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Blue Babies and Nitrate-Contaminated Well Water

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The use of nitrate-contaminated drinking water to prepare infant formula is a well-known risk factor for infant methemoglobinemia. Affected infants develop a peculiar blue-gray skin color and may become irritable or lethargic, depending on the severity of their condition. The condition can progress rapidly to cause coma and death if it is not recognized and treated appropriately. Two cases of blue baby syndrome were recently investigated. Both cases involved infants who became ill after being fed formula that was reconstituted with water from private wells. Water samples collected from these wells during the infants' illnesses contained nitrate-nitrogen concentrations of 22.9 and 27.4 mg/L. **Key words:** blue baby syndrome, methemoglobinemia, nitrate, nitrate-contaminated well water. *Environ Health Perspect* 108:675-678 (2000). [Online 6 June 2000]

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Blue baby syndrome is a potentially fatal condition that occurs when the hemoglobin (Fe^{2+}) in an infant's red blood cells is oxidized to methemoglobin (Fe^{3+}). Because methemoglobin is unable to transport oxygen, the condition produces symptoms of cyanosis. Affected infants develop an unusual blue-gray or lavender skin color and are often described as irritable or lethargic, depending on the severity of their illness. Methemoglobin levels > 50% can quickly lead to coma and death if the condition is not recognized and treated.

A variety of risk factors including inherited enzyme deficiencies, infectious and inflammatory conditions, drug reactions, and chemical exposures can increase methemoglobin levels. The most common environmental agent associated with this diagnosis is nitrate-contaminated water; however, foods that are high in nitrate or nitrite may also be involved. Infants are particularly susceptible to the condition during their first 6 months of life because they have low amounts of methemoglobin reductase, a red blood cell enzyme that converts methemoglobin back to hemoglobin. The impact of these risk factors is additive.

The association between nitrate-contaminated well water and blue baby syndrome was first described by Hunter Comly, an Iowa City physician, who treated two infants for symptoms of cyanosis during the early 1940s (1). He found that both infants became ill after they were fed formulas that were diluted

with water from shallow wells. Nitrate-nitrogen (nitrate-N) concentrations in the related wells were 90 and 150 mg/L. After Comly's findings were published, many similar cases were reported. In 1951, Walton (2) reviewed data from 278 cases that had been reported by 14 different states. Although health care providers and water quality experts have greatly reduced infant exposure to nitrate-contaminated water, emergency room physicians and pediatricians continue to diagnose and treat infants for this condition. The Wisconsin Department of Health and Family Services (Madison, Wisconsin) has an active surveillance program for methemoglobinemia. In this paper, we summarize findings from two recent case investigations.

Case Summaries

Case 1. During June 1998, public health nurses in Columbia County, Wisconsin, noted that a 6-month-old white male, who had been brought to a clinic in the Village of Cambria for immunizations, appeared cyanotic. The skin around his mouth and nose was unusually gray. According to his parents, the infant's skin color had been "gray" and he had been "crabbier than normal" for a couple of weeks. The infant also had a 6-week history of vomiting after feedings, which began shortly after the family moved to a new home that had a private water supply. Their previous residence was served by a municipal water system. The infant's daily diet consisted of 24 oz formula, 6 oz cereal,

and 4-6 oz fruit (type not specified). The formula consisted of a powdered concentrate that was diluted with water from the family's well. Because of concern that the infant's illness might have been caused by nitrate-contaminated water, a public health nurse visited the family's home the following day to collect a water sample. The laboratory analysis indicated that the well was bacteriologically safe but had a nitrate-N concentration of 22.9 mg/L. The family was notified of these results and advised to use bottled water for formula preparation. They were also urged to have the infant examined by a physician.

This infant's parents reported that his skin color and temperament improved within a week after they began using bottled water to prepare his formula. The infant was examined by a physician's assistant 12 days after being placed on bottled water. At that time he appeared healthy and had a methemoglobin level of 0.5% (normal range 0.1-1.9%). His cardiac and pulmonary functions were normal.

This family shared a well with a neighboring home. The 178-ft well was drilled in 1989 and was cased to a depth of 42 ft. The family's home is situated in an area of rolling hills that is intensively farmed. Local crops include hay, corn, and soybeans. Both homes have mound-type septic systems that comply with local and state codes. Water collected from the well during August 1998 had a nitrate-N concentration of 30.5 mg/L. First draw and flushed tap water samples were low in copper (48 and 31 $\mu\text{g/L}$, respectively).

Case 2. During April 1999, a 3-week-old white female was admitted to an emergency room in Grant County, Wisconsin. According to her parents, she had been healthy until the night before admission when she became irritable and fussy. On the

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day of her admission, the parents reported that the infant had turned "completely blue" and was having breathing difficulties. Local emergency room staff noted that the infant was dehydrated, dusky, and cold to the touch. Her temperature was 90°F and her oxygen saturations remained in the low 80s while on 100% oxygen per nasal cannula. She was given a dose of intramuscular ceftriaxone, stabilized with warming blankets and intravenous fluids, and transported by MedFlight to a regional medical center.

On arrival, the infant was described as irritable. Her skin appeared pale, cyanotic, and mottled. An echocardiogram revealed a normal functioning, well-formed heart. Laboratory studies indicated a hemoglobin concentration of 11.5 g/dL, with a methemoglobin concentration of 91.2%. Blood gas analyses also indicated a profound metabolic acidosis (pH 6.72). This infant responded rapidly to treatment with methylene blue, oral bicarbonate, and intravenous fluids.

This infant lived with her parents and grandparents on a goat dairy farm in southwestern Wisconsin. She was born at 37 weeks gestation, weighed 5 lb 2 oz at birth, and had been doing well on a liquid concentrate formula that was diluted with bottled water. She became ill 1–2 days after her parents ran out of bottled water and began using water from the farm well to prepare her formula. The parents boiled the well water several minutes before using it. Water samples collected from the well 2 days after the infant was hospitalized tested positive for *E. coli* bacteria and had a nitrate-N concentration of 27.4 mg/L. Copper and lead concentrations were low at 29 and 0.9 µg/L, respectively.

The physicians who cared for this infant concluded that her illness was caused by ingestion of nitrate-contaminated well water. Metabolic disorders were ruled out after serum amino acids, urine organic acids, and metabolic screening were all determined to be within normal limits. Infectious illnesses apparently did not contribute to her illness. She remained afebrile throughout her hospitalization and did not receive antibiotic therapy. The infant was discharged 17 days after admission. At this time her parents were instructed not to use well water to prepare her formula.

Based on available well logs, it appears that the family's well was built in 1951. The well was originally constructed to a depth of 85 ft and had 30 ft of casing. In 1952 the well was drilled deeper, from 85 ft to 228 ft. An unused tin-cased well was also located on the property approximately 200 ft from the active well and immediately downgradient from the barnyard. Potential sources of nitrate were identified as barnyard runoff, septic tank effluent, and agricultural fertilizers.

Discussion

Since 1990, the Wisconsin Department of Health and Family Services has investigated three cases of methemoglobinemia in infants who were exposed to nitrate-contaminated well water. The first of these occurred in 1992 and was described in a 1993 issue of *Morbidity Mortality Weekly Report* (3). That case involved a 6-week-old infant who was hospitalized twice for symptoms of vomiting, diarrhea, and cyanosis. On her second admission, she was found to have a methemoglobin concentration of 21.4%. A detailed investigation concluded that her illness was caused by exposure to water that contained elevated levels of nitrate and copper. Although vomiting and diarrhea are frequently signs of gastrointestinal infection, in this case there was no evidence of a concurrent infectious process. Investigators concluded that these symptoms were caused by the irritant effects of copper that had leached from the household plumbing.

The occurrence of two additional cases during 1998 and 1999 suggests that nitrate-contaminated groundwater continues to be an important infant health problem in rural Wisconsin. Although case 1 was not confirmed by a laboratory analysis, the infant's cyanotic appearance and nitrate exposure history support a presumptive diagnosis of methemoglobinemia as described by Bosch et al. (4). Spontaneous improvement of the infant's condition after he was switched to bottled water lends further support to this diagnosis. The manner in which this case was handled by the county health department is typical of public health interventions practiced throughout Wisconsin and in many other regions of the United States. In rural areas where private well use is common, awareness of blue baby syndrome is widespread. Health care providers and others who are familiar with the condition frequently advise parents of sick infants to use bottled water for formula preparation or to use prepared formula. The combination of community awareness and early intervention has reduced the number of infants who require medical treatment for the condition.

Unfortunately, this safety net is not always effective. Case 2 illustrates the devastating consequences of neonatal nitrate exposure. That case involved a 3-week-old infant who was transported by helicopter to a regional pediatric intensive care unit with a life-threatening methemoglobin concentration. The nitrate-N concentration in the well water that was used to prepare her formula was 27.4 mg/L—less than 3 times the current federal drinking water standard for this contaminant. Extensive medical diagnostics ruled out underlying metabolic disorders and

infectious illnesses as contributing factors to her illness.

Other reports of nitrate-induced methemoglobinemia. In a 1999 case report, Herman et al. (5) described the treatment of a 6-week-old infant with an intraosseous infusion of methylene blue after she was hospitalized with a methemoglobin concentration of 29.3%. Herman et al. (5) concluded that her

... methemoglobinemia was ... caused by the well water used to prepare the child's feedings, and ... may have been exacerbated by a recent diarrheal illness.

Unfortunately, their case report did not provide specific information about the well or the results of water quality tests.

The national death certificate database maintained by the Center for Disease Control and Prevention (Atlanta, GA) includes six infant deaths that were attributed to methemoglobinemia [*International Classification of Diseases, Revision 9* (ICD-9 code 289.7)] between 1979 and 1996. These included two male and four female infants who were residents of Jim Wells County, Texas (1980); Kingsbury County, South Dakota (1986); New Orleans Parish, Louisiana (1986); Henry County, Virginia (1988); Garfield County, Colorado (1994); and Mesa County, Colorado (1996). It is unclear how many of these deaths might have been caused by exposure to nitrate-contaminated water because only the case in South Dakota was reported in the literature (6). The South Dakota case involved an infant who experienced several episodes of cyanosis after her mother stopped breast-feeding and began feeding her powdered formula that was reconstituted with water from the family's private well. At 8 weeks of age, the infant became acutely ill with symptoms of vomiting, diarrhea, and severe cyanosis. Her parents rushed her to a local physician who administered oxygen for several minutes. When the infant's color did not improve, the family was referred to a hospital 33 miles away. The infant stopped breathing on the way to the hospital and could not be resuscitated. The nitrate-N concentration in a water sample collected from the family's well after her death was 150 mg/L.

Infant exposure to nitrate-contaminated water continues to be a common public health problem in Eastern Europe. Ayebo et al. (7) found methemoglobinemia incidence rates ranging from 24 to 363 cases per 100,000 live births in the Transylvania region of Romania between 1990 and 1994. The average age at diagnosis was 39 days. Investigators identified the primary cause of methemoglobinemia to be the use of polluted well water to dilute formula concentrates. Over a 14-year period, the Poison Information Center in Krakow,

Poland, investigated 239 cases of infant methemoglobinemia, and reported that 90% of these illnesses were associated with ingestion of contaminated water (8).

Regulation of nitrate in drinking water. The Safe Drinking Water Act (9) established a maximum contaminant concentration for nitrate-N of 10 mg/L. This federal standard is used to ensure the safety of public water supplies, but does not apply to private wells. According to a recent report to Congress, approximately 15 million families in the United States obtain their drinking water from unregulated, domestic wells (10). In a 1994 survey of 5,500 private water supplies in nine Midwestern states, 13% of the wells were found to have nitrate-N concentrations > 10 mg/L (11). If the rate of contamination is similar in other regions of the nation, an estimated 2 million household water supplies may fail to meet the federal standard. Based on current birth rates (12), approximately 40,000 infants < 6 months of age are expected to be living in homes that have nitrate-contaminated water supplies.

In a paper titled "Infantile Methemoglobinemia: Reexamining the Role of Drinking Water Nitrates," Avery (13) stated that

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.

Avery (13) discussed several recent reports of elevated methemoglobin levels in infants who were hospitalized because of prematurity or severe diarrhea and concluded that

... endogenous nitrite production, not exogenous nitrate contamination of drinking water, is the primary cause of methemoglobinemia.

In the final paragraph of his paper, Avery (13) wrote,

... 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.

Our findings do not support Avery's conclusions regarding the roles of gastrointestinal infections and nitrate-contaminated water in the etiology of infant methemoglobinemia, nor do they support a higher drinking water standard for nitrate. Avery's statements regarding the low incidence of nitrate-induced illness (13) are based on an assumption that all cases of infant methemoglobinemia are investigated to determine their cause and are then described in the literature. Unfortunately, this is not the case. For example, only one of the six methemoglobinemia deaths in the national death index was reported in the literature. Upon investigation, we found that the respective state and local health departments

were often unaware of these deaths. Most physicians and state and local public health officials do not have time to conduct detailed investigations and have even less time to prepare case reports for publication. These case reports, if written, might not be published if the topics were not deemed newsworthy.

Investigation during the infant illness is essential. However, cases are often identified using data systems such as electronic death certificates and hospital discharge records. Such data is typically not available until 6 months to 1 year after the illness. Retrospective investigation and analysis of these illnesses is difficult because the condition can be induced by a wide variety of chemical exposures (Table 1). It is often impossible to reconstruct an infant's exposure to environmental agents, nitrate-rich foods, contaminated water, and medications.

Almost 20 years ago Hegesh and Shiloah (15) described the role of endogenous nitrate production in the etiology of infant methemoglobinemia. They studied 58 infants (1 week to 1.5 years of age) who were hospitalized for treatment of diarrhea. After finding that some of the infants were excreting more nitrate than was provided in their diets, Hegesh and Shiloah (15) concluded that infants with diarrhea were able to synthesize up to 875 μmol (12.2 mg) nitrate-N per day. Methemoglobin levels in these infants ranged from < 0.4% to > 8%, and were positively correlated with blood nitrate concentrations. None of the infants were described as having symptoms consistent with clinically significant methemoglobinemia, such as cyanosis or tachycardia. Two conclusions can be drawn from this research: *a*) exposure to as little as 12 mg nitrate-N per day can significantly increase an infant's methemoglobin level, and *b*) infants with diarrhea are at risk of developing methemoglobinemia, even in the absence of dietary nitrate exposure.

Since Hegesh and Shiloah's research (15) was published, several similar studies have confirmed their findings (16–18). Most have found mildly elevated methemoglobin levels in infants who were hospitalized due to prematurity or gastrointestinal infections. Only a small percentage of infants in these cohorts had clinically significant methemoglobin levels. Unfortunately, none of the case reports provides detailed information about secondary risk factors such as *a*) inherited enzyme deficiencies, or *b*) exposure to methemoglobin-inducing agents such as local anesthetics (19) or nitric oxide, which is used to enhance oxygenation in premature infants (20).

Other potential health concerns. Although approximately 2 million U.S. families drink water from private wells that fail to meet the federal drinking water standard for nitrate-N,

little is known about the reproductive and chronic health effects of their exposure to nitrate. Families with nitrate-contaminated wells should not use the water to prepare infant formula. Experts disagree about the need to issue advisories to pregnant women. In a recent study in Indiana, high nitrate concentrations were found in several wells used by women who had suffered miscarriages (21). Some of the women had successful pregnancies after they stopped drinking water from these wells. Most state health agencies provide no specific guidance on the use of nitrate-contaminated water by other household members, despite recent reports that prolonged exposure might increase the risk of a variety of health problems.

Studies conducted in Spain (22), China (23), and Taiwan (24) suggest that long-term ingestion of nitrate-contaminated water may increase the risk of gastric cancer. The proposed mechanism involves the conversion of ingested nitrate to nitrite, followed by the transformation of nitrite to nitrosamines. An ecologic study of cancer incidence in the United Kingdom (25) failed to confirm an association between nitrate exposure and gastric cancer, but higher incidences of brain and central nervous system cancers were found in areas with elevated nitrate concentrations. In addition to these findings, Ward et al. (26) reported that long-term exposure to nitrate-contaminated drinking water may contribute to the risk of non-Hodgkin lymphoma.

In 1992, Kostraba et al. (27) suggested that low-level nitrate exposure may play a role in the etiology of insulin-dependent diabetes mellitus. The authors theorized that ingested nitrate damages the insulin-producing cells in

Table 1. Methemoglobin-inducing substances.

Substance	Uses
Aniline dyes	Laundry inks, markers
Benzocaine, lidocaine	Local anesthetics
Chlorates	Matches
Isobutyl nitrite	Room deodorizers
Naphthalene	Moth balls
Nitrate/nitrite	Drinking water, fruits, vegetables, cured meats
Nitric oxide	Inhalant used to treat pulmonary hypertension in newborns
Nitrobenzene	Metal cleaners
Nitroethane	Nail care products
Nitrogen oxides	Auto emissions, wood smoke, gas-burning appliances
Nitroglycerine	Angina drug, explosives
Resorcinol	Antipruritic, over-the-counter medications
Sodium nitrite	Pickling salts, boiler conditioners, cleaning solutions
Sulfonamides	Antibiotics

Adapted from the ATSDR (14).

the pancreas through the generation of free radicals. In 1994, Virtanen et al. (28) report results from a nationwide case-control study of childhood diabetes in Finland. They found that case children and their mothers had higher intakes of nitrite-rich foods than did control children and their mothers. Virtanen et al. (28) did not find an association between diabetes and exposure to nitrate-contaminated water. In a 1997 study conducted at the University of Leeds, Parslow et al. (29) reported that the risk of childhood diabetes increased from a baseline of 1.00 at nitrate concentrations < 3.22 mg/L to 1.27 at concentrations > 14.85 mg/L. These concentrations correspond to 0.7 and 3.34 mg nitrate-N per liter, respectively.

Nitrate exposure may also play a role in the development of thyroid disease. In the Netherlands, Van Maanen et al. (30) recently evaluated thyroid volume and function in populations exposed to different nitrate concentrations in their drinking water. Their research revealed a dose-dependent difference in the volume of the thyroid between low and medium nitrate-exposure groups versus high nitrate-exposure groups. The authors observed thyroid hypertrophy at nitrate concentrations > 50 mg/L (11mg/L as nitrogen) (30). An inverse relationship was established between the volume of the thyroid and serum thyroid stimulating hormone levels (30).

Conclusions

In this paper we describe two recent cases of infant methemoglobinemia, or blue baby syndrome, that were associated with the use of water from shallow private wells to dilute formula concentrates. Nitrate-N concentrations in these water supplies ranged from 22.9 to 27.4 mg/L. These cases serve as reminders of the hazard that nitrate-contaminated water poses to infants during the first 6 months of life. Chronic exposure to nitrate-contaminated drinking water has also

been linked to cancer, thyroid disease, and diabetes. In an effort to ensure the safety of rural water supplies, action should be taken to reduce nitrate inputs to groundwater. In addition, families with private water supplies should conduct annual or semiannual testing and avoid drinking the water if the nitrate-N concentration exceeds the federal drinking water standard of 10 mg/L.

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