Take Home Messages

1. Drinking water nitrosamine exposure is small relative to other sources
   - 10 to 500 times less than dietary intake, and
   - 3 to 5 orders of magnitude less than endogenous exposure

2. Chloraminated waters have higher nitrosamine levels than chlorinated waters, but those levels still represent a very small fraction of total exposure
Project Objectives: Contributions to Human NDMA Exposure

Objectives

- Develop an up-to-date assessment of total nitrosamine exposure from all relevant sources
- Reflect modern diets and current levels of nitrosamines in representative diets appropriate to the United States population
- Address diet and water exposure for children, particularly bottle fed infants
- Consider evolving understanding of endogenous nitrosamine formation

Caveats

- Incorporate our current understanding of nitrosamine occurrence in drinking water based on UCMR2
- Specifically address the difference as a function of disinfectant

- Occupational and smoking exposures, and exposures from beer were not modeled
- Endogenous formation is not well understood
Background

- Nitrosamines are a class of cancer-causing chemicals formed by the reaction of a secondary amine and a nitrosating agent

\[
\begin{align*}
\text{R} & \quad \text{N} & \quad \text{N}=\text{O} \\
\text{R'} & \quad \text{Generic} & \quad \text{nitrosamine}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 & \quad \text{N} & \quad \text{N}=\text{O} \\
\text{CH}_3 & \quad \text{N-nitroso-dimethylamine}
\end{align*}
\]

- About 90% have tested positive for carcinogenicity
- e.g. \textit{N}-nitrosodimethylamine (NDMA)
Sources of Nitrosamine Exposure

- Inhalation
  - Occupational (e.g. rubber industry)
  - Smoking (including smokeless products; up to 17,000 ng/d)
- Diet
  - Especially cured or smoked meats, smoked fish
  - Also fermented foods (e.g. sauerkraut)
- Drinking water
- Dermal
  - Cosmetics
- Endogenous synthesis
Sources of Nitrosamine Exposure

Total Nitrosamine Dose

- Nitrosamines in drinking water
- Nitrosamines in foods (including breast milk and formula)
- Nitrosamines in tobacco products
- Nitrosamines in cosmetics
- Nitrosamines in workplace environment
- Nitrosamines in beer
- Nitrosamine precursors in foods
- Endogenous formation
- Nitrosamine precursors synthesized endogenously
Estimates of Nitrosamines in Diet

1,000 ng/day (NAS, 1981)

Children: 90 ng/day NDMA
Adult: 110 ng/day NDMA

Children: 50 ng/day NDMA
Adult: 60 ng/day NDMA
(our work based on EFH 2011 consumption data from 2003-2006 NHANES)

Actions Taken
- Reduced sodium nitrite use
- Added antioxidants
- Change to indirect-fire drying of malt for beer

1980 1990 2000 2010
Endogenous Formation of Nitrosamines

- Formation is not confined to acid-catalyzed mechanism in stomach
- Precursors to nitrosamine formation are readily available in the body, independent of ingestion in food
- Changes in physiological state, inflammatory states, infections appear more important than diet
- Variation as a function of age
Estimate of Endogenous Exposure to NDMA (2012)

• Mean endogenous formation estimate for adults is approximately 1,400 to 13,000 ng/kg-day

• *If the rate of formation and metabolism are the same in infants and children as in adults*, estimates of endogenous exposure are:
  - Infant  > 8,000 ng/day
  - Child   > 44,000 ng/day
  - Adult   > 110,000 ng/day
Concentration and Rate of Exceeding MRL for NDMA in Water Supplies

<table>
<thead>
<tr>
<th>Source</th>
<th>GW – Ground Water</th>
<th>SW – Surface Water</th>
<th>MX - Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disinfectant</td>
<td>Blank – Disinfection not indicated</td>
<td>CL – Free Chlorine</td>
<td>CA – Monochloramine</td>
</tr>
<tr>
<td>Sample Location</td>
<td>EP – Entry Point to Distribution System</td>
<td>MR – Maximum Residence Time</td>
<td></td>
</tr>
</tbody>
</table>
Model of Cumulative Exposure to NDMA in the U.S.
Estimates of NDMA Intake from Drinking Water, ng/day

The mean and 95th percentile of NDMA intake from drinking water is shown for 3 age cohorts and 4 water source types.
Exogenous ADD in Infants, by Water Source and Diet

The contribution from drinking water is represented by the 95th percentile of NDMA intake from drinking water. Breast-fed infants are assumed to have no exposure to drinking water.
# Proportion of Average Daily Dose Contributed by Sources

<table>
<thead>
<tr>
<th></th>
<th>Chlorinated Ground Water</th>
<th>Chloraminated Surface Water</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Formula-fed Infant</td>
<td>Breast-fed Infant</td>
</tr>
<tr>
<td>Endogenous</td>
<td>99.94%</td>
<td>97.77%</td>
</tr>
<tr>
<td>Dietary</td>
<td>1.05%</td>
<td>2.23%</td>
</tr>
<tr>
<td>Drinking water</td>
<td>0.007%</td>
<td>0</td>
</tr>
<tr>
<td>(mean NDMA intake)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total of ADD</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Drinking water</td>
<td>0.023%</td>
<td>0</td>
</tr>
<tr>
<td>(95\textsuperscript{th} %-ile NDMA intake)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The contribution from drinking water is represented by the 95\textsuperscript{th} percentile of NDMA intake from drinking water. The decision to breast-feed or formula-feed has little impact on exposure from drinking water over a lifetime.
Proportion of Contribution from All Sources, LADD

<table>
<thead>
<tr>
<th>Source</th>
<th>Chlorinated Ground Water</th>
<th>Chloraminated Surface Water</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Formula-fed as Infant</td>
<td>Breast-fed as Infant</td>
</tr>
<tr>
<td>Endogenous</td>
<td>99.84%</td>
<td>99.83%</td>
</tr>
<tr>
<td>Dietary</td>
<td>0.16%</td>
<td>0.17%</td>
</tr>
<tr>
<td>Drinking water (mean NDMA intake)</td>
<td>0.001%</td>
<td>0.001%</td>
</tr>
<tr>
<td>Total of LADD</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Drinking water (95th %-ile NDMA intake)</td>
<td>0.003%</td>
<td>0.003%</td>
</tr>
</tbody>
</table>
Conclusions

- Depending on the source, drinking water exposure at the 95\textsuperscript{th} percentile of intake contributes
  - 4 to 50 times less NDMA than dietary intake, and
  - 2,500 to >30,000 times less than endogenous exposure

- Relative exposure as bottle-fed infants represents a minor fraction of life-time nitrosamine exposure

- Chloraminated waters have higher nitrosamine levels than chlorinated water, but those levels still represent a very small fraction of total exposure
### Range of Estimated NDMA Intake from Drinking Water

<table>
<thead>
<tr>
<th>Source</th>
<th>Median (ng/d)</th>
<th>Mean (ng/d)</th>
<th>Median (ng/d)</th>
<th>Mean (ng/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ground Water / Chlorine / Entry Point</td>
<td>0.007</td>
<td>0.082</td>
<td>0.018</td>
<td>0.189</td>
</tr>
<tr>
<td>Ground Water / Chlorine / Maximum Residence Time</td>
<td>0.064</td>
<td>0.164</td>
<td>0.152</td>
<td>0.384</td>
</tr>
<tr>
<td>Surface Water / Chlorine / Entry Point</td>
<td>0.013</td>
<td>0.199</td>
<td>0.030</td>
<td>0.467</td>
</tr>
<tr>
<td>Surface Water / Monochloramine / Entry Point</td>
<td>0.231</td>
<td>1.32</td>
<td>0.552</td>
<td>2.97</td>
</tr>
<tr>
<td>Surface Water / Monochloramine / Maximum Residence Time</td>
<td>0.631</td>
<td>2.12</td>
<td>1.51</td>
<td>4.91</td>
</tr>
<tr>
<td>Mixed / Unknown / Maximum Residence Time</td>
<td>0.373</td>
<td>2.53</td>
<td>0.891</td>
<td>6.12</td>
</tr>
</tbody>
</table>
Highest Proportional Contribution by Chlorinated Drinking Water (at 95th NDMA Intake Percentile) to Total Average Daily Dose

Chlorinated Systems Maximum Distribution System Residence Time

- Chlorinated Systems: 99.96%
- Drinking Water: 0.04%
- All other Sources: 0
Highest Proportional Contribution by Chloraminated Drinking Water (at 95th NDMA Intake Percentile) to Total Average Daily Dose

Chloraminated Systems Maximum Distribution System Residence Time

- Drinking Water: 0.3%
- All other Sources: 99.7%
Proportion of Exogenous Contribution by Drinking Water at 95th NDMA Intake Percentile, to Total Lifetime Average Daily Dose

Source
GW – Ground Water
SW – Surface Water
MX - Mixed

Disinfectant
Blank – Disinfection not indicated
CL – Free Chlorine
CA – Monochloramine

Sample Location
EP – Entry Point to Distribution System
MR – Maximum Residence Time
Concentration and Rate of Detection of NDMA in Water Supplies

**Source**
- GW – Ground Water
- SW – Surface Water
- MX - Mixed

**Disinfectant**
- Blank – Disinfection not indicated
- CL – Free Chlorine
- CA – Monochloramine

**Sample Location**
- EP – Entry Point to Distribution System
- MR – Maximum Residence Time
Mean Estimates of NDMA Intake from Drinking Water (ng/day)

- **SW/CA/MR**: 4.9
- **SW/CA/EP**: 3.0
- **SW/CL/EP**: 0.47
- **GW/CL/MR**: 0.38

Red bars represent age 20 - 49 years, and grey bars represent age 6 - 12 years.
Exogenous ADD in Infants, Chloraminated Surface Water

For chloraminated surface water sourced drinking water. Breast-fed infants are assumed to have no exposure to drinking water.
Exogenous ADD in Infants, Chlorinated Ground Water

For chlorinated ground water sourced drinking water. Breast-fed infants are assumed to have no exposure to drinking water.
Exogenous Contributions to LADD, Chloraminated Surface Water

The decision to breast-feed or formula-feed has little impact on exposure from drinking water over a lifetime.
Exogenous Contributions to LADD, Chlorinated Ground Water

The decision to breast-feed or formula-feed has little impact on exposure from drinking water over a lifetime.