

Nitrate in foods: harmful or healthy?^{1–3}

Martijn B Katan

Nitrate and nitrite are considered hazardous, and there are legal limits to their concentration in food and drinking water. Nitrate from fertilizer accumulates in vegetables and fruit, and large-scale livestock production yields huge amounts of manure rich in nitrate that seeps into groundwater. Therefore, keeping nitrate concentrations below legal limits is a struggle for farmers. In this issue of the Journal, Hord et al (1) challenge these limits. Other authors have already pointed out that the evidence for adverse effects of nitrate is inconsistent and that nitrate may actually be beneficial (2, 3). Hord et al (1) go one step further: they claim that nitrate and nitrite should be considered as nutrients.

Many food components are beneficial at low and harmful at high intakes. Hord et al (1) claim that nitrate is beneficial at intakes now considered toxic. What do we know about the health effects of nitrate and nitrite?

The World Health Organization (WHO) first set an upper limit for nitrate in food in 1962 (4). It was based on a brief report from the US Food and Drug Administration (5), which stated the following: “sodium nitrate has been fed to rats at levels up to 10% in the diet for their lifetime. Other than some depression on growth at levels above 1% of nitrate, no adverse effects were noted in these animals. Two dogs were fed 2% sodium nitrate in their diet for a period of 105 and 125 days, respectively. No adverse effects were noted” (p 136). The WHO calculated from this that daily intakes of ≤ 500 mg of sodium nitrate/kg body weight were harmless to rats and dogs. This figure was divided by 100 to yield an Acceptable Daily Intake for humans of 5 mg sodium nitrate or 3.7 mg nitrate per kg body weight, which equals 222 mg for a 60-kg adult. That figure has stood ever since.

In the United States, concerns have focused on nitrate and methemoglobinemia in infants. Bacteria in the mouth and gut convert nitrate into nitrite, and nitrite reacts with hemoglobin to produce methemoglobin, which is no longer able to carry oxygen. In the early 1950s, methemoglobinemia and cyanosis were seen in infants fed formula made with contaminated well water. The effect was ascribed to the high nitrate content of these wells (3). The US Environmental Protection Agency (EPA) therefore set a Maximum Contaminant Level for nitrate of 44 mg/L (equal to 10 mg nitrate-nitrogen/L or 10 ppm) (6).

The nitrate in the offending wells came from fecal contamination. It is now thought that methemoglobinemia was not caused by nitrate but by fecal bacteria that infected the infants and produced

nitric oxide in their gut. Nitric oxide can convert hemoglobin to methemoglobin. The key role of intestinal infection rather than nitrate was confirmed by an experiment in 1948, in which infants who were fed $100 \text{ mg nitrate} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ did not develop methemoglobinemia. When they were fed bacteria from contaminated wells, however, methemoglobinemia did develop (3). This suggests that the nitrate concentrations commonly encountered in foods and water are unlikely to cause methemoglobinemia.

The other concern about nitrate is cancer. Nitrate and nitrite themselves are not carcinogenic, but nitrite formed from dietary nitrate might react with dietary amines to form carcinogenic nitrosamines. Such effects have been shown in animal experiments, but their relevance to humans is uncertain because of the high doses and the specific amines used in these animals. In observational studies, intake of nitrate or nitrite from diet or drinking water is not associated with cancer in humans (3, 4). An effect of exogenous nitrite on cancer also seems less likely because large amounts of nitrite are formed endogenously. Fasting saliva contains ≈ 2 mg/L, and after consumption of an amount of nitrate equivalent to 200 g of spinach, the nitrite concentration in saliva may rise as high as 72 mg/L (7). That is much higher than the EPA standard for drinking water of 4.4 mg nitrite/L or the WHO Acceptable Daily Intake of 4.2 mg nitrite/d.

Thus, evidence for adverse effects of dietary nitrate and nitrite is weak, and intakes above the legal limit might well be harmless. This is not unusual in regulatory toxicology. Many chemicals and contaminants might well be safe at intakes above their legal limit. Authorities willingly accept that possibility; erring on the safe side with many chemicals is justified if it keeps just one true carcinogen out of the food supply. But the trade-off changes when excessive caution deprives us of beneficial substances, as claimed by Hord et al for nitrate. In that case, the evidence for harm needs to be weighed against the potential benefit. But what is the evidence that nitrate and nitrite are beneficial?

¹ From the Institute of Health Sciences, VU University, Amsterdam, Netherlands.

² Supported by an Academy Professorship of the Royal Netherlands Academy of Sciences.

³ Address correspondence to MB Katan, Institute of Health Sciences, VU University, De Boelelaan 1085, 1081 HV Amsterdam, Netherlands. E-mail: katan99@falw.vu.nl.

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It is undisputed that nitrate ingestion widens arteries. Bacteria in the mouth and gut reduce nitrate to nitrite, which is then converted by nitric oxide synthase into the endothelium-derived relaxing factor nitric oxide (2). That is why sublingual nitrate can resolve an episode of angina pectoris. There is also some evidence that nitrate reduces blood pressure (8). Hord et al suggest that the blood pressure-lowering effect of vegetables in the DASH (Dietary Approaches to Stop Hypertension) Trial (9) was due to the nitrate in these vegetables. However, evidence is still scant that nitrate in the amount present in vegetables lowers blood pressure. Therefore, indications that dietary nitrate or nitrite reduces cardiovascular disease risk are insufficient to relax standards for nitrate in drinking water and foods.

What we need is a trial in which volunteers are fed matched vegetables with high or low nitrate content. Lettuce grown in winter in hothouses can contain 8 times more nitrate than the same lettuce grown in summer in the field (4). The contrast can be made even larger by using organic products; these are low in nitrate because of a lack of fertilizer. A trial to investigate whether nitrate in vegetables is healthy is thus feasible. It would require a few months, a few hundred subjects, and less money than the bonus of a second-tier banker. Such a trial urgently needs to be conducted.

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