Overview of the Draft IRIS Assessment of Ammonia

Presentation for the Ammonia Augmented Chemical Assessment Advisory Committee of the Science Advisory Board
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Susan Rieth, MPH
Audrey Galizia, M.S., M.S., Dr.PH. (Assessment Manager)
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
This presentation will cover:

• Key aspects of the Ammonia Toxicological Review
• Clarification of issues raised by public commenters and CAAC panel members at the teleconference held on May 23, 2014
• RfC: 0.3 mg/m³, based on decreased lung function and respiratory symptoms found in occupational epidemiology studies
• RfD: Not derived because data are not available
• Cancer: Inadequate information to assess carcinogenic potential
## Respiratory Effects Associated with Chronic Exposure

<table>
<thead>
<tr>
<th>Epidemiology study</th>
<th>Evidence of respiratory effects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Respiratory symptoms?</td>
<td>Decreased lung function?</td>
</tr>
<tr>
<td><strong>Industrial settings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rahman et al. (2007)</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Ballal et al. (1998)</td>
<td>yes</td>
<td>[not evaluated]</td>
</tr>
<tr>
<td>Holness et al. (1989)</td>
<td>no (workplace concentration lower than other studies)</td>
<td>no (workplace concentration lower than other studies)</td>
</tr>
<tr>
<td><strong>Health care/hospital workers</strong></td>
<td>yes (asthma or respiratory symptoms)</td>
<td>yes (one study)</td>
</tr>
<tr>
<td><strong>Livestock farmers</strong></td>
<td>generally no</td>
<td>generally yes</td>
</tr>
</tbody>
</table>
**RfC Derivation**

<table>
<thead>
<tr>
<th>Principal Study / Critical Effect</th>
<th>Point of Departure (mg/m³)</th>
<th>UF</th>
<th>Chronic RfC (mg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased lung function and respiratory symptoms</td>
<td>NOAEL&lt;sub&gt;ADJ&lt;/sub&gt;: 3.1</td>
<td>UF&lt;sub&gt;H&lt;/sub&gt; = 10</td>
<td>0.3</td>
</tr>
<tr>
<td>Occupational epidemiology studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holness et al. (1989); supported by Rahman et al. (2007), Ballal et al. (1998), and Ali et al. (2001)</td>
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</tbody>
</table>

NOAEL<sub>ADJ</sub> = no-observed-adverse-effect level (workplace exposure of 8.8 mg/m³) adjusted to continuous exposure:
- Human occupational default min volume (10 m³ breathed during 8-hr workday) ÷ Human ambient default min volume (20 m³ breathed during 24-hr day)
- Exposure of 5 days out of 7 days
  = 8.8 mg/m³ x 10 m³/20 m³ x 5/7

UF = uncertainty factor (standard UF<sub>H</sub> applied for absence of data on variability of response in human population)
Not derived; available oral toxicity information considered inadequate for derivation of an RfD

- **Human studies:**
  - Case reports of intentional or accidental ingestion of household cleaning solutions or ammonia inhalant capsules

- **Animal studies:**
  - Studies in rats designed to investigate the mechanism of ammonia action on the gastric mucosa; gastric mucosal thinning reported in the absence of microscopic lesions
Inhalation:

1. The RfC should be based on the same point of departure (21 mg/m³), uncertainty factors (AEGL: UF = 1), and time adjustment factor (AEGL: no adjustment) as the Acute Exposure Guideline Level (AEGL-1). [Public comment]

2. In deriving an AEGL, is it general practice to apply an intraspecies $UF_H$ (for human variability) of 3 when the endpoint is irritation, where the $UF_H$ of 10 is split into TK and TD and the TK component is set to 1? [Question raised by CAAC Panel Member]

Oral:

1. Short-term and subchronic administration of ammonia in drinking water to rats was associated with changes in the gastric mucosa, including reduced thickness and changes in epithelial cell migration/proliferation. What is the nature of these gastric mucosal changes? Are they progressive? [Question raised by CAAC Panel Member]
### Basis of Ammonia AEGL and RfC

<table>
<thead>
<tr>
<th>Reference value type</th>
<th>Duration</th>
<th>Reference value (mg/m³)</th>
<th>Health effect</th>
<th>POD (mg/m³)</th>
<th>Duration adjustment</th>
<th>UF</th>
</tr>
</thead>
<tbody>
<tr>
<td>A EGL-1 (emergency response)</td>
<td>10 min</td>
<td>21</td>
<td>Faint nasal &amp; eye irritation in 2 of 5 healthy subjects exposed to 21 mg/m³ for 10 min (MacEwen and Vernot, 1972)</td>
<td>21</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 hr</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 hr</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 hr</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRIS RfC – proposed (chronic exposure)</td>
<td>Chronic</td>
<td>0.3</td>
<td>Decreased lung function and respiratory symptoms (Holness et al., 1989; supported by other cross-sectional epidemiology studies)</td>
<td>3.1</td>
<td>10 m³/20 m³ x 5 days/7 days</td>
<td>Total UF = 10, UF_H = 10</td>
</tr>
</tbody>
</table>
Public Comment: The RfC should be based on the same point of departure (21 mg/m³), uncertainty factors (AEGL: UF = 1), and time adjustment factor (AEGL: no adjustment) as the Acute Exposure Guideline Level (AEGL-1).
RfC: An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments.

Source: IRIS Glossary
http://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do
Acute Exposure Guideline Level (AEGL) Definitions

**CHARACTERISTICS OF AEGLs**

**HAZARD ASSESSMENT**

<table>
<thead>
<tr>
<th>THRESHOLD LEVELS</th>
<th>EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEATH</strong></td>
<td>• Increasing likelihood of death</td>
</tr>
<tr>
<td><strong>AEGL-3</strong></td>
<td>• Impairment of ability to escape</td>
</tr>
<tr>
<td></td>
<td>• Increasing severity of irreversible or other serious, long-lasting effects</td>
</tr>
<tr>
<td><strong>DISABLING</strong></td>
<td>• Increase in notable discomfort</td>
</tr>
<tr>
<td></td>
<td>• Increasing severity of reversible effects (with or without signs / symptoms)</td>
</tr>
<tr>
<td><strong>AEGL-2</strong></td>
<td>• Increasing complaints of objectionable odor, taste, sensory irritation or other mild, non-sensory or asymptomatic effects</td>
</tr>
<tr>
<td><strong>DISCOMFORT</strong></td>
<td>• Notable discomfort</td>
</tr>
<tr>
<td><strong>AEGL-1</strong></td>
<td>• Notable irritation</td>
</tr>
</tbody>
</table>

**AEGL-1:** the airborne concentration (ppm or mg/m³) above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort (such as odor detection), irritation, or certain asymptomatic non-sensory effects. Effects are not disabling and are transient and reversible upon cessation of exposure.

**AEGL-2:** the airborne concentration above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

**AEGL-3:** the airborne concentration above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Source: AEGL Standard Operating Procedures (SOPs)

http://www.epa.gov/oppt/aegl/pubs/sop.htm
• AEGLs are developed with an assumption of a “once-in-a-lifetime” exposure scenario

• AEGLs do not take into account:
  – Potential for repeated spikes in exposure
  – Repeated injury leading to the potential for a cumulative increase in effect
Ammonia: Comparison of Reference Values

- **ACUTE**
- **Short Term**
- **Subchronic**
- **Chronic**

*Indicates an occupational value: expert judgment necessary prior to applying these values to the general public.
CAAC Question: In deriving an AEGL, is it general practice to apply an intraspecies $U_{FH}$ (human variability) of 3 when the endpoint is irritation, where the $U_{FH}$ of 10 is split into TK and TD and the TK component is set to 1?

AEGL SOPs:

- “In general, in the absence of data or information to the contrary, the default value for the intraspecies UF is 10. However, a UF of 3, or even 1, may be used if credible information or data are available.” (SOPs; Section 2.5.3.4)

- For some AEGL values, $U_{FH}$ may take TK and TD into consideration, but there is no general policy on doing so.
Intraspecies UF Values for Irritants

• AEGL SOPs do not offer specific guidance on the UFₜ to use for irritants.

• UFₜ for sensory irritants -- typically a UF of 3
  – For many irritants (including ammonia, chlorine, hydrochloric acid), UFₜ = 1

• Rationale for applying a UFₜ of 1 for AEGL-1 and AEGL-2 for ammonia:
  – “Ammonia is a contact irritant and is efficiently scrubbed in the upper respiratory tract, particularly at the low AEGL-1 concentration; therefore, members of the population are not expected to respond differently to effects confined to the upper respiratory tract. Atopics, including asthmatics, and nonatopics responded similarly to a brief nasal exposure to ammonia. Exercising subjects showed only a clinically nonsignificant decrease in pulmonary function after exposure to ammonia.”

Source: Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 6 (Appendix B)
CAAC Question: Short-term and subchronic administration of ammonia in drinking water to rats was associated with changes in the gastric mucosa, including reduced thickness and changes in epithelial cell migration/proliferation. What is the nature of these gastric mucosal changes? Are they progressive?

Overview of ammonia literature related to gastric effects:

- Three in vivo drinking water studies of ammonia in the rat
  - Designed to investigate the role of ammonia in the pathogenesis of chronic atrophic gastritis caused by *Helicobacter pylori*
    - *H. pylori* is a bacterium that produces urease that increases ammonia production in the stomach
    - Responsible for gastric disease in human populations
  - Study designs:

<table>
<thead>
<tr>
<th>Study</th>
<th>Drinking water conc (ppm)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kawano et al. (1991)</td>
<td>0, 0.01, 0.1%</td>
<td>2, 4 wks</td>
</tr>
<tr>
<td>Tsujii et al. (1993)</td>
<td>0, 0.01%</td>
<td>3 days, 1, 2, 4, 8 wks</td>
</tr>
<tr>
<td>Hata et al. (1994)</td>
<td>0, 0.02, 0.1%</td>
<td>1, 3, 5 days, 1, 4, 8, 12, 24 wks</td>
</tr>
</tbody>
</table>
H. pylori-induced gastric changes

- Chronic gastritis: gastric atrophy (loss of glands) and chronic inflammation
- Progression:
  → ulcer
  → metaplasia and gastric cancer
- Pathogenesis is complex, multifactorial

Ammonia-induced gastric changes

- Concentration- and duration-related changes in:
  - gland height/thickness (mucosal atrophy) [presented as morphometric change]
  - PAS-positive mucus
  - cell cycling, rate of epithelial cell migration/proliferation
- Evidence of lack of progression:
  - Kawano et al. (1991) and Tsujii et al. (1993): “No mucosal lesions were found macroscopically or microscopically in the stomach…”
  - Hata et al. (1994): “Histological observation did not reveal inflammatory cell invasion or ulceration of the mucosa…”
Interpretation of gastric mucosal changes should take into consideration:

- Context: e.g., severity, incidence, associated changes
- Quality of the study, including documentation of slide review by a qualified pathologist

In the absence of reported histopathology, ammonia-associated gastric effects in the rat are difficult to interpret.
Summary of Major Issues Raised during June 2 Teleconference

- Public commenter recommended that the RfC be based on the same POD, UF, and time adjustment factor as the AEGL-1.
  - By definition RfCs and AEGLs are not the same; RfCs apply to chronic (lifetime) exposures, while AEGLs are used for emergency response situations and apply to acute (10-minute to 8-hour) exposures.
  - Study used to derive the ammonia AEGL-1 is not an appropriate basis for the chronic RfC:
    - Irritation only evaluated in 5 subjects exposed to ammonia for 10 minutes (MacEwen and Vernot, 1972)

- CAAC Question: Is it general practice to apply an intraspecies UF\textsubscript{H} (human variability) of 3 when the endpoint is irritation, where the UF\textsubscript{H} of 10 is split into TK and TD and the TK component is set to 1?
  - AEGL SOPs:
    - Default value for UF\textsubscript{H} is 10; however, UF \leq 3 may be used if credible information or data are available.
    - No specific guidance on the UF\textsubscript{H} to use for irritants; for sensory irritants, typically UF\textsubscript{H} = 1 or 3 applied
    - No general policy for taking TK and TD components of UF\textsubscript{H} into consideration.
  - RfC for ammonia based on respiratory symptoms and lung function changes (not specifically irritation)

- CAAC Question: What is the nature of changes to the gastric mucosa associated with short-term and subchronic administration of ammonia in drinking water to rats? Are such changes progressive?
  - Ammonia exposure associated with concentration- and duration-related changes in: gland height/thickness, PAS-positive mucus, epithelial cell migration/proliferation
  - Evidence of lack of progression (no histopathological lesions identified)
  - Insufficient information to characterize the adversity of gastric mucosal changes