Nitrates and Nitrites

TEACH Chemical Summary

U.S. EPA, Toxicity and Exposure Assessment for Children's Health

This TEACH Chemical Summary is a compilation of information derived primarily from U.S. EPA and ATSDR resources, and the TEACH Database. The TEACH Database contains summaries of research studies pertaining to developmental exposure and/or health effects for each chemical or chemical group. TEACH does not perform any evaluation of the validity or quality of these research studies. Research studies that are specific for adults are not included in the TEACH Database, and typically are not described in the TEACH Chemical Summary.

I. INTRODUCTION

Nitrates and nitrites are chemicals used in fertilizers, in rodenticides (to kill rodents), and as food preservatives (1-5). Nitrates and nitrites come in various forms, but when dried are typically a white or crystalline powder. Nitrate (NO_3^-) and nitrite (NO_2^-) are also naturally-occurring compounds that are a metabolic product of microbial digestion of wastes containing nitrogen, for example, animal feces or nitrogen-based fertilizers (2, 4). Sodium and potassium nitrates are used as fumigants in canisters, which are placed underground in rodent dens and holes, and then ignited to explode and release gases that kill the rodents (1, 3). Sodium nitrite is a food additive that is used as a preservative (4, 5).

Likely exposure pathways for children include ingesting contaminated drinking water, most commonly of concern for private wells (4); and foods containing preservatives, particularly cured meats such as hot dogs and lunch meats (4-7). Nitrates have also been detected in fruits and vegetables (6, 8-10).

Exposure to nitrates and nitrites at levels above health-based risk values (see Section VI in this Chemical Summary) has been reported to have adverse health effects on infants and children. The health effect of most concern to the U.S. EPA for children is the "blue baby syndrome" (methemoglobinemia) seen most often in infants exposed to nitrate from drinking water used to make formula (11). Infants of ages 0-3 months are at highest risk for blue baby syndrome because their normal intestinal flora contribute to the generation of methemoglobin; older children and adults can experience this syndrome, but at higher concentrations of nitrates (2, 4). The blue baby syndrome is named for the blue coloration of the skin of babies who have high nitrate concentrations in their blood. The nitrate binds to hemoglobin (the compound which carries oxygen in blood to tissues in the body), and results in chemically-altered hemoglobin (methemoglobin) that impairs oxygen delivery to tissues, resulting in the blue color of the skin (4, 12). The blue coloration can be seen in the lips, nose, and ears in early stages of blue baby syndrome, and extend to peripheral tissues in more severe cases. Reduced oxygenation of the tissues can have numerous adverse implications for the child, the most severe of which are coma and death (4).

Exposure to higher levels of nitrates or nitrites has been associated with increased incidence of cancer in adults, and possible increased incidence of brain tumors, leukemia, and nasopharyngeal (nose and throat) tumors in children in some studies (8, 9, 11, 13-19) but not others (20-29). The U.S. EPA concluded that there was conflicting evidence in the literature as to whether exposures to nitrate or nitrites are associated with cancer in adults and in children (1, 2).

II. EXPOSURE MEDIA AND POTENTIAL FOR CHILDREN'S EXPOSURE[1]

Exposure Media	Relative Potential for Children's Exposure[2,3]	Basis[4]
Diet	Higher	Use of nitrate fertilizer on crops can result in higher concentrations in some foods. Nitrites and, less often, nitrates are used as preservatives in foods such as cured meats, for example, bacon and salami. Nitrates have been found in vegetables and some baby foods that contain vegetables.
Groundwater	Medium	Nitrates and nitrites in fertilizers readily migrate from fertilized soil to groundwater.
Drinking Water	Medium	For many situations, the potential for children's exposure from drinking water is medium to low. The potential can be higher when private wells become contaminated with nitrates from feed lot and agricultural runoff, and contaminated groundwater. Some geographic areas are at higher risk of drinking water contamination of private wells with nitrates.
Sediment	Lower	Nitrates and nitrites are highly water soluble and therefore less likely to partition to sediment.
Soil	Lower	Nitrates and nitrites are not retained in soil and quickly partition to any water phase.
Ambient Air	Lower	Nitrates and nitrites are not volatile and are not generally released into the air. Registered users of fumigant canisters containing nitrates for killing of rodents follow strict use protocols that limit exposure to fumes from its use.
Indoor Air	Lower	Nitrates and nitrites are not usually released in indoor air. Use of nitrite or nitrate inhalants from commercial products in the home may be a concern for adolescents.

[1] For more information about child-specific exposure factors, please refer to the Child-Specific Exposure Factors Handbook (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55145).

[2] The Relative Potential for Children's Exposure category reflects a judgment by TEACH Workgroup, U.S. EPA, that incorporates potential exposure pathways, frequency of exposure, level of exposure, and current state of knowledge. Site-specific conditions may vary and influence the relative potential for exposure. For more information on how these determinations were made, go to http://www.epa.gov/teach/teachprotocols_chemsumm.html.

[3] Childhood represents a lifestage rather than a subpopulation, the distinction being that a subpopulation refers to a portion of the population, whereas a lifestage is inclusive of the entire population.

[4] Information described in this column was derived from several resources (e.g., 1-5) including studies listed in the TEACH Database (http://www.epa.gov/teach).

III. TOXICITY SUMMARY[5, 6]

Reduced oxygenation of hemoglobin (methemoglobinemia) has been reported after exposure to nitrate- and nitrite-contaminated drinking water; also called the "blue baby syndrome" because of the cyanotic (oxygen-deficient) symptoms that result from the reduced oxygenation of the blood (2, 4). Infants less than 4 months old are the most sensitive population for methemoglobinemia following exposure to nitrates and nitrites, but it does occur in older age groups (12, 13, 30-33). Severe methemoglobinemia can lead to coma or death (2, 4).

Other health effects following fetal exposure to elevated levels of nitrates in drinking water included intrauterine growth retardation (34), increased incidence of Sudden Infant Death Syndrome (SIDS) (35), cardiac defects (36), and increased risk of nervous system defects (37-40).

The U.S. EPA concluded that there was conflicting evidence in the literature as to whether exposures to nitrate or nitrites are associated with cancer in adults and in children (1, 2). The types of cancers studied included non-Hodgkin's lymphoma as well as stomach and gastric cancers in adults (11); and brain tumors, leukemia, and nasopharyngeal cancers in children (13-18, 20-25, 28, 29). Maternal (during pregnancy) or child consumption of nitrite-containing meats may be associated with increased incidence of brain tumors in children (for more details, see Human Exposures and Effects section) (13, 15-17).

A few studies have reported other health effects that are possibly associated with nitrate exposure in children, including increased incidence of childhood diabetes (41), recurrent diarrhea (42), and recurrent respiratory tract infections (43). Other reported effects of chronic exposure reported in adults include frequent urination and spleen hemorrhaging (bleeding) (2, 4). Acute high dose ingestion exposure to nitrates can cause abdominal pain, muscle weakness, blood in stools and urine, fainting, and death (4).

Carcinogenicity Weight-of-Evidence Classification[7]: There is no weight-of-evidence classification in the U.S. EPA IRIS file available at this time for either nitrates (http://www.epa.gov/iris/subst/0076.htm) or nitrites (http://www.epa.gov/iris/subst/0078.htm). The World Health Organization International Agency for Research on Cancer (IARC) ranked nitrates and nitrites high on the priority list for upcoming review of possible carcinogenicity of ingested nitrates and nitrites (http://monographs.iarc.fr/ENG/Meetings/prioritylist.pdf).

[5] Please refer to research article summaries listed in the TEACH Database for details about study design considerations (e.g., dose, sample size, exposure measurements).

[6] This toxicity summary is likely to include information from workplace or other studies of mature (adult) humans or experimental animals if child-specific information is lacking for the chemical of interest. Summaries of articles focusing solely on adults are not listed in the TEACH Database because the TEACH Database contains summaries of articles pertaining to developing organisms.

[7] For recent information pertaining to carcinogen risk assessment during development, consult "Guidelines for Carcinogen Risk Assessment and Supplemental Guidance on Risks from Early Life Exposure" at *http://www.epa.gov/cancerguidelines*.

IV. EXPOSURE AND TOXICITY STUDIES FROM THE TEACH DATABASE

This section provides a brief description of human and animal studies listed in the TEACH Database. These descriptions generally include the overall conclusion in each study without evaluation or assessment of scientific merit by TEACH. For more details about doses and exposure levels, query the TEACH Database. Any consideration of adverse events should include an understanding of the relative exposure on a body weight basis. In many cases, exposure levels in animal studies are greater than exposure levels normally encountered by humans.

A. *HUMAN EXPOSURE AND EFFECTS*

- Nitrate contamination of drinking water is of special concern in agricultural areas (4, 12, 30, 44, 45). Nitrate-contaminated drinking water often arises as a result of fertilizers applied to crops, which are converted to nitrate in the soil and then seep into groundwater and into private residential wells. Of particular concern is proximity of animal feed lots to some groundwater sources of drinking water, which may lead to groundwater contamination with nitrates from run-off from these feed lots (3, 6, 11, 12).
- Nitrates have been measured in foods, and have been detected in vegetables and preserved meats (6-8, 10, 13, 46, 47), and baby foods (9, 48, 49). Nitrate and nitrite intakes for children in Estonia were estimated from measures of nitrate and nitrite concentrations in meat products (50) and in vegetables (10).
- Nitrates have been detected in breast milk, and concentrations increased with increasing consumption of nitrates by the mother (51). Nitrates have also been measured in blood and stools of children (46).
- Nitrite exposure of teens from use of nitrite inhalants (e.g., “poppers” also called amyl nitrate, gasoline, shoe polish, halothane, whippets, and spray paints) has been reported in a survey of teens (52) (See Considerations for Decision Making).
- Measurement of methemoglobin concentrations in blood has been used as a biomarker of effect for infants and children (43). Some studies found an association between concentrations of methemoglobin in blood and nitrate exposure (33, 53), but other studies did not (45, 54).
- Health effects that were significantly associated with nitrate or nitrite exposure during pregnancy include increased incidence of intrauterine growth retardation (34), cardiac defects (36), central nervous system defects (37-40), Sudden Infant Death Syndrome (SIDS) (35), and miscarriage (55).
- The most sensitive health effect endpoint for nitrate exposure is methemoglobinemia in infants, also called “blue baby syndrome”. When humans metabolize nitrate, an alternative form of hemoglobin, called methemoglobin, is formed and is detectable in blood. Infants with blue baby syndrome turn blue because their red blood cells, which contain methemoglobin, have a decreased ability to carry oxygen. Blue baby syndrome has been reported following exposure of infants to nitrate-contaminated drinking water (12, 30-33). Infants of ages 0-3 months are at higher risk for blue baby syndrome because their normal intestinal flora contribute to the generation of methemoglobin; older children and adults can experience this syndrome, but at higher concentrations of nitrates (2, 4).

- The U.S. EPA concluded that there was conflicting evidence in the literature as to whether exposures to nitrate or nitrites are associated with cancer in adults and in children (1, 2). Exposures to nitrates or nitrites during pregnancy, and possible associations with incidence of cancer in children, have been studied. Two studies reported that increased risk of brain tumors in children was significantly associated with increased maternal consumption of increasing amounts of cured meats (containing nitrates and nitrites) during pregnancy (13, 17).
- Possible associations between childhood nitrate exposure and cancer have been investigated. Children living in areas with higher nitrate levels in drinking water had higher levels of some forms of chromosomal damage than control children living in areas with lower nitrate levels (56). In some studies, increased incidence of childhood brain cancer (13, 15-18) and nasopharyngeal cancer (21) correlated with childhood nitrate exposure in the diet or drinking water, though other studies found no such correlations for some of the same cancers (20-27). An association between nitrate exposure and incidence of childhood leukemias was found in one study (57) but not in two others (28, 29). Living in areas with high nitrate levels in drinking water during childhood was associated with a higher incidence of testicular cancer (58) or urothelial cancer (a specific cancer of the urogenital tract) (23).
- Effects on other systems in humans have been associated with childhood exposure to nitrates or nitrites (41-43, 59-62). Exposure of children to nitrates or nitrites was associated with increased incidence of childhood diabetes in one study (41), but not others (59-61). Single studies have reported associations between children's exposure to nitrates or nitrites, and recurrent respiratory tract infections (43), increased risk for thyroid disorders during adulthood (59), or recurrent diarrhea (42).

B. EXPERIMENTAL ANIMAL EXPOSURE AND EFFECTS

- Several experimental animal studies of health effects following prenatal exposure to nitrates or nitrites have been reported (all studies summarized here involved exposure via maternal ingestion). Results of studies of teratogenic effects in offspring following maternal exposure to nitrates or nitrites during pregnancy were equivocal. For example, adverse effects were observed in offspring following prenatal exposure, including delays in brain development in the hippocampal region (63), decreased fetal weight gain (64, 65), increased fetal mortality (64), and delayed acquisition of certain behaviors (66). However in other studies, prenatal exposure resulted in no observable teratogenic effects following prenatal exposure to nitrate (67, 68) or nitrite (67, 69).
- Effects of prenatal exposure of mice to nitrites on the hematopoietic (blood cell formation) system revealed increased liver hematopoiesis in fetuses in one study (70). The liver is a major organ for blood cell development in fetuses. In another study, increased levels of methemoglobin were observed in pregnant mothers but not their fetuses following prenatal exposure to nitrite (71).

- Prenatal exposure to mixtures of sodium nitrite with other chemicals may have different effects than each chemical alone. For example, sodium nitrite administered together with ethylurea induced malformations in fetuses, including eye, brain, kidney, and skeletal defects; such malformations were not induced by administration of either chemical alone in this study (72). Increased incidence of brain tumors was observed in hamster offspring following concurrent maternal exposure to nitrite and ethylurea during pregnancy (73, 74). Nitrite and ethylurea are thought to chemically react in the gastrointestinal tract to form the potent carcinogen, ethylnitrosourea (73). Female offspring had a higher incidence of tumors than male offspring (74).

V. CONSIDERATIONS FOR DECISION-MAKERS

This section contains information that may be useful to risk assessors, parents, caregivers, physicians, and other decision-makers who are interested in reducing the exposure and adverse health effects in children for this particular chemical. Information in this section focuses on ways to reduce exposure, assess possible exposure, and, for some chemicals, administer treatment.

- The most likely exposure pathways for children are ingestion of contaminated drinking water and ingestion of food containing preservatives, such as cured meats and hot dogs (2, 4, 5).
- General consumer information on preservatives in food is available from the U.S. FDA (75, 76).
- Some nitrites in household products have been used as inhalants by adolescents and adults to enhance sexual performance, and are commonly called "poppers" (77). Compounds include amyl, butyl, isobutyl, and cyclohexyl nitrites, and are often sold in small brown bottles and labeled as "video head cleaner," "room odorizer," "leather cleaner," or "liquid aroma" (77).
- The U.S. EPA Oral Reference Dose (RfD) and the Maximum Contaminant Level (MCL) for drinking water (see Toxicity Reference Values in this document) are set to prevent methemoglobinemia in infants, the most sensitive health endpoint in children (78).
- The MCL is 1 mg/L for nitrites and 10 mg/L for nitrates in drinking water. As a potential health effect, the U.S. EPA states that, "Infants below the age of six months who drink water containing nitrate in excess of the MCL could become seriously ill and, if untreated, may die" (78). The U.S. EPA makes the same statement for nitrite in water (78).
- Caregivers may consider an alternate water supply, e.g. bottled water, where nitrate-contaminated ground water may be impacting drinking water.
- The U.S. EPA regulates public water systems, and does not have the authority to regulate private drinking water wells that serve fewer than 25 people (79). Some states may have rules to protect users of these wells. The U.S. EPA urges owners of private wells to have their well water tested annually and more often if someone in the household is pregnant or nursing. The U.S. EPA urges owners to test their well water for nitrate concentrations and several other contaminants (80).
- Nitrates are not filtered out of drinking water using filtration devices that utilize only carbon or activated carbon filtration. Nitrates can be filtered from drinking water using ion exchange, reverse osmosis, or electrolysis methods (81).

- A Nitrate/Nitrite Toxicity Case Study in Environmental Medicine is available from the U.S. Agency for Toxic Substances and Diseases Registry (ATSDR), which provides clinical information for physicians on the diagnosis and treatment of nitrate and nitrite toxicity. Details of a case study of a 2 month-old infant with blue baby syndrome is included (4).
- Consult the "Child-Specific Exposure Factors Handbook," EPA-600-P-00-002B, for factors to assess children's drinking water consumption rates (82). An updated External Draft of the 2006 version of this handbook is available (83).

VI. TOXICITY REFERENCE VALUES

Oral/Ingestion

U.S. EPA Reference Dose (RfD) for Chronic Oral Exposure:

Nitrate, 1.6 mg/kg-day, based on the critical effect of early clinical signs of methemoglobinemia in infants (excess of 10%) 0-3 months of age exposed to nitrate in infant formula (http://www.epa.gov/iris/subst/0076.htm, I.A.I.) (11). Last agency verification date 8/22/90.

Nitrite, 1E-1 (or 0.1) mg/kg-day, based on methemoglobinemia in infants chronically exposed to nitrite in drinking water (http://www.epa.gov/iris/subst/0078.htm, I.A.I.) (84). Last agency verification date 2/26/86.

U.S. EPA Drinking Water Advisories (4 kg child):

Nitrate, 1 day=10 mg/kg and 10 day=10 mg/kg;

Nitrite, 1 day=1 mg/kg and 10 day=1 mg/kg (http://www.epa.gov/ost/drinking/standards/dwstandards.pdf, p. 9) (85). Last revised Winter, 2006.

U.S. EPA Maximum Contaminant Level (MCL) for Drinking Water:

Nitrate, 10 mg/L; nitrite, 1 mg/L.

Both are based on potential health effects of shortness of breath and blue baby syndrome in infants (http://www.epa.gov/safewater/mcl.html#mcls) (86). Last revised 7/02.

U.S. EPA Maximum Contaminant Level Goal (MCLG):

Nitrate, 10 mg/L; nitrite, 1 mg/L.

Both are based on potential health effects of shortness of breath and blue baby syndrome in infants (http://www.epa.gov/safewater/mcl.html#mcls) (86). Last revised 7/02.

VII. U.S. FEDERAL REGULATORY INFORMATION

- The reference value, U.S. EPA Drinking Water Advisory for a 4 kg Child, for both nitrate and nitrite were recently revised. The 1-day and 10-day values for nitrate are both 10 mg/kg, and for nitrite are both 1 mg/kg (see Toxicity Reference Values).
- The U.S. EPA regulates drinking water for public water systems and drinking water wells that serve at least 25 people (79); information is available for owners of private wells (80).
- Nitrite and nitrate are listed as number 216 and 219 respectively out of 275 chemicals on the 2005 Priority List of Hazardous Substances for the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) section 104 (i), as amended by the Superfund Amendments and Reauthorization Act (SARA). This is a list in the order of priority of concern of substances most commonly found at sites listed on the National Priorities list (NPL); there are currently 275 substances on this list (87).
- The U.S. EPA requires reporting of quantities of certain chemicals that exceed a defined reportable quantity, and that quantity varies for different chemicals. Under the Emergency Planning and Community Right-to-Know Act (EPCRA) Section 313 "Toxic Chemicals," quantities of nitrate compounds (water soluble) or sodium nitrite greater than 25,000 pounds manufactured or processed, or greater than 10,000 pounds otherwise used, is required; under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), reporting releases of sodium nitrite of any quantity exceeding 100 pounds is required (88).

VIII. BACKGROUND ON CHEMICAL

A. CAS Number: Nitrate 14797-55-8; **Nitrite** 14797-65-0.

B. Physicochemical Properties: Nearly all nitrate and nitrite salts are soluble in water, and occur as a whitish powder when not dissolved in water (5). Go to the National Library of Medicine ChemID Web site (*http://chem.sis.nlm.nih.gov/chemidplus*) and search for nitrate or nitrite.

C. Production: Fertilizers comprise the majority of environmental releases of inorganic sources of nitrates (5). Total U.S. reported releases of nitrate compounds totaled over 291 million pounds in 2005 (89).

D. Uses: Primary sources of organic nitrates in the environment include human sewage and livestock manure (5). Sources of inorganic nitrates in the environment include potassium nitrate and ammonium nitrate, which may leach to ground water and contaminate private residential drinking water wells (3, 5). Potassium nitrates are mainly used as fertilizers and may also be used in heat transfer salts, glass and ceramics, rodenticides, and in matches and fireworks (2). Ammonium nitrates are mostly used as fertilizers, but also in explosives and blasting agents (2).

E. Environmental Fate: Nitrates are very mobile in soil and have a high potential to migrate to ground water due to high solubility in water and weak retention by soil (3, 5). Nitrates and nitrites do not volatilize and therefore are likely to remain in water until consumed by plants or other organisms (3). Ammonium nitrate is taken up by bacteria, and nitrate degradation is fastest under anaerobic conditions (5). Nitrite is easily oxidized to nitrate, and nitrate is the more predominant compound of the two detected in groundwater (4).

Additional information on nitrates and nitrites is available in the TEACH Database and at the following Web sites:

www.epa.gov/iris/subst/0076.htm
www.epa.gov/iris/subst/0078.htm
www.epa.gov/safewater/dwh/c-ioc/nitrates.html

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