Overview of the Draft IRIS Assessment of Ammonia

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Outline of Presentation

This presentation will cover:

- Implementation of 2011 NRC recommendations in the ammonia assessment
- General information on ammonia
- Overview of the Toxicological Review
- Major public comments and EPA's responses to those comments

Implementation of 2011 NRC Recommendations

The new document structure enhances clarity, reduces volume, addresses redundancies and inconsistencies, and includes:

- A Preamble that describes the assessment methods
- An executive summary that concisely summarizes major conclusions
- A detailed literature search strategy and study selection section
- Use of the HERO database
- Distinct sections on hazard identification and dose-response assessment
- Standardized evidence tables in place of long text descriptions
- Standardized study evaluation (describing strengths and weaknesses) by including more systematic synthesis and integration of information by health outcome
- A dose-response section with a toxicity value derived from the combination of multiple studies
- Clear description of decision points

Implementation of 2011 NRC Recommendations

Recommendations to be implemented in future IRIS assessments:

- More transparent and systematic approaches to evidence identification
- Systematic approaches for evaluation of human, experimental animal, and mechanistic studies
- A systematic approach for evidence integration
- Development of uniform language to describe weight-of-evidence for noncancer effects
- Advanced approaches for quantitative assessment
- Expanded approaches for characterizing uncertainty and variability

General Information

Uses of ammonia

- In agricultural fertilizers
- As a corrosion inhibitor, household cleaner, antimicrobial agent in food products, refrigerant, in water purification
- To reduce nitrogen oxide (NOx) emissions from the exhaust of stationary combustion sources and diesel vehicles

Exposures

- Exposures (largely inhalation and dermal) can occur through:
  - Use of cleaning products
  - Manufacture and application of fertilizers
  - Work in swine and poultry confinement areas
- ~159 million pounds released annually from facilities required to report releases (TRI, 2012)
- Identified at a number of National Priority List (NPL) waste sites, listed as a hazardous substance under CERCLA ("Superfund"), and subject to reporting requirements under the Emergency Planning and Community Right-to-Know Act and to emergency planning requirements under the Clean Air Act

Scope of the Toxicological Review

- Critical review of publicly available scientific literature on ammonia (gaseous) and ammonium hydroxide (ammonia dissolved in water)
- Does not include evaluation of ammonium salts literature
  - Uncertainty regarding the influence of the anion of the salt on the toxicity of the ammonium compound (addressed in Appendix C)

Literature Search Strategy

Initial keyword search (*see Table LS-1 and Figure LS-1*): **~22,400** references

Secondary keyword search:
~13,270 references **excluded**

~9,130 references

Preliminary manual screen (titles/abstracts):
~8,700 references **excluded**

Other search strategies
- Forward/backward searching
- Focused search in cleaning/health care settings

Considered for inclusion in the Toxicological Review: **1,032** references

Manual review (abstracts/papers):
737 references **excluded**

Cited in the Toxicological Review: **295** references

Literature search output and references available on HERO (https://hero.epa.gov)

Ammonia Database

	Humans	Experimental				
		Chronic	Subchronic	Two-gen repro/ developmental	Mechanistic information	Toxico-kinetics
Oral			✓		✓	✓
Inhalation	✓		✓			✓

Ammonia database also includes:

- Limited cancer bioassays (oral exposures)
- Numerous case reports (acute oral and inhalation exposures)
- Controlled-exposure volunteer studies (≤4 hour inhalation exposures)

Hazard Identification

- Noncancer effects
  - Respiratory (inhalation exposure)
  - Gastrointestinal (oral exposure)
  - Immune system
    - Unclear if evidence of elevated bacterial colonization is the result of damage to the protective mucosal epithelium of the respiratory tract or suppressed immunity
  - Other systemic effects
    - Inconsistent evidence from older (1939-1970) toxicological literature
- Cancer weight-of-evidence descriptor
  - Inadequate information to assess carcinogenic potential

Selection of Studies for RfC Derivation

- Cross-sectional epidemiology studies

Study	Industrial setting	Respiratory effects	
		No effects observed (mg/m^3)	Effects observed (mg/m^3)
Rahman et al. (2007)	Urea fertilizer plant	4.9 (mean)	18.5 (mean)
Ballal et al. (1998)	Urea fertilizer plant	0.2–7	2–27.1
Ali et al. (2001)	Urea fertilizer plant	≤50 mg/m^3-yr (cumulative exposure)	>50 mg/m^3-yr (cumulative exposure)
Holness et al. (1989)	Soda ash plant	~8.8	--

- Respiratory effects in experimental animals generally observed at higher concentrations than epidemiology studies

RfC Derivation

Principal Study / Critical Effect	Point of Departure (mg/m^3)	UF	Chronic RfC (mg/m^3)
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)	$NOAEL_{ADJ}$: 3.1	$UF_H = 10$	0.3

NOAEL = no-observed-adverse-effect level

UF = uncertainty factor (standard UF_H applied for absence of data on variability of response in human population)

$NOAEL_{ADJ}$ = NOAEL based on workplace exposure (8.8 mg/m^3) adjusted to continuous exposure:

- ratio of VEho (human occupational default min volume of 10 m^3 breathed during 8-hr workday) to VEh (human ambient default min volume of 20 m^3 breathed during 24-hr day)
- exposure of 5 days out of 7 days

$= 8.8\ mg/m^3 \times 10\ m^3/20\ m^3 \times 5/7$

Advances in Integration and Analysis of Epidemiology and Toxicokinetic Data

Principal Study / Critical Effect	Point of Departure (mg/m^3)	UF	Chronic RfC (mg/m^3)
RfC currently on IRIS (1991): • Lack of evidence of decreased pulmonary function or changes in subjective symptomatology; Holness et al. (1989)—occupational epidemiology study	$NOAEL_{ADJ}$: 2.3	Total UF = 30 UF_H = 10 UF_{DB} = 3	0.1
Proposed RfC (2013): • Decreased lung function and respiratory symptoms; Holness et al. (1989)—occupational epidemiology study; supported by Rahman et al. (2007), Ballal et al. (1998), and Ali et al. (2001)	$NOAEL_{ADJ}$: 3.1	Total UF = 10 UF_H = 10	0.3

2013 draft assessment:

- Reanalyzes Holness et al. (1989); higher POD identified
- Integrates findings from multiple occupational epidemiology studies
- Presents a more thorough analysis of toxicokinetic data; database UF removed

RfD

Data inadequate for derivation of an RfD

- Human studies
  - Case reports
    - Involved intentional or accidental ingestion of household cleaning solutions or ammonia inhalant capsules
    - Provide anecdotal evidence of effects on the gastrointestinal tract

- Animal studies
  - Studies in rats designed to investigate the mechanism of ammonia action on the gastric mucosa; no evidence of microscopic lesions, gastritis, or ulceration

Key Scientific Issue: Endogenously-produced Ammonia

- EPA's analysis shows that ammonia concentrations in exhaled breath depend on where it is measured (see Appendix E).
  - In the mouth: 0.09–2.1 mg/m^3
    - Largely attributable to bacterial degradation of food proteins
  - In the nose or trachea: 0.009–0.1 mg/m^3
    - More representative of systemic levels of ammonia
    - Better represents levels at the alveolar interface of the lung
  - Exhaled (endogenous) ammonia is likely to be rapidly diluted in ambient air
    - Representative ambient concentrations (see Appendix E):

      Indoors: 0.002–0.06 mg/m^3; Outdoors: 0.0004 mg/m^3
  - Proposed RfC = 0.3 mg/m^3

Major Public Comments and EPA's Response

Comment: The literature search strategy is not transparent or sufficiently detailed.

EPA's Response:

- Additional literature search documentation, including the search string and details of additional focused searches, were added to the Supplemental Materials (Appendix D).
- Ammonia is one of the first IRIS assessments to apply a systematic review approach to evidence identification; EPA is working to more fully implement systematic review practices, including literature search documentation, in other on-going assessments.

Major Public Comments and EPA's Response

Comment: EPA should provide more specific information as to how and why studies were selected from the literature search for further consideration.

EPA's Response:

- The Literature Search Strategy | Study Selection section was expanded to include a more detailed discussion of study selection process (for human and animal studies).
- A study-by-study tabulation of methodological considerations that inform study quality for epidemiology studies was added (Appendix D).

Major Public Comments and EPA's Response

Comment: A qualitative discussion of potential confounding factors (e.g., co-exposure to other chemicals) should be included.

EPA's Response:

- Consideration of potential confounding was added to Appendix D (methodological evaluations of individual epidemiology studies) and to the Literature Search Strategy | Study Selection section.
- Consideration of co-exposure to other agents in livestock farmer studies in Appendix E was expanded.

Major Public Comments and EPA's Response

Comment: Selection of Holness et al. (1989) as the principal study was not supported. This worker study found no relationship between level or duration of ammonia exposure and lung function changes.

EPA's Response:

- Holness et al. (1989) was selected as the principal study in the context of the entire database, with support from 3 other cross-sectional occupational studies.
- Confidence in Holness et al. (1989) was higher because of:
  - Higher confidence in the exposure measures
  - Evaluation of both respiratory symptoms and lung function
  - Higher estimate of the NOAEL
- Support for the selection of the principal study was expanded (Section 2).

Major Public Comments and EPA's Response

Comment: An alternative POD should be selected as the basis for the RfC; the POD should be consistent with the Acute Exposure Guideline Level (AEGL)-1 value of 21 mg/m^3.

EPA's Response:

- The AEGL-1 of 21 mg/m^3 for ammonia is not a scientifically sound POD for the chronic RfC.
  - AEGLs are applicable to emergency exposures (10 minutes to 8 hours), whereas IRIS reference values are used to assess chronic exposures.
  - The AEGL-1 for ammonia is based on a study in which 2 of 6 human volunteers experienced upper respiratory tract irritation after exposure to 21 mg/m^3 for 10 minutes.
- The rationale for selecting the POD from the Holness et al. (1989) study (NOAEL of 8.8 mg/m^3) was expanded (Section 2).

Summary

The ammonia assessment:

- Provides an updated RfC for ammonia
- Integrates findings from multiple epidemiological studies to derive the RfC
- Uses toxicokinetic data to reduce database uncertainty
- Addresses public comments
- Represents a significant advance for the IRIS Program in implementing the 2011 NRC recommendations

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