IRIS Public Science Meeting

May 23, 2018

Welcome and Logistics

- Keep your phone **muted** throughout the webinar.
- **To ask a question or provide a comment**, use the “Q&A” pod of the Adobe Connect Webinar to inform the meeting host of your question. Questions and comments (webinar) will be posed at the end of each issue discussion.
- **To report technical difficulties or webinar issues to the meeting host,** use the “chat” pod of the Adobe Connect Webinar.

INTRODUCTION AND ROLE OF ASSESSMENT PLANS IN THE IRIS PROCESS

Kris Thayer
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Office of Research and Development
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- **Created in 1985 to foster consistency in the evaluation of chemical toxicity across the Agency.**
- **IRIS assessments contribute to decisions across EPA and other health agencies.**
- **Toxicity values**
  - Noncancer: Reference Doses (RfDs) and Reference Concentrations (RfCs).
  - Cancer: Oral Slope Factors (OSFs) and Inhalation Unit Risks (IURs).
- **IRIS assessments have no direct regulatory impact until they are combined with**
  - Extent of exposure to people, cost of cleanup, available technology, etc.
  - Regulatory options.
  - Both of these are the purview of EPA's program offices.

IRIS Provides Scientific Foundation for Agency Decision Making

IRIS

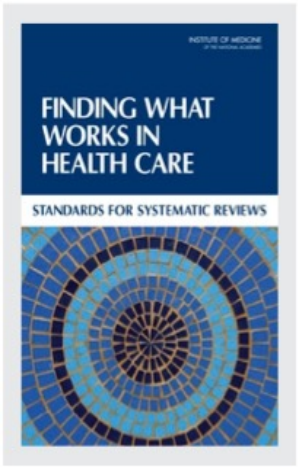
- Clean Air Act (CAA)
- Safe Drinking Water Act (SDWA)
- Food Quality Protection Act (FQPA)
- Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)
- Resource Conservation and Recovery Act (RCRA)
- Toxic Substances Control Act (TSCA)

Broad Input to Support

- Agency Strategic Goals
- Children's Health
- Environmental Justice

Systematic Review

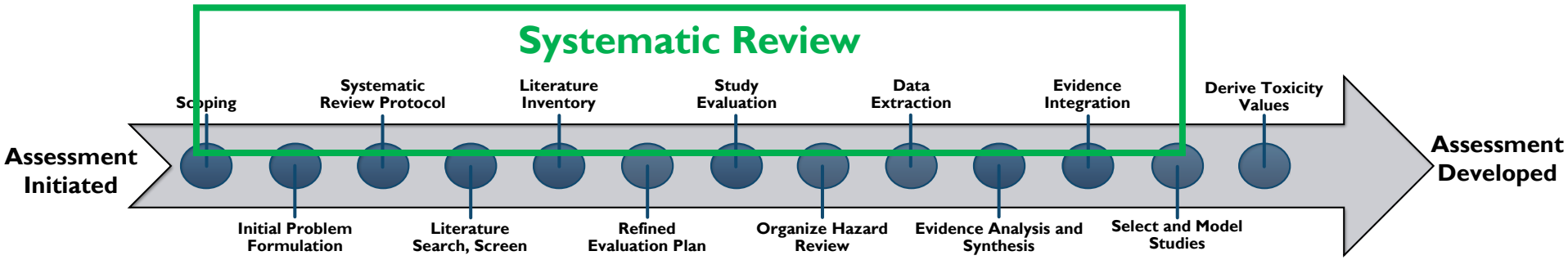
A structured and documented process for transparent literature review



"As defined by IOM [Institute of Medicine][1], systematic review 'is a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies."

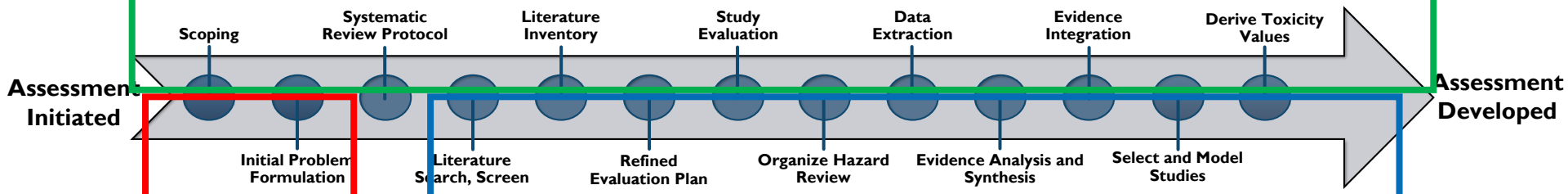
[1] Institute of Medicine. Finding What works in Health Care: Standards for Systematic Reviews. p.13-34. The National Academies Press. Washington, D.C. 2011

Systematic Review in IRIS Assessments



IRIS Systematic Review Documents

IRIS Handbook: Approaches and considerations for applying principles of systematic review to IRIS assessments, general frameworks, and examples.



Assessment Plans: What the assessment will cover

Protocols: How the assessment will be conducted (specific procedures and approaches for each assessment component, with rationale where needed)

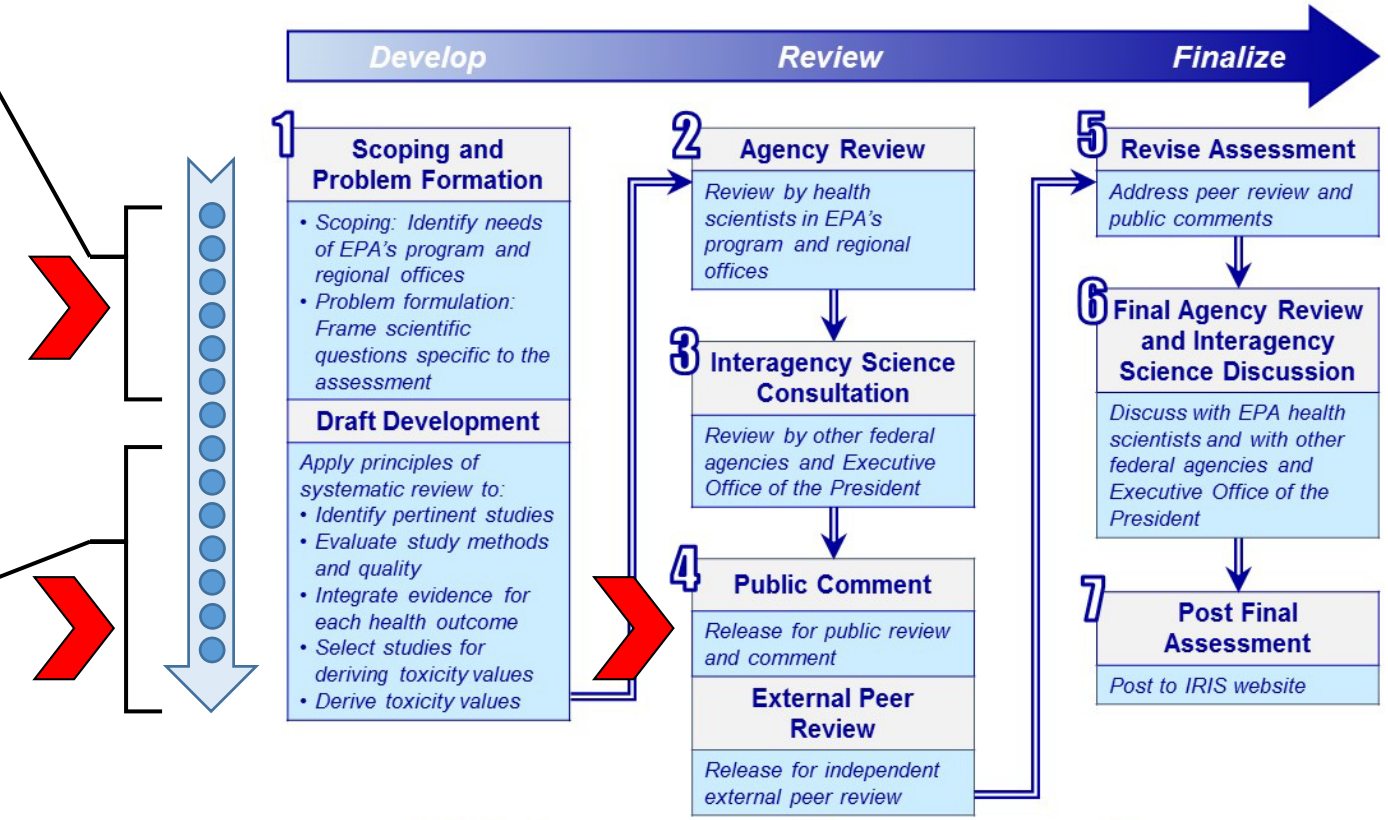
IRIS Assessment Plans, Protocols, and 7-Step IRIS Process

Early Step 1: IRIS Assessment Plans

- What the assessment covers
- 30-day public comment period + public science meeting

Mid-Step 1: Protocols

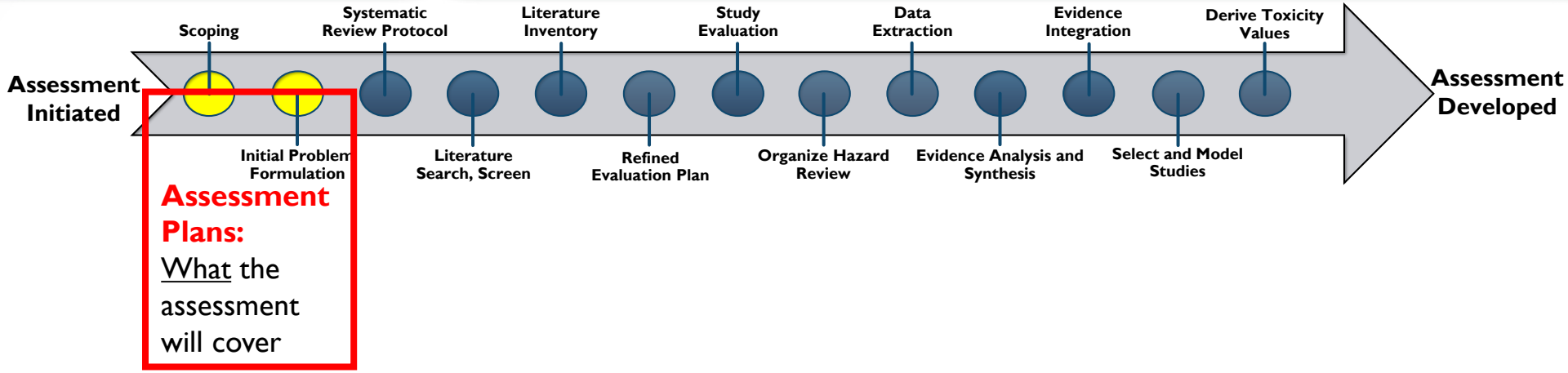
- How the assessment will be conducted
- 30-day public comment



Opportunities for Public Comment

https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#process

IRIS Assessment Plan (IAP)



- Scoping and initial problem formulation determinations
  - Background and Agency need, exposure context, objectives and specific aims, key areas of scientific complexity
  - Includes draft PECO (Populations, Exposures, Comparators, and Outcomes) criteria which outlines evidence considered most pertinent
  - Internal review of IAP fosters early and focused Agency engagement
- Released for a 30-day public comment period + public science discussion (beginning of IRIS Step 1)
- Ammonia IAP released for public comment on April 16, 2018

IRIS Assessment Plan (IAP) Content

Table 1. EPA program and regional office interest in an assessment of oral exposure to ammonia

EPA program or regional office[a]	Oral	Inhalation	Statutes/regulations	Anticipated uses/Interest
Office of Water	Need	Completed, 2016	Safe Drinking Water Act: to inform the Office of Water Health Advisories,	Ammonia is certified for use in water and wastewater treatment, most notably in disinfection of drinking water by chloramination.

- ammonium hydroxide (1336-21-6)
- ammonium acetate (631-61-8)
- ammonium chloride (12125-02-9)
- ammonium sulfate (7783-20-2)
- ammonium

also a high-priority contaminant due fertilizers and presence in runoff agricultural fields.

orities need a reference dose to ection of public health after spills or contamination situations.

ated ources.

2.4. KEY SCIENCE ISSUES

Based on the preliminary survey of health agency assessments and authoritative review articles, several key science issues will warrant consideration in the assessment.

Attribution of responses to the ammonium cation or to the anion (for example, is a response to ammonium chloride due to its ammonium cation or to its chloride anion?): Some studies included an anion control (for example, a study of ammonium chloride that included control animals exposed to equimolar concentrations of potassium chloride). These studies will be especially informative for determining whether responses are attributable to the ammonium ion or to the anion (in this example, the chloride ion).

The palatability of ammonia to experimental animals: Ammonia is unpalatable to humans, which suggests that ammonia in food or water might cause experimental animals to reduce intake, leading to adverse health outcomes that would not necessarily be due to ammonia toxicity. The assessment will examine dose-related trends in body weight and in food or water intake to estimate concentrations of ammonia that make food or water unpalatable to experimental animals. In addition, the assessment will consider studies in which ammonia was administered directly via oral gavage, in which the dose of ammonia does not depend on food or water intake.

Endogenous production of ammonia: The body produces ammonia during the metabolism of amino acids. Most production occurs in the intestines during the digestion of meat and other sources of protein, and a smaller amount occurs in the mouth from the reaction of saliva with food particles. The rate of production of ammonia in the intestines is substantially higher than typical intake rates (see Section 2.1). Ammonia is a toxic product with no apparent health benefits; the body converts ammonia to urea and eliminates it.

3. OVERALL OBJECTIVE, SPECIFIC AIMS, AND DRAFT POPULATIONS, EXP AND OUTCOMES (P

The overall objective of this assess exposure to ammonia and ammonium sal derive an oral reference dose. The assess pertinent epidemiologic and experimenta mechanistic evidence. The evaluations co relevant EPA guidance.[9] The systematic r draft assessment plan and will reflect cha response to public input.

3.1. SPECIFIC AIMS

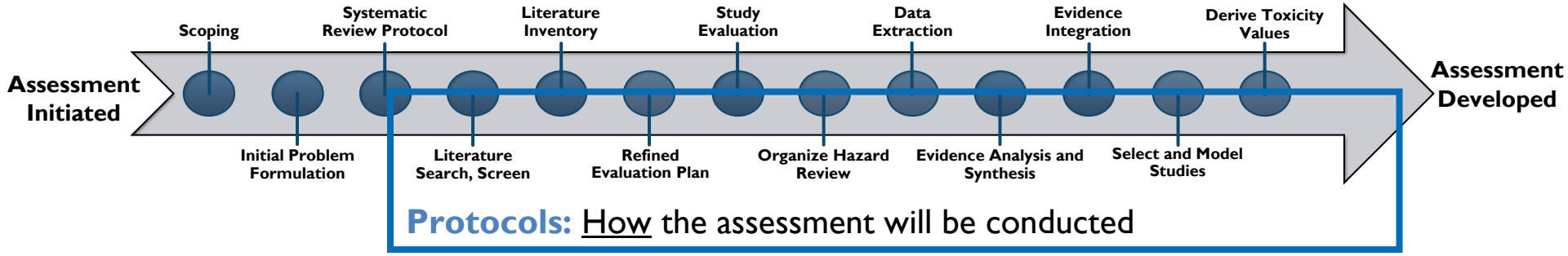
- Identify epidemiologic and experi ammonia, as outlined in the PECO exposure to ammonia or ammoniu considered critical for this assessr Other published authoritative sou review articles, will be the primar assessment.
- Conduct study evaluations (risk o experimental animal studies. Stud uninformative and will not be con
- Extract data on relevant health ou studies included based on the stud

Table 3. Draft PECO (Populations, Exposures, Comparators, Outcomes) Criteria for assessing noncancer hazards of oral exposure to ammonia and ammonium salts

PECO element	Evidence
Populations[a]	Human: Any population and life stage (occupational or general population, including children and other potentially susceptible populations or life stages). The following study designs will be considered most informative: controlled exposure, cohort, case-control, cross-sectional, and ecological. Note: Case reports and case series will be tracked during study screening, but are not the primary focus of this assessment. They may be retrieved for full-text review and subsequent evidence synthesis if no or few informative study designs are available. Case reports also can be used as supportive information to establish biologic plausibility for some target organs and health outcomes.
	Animal: Nonhuman mammalian animal species (whole organism) of any life stage (including preconception, in utero, lactation, peripubertal, and adult stages).
Exposures	• Ingested ammonia (7664-41-7) or ammonium salts, including ammonium hydroxide (1336-21-6), ammonium acetate (631-61-8), ammonium chloride (12125-02-9), ammonium sulfate (7783-20-2), ammonium phosphate (7783-28-0), ammonium dihydrogen phosphate (7722-76-1), ammonium carbonate (506-87-6), ammonium bicarbonate (1066-33-7), and ammonium citrate (7632-50-0) • Studies of urea or of mixtures containing ammonia are not expected to be useful for deriving toxicity values. These are outside the scope of the assessment. • Studies of complex ammonium salts in which the non-ammonium moiety could contribute significant toxicity (e.g., aluminum ammonium sulfate, ammonium metavanadate, ammonium perchlorate; see Section 2.2) are not expected to be useful for deriving toxicity values for ammonia. These are outside the scope of the assessment.
	Human: Exposure based on biomonitoring data (e.g., urine, blood, or other specimens), environmental or occupational-setting measures (e.g., air, water levels), or job title, or residence. Occupations in which exposure to ammonia is expected include brewers, janitors, cleaners, exterminators, cosmetologists, hairstylists, morticians, embalmers, agricultural workers, farmworkers, and fertilizer manufacture. All single-dose human studies will be included.
	Animal: Exposure routes to ammonia via dietary, drinking water, gavage, or intraperitoneal administration. Studies employing one or more exposed groups will be considered the most informative (i.e., studies with multiple doses and multiple durations of exposure). Other exposures (e.g., including single-dose studies) will be tracked during title and abstract as "supplemental material." Studies involving exposures to mixtures will be included only if they include an arm with exposure to ammonia or an ammonium salt alone.
Comparators	Human: A comparison or reference population exposed to lower levels (or no exposure/exposure below detection levels) of ammonia (or ammonia salts) or for shorter periods.
	Animal: Quantitative exposure vs. lower or no exposure or for a shorter duration with vehicle control. Historical controls, preferably from the same laboratory and close in time, may be considered if needed.

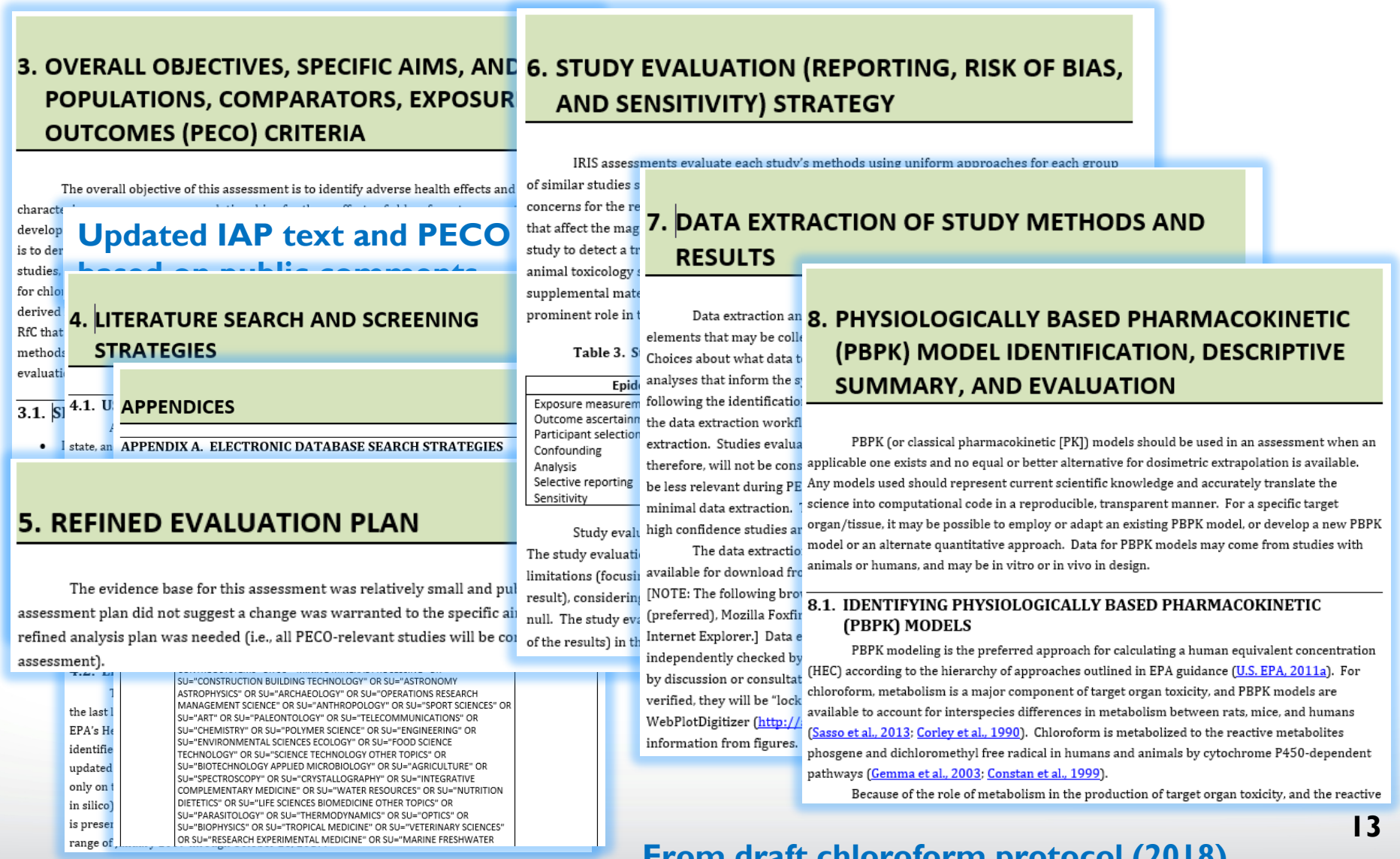
From draft ammonia IAP (2018)

IRIS Protocol



- In IRIS, comments received on IAP are considered when preparing the protocol (updated IAP text is included in the protocol) and protocols are released for 30-day public comment period
- Protocol is iterative – Public comment and knowledge gained during implementation may result in revisions to the protocol to focus on the best available evidence. Major revisions are documented via updates, e.g., changes to specific aims or PECO
- List of included, excluded, and studies tagged as supplemental are disseminated through protocols (either during initial release or as an update)

IRIS Protocol Content



From draft chloroform protocol (2018)

IRIS Protocol Content

9. SYNTHESIS WITHIN LINES OF EVIDENCE

For each potential health effect
outcomes; or a broad hazard category),
effect evidence, ar
written to empha
the evidence inte
studies or group c
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9.1. SYNTHE

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Table 9. Primar
syntheses[a]

Consideration	
Consistency	Repeated exist, the "differing" *Stronger h* *Stronger c*
Biological gradient (dose-response)[b]	Increases concentrat or comple necessarily considered
Strength (effect magnitude) and precision	Given wha particularl small effe may consi other expl errors and results acr (i.e., low p
Mechanistic evidence related to biological plausibility	Supporting effects; changes in established biol evidence strength. While a lack of strength, it may do so if findings de *Human evidence:* studies in expose *Animal evidence*: studies in exposed animals
Coherence[c]	Findings across the database that fit into a co similarity in results for related effects within a dose-dependent progression of linked effects Conversely, an observed lack of changes that subsequently) with the effect of interest coul informed by the known biological developme toxicokinetic/dynamic understanding of the c
Natural experiments	*Human evidence only*: Reductions in effect th Although rare, such reductions can provide c
Temporality	*Human evidence only:* The exposure occurs be evaluation of exposure measures for each stu

10. INTEGRATION ACROSS LINES

For the analysis of most health outcomes, IRIS assessme
and mechanistic evidence. Depending on the assessment scope a
animal evidence, conclusions for mechanistic evidence may be b
mechanistic st
are drawn as f

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- In para the che

WITHIN STREAM CONCLUSIONS

HUMAN EVIDENCE STREAM CONCLUSION

The synthesis of evidence about health effects and mechanisms from human studies is combined (integrated) to draw a conclusion about effects within the stream

Studies and interpretation	Factors that increase confidence	Factors that decrease confidence	Summ
[Health Effect or Outcome Grouping]			
Evidence from Human Studies (Route)			
· References · Study confidence (based on evaluation of risk of bias and sensitivity) and explanation · Study design description	· Consistency · Dose-response gradient · Coherence of observed effects (apical studies) · Effect size (magnitude, severity) · Biological plausibility · Low risk of bias/ high quality · Insensitivity of null/ negative studies · Natural experiments · Temporality	· Unexplained inconsistency · Imprecision · Indirectness/ applicability · Poor study quality/ high risk of bias · Other (e.g., Single/Few Studies; small sample size) · Evidence demonstrating implausibility	Results infor affected/ una Human evid plausibility: d data influenc judgement (e precursors in Could be multiple rows (e.g study confidence or popul informs results hetero
Evidence for an Effect in Animals (Route)			
· References · Study confidence (based on evaluation of risk of bias and sensitivity) and explanation · Study design description	· Consistency and Replication · Dose-response gradient · Coherence of observed effects (apical studies) · Effect size (magnitude, severity) · Biological plausibility · Low risk of bias/ high quality · Insensitivity of null/ negative studies	· Unexplained inconsistency · Imprecision · Indirectness/ applicability · Poor study quality/ high risk of bias · Other (e.g., Single/Few Studies; small sample size) · Evidence demonstrating implausibility	Results information (gene affected/ unaffected) acro Evidence informing biolo plausibility for effects in a discuss how mechanistic influenced the within stream judgement (e.g., evidence of coherent molecular changes in animal studies) Could be multiple rows (e.g., by study confidence, species, or exposure duration) if this informs results heterogeneity

+ + + Strongestevidence
+ + ○
+ ○ ○ Weakest evidence
○ ○ ○ Inadequate
– – – Convincing evidence of no effect

Figure 4. Evidence profile table template.

11. DOSE-RESPONSE ASSESSMENT: STUDY SELECTION AND QUANTITATIVE ANALYSIS

The previous sections of this protocol describe how systematic review principles are applied to support transparent identification of health outcomes (or hazards) associated with exposure to the chemical of interest in conjunction with evaluation of the quality of the studies considered during hazard identification. Selection of specific data for dose-response assessment and performance of the dose-response assessment is conducted after hazard identification is complete, and builds off this step in developing the complete IRIS assessment. The dataset selection process involves database- and chemical-specific biological judgments that are beyond the scope of this protocol, but are discussed in existing EPA guidance and support documents. This section of the protocol provides an overview of points to consider when conducting the dose-response assessment, particularly statistical considerations specific to dose response analysis that support quantitative risk assessment. Importantly, the considerations outlined in this protocol do not supersede existing EPA guidance. Several EPA guidance and support documents provide more detailed considerations for the development of EPA's traditional dose-response values, especially EPA's *Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002), EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012b), *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), and *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b).

For IRIS toxicological reviews, dose-response assessments are typically performed for both

12. PROTOCOL HISTORY

Release date: (January 2018 [*chloroform protocol version 1*])

From draft chloroform protocol (2018)

IRIS Assessment Plan for Oral Exposure to Ammonia and Selected Ammonium Salts

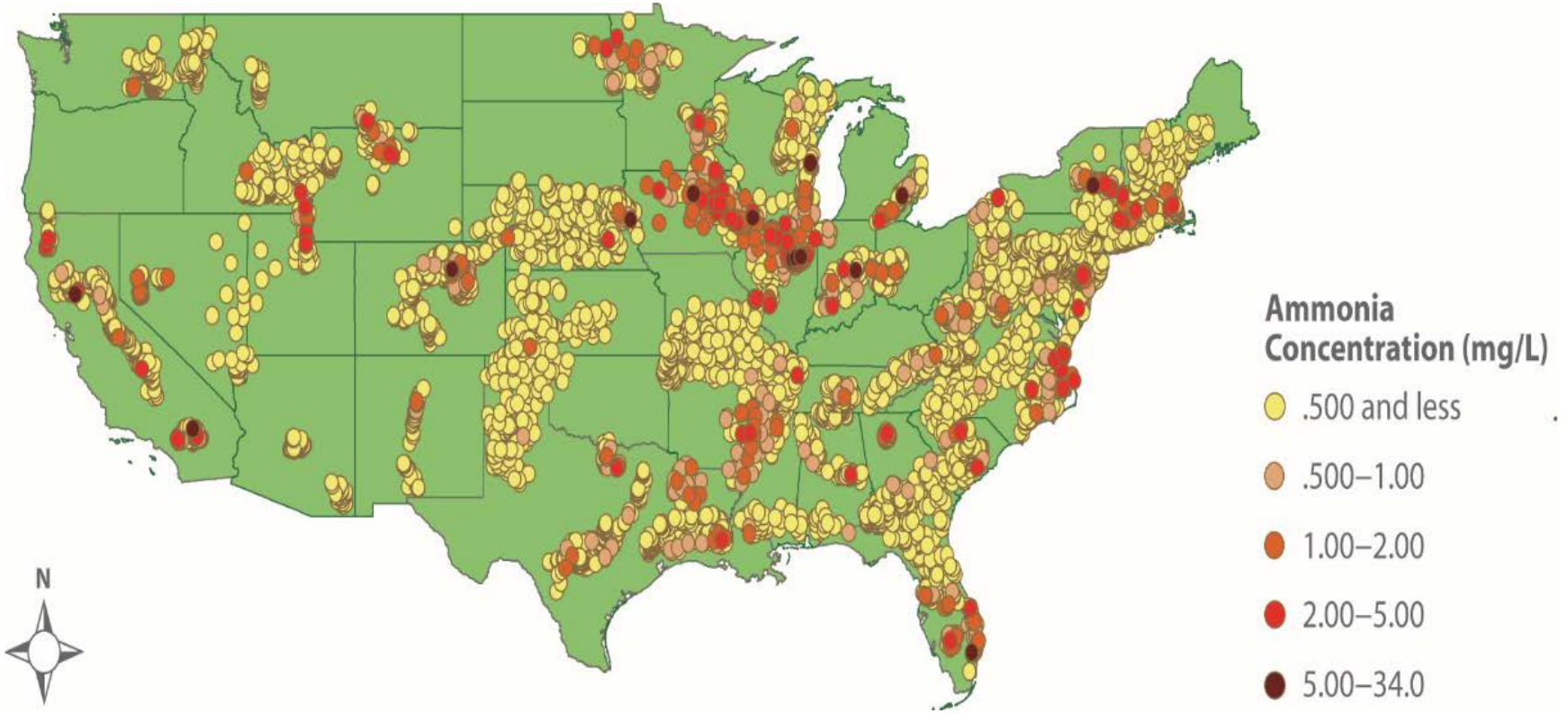
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency

Background

- **Ammonia is a caustic gas, highly soluble in body fluids**
- **Production: 10s of billions of lbs/yr in the U.S.**
- **Uses**
  - drinking-water disinfection by the process of chloramination
  - other water and wastewater treatment operations
  - fertilizers for agriculture (major use)
  - production of explosives (ammonium nitrate)
  - food additives, prescription drugs, pesticides (smaller amts)
- **Typical concentrations (variable by place and season)**

  <0.5 mg/L (water), <0.25 mg/m^3 (air)
- **Typical intake (mg/d):** <1 (water), <0.5 (air); 18 (foods)
- **Endogenous production (mg/d):** 4000, mostly intestinal

Ammonia in groundwater: spatial heterogeneity



Source: Map created for U.S. EPA based on U.S. Geological Survey National Water-Quality Assessment Program data from 2011

Scope of the assessment

- **Focus on oral exposure**

  (an inhalation assessment was completed in Sept 2016)

- **Focus on soluble ammonium salts**
  - These yield the ammonium ion (NH_4^+) in the body
  - Studies are available on several salts whose toxicity is reasonably attributed to NH_4^+

    (ammonium hydroxide, acetate, chloride, sulfate, etc.)
  - Excludes more complex compounds where the rest of the molecule is expected to be toxic

    (e.g., ammonium perchlorate, ammonium metavanadate)
- **Derive reference doses in terms of the ammonium ion**

Health outcomes to be evaluated

- **Gastric irritation**
- **Systemic toxicity (body weight)**
- **Metabolic acidosis* (and potentially musculo-skeletal toxicity)**
- **Hyperammonemia* (and potentially neurotoxicity)**
- **Developmental toxicity**

** these hazards are well established in the medical literature; focus will be on dose–response assessment*

- **No cancer evaluation (science topic 3, later)**

Potentially susceptible populations and lifestages

- Individuals with impaired liver or kidney function *(the liver converts ammonia to urea, which is excreted by the kidneys)*
- Infants and children *(ammonia can cross the blood–brain barrier)*
- Individuals at risk for osteoporosis *(metabolic acidosis can cause bone loss)*
- Individuals infected with *Helicobacter pylori (this bacterium produces ammonia and causes stomach irritation and most non-cardia stomach cancers)* (science topic 2, later)

Public comments

- Limit the assessment to ammonia and *selected* ammonium compounds where toxicity is attributable to ammonia and not the rest of the molecule
- Good to see discussion of endogenous production; experts in that field should be consulted (science topic 1, later)
- Comments pertinent to systematic review: PECO, study selection, study evaluation, general operating procedures
- Further comments on the assessment of inhalation exposure to ammonia (completed in 2016)

Specific aims

- Literature searches to identify pertinent epidemiologic and experimental studies for each health outcome
- Study evaluation (risk of bias and insensitivity)
- Data extraction
- For each health outcome, synthesize the human and animal evidence separately, then integrate the evidence overall
- Derive oral reference doses for chronic and for less-than-chronic exposure
- Characterize strengths and limitations of the database, uncertainties, and key data gaps

Systematic review topic

- Are the assessment objectives and specific aims articulated clearly?
- Does the background information and context that is provided support the objectives for the assessment presented in plan?
- Does the proposed PECO framework identify the most pertinent evidence to address the stated needs of the Agency programs and regions?

Science topic 1: Endogenous production

- Ammonia is produced during the metabolism of amino acids. Most occurs in the intestines during the digestion of meat and other sources of protein, and a smaller amount occurs in the mouth from the reaction of saliva with food particles.
- Many animal studies have investigated the effect of oral exposure to ammonia on upper-digestive-tract irritation, on hyperammonemia, or on metabolic acidosis. These studies have reported clear dose–response relationships and have not attributed any part of these effects to endogenous production.

- *The assessment will consider whether endogenous production of ammonia might complicate dose–response relationships for irritation, hyperammonemia, or metabolic acidosis, and if so, how to disentangle the effects of oral exposure to ammonia and its endogenous production.*

Science topic 2: *Helicobacter pylori*

- Endogenous production of ammonia also occurs in individuals infected with *H. pylori*, which survives in the stomach by producing ammonia to reduce stomach acidity.
- In individuals infected with *H. pylori*, oral exposure to ammonia would add to the concentration of ammonia in the stomach associated with *H. pylori* infection.
- Some studies in uninfected rats have investigated stomach irritation from oral exposures that correspond to stomach concentrations of ammonia in humans infected with *H. pylori*.

- *The assessment will consider the use of these oral studies in uninfected rats in developing reference doses for oral exposure.*

Science topic 3: Potential carcinogenicity

- There are several studies pertinent to an evaluation of potential carcinogenicity, including two occupational case–control studies, four studies of cancer in experimental animals, and three initiation–promotion studies (see section 2.2 of the assessment plan).

- *Because these studies are not likely to be useful for deriving toxicity values for cancer, the assessment plan has chosen to limit the scope of the assessment by not pursuing an evaluation of potential carcinogenicity.*