1. PUBLIC HEALTH STATEMENT FOR NITRATE AND NITRITE

This Public Health Statement summarizes the Agency for Toxic Substances and Disease Registry's (ATSDR) findings on inorganic nitrate and nitrite, including chemical characteristics, exposure risks, possible health effects from exposure, and ways to limit exposure. Nitrate and nitrite can be present in organic or inorganic compounds, depending on their chemical structures. This profile pertains to inorganic nitrate and nitrite, specifically the ionic forms of both nitrate and nitrite.

The U.S. Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are sites targeted for long-term federal clean-up activities. Nitrate and nitrite are ubiquitous in the environment. Specific forms of nitrate and nitrite have occasionally been identified in hazardous waste sites. Ammonium nitrate, sodium nitrate, and sodium nitrite were identified in 7, 3, and 2 of the 1,832 hazardous waste sites, respectively, that have been proposed for inclusion on the NPL. The total number of NPL sites evaluated for nitrate and nitrite is not known. But the possibility remains that as more sites are evaluated, the number of sites at which nitrate and/or nitrite are found may increase. This information is important because these future sites may be sources of exposure, and overexposure to nitrate and/or nitrite may be harmful.

If you are exposed to nitrate and/or nitrite, many factors determine whether you'll be harmed. These include how much you are exposed to (dose), how long you are exposed (duration), how often you are exposed (frequency), and how you are exposed (route of exposure). You must also consider the other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

WHAT ARE NITRATE AND NITRITE?

Nitrate and nitrite are naturally occurring ionic species that are part of the earth's nitrogen cycle. They typically exist in the environment in highly water-soluble forms, in association with other ionic species such as sodium and potassium. Nitrate and nitrite salts completely dissociate in aqueous environments. Nitrite is readily oxidized (combines with oxygen) to form nitrate. Nitrate is generally stable in the environment; however, it may be reduced to nitrite through biological processes involving plants, microbes, etc.

In nature, plants utilize nitrate as an essential (key) nutrient. In commerce, the majority of nitrate is used in inorganic fertilizers. Additional uses of commercial nitrate and nitrite include food preservation and

the production of munitions and explosives. Sodium nitrite is also being used in medicines and therapeutics; for example, as an antidote for cyanide poisoning and as a treatment for pulmonary arterial hypertension.

WHAT HAPPENS TO NITRATE AND NITRITE WHEN THEY ENTER THE ENVIRONMENT?

Nitrate and nitrite ions naturally occur in the terrestrial (soil) and aquatic (water) environment as part of the earth's nitrogen cycle (see Figure 5-1) and can therefore be found in both soil and water. In nature, nitrate and nitrite can also be found in igneous and volcanic rocks. Nitrate is formed naturally as an end product of vegetable and animal decomposition, making this a principal source for nitrate ion in both terrestrial (soil) and aquatic (water) environments. Nitrate and nitrite can also be released into the atmospheric (air), terrestrial (soil), and aquatic (water) environments at places where human-made materials such as fertilizers are produced or used. Human and animal wastes are important sources of ammonia, a compound containing nitrogen, which undergoes chemical reaction to produce nitrite and subsequently nitrate. In aerobic (containing oxygen) environments, ammonia is readily oxidized to nitrite by ammonia-oxidizing bacteria; nitrite is oxidized to nitrate by nitrite-oxidizing bacteria. This two-stage process is known as nitrification. Both human-made and natural sources of nitrogen may contribute to nitrate aerosols in the atmosphere, as well as nitrate and nitrite ions in terrestrial (soil) and aquatic (water) environments.

Nitrate and nitrite have been detected in surface waters, drinking water (including public and private wells), and groundwater. Nitrate accounts for the majority of the total available nitrogen in surface waters. Contamination of waters is a result of agricultural runoff (use of chemical fertilizer or animal manure) and discharges from septic systems and municipal waste water treatment facilities. Nitrogen exists naturally in soils, typically bound to organic matter or mineral soil material such as rocks. Available forms of nitrogen, including nitrate and nitrite, are present in soils at a few kilograms (kg)/hectare.

Nitrate and nitrite are a normal part of the human diet and can be found in vegetables, fruits, cured meats, fish, dairy products, beers, cereals, and cereal products. Some salts, such as sodium nitrite, are intentionally added to foods and beverages to preserve or cure them; inhibiting the formation of microorganisms that may cause disease such as botulism. Additionally, nitrites and nitrates may be present in some medicines as they can be employed in medicinal and therapeutic uses.

HOW MIGHT I BE EXPOSED TO NITRATE AND NITRITE?

The major source of overexposure of the general population to nitrate and nitrite is via ingestion of water, foods, beverages, and/or medicines that contain nitrate and/or nitrite naturally or as an added preservative. Nitrate and nitrite can be taken up by plants, especially leafy vegetables such as lettuce and spinach and beet roots; vegetables account for about 80% of the nitrate in a typical human diet. Cured meats, meat products, cheeses, and beverages may contain sodium nitrate and/or sodium nitrite as preservatives. Relatively high nitrate concentrations are found in some privately owned wells with shallow depths and permeable soils. Drinking of water from such sources, combined with nitrate intake from the diet, may result in overexposure to nitrate in some individuals. Release of nitrate and/or nitrite to soil and water at waste disposal sites could result in contamination of drinking water sources and increased uptake by plants used for the human diet. Inhalation of nitrate or nitrite is not a likely exposure route of concern for the general population, although inhalation of dust from fertilizer products containing nitrate salts is possible. Dusts may also dissolve in sweat on skin, increasing the potential for dermal exposure.

HOW CAN NITRATE AND NITRITE ENTER AND LEAVE MY BODY?

Nitrate and nitrite could enter your body from the air you breathe; however, you are not likely to be exposed to amounts of nitrate or nitrite in the air that might cause adverse health effects. Nitrate and nitrite enter your body when you drink water or eat foods that contain these substances. Nitrate and nitrite are also present in smokeless tobacco products. Certain bacteria and fungi in these products can convert nitrate to nitrite, which can lead to the formation of carcinogenic nitrosamines. Neither nitrate nor nitrite is likely to enter your body from soil. However, nitrate or nitrite in soil could enter the body of young children if they put soil containing nitrate or nitrite in the mouth. Intake of some nitrate is a normal part of the nitrogen cycle in humans. Both nitrate and nitrite can be produced inside the body as well. Some of the nitrate in your body moves from blood to the salivary glands where some of it is changed to nitrite. Nitrate and nitrite are widely distributed in the body. Nitrate and nitrite that enter your body are no different chemically than nitrate and nitrite produced inside your body. Most nitrate in your body leaves in the urine the same day it enters your body. Some nitrite in the stomach forms other substances, some of which may be harmful. Nitrite in your blood can react with hemoglobin (which carries oxygen to body tissues) and reduce the ability of hemoglobin to carry oxygen. Nitrite can also form nitric oxide, which may be beneficial in some instances.

HOW CAN NITRATE AND NITRITE AFFECT MY HEALTH?

Most people are not exposed to levels of nitrate and/or nitrite that would cause adverse health effects. Young infants (<6 months of age) appeared to be particularly sensitive to the effects of nitrite on hemoglobin after consuming formula prepared with drinking water that contained nitrate at levels higher than recommended limits; some of these infants died. The cause of methemoglobinemia (a change to hemoglobin that decreases the ability to transport oxygen to tissues) in many of these infants may have been gastroenteritis from bacteria or viruses in the drinking water or from other sources not related to nitrate. Some children and adults who ate food or drank fluids that contained unusually high levels of nitrite experienced decreases in blood pressure, increased heart rate, reduced ability of the blood to carry oxygen to tissues, headaches, abdominal cramps, vomiting, and even death.

There is limited evidence that nitrite may cause some cancers of the gastrointestinal tract in humans and mice. Cancer could result from reactions between nitrite and certain other chemicals that may produce cancer-causing substances. The International Agency for Research on Cancer (IARC) determined that there is inadequate evidence for the carcinogenicity of nitrate in food or drinking water and limited evidence for the carcinogenicity of nitrite in food (based on association with increased incidence of stomach cancer). IARC determined that there is inadequate evidence for the carcinogenicity of nitrate, limited evidence for the carcinogenicity of nitrite *per se*, and sufficient evidence for the carcinogenicity of nitrite in combination with amines or amides. The overall conclusions of IARC were that "ingested nitrate and nitrite under conditions that result in endogenous nitrosation is probably carcinogenic to humans (Group 2A)." IARC noted that: (1) the endogenous nitrogen cycle in humans includes interconversion of nitrate and nitrite; (2) nitrite-derived nitrosating agents produced in the acid stomach environment can react with nitrosating compounds such as secondary amines and amides to generate N-nitroso compounds; (3) nitrosating conditions are enhanced upon ingestion of additional nitrate, nitrite, or nitrosatable compounds; and (4) some N-nitroso compounds are known carcinogens.

The U.S. EPA Integrated Risk Information System does not include a carcinogenicity evaluation for nitrate or nitrite.

See Chapters 2 and 3 for more information on health effects of nitrate and nitrite.

HOW CAN NITRATE AND NITRITE AFFECT CHILDREN?

This section discusses potential health effects of nitrate and nitrite exposure in humans from when they're first conceived to 18 years of age.

Children can experience the same effects as adults from overexposure to nitrate and/or nitrite. Young infants (<6 months of age) who were fed formula prepared using nitrate-contaminated drinking water sources appear to be particularly sensitive to the effects of nitrate on hemoglobin (i.e., methemoglobinemia), although bacterial infections may have been at least partially responsible for increased sensitivity in these infants. It is not known whether nitrate or nitrite can cause birth defects. Results of some studies suggest that ingestion of relatively high levels of nitrate or nitrite could cause developmental effects, but other studies found no evidence for nitrate- or nitrite-related developmental effects.

HOW CAN FAMILIES REDUCE THE RISK OF OVEREXPOSURE TO NITRATE AND NITRITE?

If your doctor finds that you have been exposed to significant amounts of nitrate and/or nitrite, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate. You may also contact the state or local health department with health concerns.

Much of the diet contains food with nitrate and possibly small amounts of nitrite. Some processed food contains nitrate and/or nitrite as preservative. If you think that you are getting too much nitrate or nitrite in your diet, consider eating less of those foods that contain high levels of nitrate or nitrite. This consideration is particularly relevant to infants and small children. Don't drink water containing levels of nitrate or nitrite higher than guideline levels for drinking water.

ARE THERE MEDICAL TESTS TO DETERMINE WHETHER I HAVE BEEN OVEREXPOSED TO NITRATE AND/OR NITRITE?

Methods are available to detect nitrate and nitrite in plasma and urine; however, these are usually not available at a doctor's office and are not clinically useful.

Routine blood tests are available to detect a condition known as methemoglobinemia, which is caused by the presence of higher-than-normal levels of a form of hemoglobin. However, these tests cannot tell

whether the high methemoglobin levels were caused by nitrate and nitrite or by some other substance or disease.

For more information on the different substances formed by nitrate and nitrite breakdown and tests to detect these substances in the body, see Chapters 3 and 7.

WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but are not enforceable by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed as "not-to-exceed" levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (e.g., an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that issued the regulation or recommendation.

The EPA lists maximum contaminant levels (MCL) and maximum contaminant level goals (MCLG) of 10 mg/L (or ppm) for nitrate (as nitrate-nitrogen; ~44 mg nitrate/L) and 1 mg/L (or ppm) for nitrite (as nitrite-nitrogen; ~3.3 mg nitrite/L) in the 2012 Edition of the Drinking Water Standards and Health Advisories. The FDA lists 10 mg/L nitrate (as nitrogen; ~44 mg nitrate/L), 1 mg/L nitrite (as nitrogen; ~3.3 mg nitrite/L), and 10 mg/L total nitrate and nitrite (as nitrogen) as allowable levels in bottled water. OSHA has not set a legal limit for nitrate or nitrite in air. NIOSH has not set a recommended limit for nitrate or nitrite in air.

WHERE CAN I GET MORE INFORMATION?

If you have any questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below. You may also contact your doctor if experiencing adverse health effects or for medical concerns or questions. ATSDR can also provide publicly available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

- Call the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636) or

- Write to:

  Agency for Toxic Substances and Disease Registry
  Division of Toxicology and Human Health Sciences
  1600 Clifton Road NE
  Mailstop F-57
  Atlanta, GA 30329-4027

Toxicological profiles and other information are available on ATSDR's web site: http://www.atsdr.cdc.gov.