

Infantile Methemoglobinemia: Reexamining the Role of Drinking Water Nitrates

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Ingestion of nitrates in drinking water has long been thought to be a primary cause of acquired infantile methemoglobinemia, often called blue baby syndrome. However, recent research and a review of historical cases offer a more complex picture of the causes of infantile methemoglobinemia. Gastrointestinal infection and inflammation and the ensuing overproduction of nitric oxide may be the cause of many cases of infantile methemoglobinemia previously attributed to drinking water nitrates. If so, current limits on allowable levels of nitrates in drinking water, which are based solely on the health threat of infantile methemoglobinemia, may be unnecessarily strict. **Key words:** blue baby syndrome, diarrhea, drinking water, gastrointestinal disturbance, methemoglobinemia, nitrates, nitric oxide. *Environ Health Perspect* 107:583-586 (1999). [Online 10 June 1999]

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Methemoglobin is a form of hemoglobin in which the heme iron is reduced to its ferric state and is unable to deliver oxygen. Methemoglobinemia results when amounts of methemoglobin in the blood become high enough to manifest clinical symptoms of cyanosis, usually about 15% of total circulating hemoglobin. Methemoglobinemia occurs for various reasons, including genetic deficiencies in key methemoglobin-reducing enzymes, genetic abnormalities in hemoglobin that make the protein more susceptible to oxidation, and exposure to oxidant drugs and chemicals, including nitrite. Infants under 6 months of age are particularly susceptible to methemoglobinemia because they have lower amounts of a key enzyme, NADH-cytochrome b_5 reductase (methemoglobin reductase), which converts methemoglobin back to hemoglobin. Infants begin making adult levels of this enzyme by about 6 months of age (1). Although it has often been reported that high levels of fetal hemoglobin in the blood of young infants contributes to their increased susceptibility to methemoglobinemia, it has been demonstrated that fetal hemoglobin has the same redox potential and rate of auto-oxidation as hemoglobin A and therefore does not contribute to the increased vulnerability (1).

For over 40 years, there has existed a widespread belief that nitrates in drinking water are a primary cause of infantile methemoglobinemia. Hunter Comly originally proposed this theory in 1945 in a report in the *Journal of the American Medical Association* after treating several infantile methemoglobinemia victims

exposed to nitrate-contaminated water (2). Comly proposed that because nitrites (NO_2^-) are known to react directly with hemoglobin to form methemoglobin, nitrates (NO_3^-) from drinking water must be converted to nitrites within the gastrointestinal tract of infants. Because many infants did not appear susceptible to methemoglobinemia from nitrate-contaminated water, Comly (2) suggested that the nitrate-to-nitrite conversion might only occur in the presence of a bacterial infection of the upper gastrointestinal tract, where such reactions could occur before nitrates are absorbed. These nitrate-derived nitrites could then react with hemoglobin to form methemoglobin and, in sufficient quantities, lead to the cyanosis of methemoglobinemia. This theory was reinforced by the fact that cyanosis typically subsided once an infant was switched to an uncontaminated water supply.

Comly's hypothesis (2) became widely accepted as further research revealed a consistent pattern of elevated well water nitrate levels in infantile methemoglobinemia cases. Limiting infant exposure to nitrates was thus decided to be the most prudent approach to protecting infant health, and a committee from the American Public Health Association (APHA) conducted a nationwide survey to determine a safe level of nitrates in water. A total of 278 cases with 39 deaths were compiled. The results showed that methemoglobinemia incidence correlated with increasing nitrate levels (Table 1) (3). Because no infantile methemoglobinemia cases were observed with concentrations < 10 ppm nitrate-nitrogen

(nitrate-N), the United States and the World Health Organization established a maximum contaminant level (MCL) of 10 ppm nitrate-N for nitrate in drinking water.

Over the last 20 years, however, a more complex picture of infantile methemoglobinemia causation has emerged which indicates that current limits on drinking water nitrates may be unnecessarily strict. It is now well established that diarrheal illness and some gastrointestinal disturbances, typically accompanied by diarrhea and/or vomiting, can lead to methemoglobinemia in young infants without exposure to high-nitrate drinking water or exposure to abnormal levels of nitrates through food. There are literally dozens of reported infantile methemoglobinemia cases associated with diarrhea without exposure to nitrate-contaminated water (4-10). Because diarrhea was a prominent symptom in the majority of drinking water-linked methemoglobinemia cases, the evidence suggests that diarrhea and/or gastrointestinal infection/inflammation, not ingested nitrates, are the principle causative factor in infantile methemoglobinemia; a survey in Germany found that 53% of 306 infantile methemoglobinemia cases reported diarrhea (11). (Contrary to some reports, diarrhea and vomiting are not symptoms that typically accompany cyanosis, methemoglobinemia due to oxidant drug exposure, or genetic abnormalities in hemoglobin.)

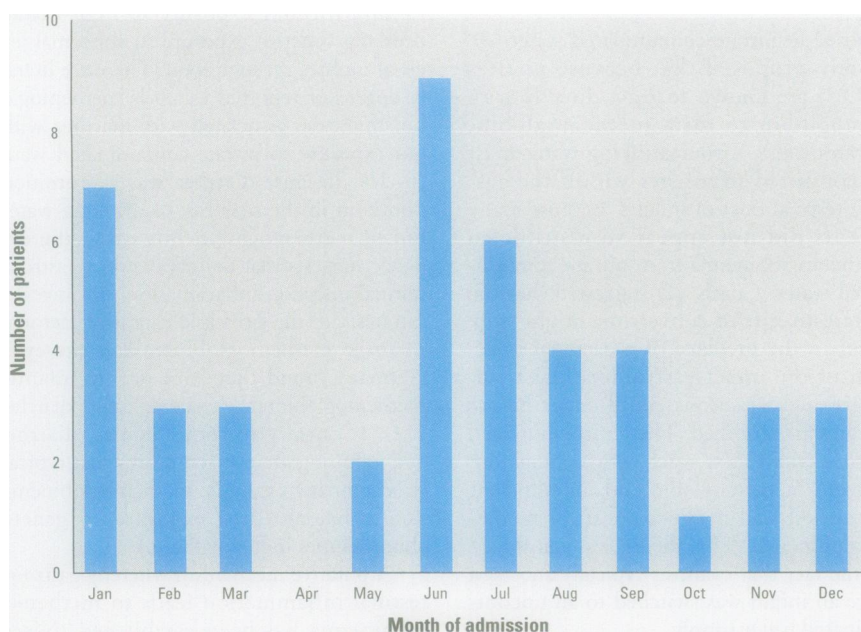
A putative mechanism whereby gastrointestinal inflammation leads to methemoglobinemia has been established. Nitric oxide (NO) is produced by several tissues in response to infection and inflammation. Increased expression of an inducible nitric oxide synthase (iNOS) mRNA has been observed in young children with inflammatory bowel disease during periods of colonic inflammation, but not, however, in the absence of colonic inflammation (12,13). A rapid up regulation of iNOS mRNA is also seen in colon epithelial cells upon infection

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Table 1. Reported cases of nitrate water-induced infant methemoglobinemia classified according to nitrate-nitrogen (nitrate-N) concentration of water used in feeding formula.^a

State	Methemoglobinemia		Number of cases associated with indicated ranges of nitrate-N concentration (ppm)						Cases with available data (n)
	Reported cases	Reported deaths	0-10	11-20	21-30	31-50	51-100	100+	
California	1	0	0	0	0	0	1	0	1
Georgia	6	3	-	-	-	-	-	-	0
Illinois	75	6	0	1	2	2	12	11	28
Indiana	1	0	0	0	0	0	1	0	1
Iowa	Several	11	0	0	0	0	1	1	2
Kansas	13	3	0	0	1	1	2	8	12
Michigan	7	0	0	0	0	0	0	7	7
Minnesota	139	14	0	2	25	53	49	129	129
Missouri	2	0	0	0	0	0	0	2	2
Nebraska	22	1	0	1	0	4	9	8	22
New York	2	0	0	0	0	0	1	0	1
North Dakota	9	1	0	1	1	0	0	6	8
Ohio	0	0	0	0	0	0	0	0	0
Oklahoma	0	0	0	0	0	0	0	0	0
South Dakota	Several	0	-	-	-	-	-	-	-
Texas	0	0	0	0	0	0	0	0	0
Virginia	1	0	0	0	0	0	1	0	1
Total	278+	39	0	5	36	81	92	214	214
Percent of total			0.0	2.3	16.8	37.8	43.1	100	

^aBased on Table 1 from Walton (3).**Figure 1.** The seasonal variation in the incidence of methemoglobinemia in a region of Israel during a 12-year period (1980-1992). Data from Hanukoglu and Danon (19).

with enteroinvasive bacteria (14). Nitrite is a product of nitric oxide metabolism, and increased expression of iNOS mRNA from colonic inflammation is accompanied by increased stool and plasma nitrate/nitrite levels (13). In young infants, overexpression of nitric oxide may lead to nitrite production sufficient to overwhelm the underdeveloped methemoglobin-reducing system, resulting in methemoglobinemia. Indeed, methemoglobinemia is a well-known side effect of nitric oxide therapy for acute respiratory distress syndrome and persistent pulmonary hypertension in newborns, and

such therapy requires close monitoring of methemoglobin levels (15).

This hypothesis is supported by observations that infants suffering from diarrhea and methemoglobinemia (without exposure to nitrate-contaminated water) excrete up to 10 times more nitrate daily than they ingest through food or water (16). As nitrites are metabolized to nitrates before excretion, excess nitrate excretion is an indicator of endogenous nitrite production. Infants with methemoglobinemia associated with gastroenteritis and/or dehydration also have significantly longer average hospital

stays than infants with methemoglobinemia secondary to oxidant drug exposure, indicating chronic, endogenous oxidant stress—presumably endogenous nitrite production from nitric oxide (17). Despite similar initial methemoglobin levels in the endogenous (mean, 29%) and exogenous (mean, 28%) groups, children in the endogenous group stayed an average of 19 days in the hospital, whereas in the exogenous group, methemoglobinemia resolved within 1 day. As Avner et al. (17) stated,

The shorter, more benign course of illness [of children with methemoglobinemia due to acute poisoning] may reflect a relatively brief exposure to the oxidant stress ... compared with ongoing exposure over a prolonged period in children with methemoglobinemia associated with gastroenteritis and dehydration.

Protein intolerance accompanied by diarrhea and/or vomiting has also been proven to cause methemoglobinemia in infants less than 6 months of age without excessive intake of nitrates through food and water (18,19). Methemoglobin levels over 35% have been recorded in protein-intolerant infants following brief exposure to the offending protein (18). Moreover, although over 90% of exogenous nitrate exposure comes from food, the only methemoglobinemia cases linked to food have involved high levels of nitrite contamination. For example, a typical case involved carrot juice containing 775 ppm nitrite-N, which is over 700 times the MCL for nitrites (20). All of these observations strengthen the view that endogenous nitrite production, not exogenous nitrate contamination of drinking water, is the primary cause of methemoglobinemia.

Epidemiological evidence suggests that infantile methemoglobinemia may also have an infectious etiology. A 54-year-old woman who suffered chronic methemoglobinemia for 15 years saw a disappearance of the condition after a 10-day course of neomycin (21). Infantile methemoglobinemia resulting from urinary tract infection has been reported in over a dozen instances (22,23). Infectious bacterial and viral gastroenteritis may underlie many infantile methemoglobinemia cases. Several methemoglobinemia cases have been reported as resulting specifically from bacterial enteritis or suspected bacterial sepsis without exposure to high nitrate water (24-26). Further, an Israeli study of 45 infant methemoglobinemia cases over a 12-year period (all from urban areas with normal concentrations of nitrate in the drinking water) revealed a seasonal variation in methemoglobinemia incidence (19). The incidence of methemoglobinemia showed

two peaks, in January ($n = 7$, 16%) and in the summer months ($n = 23$, 51%; Figure 1). As Hanukoglu and Danon (19) noted,

these [incidence] peaks correspond to times when infectious gastroenteritis is common (viral agents, especially rotavirus, in winter and bacterial agents in summer).

Hanukoglu and Danon (19) further noted that the declining incidence of methemoglobinemia observed over a decade also supported an infectious etiology (Figure 2).

The incidence of methemoglobinemia was highest before 1980 and decreased significantly to a minimum during the last 6 years of our survey. This was paralleled by a significant decrease in infant morbidity and hospitalization rates of patients with infantile diarrhea due to bacterial pathogens in our hospital during the same period, despite the increase in the pediatric population in the area served by our hospital. Presumably the morbidity of non-bacterial gastroenteritis is also decreasing. A similar trend was also observed over the whole country.

This observation is striking in that a similar drop in methemoglobinemia incidence appears to have occurred in the United States during the 1950s and 1960s. Although no data on diarrheal disease incidence for infants could be obtained for this time period, either at the state or national level, reports in the literature of infantile methemoglobinemia decreased dramatically over this time period. Reports of infantile methemoglobinemia linked to contaminated drinking water are now virtually non-existent in the United States, with only two cases reported since the mid-1960s. This drop in infantile methemoglobinemia incidence cannot be attributed solely to decreased exposure to nitrate-contaminated water supplies. The U.S. Environmental Protection Agency estimated in 1990 that 66,000 infants are exposed annually in the United States to drinking water that exceeds the federal standard of 10 ppm nitrate-N (27).

While it is often speculated that the low incidence rate for infantile methemoglobinemia could be due to a lack of reporting, that seems an unsatisfactory explanation considering the amount of attention given by health authorities and the media to infant health threats. Both of the last two reported infantile methemoglobinemia cases linked to nitrate-contaminated drinking water in the United States received extensive coverage by health authorities and the media (28,29). The first of these, in 1986, even prompted a reprint of Comly's original 1945 report (2) in the *Journal of the American Medical Association*.

If infantile methemoglobinemia is caused primarily by the endogenous overproduction of nitric oxide, an explanation must still be

found for the correlation between nitrate contamination and methemoglobinemia incidence seen in the APHA study. One possible explanation is that nitrate contamination is merely an indicator of bacterial contamination. Based on the descriptions of the drinking water wells and the prevalence of diarrhea and vomiting in the historical cases, bacterial and viral gastroenteritis were probably common in infantile methemoglobinemia cases seen in the United States during the 1940s and 1950s. The vast majority of these cases were from rural farm households served by poorly constructed wells. Often these wells were shallow, contaminated with bacteria, and close to a source of both bacterial contamination and nitrates, such as a barnyard, cesspool, leaking septic tank, or manure storage facility.

Perhaps a better explanation for the correlation between nitrate contamination and infantile methemoglobinemia incidence illustrated in Table 1 is that conditions of gastrointestinal inflammation and/or infection establish an environment predisposing toward methemoglobin production through the endogenous production of nitrites from nitric oxide. Under such conditions, exogenous nitrates exacerbate the formation of nitrite while inhibiting conversion of nitrite to ammonia and other nonharmful products. The bacterial enzyme nitrite reductase, for example, which converts nitrite to ammonia, is inhibited by an elevated concentration of nitrate (30). Higher concentrations of ingested nitrates, therefore, drive chemical reactions toward nitrite production, increasing the potential for nitrite accumulation sufficient to overwhelm the young infant's methemoglobin reduction mechanisms. Although this may only be a variation of Comly's original hypothesis (2) and the prevailing wisdom, the difference is important in that nitrates from drinking water are not the cause of the condition.

Importantly, this hypothesis offers an explanation for the wide variability in susceptibility to methemoglobinemia seen among infants. This variability has been one of the most puzzling aspects of infantile methemoglobinemia. Research conducted in the late 1940s revealed that healthy infants fed high-nitrate water (100 mg nitrate/kg body weight/day; roughly equivalent to consumption of water contaminated at 100 ppm nitrate-N) showed virtually no increase in methemoglobin levels. However, when infants who had previously suffered methemoglobinemia associated with drinking water were fed the same high-nitrate water (100 mg/kg body weight/day), their methemoglobin levels rose moderately (to a high of 11–12%) over 3 days of feeding (31). Even these previously susceptible infants exhibited

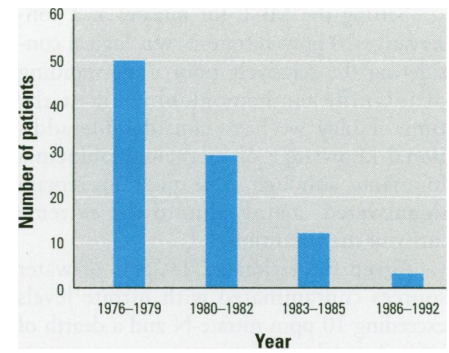


Figure 2. The number of patients hospitalized for methemoglobinemia in a region of Israel from 1980 to 1992. Data from Hanukoglu and Danon (19).

only mild increases in methemoglobin levels when subjected to a high dose of nitrates (10 times the current MCL). This may be the strongest evidence of all that exogenous nitrates do not cause methemoglobinemia and probably play a role only in the potential severity of methemoglobinemia.

Thus, limiting nitrate exposure through drinking water may not be the most protective or cost effective approach to infant health. The current strict MCL for nitrate in drinking water contributes to the widespread misperception that this is the primary cause of infantile methemoglobinemia. In fact, such cases are virtually nonexistent today, and the vast majority of cases appear related to infection and gastrointestinal problems. The strict standard also contributes to the misperception that high-nitrate foods may cause methemoglobinemia, when in all such cases the food has been shown to contain high levels of nitrite (20,32–35). These two misperceptions are potentially dangerous, as they lead pediatric physicians away from the major causes of methemoglobinemia. A more protective approach would be to inform both physicians and public health professionals of the link between methemoglobinemia and diarrhea, gastrointestinal infections, protein intolerance, and other health problems in infants under 6 months of age. This is not meant to advocate a complete abolishment of a drinking water nitrate standard, only a reassessment of the MCL for nitrate. The current limit of 10 ppm nitrate-N was based on a review of only 214 cases in the APHA study for which nitrate levels were known (36). The APHA committee itself noted that most of these cases occurred with water contaminated at greater than 40 ppm nitrate-N. However, due to the wide variation in nitrate contamination, the committee (3) remarked that

It is impossible at this time to select any precise concentration of nitrates in potable waters fed infants which definitely will distinguish between waters which are safe or unsafe.

Setting the MCL for nitrates at a conservative 10 ppm nitrate-N was logical considering the relatively poor understanding of infantile methemoglobinemia at the time. Today we have considerable additional knowledge of methemoglobinemia in infants, although some questions remain unanswered, mainly due to the extreme rarity of the condition.

Given the estimated 1–2.4% of water sources contaminated with nitrate levels exceeding 10 ppm nitrate-N and a dearth of infantile methemoglobinemia cases connected to such water sources, there is little indication that relaxing the drinking water standard for nitrate (not nitrite) to 15 or 20 ppm nitrate-N would increase the health risk to infants (27). (This is not to be confused with the MCL for nitrite. Because nitrite reacts directly with hemoglobin and has been shown to be inherently more dangerous than nitrate, the MCL for nitrite should remain unchanged.) However, raising the MCL to this level would drastically reduce the need for expensive water treatment in several large U.S. cities and countless small communities that are currently spending large sums of money to comply with the current MCL, often for only mild, seasonal spikes in nitrate levels. For example, Lake Decatur, which supplies drinking water to the city of Decatur, Illinois, has seen peak nitrate contamination of between 15 and 18 ppm nitrate-N over the past decade (37). A complete review of the drinking water nitrate standard should be conducted. The National Research Council conducted a review of the nitrate standard in the early 1990s with the purpose of determining if the current standard was adequate to protect human health; it did not address whether the standard was overly protective (36). Moreover, much has been learned since that review, especially the mechanisms of nitric oxide production, its metabolism, and the conditions under which nitrite is produced.

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