Nitrate in drinking water and cancer risk

Mary H. Ward, M.S., Ph.D.
Occupational and Environmental Epidemiology Branch
Division of Cancer Epidemiology & Genetics
NCI, NIH

Challenges to Providing Safe Drinking Water in the Midwest:
A Symposium, Des Moines, Iowa
September 21, 2017
Overview

• N-Nitroso compound (NOC) precursors
  ❖ Dietary nitrite/nitrate
  ❖ Nitrate from drinking water - Public water supplies (measurement data)

• Approaches for estimating nitrate in private wells
Nitrate in drinking water: Sources and exposures

• Nitrogen fertilizers, animal and human waste

• Regulatory limit (Maximum Contaminant Level [MCL]):
  • 10 mg/L as NO$_3$-N (USA)
  • 50 mg/L as NO$_3$ (EU)

• Highest exposures:
  • Private well users
  • Few measurements
Probability of nitrate-N > 4 mg/L NO$_3$-N

Probability that nitrate exceeds 4 mg/L

0 - .17
>.17 - .33
>.33 - .50
>.50 - .67
>.67 - .83
>.83 - 1

Probability of Nitrate Contamination of Recently Recharged Groundwaters in the Conterminous United States
B.T. Nolan, K.J. Hitt, and B.C. Ruddy
Environmental Science & Technology Vol. 36, No. 10, Page 2142
Nitrite + stomach acid

$N_2O_3 + $ amines/amides

NOC

Oral bacteria: Nitrate $\rightarrow$ nitrite

Heme iron (red meat)
Thiocyanate (smoking)

Antioxidants (vitamin C)

Endogenous NOC formation from ingested nitrate (drinking water & diet)
Competitive inhibition of iodide uptake by nitrate

Inhibition of iodide uptake in thyroid

Plasma $T_3$, $T_4$, ↓ plasma TSH ↑

Thyroid hypertrophy/hyperplasia

Hypothyroidism

Metabolic effects (any age)

Impaired development and growth (fetus, child)

=> Cancer??
Nitrate in drinking water and hypothyroidism

1. Subclinical hypothyroidism was increased in children in Slovakia with high nitrate drinking water (Tajtakova et al, 2006)

2. Postmenopausal women in Iowa with higher nitrate ingestion (diet and drinking water) had higher prevalence of hypothyroidism (Ward et al, 2010)

3. Amish women (but not men) with drinking water nitrate >6 mg/L NO$_3$-N had higher serum TSH & subclinical hypothyroidism (Aschebrook-Kilfoy et al, 2012)
Ingested Nitrate and Nitrite (IARC vol. 94): 2A - **probably carcinogenic to humans under conditions favorable for endogenous nitrosation**

- Animal studies
- Human mechanistic studies
- Epidemiologic studies
  - Diet
  - Drinking water

Animal Studies: NOC and Cancer

- ~ 300 NOCs were tested in animal studies: 90% were carcinogenic (IARC 1995)
- Carcinogenic in 39 animal species including all species of nonhuman primates
- Cause tumors in multiple organs: lung, GI tract, bladder, kidney, breast, ovary, thyroid
  - Individual NOCs (e.g. NDMA, NDEA, NPyr)
  - Nitrite plus amine source via diet
Human mechanistic studies

- Humans 5-8% of ingested nitrate reduced to nitrite (oral bacteria)

- Drinking water nitrate increases endogenous formation of NOC at levels:
  - >10 mg/L NO₃⁻ (≈45 mg/L NO₃⁻) (Mirvish 1992; Moller et al. 1989)
  - But not at levels <5 mg/L (Levallois, 2000)
Direct relationship between nitrate ingestion & formation of NDMA

- Nitrate via drinking water at ADI (3.67 mg/kg NO3-) and dietary amine source (fish)

Vermeer et al., 1998
Epidemiologic Studies (IARC 2010):
Dietary Nitrate and Nitrite

• Inadequate evidence for dietary nitrate
  o Sources: green leafy and root vegetables
  o Stomach and esophagus: **inverse or no association**
  o Protective effect of micronutrients in vegetables (vitamin C, polyphenols)

• Limited evidence for dietary nitrite especially from processed meats:
  o Stomach and esophagus: **positive associations**
  o Since review, increased risk for additional cancers: studies of colorectal, kidney, thyroid, ovarian cancer
  o IARC 2016: Processed meat (usually preserved with nitrate/nitrite) is a human carcinogen
Epidemiologic Studies (IARC 2010): Drinking Water Nitrate

- Inadequate evidence of carcinogenicity in humans for nitrate in drinking water

- “Epidemiological studies of any one cancer site were few, exposure levels were low, and endogenous nitrosation was not often considered”
Drinking water nitrate – epidemiology studies

• Case-control studies:
  ❖ Positive associations with stomach, colon, kidney cancers:
  ❖ No association with brain, bladder:
    Ward et al. 2003; Ward et al. 2005; Espejo-Herrera et al. 2015
Recent and ongoing research: Drinking water nitrate and cancer in two cohorts

1. Iowa Women’s Health Study (IWHS):
   - Postmenopausal women
   - 73% use public supplies, 25% private well users

2. Agricultural Health Study (AHS):
   - Pesticide applicators, spouses in 2 agricultural states (Iowa & North Carolina)
   - ~60% use private wells for drinking water
1. Iowa Women’s Health Study

- 42,000 postmenopausal women
- Selected from DMV records
- Drinking water source and duration in 1989
- 73% use public supplies, 25% private wells
Iowa Women’s Health Study: Public water supply exposure assessment


NO₃-N

Total Trihalomethanes (THMs)

City
N = 473

Median duration (years)
4
8
16
34

Exposure Metrics
Average NO₃-N and THMs
Years >1/2 Maximum Contaminant Level

82% used supply 16+ years
Drinking water nitrate and cancer risk: previous results from the IWHS

- Weyer et al. (2001)

**Ovarian cancer** (n = 109)
- Public water: \( \text{HR}_{Q4\text{vs.}Q1} = 2.0 \ (1.01 - 4.1) \)
- Private well users (vs Q1): \( \text{HR} = 1.6 \ (0.8 - 3.1) \)

**Bladder cancer** (n=57)
- Public water: \( \text{HR}_{Q4\text{vs.}Q1} = 2.8 \ (1.1 - 7.2) \)
- Private well users (vs Q1): \( \text{HR} = 1.3 \ (0.5 - 3.5) \)
Ovarian and Bladder Cancers

• >20 years of follow-up:
  – 315 ovary, 263 bladder cases

• Exposure assessment:
  – Duration specific metrics
  – THMs ($\rho=0.24$ with nitrate)
  – Dietary nitrite

• Adjustment, Effect modification:
  – Vitamin C and red meat
  – Smoking (bladder)
Ovarian Cancer
Average nitrate (mg/L) and ovarian cancer

- Inoue-Choi..Ward Int J Cancer 2015

- \( P\text{-trend}=0.003 \)

- Adjusted for age, BMI, hormone use, reproductive factors, THMs

- \( \text{NO}_3\text{-N mg/L in Public Water} \)
Average nitrate and ovarian cancer, by vitamin C intake

Inoue-Choi..Ward, *Int J Cancer* 2015
Bladder Cancer
Years >5 mg/L NO$_3$-N and bladder cancer

Not adjusted for THMs

Adjusted for THMs

$P$-trend=0.03

Jones et al. EHP, 2016
Average water nitrate and bladder cancer risk by smoking history

$p_{interaction}=0.03$

*adjusted for age, pack-years of smoking (current, former smokers)  

Jones et al. EHP; 2016
Thyroid cancer
Nitrate in drinking water and thyroid cancer

<table>
<thead>
<tr>
<th>Public supplies</th>
<th>Average nitrate (1955-89) mg/L</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.4</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>0.4-&lt;1.0</td>
<td></td>
<td>0.5 (0.1-2.0)</td>
</tr>
<tr>
<td>1.0-&lt;2.5</td>
<td></td>
<td>1.5 (0.4-3.7)</td>
</tr>
<tr>
<td>2.5+</td>
<td></td>
<td>2.2 (0.8-5.8)</td>
</tr>
</tbody>
</table>

P for trend=0.02

| Private wells | >10 years | 1.1 (0.8 – 3.7) |

adjusted for age, diet nitrate, vitamin C, calories, smoking, education, physical activity, BMI

Ward et al, 2010
Additional drinking water analyses in the IWHS

Kidney
N=125
• Average and ≥4 years >½ MCL nitrate increased risk
  Jones et al., *Epidemiology*; 2017

Colon & Rectum
N=624      N=158
• No associations with drinking water nitrate
• Positive association, rectal cancer & TTHM
  Jones et al., *In prep*

Pancreas
N=153
• No associations with drinking water nitrate or TTHM
  Quist et al. *in press*
2. Agricultural Health Study - Drinking water nitrate exposure

- Applicators and spouses in Iowa (N=~60,000)
- Drinking water source: >60% use private wells
- Measurement data not available
- Geocoded residential histories (Jones et al. IJHG 2014)
Model of nitrate in private wells

- ~34,000 nitrate measurements (1980-2000s)
- Evaluated >150 variables (e.g., land use, animal feeding operations, geology, soils)
Predicted NO$_3$-N mg/L

Overall:

Median (IQR): 1.6 (0.9-5.1)

13% >10 mg/L
Ongoing research –
Drinking water nitrate

Iowa Women’s Health Study:
• Ongoing analyses of gastrointestinal tract cancers (stomach, liver, gall bladder)

Agricultural Health Study:
• Analyses of gastrointestinal and urinary tract, thyroid, ovarian cancers and thyroid disease
• Results should help clarify cancer risk at levels between 5 – 10 mg/L and >10 mg/L NO$_3$-N
Research gaps

• Clarify relationship between nitrate ingestion & NOC formation below MCL in controlled studies

• Evaluate additional factors that influence endogenous nitrosation
  – E.g. oral microbiome can be measured in buccal samples
  – Incorporate biomarkers (urinary NOC, nitrate) in nested case-control studies

• Other contaminants that co-occur with nitrate, mixtures

• More studies in populations, high exposures
Acknowledgements

NCI/OEEB
Laura Beane Freeman
Kenneth Cantor
Curt DellaValle
Abby Flory
Maki Inoue-Choi
Rena Jones

U.S. Geologic Survey
Tom Nolan

University of Iowa
Peter Weyer, Jim Giglierano, Gerry Rushton

University of Minnesota
Kristin Anderson, DeAnn Lasovich, Kim Robien

Mayo College of Medicine
James Cerhan

Virginia Commonwealth University
David Wheeler

Colorado State University
John Nuckols