# Nitrate Toxicology:
# Status of a Commonly Underappreciated Health Risk

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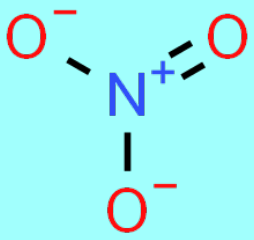
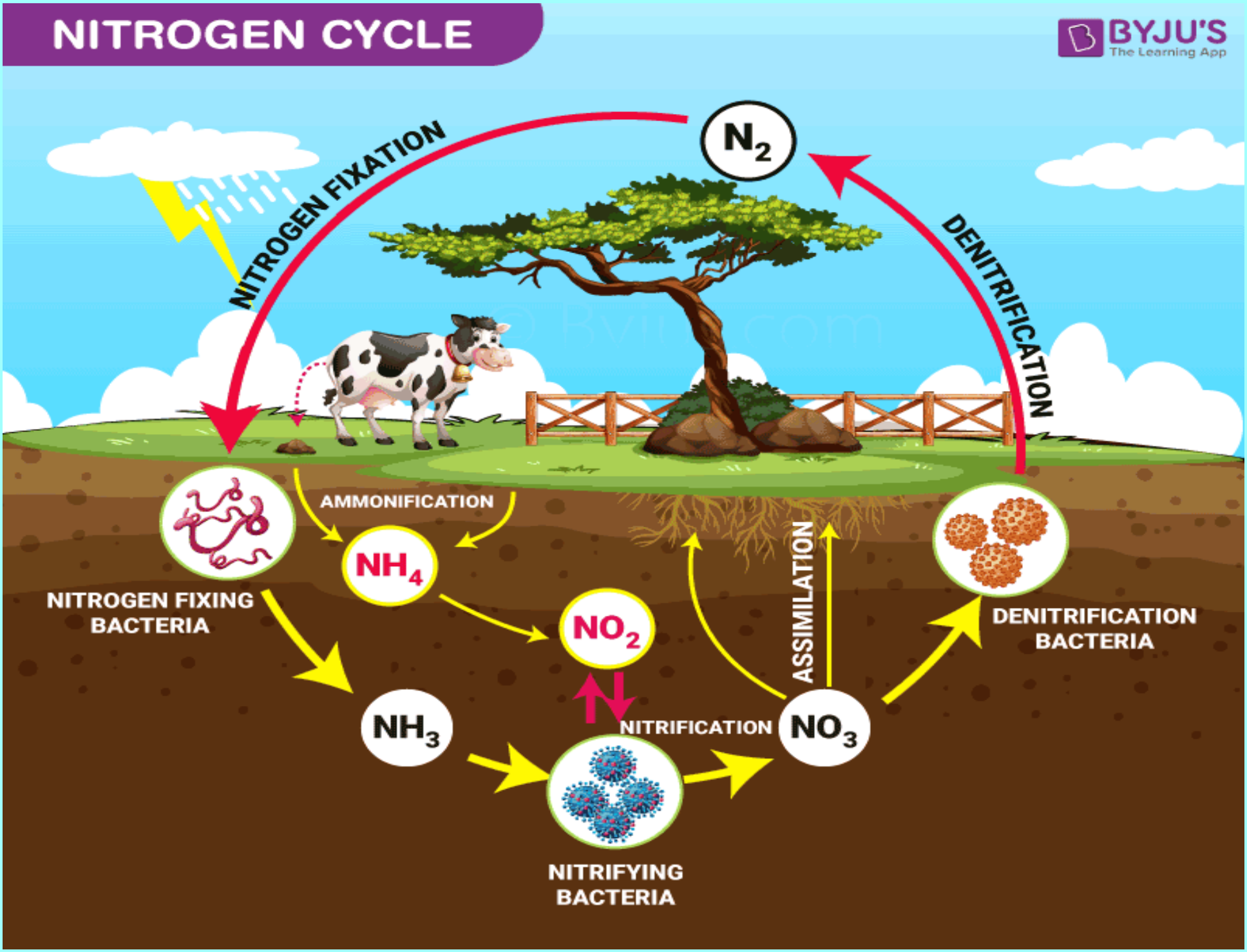
# Nitrate




- Relatively stable form of N;  part of environmental nitrate, nitrite, $NH_3$ balance
- Nitrogen is essential to maintenance of human health
- Component of cardiac medications (nitroglycerin, isosorbides)
- Essential as plant nutrients in various forms
- Nitrate occurs naturally in some fruits and vegetables, other diet items
- Occurs in animal manure, agricultural products, septic system discharge
- Thus, a common contaminant found in soil, groundwater, surface water
- Related nitrite ($–NO_2$) may be formed from nitrate under reducing conditions (low $O_2$) in the environment and mammalian gastrointestinal system


NITROGEN CYCLE
BYJU'S
The Learning App
$N_2$
NITROGEN FIXATION
DENITRIFICATION
AMMONIFICATION
$NH_4$
NITROGEN FIXING BACTERIA
$NO_2$
ASSIMILATION
DENITRIFICATION BACTERIA
$NH_3$
NITRIFICATION
$NO_3$
NITRIFYING BACTERIA

# Exposure and Toxicology - 1

- Greatest human exposure potential is ingestion of impacted drinking water, fruits/vegetables (*spinach, lettuce, root crops*), preserved meats
- 10 mg/L (10,000 ug/L) drinking water standard currently in place for nitrates, 1 mg/L for nitrites
- Long-term exposure can lead to thyroid dysfunction (*e.g., hypothyroidism*), and reproductive effects (*e.g., spontaneous abortion, intrauterine growth restriction, selected birth defects*)
- Increased cancer risks (e.g., colorectal, thyroid, stomach) reported associated with increased nitrate/nitrate intake

# Exposure and Toxicology - 2

- The 10 mg/L Maximum Contaminant Level Goal (MCLG, a *recommendation*) and MCL (a *regulation*) were established over 3 decades ago (1991) to protect against methemoglobinemia ("*blue baby syndrome*") in infants, gastroenteritis patients
- Those criteria have been under review for a considerable period by ATSDR/USEPA to assess other potentially relevant toxicological endpoints, including cancers
- The review process is slow, and the consequences are large, given environmental ubiquity and remedial cost considerations

# Methemoglobinemia

- Infants under 6 months most sensitive due to increased $O_2$ requirements and GI characteristics which favor nitrite formation
- Ingestion of formula made with nitrate-contaminated water can cause decreased $O_2$ capacity of hemoglobin
- Symptoms include cyanosis, fatigue, CNS depression; may arise from acute exposure and may result in death if untreated
- Severe methemoglobinemia (*dizziness, hypotension, stomach cramps, vomiting*) reported in older children, adults following ingestion of food or water contaminated with nitrate/nitrite
- Increased risk for individuals with congenital $O_2$–carrying deficiencies, as well as enzyme deficiencies such as G6PD and other genetic factors

# Significant Non-Cancer Effects

- Thyroid dysfunction (*hypothyroidism, increased thyroid weight, thyroid lesions*) – suggestive evidence in humans and sufficient evidence in animals following ingestion studies with nitrate-contaminated water or foods
- Reproductive effects – older studies reported mixed results linking nitrate ingestion during pregnancy with spontaneous abortion
- Positive associations have been postulated in historical and more recent studies of various congenital anomalies/neural tube defects (*e.g., spina bifida, limb deficiencies, cleft palate*)

# Potential Cancer Effects

- Cancer potential is primarily related to nitrosamine formation *in vivo* (endogenous nitrosation) or in the environment
- Increased colorectal cancer risk has been shown in multiple human studies of populations exposed to nitrate levels greater than or less than the MCL
- Increased risk of thyroid cancer reported with increasing nitrate levels in drinking water >5 mg/L (*less than the MCL*)
- Non-Hodgkins Lymphoma
- "Since 1987 a growing body of literature indicates potential associations between nitrate/nitrite exposure and other noncancer health effects. Some epidemiological studies also suggest an increased risk of cancer especially gastric cancer associated with dietary nitrite exposure." (USEPA, 2017; USEPA 2023)

# Regulatory Timeline

- 1991 - MCLG/MCL established for nitrates (10 mg/L) and nitrites (1 mg/L)
- 2015 - Nitrate and nitrite identified by USEPA/ATSDR as high priority substances for reevaluation
- 2017 - USEPA announced reassessment of drinking water criteria for nitrate/nitrite
- 2023 USEPA releases draft toxicology review document "Protocol for the Nitrate and Nitrite Assessment (Oral)"
- More as it develops

# Case Study

- Historical and ongoing local and downgradient groundwater impacts from large scale feedlot and waste management facilities
- Groundwater private residence usage common and widespread in the region; characterization ongoing
- Broad groundwater user communications ongoing; historical and new provision of reverse osmosis (RO) systems ongoing
- Questions remain about RO systems maintenance, uses of groundwater vs RO water for nondrinking water residential uses (e.g., bathing, toohbrushing, food prep and cleanup, infant formula preparation)

# Summary

- Demonstrable health effects exist and are acknowledged in MCLG / MCL, as well as in state criteria in many locations
- Clear causation and suggestive associations with cancer and noncancer effects exist
- Effects occur at less than current MCL
- USEPA has prioritized revisiting the drinking water guidelines for nitrate/nitrate and that process is underway – stay tuned
- These substances are an example of “familiarity breeds avoidance”. The implications of more restrictive criteria are potentially very large


Questions or Comments?
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