Drinking-Water Nitrate, Methemoglobinemia, and Global Burden of Disease: A Discussion

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On behalf of the World Health Organization (WHO), I have undertaken a series of literature-based investigations examining the global burden of disease related to a number of environmental risk factors associated with drinking water. In this article I outline the investigation of drinking-water nitrate concentration and methemoglobinemia. The exposure assessment was based on levels of nitrate in drinking water greater than the WHO guideline value of 50 mg/L. No exposure–response relationship, however, could be identified that related drinking-water nitrate level to methemoglobinemia. Indeed, although it has previously been accepted that consumption of drinking water high in nitrates causes methemoglobinemia in infants, it appears now that nitrate may be one of a number of co-factors that play a sometimes complex role in causing the disease. I conclude that, given the apparently low incidence of possible water-related methemoglobinemia, the complex nature of the role of nitrates, and that of individual behavior, it is currently inappropriate to attempt to link illness rates with drinking-water nitrate levels. ***Key words:*** **burden of disease, drinking water, methemoglobinemia, nitrates.** ***Environ Health Perspect*** **112:1371–1374 (2004). doi:10.1289/ehp.7216 available via** ***http://dx.doi.org/*** **[Online 22 July 2004]**

The Global Burden of Disease project, coordinated by the World Health Organization (WHO), is an attempt to quantify and compare the level of illness at both world and regional levels. This can be done on a disease-by-disease basis (Murray and Lopez 1996) or in relation to various risk factors such as malnutrition; exposure to poor water, sanitation, and hygiene; or indoor air pollution (Murray and Lopez 1996; Prüss et al. 2002; WHO 2002). Information relating to environmental risk factors, such as the amount of illness attributable to lead in the environment (Fewtrell et al. 2004), can be very powerful in terms of informing policy decisions. Disease burden, in relation to environmental risk factors, is generally determined by establishing the exposure of the population (on a regional basis) to the chosen risk factor and combining these data with exposure–response relationships for the selected health outcomes to estimate the number of people affected with each outcome. This may then be converted into disability-adjusted life years, accounting for the severity and duration of each health outcome.

Nitrate pollution of drinking water (which has been linked with certain health outcomes) is known to be increasing (Croll and Hayes 1988; Tandia et al. 2000; WHO 1985; Young and Morgan-Jones 1980). WHO therefore considered it useful to determine whether it was possible to establish a disease burden estimate.

Health Outcomes

Nitrate is a naturally occurring ion, which makes up part of the nitrogen cycle. The nitrate ion (NO_3^-) is the stable form of combined nitrogen for oxygenated systems. Although it is chemically unreactive, it can be microbially reduced to the reactive nitrite ion. Nitrate has been implicated in methemoglobinemia and also a number of currently inconclusive health outcomes. These include proposed effects such as cancer (via the bacterial production of *N*-nitroso compounds), hypertension, increased infant mortality, central nervous system birth defects, diabetes, spontaneous abortions, respiratory tract infections, and changes to the immune system [Centers for Disease Control and Prevention (CDC) 1996; Dorsch et al. 1984; Gupta et al. 2000; Hill 1999; Kostraba et al. 1992; Kozliuk et al. 1989; Malberg et al. 1978; Morton 1971; Super et al. 1981]. Although the role of *N*-nitroso compounds and nitrite in the promotion of cancer would appear to be incontrovertible, the evidence relating to the role of nitrates is less clear (Pobel et al. 1995). Thus, methemoglobinemia was the only health outcome I considered further in this investigation.

Methemoglobin (MetHb) is formed when nitrite (for our purposes, formed from the endogenous bacterial conversion of nitrate from drinking water) oxidizes the ferrous iron in hemoglobin (Hb) to the ferric form (Fan et al. 1987). MetHb cannot bind oxygen, and the condition of methemoglobinemia is characterized by cyanosis, stupor, and cerebral anoxia (Fan et al. 1987). Under normal conditions, < 2% of the total Hb circulates as MetHb (Fan et al. 1987). Signs of methemoglobinemia appear at 10% MetHb or more, as shown in Table 1 [Craun et al. 1981; Kross et al. 1992; National Academy of Sciences (NAS) 1981]. Symptoms include an unusual bluish gray or brownish gray skin color, irritability, and excessive crying in children with moderate MetHb levels and drowsiness and lethargy at higher levels (Brunning-Fann and Kaneene 1993). Diagnosis is through the observation of chocolate-colored blood or a laboratory test showing the presence of elevated MetHb levels (Brunning-Fann and Kaneene 1993).

Infant methemoglobinemia was first linked to nitrates in drinking water by Hunter Comly in the United States in 1945. He reported on two cases and concluded that methemoglobinemia may occur in an infant after ingestion of water high in nitrates, especially if the infant was suffering from a gastrointestinal disturbance (Comly 1945). Fan et al. (1987) have noted since then that microbially poor water (i.e., high in microbes) and high drinking-water nitrate levels often go "hand in hand," and gastrointestinal illness, as a result of exposure to poor water quality, may play a role in methemoglobinemia.

Nitrate-related drinking-water methemoglobinemia is principally a disease of young children, with bottle-fed or weaned infants < 4 months of age being the most susceptible. This age group is the most susceptible because of a combination of factors (Ayebo et al. 1997), including:

- A higher gastric pH, which allows greater bacterial invasion of the stomach and hence an enhanced conversion of ingested nitrate to nitrite
- A greater fluid intake relative to body weight
- A higher proportion of fetal Hb (which may be more rapidly oxidized to MetHb than adult Hb)
- Lower NADH-dependent MetHb reductase activity (the enzyme that converts MetHb to Hb).

However, although the gastric pH in infants may be higher than that seen in adults, L'hirondel and L'hirondel (2002) have suggested that the general stomach conditions are still not really suitable for the microbial conversion of nitrate to nitrite.

Exposure Assessment

Methemoglobinemia has several causes, as shown in Table 2, including exposure to

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