitrate concentrations within the body are natural physiological responses that are devoid of harmful effects (Erzurum et al., 2007). These natives have as much as 100 times more nitrate and nitrite in their bloodstream than people living at sea level with no gross deformities from cancer or any other health concerns. There should be a reevaluation of current nitrite and nitrate consumption analysis based on 21st century dietary habits. The strategy imposed in the 1970s of avoiding nitrite- and nitrate-rich foods due to the propensity to form N-nitrosamines may prove to be unwarranted and even detrimental to cardiovascular health.

The emerging physiological data on nitrite are strikingly analogous to a vitamin. A vitamin is by definition any of a group of organic substance essential in small quantities to normal metabolism, found in minute amounts in natural foods or sometimes produced synthetically; deficiencies of vitamins produce specific disorders. We know that nitrite is produced in relatively small quantities in normal metabolism of L-arginine and NO and is found in minute amounts in natural foods. Could it be then that if one does not eat sufficient foods rich in nitrite and nitrate, specific disorders occur? I would argue yes. Our animal studies reveal that nitrite insufficiency exacerbates ischemia/reperfusion injury, and a host of cardiovascular diseases are associated with decreased NO availability as measured by nitrite in biological fluids. Becoming more evident is the enormous benefit of exogenous dietary nitrite and nitrate in a number of disease models. A simple ubiquitous molecule we have been advised to avoid may be an indispensable nutrient that many are lacking. As with any nutrient or treatment strategy, a risk–benefit evaluation should be considered. The now recognized and undisputed benefits of dietary nitrite and nitrate should be put in context to the very weak associations to its potential risks.

**REFERENCES**


