



# 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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## Outline of Presentation

### **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



## Key Aspects of Assessment

- RfC: 0.3 mg/m<sup>3</sup>, 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

Epidemiology study	Evidence of respiratory effects	
	Respiratory symptoms?	Decreased lung function?
Industrial settings		
Rahman et al. (2007)	yes	yes
Ballal et al. (1998)	yes	[not evaluated]
Ali et al. (2001)	[not evaluated]	yes
Holness et al. (1989)	no (workplace concentration lower than other studies)	no (workplace concentration lower than other studies)
Health care/hospital workers	yes (asthma or respiratory symptoms)	yes (one study)
Livestock farmers	generally no	generally yes



## RfC Derivation

Principal Study / Critical Effect	Point of Departure (mg/m <sup>3</sup> )	UF	Chronic RfC (mg/m <sup>3</sup> )
Decreased lung function and respiratory symptoms  Occupational epidemiology studies  Holness et al. (1989); supported by Rahman et al. (2007), Ballal et al. (1998), and Ali et al. (2001)	NOAEL <sub>ADJ</sub> : 3.1	UF <sub>H</sub> = 10	0.3

NOAEL<sub>ADJ</sub> = no-observed-adverse-effect level (workplace exposure of 8.8 mg/m<sup>3</sup>) adjusted to continuous exposure:

- Human occupational default min volume (10 m<sup>3</sup> breathed during 8-hr workday) ÷ Human ambient default min volume (20 m<sup>3</sup> breathed during 24-hr day)
  - Exposure of 5 days out of 7 days
- = 8.8 mg/m<sup>3</sup> × 10 m<sup>3</sup>/20 m<sup>3</sup> × 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



## Major Public / CAAC Comments

### Inhalation:

1. The RfC should be based on the same point of departure ( $21 \text{ mg/m}^3$ ), 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

Reference value type	Duration	Reference value (mg/m <sup>3</sup> )	Health effect	POD (mg/m <sup>3</sup> )	Duration adjustment	UF
AEGL-1 (emergency response)	10 min	21	Faint nasal & eye irritation in 2 of 5 healthy subjects exposed to 21 mg/m <sup>3</sup> for 10 min (MacEwen and Vernot, 1972)	21	none	Total UF = 1 UF <sub>H</sub> = 1
	30 min	21				
	1 hr	21				
	4 hr	21				
	8 hr	21				
IRIS RfC – proposed (chronic exposure)	Chronic	0.3	Decreased lung function and respiratory symptoms (Holness et al., 1989; supported by other cross-sectional epidemiology studies)	3.1	10 m <sup>3</sup> /20 m <sup>3</sup> x 5 days/7 days	Total UF = 10 UF <sub>H</sub> = 10



## Inhalation Issue #1

- **Public Comment:** The RfC should be based on the same point of departure ( $21 \text{ mg/m}^3$ ), uncertainty factors (AEGL:  $UF = 1$ ), and time adjustment factor (AEGL: no adjustment) as the Acute Exposure Guideline Level (AEGL-1).



## RfC: Definition

**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.**

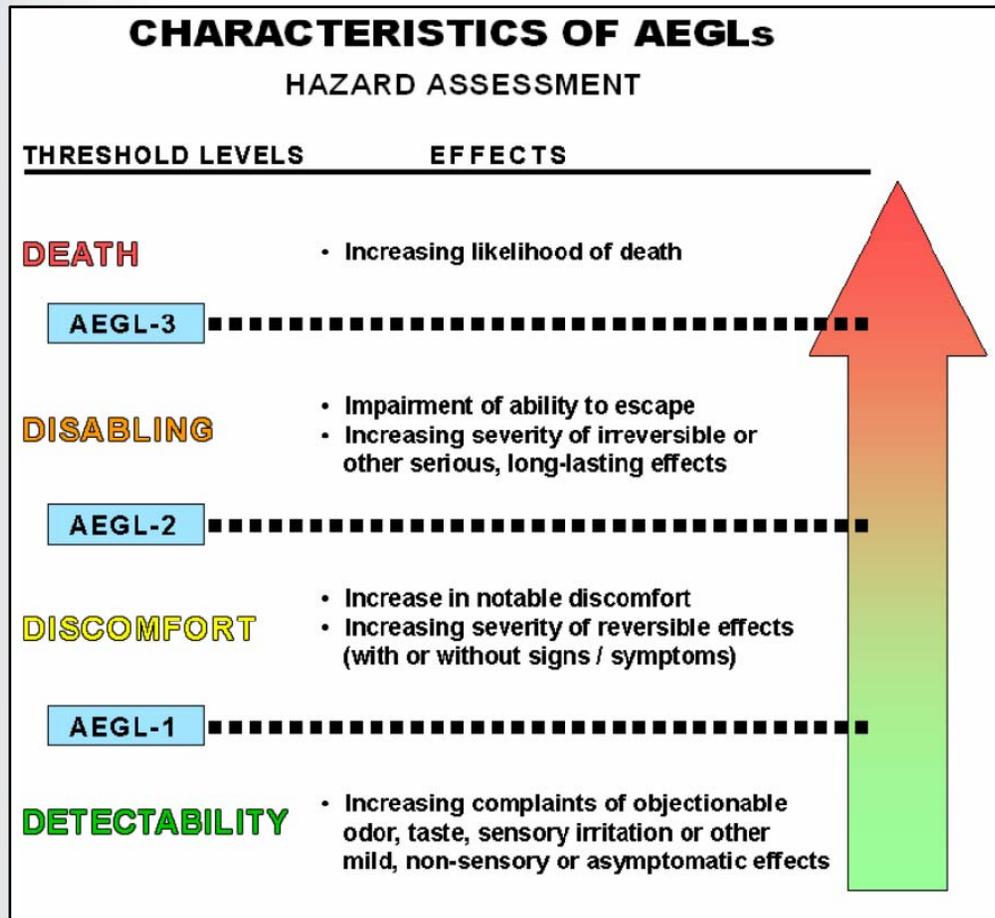
It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments.

Source: IRIS Glossary

[http://ofmpub.epa.gov/sor\\_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do](http://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do)



# Acute Exposure Guideline Level (AEGL) Definitions



**AEGL-1:** the airborne concentration (ppm or mg/m<sup>3</sup>) 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>





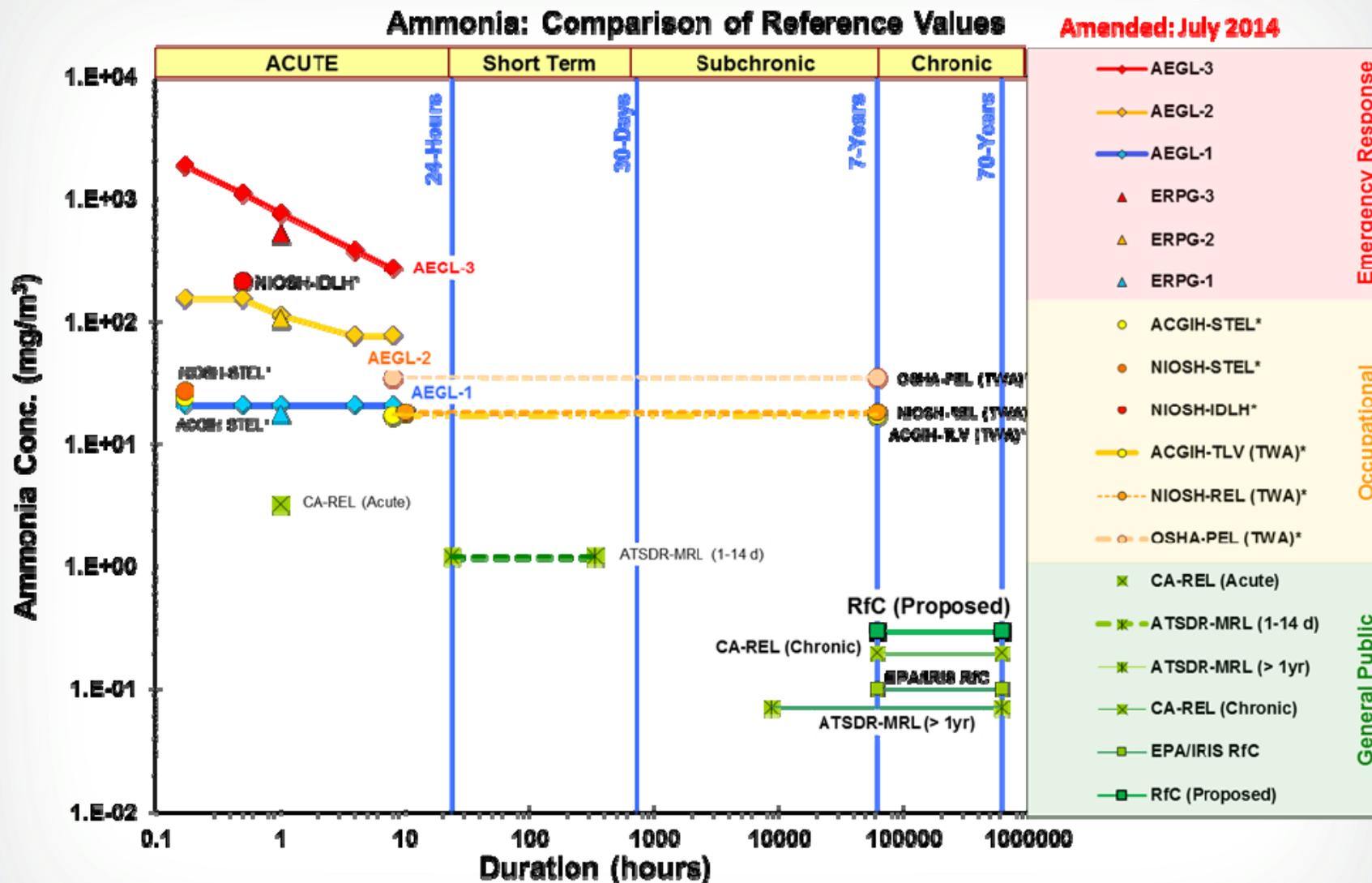
## Acute Exposure Guideline Level (AEGL) Features

- 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



May 2009

Amended: July 2014



\* Indicates an occupational value: expert judgment necessary prior to applying these values to the general public.



## Inhalation Issue #2

**CAAC Question:** In deriving an AEGL, is it general practice to apply an intraspecies  $UF_H$  (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?

### **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,  $UF_H$  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  $UF_H$  to use for irritants.
- $UF_H$  for sensory irritants -- typically a UF of 3
  - For many irritants (including ammonia, chlorine, hydrochloric acid),  $UF_H = 1$
- Rationale for applying a  $UF_H$  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)  
[http://www.epa.gov/oppt/aegl/pubs/ammonia\\_final\\_volume6\\_2007.pdf](http://www.epa.gov/oppt/aegl/pubs/ammonia_final_volume6_2007.pdf)



## Oral Issue #1

**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:

Study	Drinking water conc (ppm)	Duration
Kawano et al. (1991)	0, 0.01, 0.1%	2, 4 wks
Tsujii et al. (1993)	0, 0.01%	3 days, 1, 2, 4, 8 wks
Hata et al. (1994)	0, 0.02, 0.1%	1, 3, 5 days, 1, 4, 8, 12, 24 wks



## Oral Issue #1 (con't)

### ***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...”



## Oral Issue #1 (con't)

- 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, UFs, 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  $UF_H$  (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?**
  - AEGL SOPs:
    - Default value for  $UF_H$  is 10; however,  $UF \leq 3$  may be used if credible information or data are available.
    - No specific guidance on the  $UF_H$  to use for irritants; for sensory irritants, typically  $UF_H = 1$  or 3 applied
    - No general policy for taking TK and TD components of  $UF_H$  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