



IRIS Assessment Plan for Nitrate/Nitrite

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Outline of the Presentation

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- Scoping Summary
- Initial Problem Formulation
- Overall Objective, Specific Aims, and PECO Framework
- Key Science Issues

- Nitrate (NO_3^-) and nitrite (NO_2^-) are naturally occurring ions in the environment; they play an essential role in Earth's nitrogen cycle.
- Human sources of reactive N substantially increased since ~1950.
- Major uses
 - Nitrate: fertilizers, explosives, fireworks, glass making
 - Nitrite: preservatives for meat and fish curing, color fixatives

Exposure

- Nitrate
 - Food:
 - Leafy vegetables (~80% of total nitrate exposure)
 - Cured meats/fish, cereal grains, dairy products, beer
 - Drinking water -- median conc in surface/ground water = 2-3 mg/L (as N); max conc = 99 mg/L (as N) (U.S. EPA, 2009)
 - Populations served by private/shallow wells in agricultural areas
- Nitrite
 - Exogenous sources:
 - Food -- relatively higher percentage of nitrite intake comes from cured meats
 - Drinking water -- minor source [median conc in surface/ground water = 0.02 mg/L (as N)]
 - Endogenous sources:
 - ~80% of nitrites in the body generated endogenously (5–8% of ingested nitrates are converted to nitrites)

Complexities in characterizing exposure

- Endogenous nitrosation: nitrate reduced to nitrite in the mouth → reacts with proteins/amines/amides in the stomach to form *N*-nitroso compounds (NOC)
- Leafy vegetables:
 - Major source of nitrate exposure
 - Also source of dietary antioxidants that inhibit endogenous NOC formation
- Epidemiology studies need to consider factors that influence nitrite formation and nitrosation
 - Co-exposures in the diet and drinking water differ
 - Influence of various medical conditions



Background: Existing Nitrate/Nitrite IRIS Assessments

- Existing IRIS assessments posted in 1987 (nitrite) and 1991 (nitrate)
 - Oral reference doses (RfDs) based on surveys of methemoglobinemia in infants (Walton, 1951; Bosch et al., 1950)
 - No assessment of the RfC or carcinogenicity
- 1987+: evidence for potential associations between nitrate/nitrite and other health effects



Scoping Summary

During scoping, the IRIS Program met with EPA program and regional offices that had interest in an updated IRIS assessment for nitrates and nitrites to discuss specific assessment needs.



Scoping Summary (cont'd)

EPA program or regional office interest in nitrate/nitrite assessment

EPA program or regional office	Oral	Inhalation	Statutes/ Regulations	Anticipated uses/interest
Office of Water	✓		Safe Drinking Water Act (SDWA) – Section 1412	Six-year review of the NPDW regulations.
Region 5	✓		National Primary Drinking Water [NPDW] regulations, 40 CFR 141, 142	Evaluation of special provision of the NPDW regulation [40 CFR 141.11(d)] allowing, at the discretion of the state, non-community water systems to exceed the nitrate maximum contaminant level (MCL).

National Primary Drinking Water [NPDW] regulations

- Maximum contaminant levels (MCLs):
 - Nitrate: 10 mg/L (as N)
 - Nitrite: 1 mg/L (as N)

- Special provision for non-community water systems
 - At the discretion of the state, nitrate levels, not to exceed 20 mg/L, may be allowed in a non-community water system if the supplier of water demonstrates to the satisfaction of the State that:
 - (1) Such water will not be available to children under 6 months of age
 - (2) The non-community water system is meeting the public notification requirements under §141.209, including continuous posting of the fact that nitrate levels exceed 10 mg/L and the potential health effects of exposure
 - (3) Local and state public health authorities will be notified annually of nitrate levels that exceed 10 mg/L
 - (4) No adverse health effects shall result.

IRIS health assessment to address:

- Inorganic forms of nitrate and nitrite
 - Ammonium nitrate, sodium nitrate and nitrite, potassium nitrate and nitrite
- Oral route only
- Noncancer
 - Methemoglobinemia is established causal association; focus will be on other health outcomes not evaluated in the existing IRIS assessment
- Cancer
 - Qualitative assessment
 - Feasibility of quantitative assessment to be explored

- Preliminary literature survey of other health agency assessments
 - ATSDR, Health Canada, WHO, IARC, Cal EPA
- Relied on ATSDR (2017) *Toxicological Profile for Nitrate and Nitrite* and IARC (2010) Monograph on Ingested Nitrate/Nitrite to identify pertinent health effects literature published through 2016.



Initial Problem Formulation (cont'd)

Outcomes	Human Studies				Animal Studies					
	Occupational epid. studies	General population epid. studies	Controlled exposure studies	Case reports and case series reports	Chronic	Subchronic	Short-term	Acute	Multi-generational	Gestational
Cancer		>60 ^b			18					
Hematological		>25	3	>10	4	6	3	1		
Developmental		14							2	6
Endocrine (thyroid)		6	1		4	3	1			
Gastrointestinal	1	1	1	7	5	1				
Other systemic toxicity (body wt.)					10	2	1		1	
Neurological and sensory			2	6	1	1			1	
Metabolic disease (type 1 diabetes)		8								
Reproductive			3	1	2	3			1	
Hepatic					3			2		
Cardiovascular		1	1	3						
Dermal and ocular				1						
Renal					1					
Immunological										
Musculoskeletal										
Respiratory										

Source: ATSDR (2017), IARC (2010)

- Based on preliminary literature survey, systematic reviews anticipated for:
 - Cancer
 - Hematological effects
 - Developmental effects
 - Thyroid effects (endocrine effect)
 - Type 1 diabetes (metabolic effect)
 - Reproductive effects
- Systematic review for other health effect categories -- only if additional new evidence suggests that such a review is warranted.
- Cardiovascular and infectious disease outcomes -- evidence of beneficial effects associated with nitrate/nitrite exposure will be not be included in assessment.



Overall Objective

The overall objective of this assessment is to identify adverse health effects and characterize exposure-response relationships for nitrate and nitrite to support development of toxicity values.

- **Identify** literature reporting exposure to nitrate/nitrite as outlined in the PECO framework and flag mechanistic studies for use in understanding potential human health hazards.
 - ATSDR (2017) *Toxicological Profile of Nitrate and Nitrite* and IARC (2010) monograph will be used to identify literature through 2016.
 - Literature search update (2016 to present)
- **Conduct** study evaluation (risk of bias and sensitivity) for individual human and animal studies.
- **Extract** data on relevant health outcomes from human and animal studies based on the study evaluation.
- **Synthesize** the evidence across studies assessing similar health outcomes.



Specific Aims (cont'd)

- **Evaluate** confidence in conclusions from across studies (or sub-sets of studies) within human and animal evidence streams for each health outcome.
- **Integrate** results across evidence streams for each health outcome to conclude whether it is a hazard to humans.
- **Identify** and discuss issues concerning potentially susceptible populations and life stages.
- **Derive** toxicity values as supported by the available data. For nitrate and nitrite anions:
 - Separate RfDs for nitrate and nitrite
 - Cancer slope factor, if feasible
- **Characterize** uncertainties and identify key data gaps and research needs.



PECO Framework

PECO element	Evidence
<u>Populations</u>	<p>Human: All population and life stage.</p> <p>Animal: Nonhuman mammalian animal species (whole organism) of any life stage.</p> <p>In vitro: Nonmammalian model systems; human or animal cells, tissues, or biochemical reactions; bioinformatics pathways of disease analysis; or high-throughput screening data.</p>
<u>Exposures</u>	<p>Exposure to specific nitrate/nitrite compounds, including: ammonium nitrate, potassium nitrate, potassium nitrite, sodium nitrate, sodium nitrite, inorganic nitrate/nitrite in drinking water and inorganic nitrate/nitrite in foods.</p> <p>Human and animal: Any oral exposures. Where possible, exposures assessed separately for drinking water and dietary nitrate/nitrite.</p> <p>In vitro: Exposure via growth or assay medium.</p>
<u>Comparators</u>	<p>Human: Any comparison or reference group exposed to no or lower nitrate/nitrite levels or to nitrate/nitrite for shorter periods of time.</p> <p>Animal: Quantitative exposure versus lower or no exposure with concurrent vehicle control group.</p> <p>In vitro: Quantitative exposure versus lower or no exposure with concurrent vehicle control group.</p>
<u>Outcomes</u>	All health outcomes (both cancer and noncancer).

Based on the preliminary literature survey, the following key scientific issues were identified that warrant evaluation in the assessment:

- Role of endogenous versus exogenous nitrate/nitrite
- Susceptible populations and life stages
- Human PBPK model for simulating the kinetics of methemoglobinemia formation after oral exposure to nitrate in adults; utility of this model will be explored.
- Issues related to cancer risk
 - Potential effect modification from co-exposures
 - Potentially susceptible populations