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IRIS Assessment Plan
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IRIS Assessment Plan for Ammonia and Ammonium Salts: Noncancer Assessment for Oral Exposure (Scoping and Problem Formulation Materials)

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ABBREVIATIONS

CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
IAP	IRIS Assessment Plan
IRIS	Integrated Risk Information System
PECO	populations, exposures, comparators, and outcomes
SAB	Science Advisory Board
WHO	World Health Organization

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1. INTRODUCTION

The Integrated Risk Information System (IRIS) Program is undertaking an assessment of the noncancer effects of oral exposure to ammonia. Ammonia (oral exposure) was included on the December 2015 IRIS Program multiyear agenda[1] as a high priority for assessment development. Oral exposure was specified because the IRIS Program was at that time completing an evaluation of the noncancer hazards of inhalation exposure to ammonia (U.S. EPA, 2016). IRIS assessments provide high quality, publicly available information on the toxicity of chemicals to which the public might be exposed. These assessments are not regulations, but provide a critical part of the scientific foundation for decisions made in Environmental Protection Agency (EPA) program and regional offices to protect public health.

Prior to efforts to develop an IRIS assessment of oral exposure to ammonia, EPA's Office of Water had been preparing a Health Advisory for ammonia and ammonium salts as technical guidance for federal, state, and local officials, as well as managers of public or community water systems in protecting public health should emergency spills or contamination situations occur. The draft Health Advisory (U.S. EPA, 2013a) was superseded by the IRIS effort to address these needs.

The peer-review draft of the 2016 IRIS assessment (U.S. EPA, 2013c) had included evaluations of both oral and inhalation exposure to ammonia and ammonium hydroxide. In its review of that draft, EPA's Science Advisory Board (SAB) recommended that the revised assessment consider studies of ammonium salts and the potential for increased ammonia in blood to induce neurotoxicity, especially in individuals with abnormal liver function (U.S. EPA, 2015b). Because these recommendations would entail new analyses and further peer review for oral exposure, the IRIS Program separated and expedited the inhalation module (U.S. EPA, 2016), which was completed and released in September 2016.

As part of the initial steps in assessment development, the IRIS Program undertakes scoping and initial problem formulation activities. During scoping activities, the IRIS Program consults with EPA program and regional offices to identify the nature of the hazard characterization needed, the most important exposure pathways, and the level of detail required to inform Agency decisions. A broad, preliminary literature survey may also be conducted to assist in identifying the extent of the evidence and health effects that have been studied for the chemical of interest.

Based on the preliminary literature survey and the scope defined by EPA, the IRIS Program undertakes problem formulation activities to frame the scientific questions that will be the focus of the assessment. A summary of the IRIS Program's scoping and problem formulation conclusions are contained in the **IRIS Assessment Plan (IAP)**.

[1]IRIS multiyear agenda: https://www.epa.gov/iris/iris-agenda

The IAP is followed by development of a **Systematic Review Protocol**, which presents detailed methods for conducting the full systematic review and dose-response analysis, including any adjustments made to the IAP in response to public input. The IAP describes what will be assessed, and the chemical-specific protocol describes how the assessment will be conducted. Figure 1 graphically displays the context of the IAP and Systematic Review Protocol in the systematic review process.

This document presents the draft IAP for oral exposure to ammonia—a summary of the IRIS Program's scoping and initial problem formulation conclusions. It describes Agency need for the assessment; objectives and specific aims of the assessment; draft Populations, Exposures, Comparators, and Outcomes (PECO) criteria that outline the evidence considered most pertinent to the assessment; and identification of key areas of scientific complexity. Brief background information on uses and potential for human exposure is provided for context.

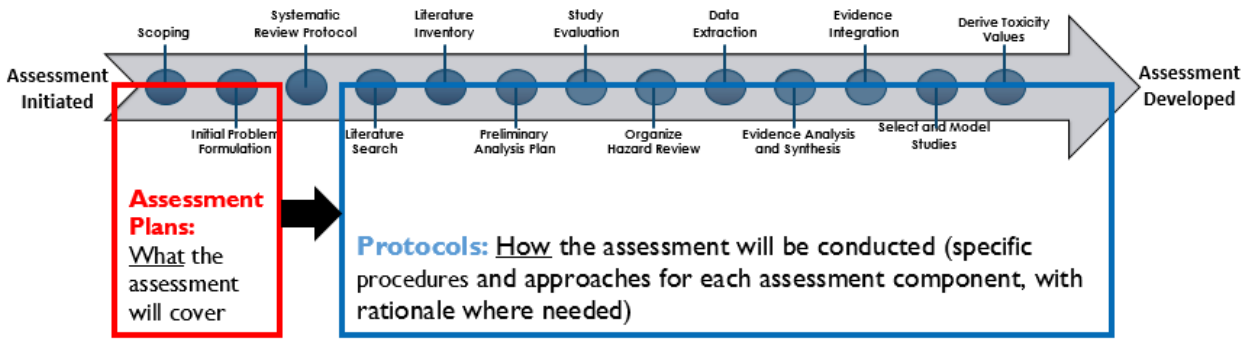

Figure 1. Integrated Risk Information System systematic review problem formulation and method documents.

2. SCOPING AND INITIAL PROBLEM FORMULATION

2.1. BACKGROUND

Ammonia (NH_3) is a clear caustic gas with a pungent odor. It is highly soluble in water and in blood, with solubility decreasing as temperature or pH increases. The water-based solution is called ammonium hydroxide or aqueous ammonia. The gas is also called anhydrous ammonia.

Ammonia is used in the disinfection of drinking-water by the process of chloramination, whereby chlorine and ammonia are added to water to form the disinfectant chloramine (NH_2Cl). The use of ammonia in drinking-water disinfection limits the production of chlorinated byproducts (mainly trihalomethanes and haloacetic acids) that are suspected of causing cancer. Ammonia, ammonium chloride, ammonium hydroxide, and ammonium sulfate are certified as treatment chemicals in drinking water for the purposes of disinfection, chloramination, oxidation, ozone reduction, pH adjustment, and as an antioxidant (NSF, 2012). Ammonia is also used in other areas of water or wastewater treatment.

U.S. production of ammonia and ammonium salts totals tens of billions of pounds per year. The major use is in fertilizers for agriculture. Ammonium nitrate is also used to produce explosives.

Ammonia has many other uses in smaller amounts. For example, several ammonium salts[2] are used as food additives and in food processing, and the Food and Drug Administration (FDA) has determined these uses to be "Generally Recognized as Safe" (FDA, 1974). Ammonium chloride is an FDA-approved prescription drug for lowering excess alkalinity in the blood. In addition, ammonia and ammonium sulfate are EPA-registered pesticides for controlling micro-organisms (algae, bacteria, fungi), and ammonium sulfamate was an EPA-registered herbicide. Several ammonium compounds are inert ingredients in pesticide formulations.

[2]Ammonium bicarbonate, ammonium carbonate, ammonium chloride, ammonium hydroxide, mono and dibasic ammonium phosphate, and ammonium sulfate.

Occurrence in environmental media is difficult to summarize, as concentrations depend on proximity to agriculture and season of the year, and measurements often reflect specific local conditions that are not widely representative. The U.S. Geological Survey reported that ammonia concentrations are usually less than 0.1 mg/L in groundwater and stream samples from background sites (Mueller and Helsel, 2016). Figure 2 shows a range of ammonia concentrations in groundwater in the United States, with most values in the lowest category, but elevated in some areas. A World Health Organization report prepared by EPA estimated typical concentrations of ammonia in surface water at 0.2–0.5 mg/L, but up to 12 mg/L near farms. Concentrations in outdoor air were estimated at 5–25 μg/m^3 in urban areas, 2–6 μg/m^3 in nonagricultural rural areas, and up to some hundreds of μg/m^3 in agricultural areas (IPCS, 1986).[3] Ammonia is present in cigarette smoke, with a median yield in mainstream smoke of 37 μg per cigarette and a range of 10–88 μg (IARC, 2012). Comparison of oral exposure to exposure in air shows that oral exposure generally is the principal route of human exposure.

[3]IPCS (1986) appears to be the most recent survey of ammonia occurrence in environmental media. It is the primary reference cited for this purpose by WHO (2003), by ATSDR (2004), by a draft Health Advisory prepared by EPA's Office of Water (U.S. EPA, 2013a), and by a summary of environmental concentrations prepared by EPA's National Center for Environmental Assessment (U.S. EPA, 2013b). Recent reports (see table in this footnote) are consistent with the ranges reported by IPCS.

Recent reports of ammonia in surface water or groundwater

Concentration of ammonia	Location	Reference
31–43 ppb (head of bay) 8.5–26 ppb (mouth of bay)	Ochlocknee Bay, Florida	Seitzinger (1987) as cited by ATSDR (2004)
<1 mg/L (upstream) 16 mg/L (downstream, peak)	Municipal-sewage-treatment facility, South Skunk River, Iowa	Crumpton and Isenhart (1988) as cited by ATSDR (2004)
0–2.3 mg/L (1.2 m depth) Nondetect (12.6 m depth)	Groundwater in The Netherlands	Krajenbrink et al. (1988) as cited by ATSDR (2004)
>0.020 mg/L for >6 months 0.3 mg/L often exceeded	Hamilton Harbour, Ontario	Barica (1990) as cited by ATSDR (2004)
As high as 3 mg/L	Groundwater rich in humic substances or iron, or in forests	Dieter and Möller (1991) as cited by WHO (2003)
0.0025 mg/L (municipal well) 3.25 mg/L (deep private well)	Area in Idaho with high nitrogen concentrations	Wicherski (2000) as cited by ATSDR (2004)
>2 mg/L in >50% of wells >5 mg/L in >5% of wells	Groundwater wells (Quaternary) in Iowa	Schilling (2002)
>2 mg/L in ~5% of bedrock wells	Groundwater wells (bedrock) in Iowa	Schilling (2002)
3.3 mg-nitrogen/L (mean)	Palo, Iowa	U.S. EPA (2014)
Up to 5–10 mg/L	Groundwater wells in Iowa	U.S. EPA (2014)

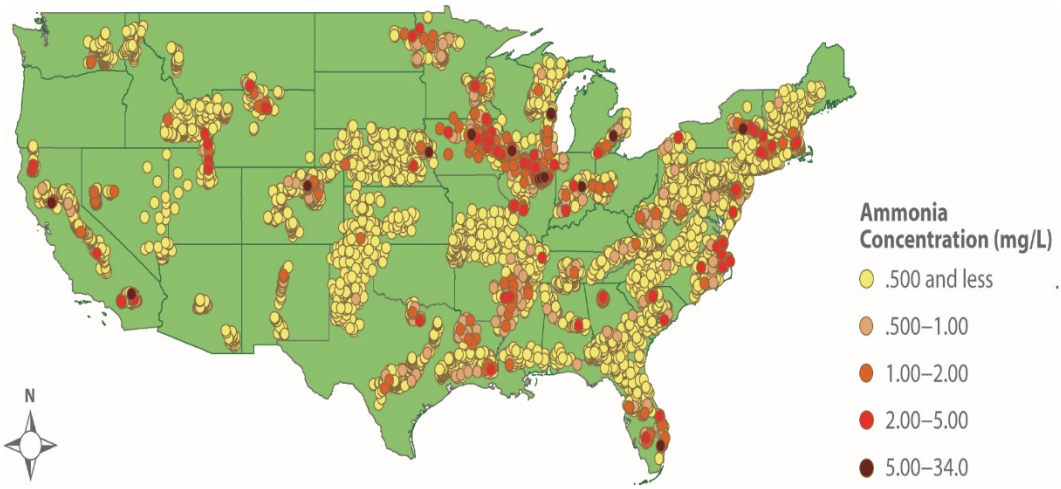

Figure 2. Ammonia concentrations in groundwater in the United States.

Source: Map created for U.S. EPA (2013a), based on U.S. Geological Survey National Water-Quality Assessment Program data from 2011

Based on the ranges reported by the World Health Organization (WHO), and in the absence of sources that would cause ammonia concentrations to be elevated, typical human intake would be estimated at less than 1 mg/day from drinking water (but could exceed 20 mg/day near farms) and less than 0.5 mg/day by inhalation (but proximity to farms or to cigarette smoke can add several times that amount).[4] Average intake of ammonium salts in foods was estimated at 18 mg/day (IPCS, 1986).

Ingested ammonia is transferred to the liver, where it is converted to urea ($C(NH_2)_2O$), which is excreted by the kidneys. Ammonia can enter the systemic circulation and cross cell membranes; it can also cross the blood-brain barrier.

Ammonia is also produced in the body at rates (more than 4 g/day) that are substantially higher than typical intake rates (approximately 20 mg/day, discussed above). Most of this endogenous ammonia is produced in the intestines during digestion of meat and other sources of protein. A smaller amount is produced in the mouth in the presence of food particles.

Oral exposure to ammonia has been linked to chemical burns in the mouth, throat, and stomach (ATSDR, 2004) and metabolic acidosis (PHE, 2015), but no national or international health agency has yet derived a health-based reference value for chronic oral exposure. Chronic inhalation exposure to ammonia can increase the risk of respiratory irritation, impaired lung function, and other respiratory symptoms (U.S. EPA, 2016; PHE, 2015; ATSDR, 2004; CalEPA, 1999; U.S. EPA, 1987), but also adverse effects in the liver, kidney, and spleen (U.S. EPA, 1989). IRIS has derived an

[4]Calculated as follows: surface-water concentrations of 0.2–0.5 mg/L times 2 L/day high-end drinking-water intake yields a high-end estimate of 0.4–1 mg/day intake via drinking water; ambient air concentrations of 5–25 mg/m^3 times 20 m^3 air intake yields an estimate of 0.1–0.5 mg/day intake via air.

inhalation reference concentration of 0.5 mg/m^3 based on decreased lung function and increased respiratory symptoms in exposed workers (U.S. EPA, 2016). Short-term exposure to high air concentrations can not only cause irritation and serious burns in the respiratory tract and eyes, but also convulsions, pulmonary edema, coma, and death (U.S. EPA, 1989). To date, no health agency has concluded that there is evidence of carcinogenic potential by any route of exposure.

In general, most health agencies have concluded that ammonia does not pose a direct health concern at concentrations expected in drinking water (that is, below 0.2 mg/L) (WHO, 2003), but some regions in the United States have elevated levels in their drinking-water sources (U.S. EPA, 2014), and there is also a concern for higher concentrations that might follow emergency spills or contamination situations (U.S. EPA, 2013a).

2.2. SCOPING SUMMARY

During scoping, the IRIS Program consults with EPA program and regional offices that had interest in an IRIS assessment of oral exposure to ammonia to discuss specific assessment needs. Table 1 provides a summary of input from this outreach.

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, which serve as technical guidance to assist federal, state, and local officials, as well as managers of public or community water systems in protecting public health when emergency spills or contamination situations occur Clean Water Act: potential human health criteria development	Ammonia is certified for use in water and wastewater treatment, most notably in disinfection of drinking water by chloramination. Ammonia is also a high-priority contaminant due to its use in fertilizers and presence in runoff water from agricultural fields. Health authorities need a reference dose to ensure protection of public health after emergency spills or contamination situations. Elevated ammonia is associated with elevated nitrate concentrations in drinking water sources.

[a]EPA's Office of Land and Emergency Management also has an interest in ammonia. Ammonia and several ammonium compounds (ammonium acetate, benzoate, bicarbonate, bichromate, bifluoride, bisulfite, carbamate, carbonate, chloride, chromate, citrate [dibasic], fluoborate, fluoride, hydroxide, oxalate, picrate, silicofluoride, sulfamate, sulfide, sulfite, tartrate, thiocyanate, vanadate) are listed as hazardous substances under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) section 102(a) (U.S. EPA, 2015a). Ammonia is a chemical of concern at 135 sites on the National Priorities List for EPA's Superfund program (ATSDR, 2015), and risk assessments for these sites conducted by EPA regional offices or by state environmental agencies are often based on less-than-lifetime exposure scenarios. In addition, many regions in the United States have excessive levels of ammonia in their drinking-water sources (ground and surface waters) (U.S. EPA, 2014).

The assessment will meet the Office of Water's need for an evaluation of oral exposure to ammonia and ammonium salts. In doing so, the assessment also will be mindful of the Science Advisory Board's outstanding recommendations on oral exposure (U.S. EPA, 2015b). The scope of the assessment is to develop an oral reference dose for noncancer effects (including neurotoxicity, which the SAB had stressed as important). This will be the first oral reference dose for ammonia under the IRIS Program.[5]

Ammonia is highly soluble in water and in blood, consequently, it will occur in the body as the ammonium ion (NH_4^+). Many ammonium salts also are soluble in water and in blood, and the ammonium moiety will dissociate and occur in the body as the ammonium ion. Accordingly, the assessment will derive a reference value in terms of the ammonium ion. This may be converted

[5]EPA's *Health Effects Assessment for Ammonia* (U.S. EPA, 1987) derived reference values based on taste and odor thresholds, but not on health hazards.

into a reference value for each ammonium salt by considering the fraction, by weight, of the molecule that dissociates into an ammonium ion.

The reference value for the ammonium ion will be derived from results from suitable studies of ammonia and various ammonium salts. In addition to ammonia (7664-41-7), studies have been found on several ammonium salts in which the responses may be reasonably attributable to the ammonium moiety.

- ammonium hydroxide (1336-21-6)
- ammonium acetate (631-61-8)
- ammonium chloride (12125-02-9)
- ammonium sulfate (7783-20-2)
- ammonium phosphate (diammonium phosphate) (7783-28-0)
- ammonium dihydrogen phosphate (7722-76-1)
- ammonium carbonate (506-87-6)
- ammonium nitrate (6484-52-2)
- ammonium bicarbonate (1066-33-7)
- ammonium citrate (7632-50-0)

There are also numerous complex ammonium compounds in which the non-ammonium moiety is expected to be toxic. Although there are toxicity studies of several such compounds (e.g., aluminum ammonium sulfate, ammonium metavanadate, ammonium perchlorate), disentangling the toxicity of the ammonium and non-ammonium moieties would be difficult. Accordingly, the assessment will not review studies of such ammonium compounds, especially as toxicity studies are available for compounds where the non-ammonium moiety is relatively nontoxic (e.g., ammonium hydroxide and acetate).

The assessment will not undertake an evaluation of carcinogenicity. The cancer studies identified by preliminary survey of assessments from national and international health agencies (see Section 2.3) identified no studies that could be used to derive cancer toxicity values. Briefly, this information includes:

- Two occupational case-control studies that mention ammonia in the abstract:
  - one found an association with non-Hodgkin lymphoma in males in Montreal (Fritschi and Siemiatycki, 1996).

- one found an association with colon cancer in males in British Columbia (Fang et al., 2011).

The complex exposures inherent in the occupations and the small numbers of cases make it unlikely that these cancers can be confidently attributed to ammonia. Moreover, there are no quantitative exposure estimates that could be used to characterize exposure-response relationships.

- Four studies of cancer in experimental animals:
  - ammonium hydroxide in the drinking water of both sexes of Swiss mice (Toth, 1972).
  - ammonium hydroxide in the drinking water of both sexes of C3H mice (Toth, 1972).
  - ammonium chloride in the diet of both sexes of Wistar rats (Lina and Kuijpers, 2004).
  - ammonium sulfate in the diet of both sexes of F344 rats (Ota et al., 2006).

Each study found no increase in tumors. EPA has not derived cancer toxicity values from negative studies of carcinogenicity.

- Three initiation-promotion studies:
  - drinking-water administration of ammonia promoted gastric cancer in initiated Sprague-Dawley rats (Tsujii et al., 1995; Tsujii et al., 1992).
  - intrarectal administration of ammonium acetate promoted colon cancer in initiated Sprague-Dawley rats (Clinton et al., 1988).

EPA has not derived cancer toxicity values from initiation-promotion studies. Moreover, it would be difficult to translate the quantitative effect of initiation in rats to a human population.

As there are no studies that can be used to derive toxicity values for cancer, the assessment will not evaluate carcinogenicity.

2.3. PROBLEM FORMULATION

The literature searches conducted for the 2016 IRIS assessment of inhalation exposure were insufficient to assess oral exposure. Although the searches conducted before 2013 did include oral studies (because the 2013 peer-review draft addressed oral and inhalation exposures), no systematic search for studies on ammonium salts was conducted (because the 2016 assessment addressed only ammonia and ammonium hydroxide).

To obtain information on the ammonium salts, a preliminary survey began with a review of assessments from national and international health agencies, including FDA (1974), IPCS (1986), U.S. EPA (1987), U.S. EPA (1989), CalEPA (1999), ATSDR (2004), PHE (2015), and U.S. EPA (2016). These assessments were reviewed to identify health outcomes that have been associated with oral

exposure to ammonia or ammonium salts, and to identify the studies that provided the principal support for these findings.

The preliminary survey also included a review of articles on the ability of some ammonium salts to induce metabolic acidosis[6] or hyperammonemia.[7] These articles discuss the linkage between metabolic acidosis and the subsequent development of bone loss or osteoporosis, and the linkage between hyperammonemia and the subsequent development of hepatic encephalopathy or other manifestations of neurotoxicity. Metabolic acidosis and hyperammonemia are well established in the medical literature as hazards of exposure to high doses of ammonia. Accordingly, this assessment will not expend resources on systematic reviews of the evidence for these hazards. Rather, the assessment will accept that metabolic acidosis and hyperammonemia are known hazards of ammonia exposure and will focus the review of these studies at a survey level to characterize the doses or durations of exposure that could induce these effects.

To identify studies of these and other possible health hazards, literature search strategies are using key terms and words related to the forms of ammonia outlined in the PECO criteria (see Section 3). Literature search strategies were developed for the PubMed, Web of Science, and Toxline databases, tailoring the strategies to the unique search functionality of each database. No date or language restrictions are being applied. The initial search was conducted in May 2017 and returned approximately 39,000 studies.

Given the size of the evidence base, refined searches were conducted to focus on standard experimental animal species (e.g., *rats, mice, rabbits, hamsters, dogs, monkeys*), oral administration (e.g., *oral, ingestion, gavage, diet, food, feed, drinking water*), and on a subset of ammonium salts (e.g., *hydroxide, acetate, bicarbonate, carbonate, chloride, phosphate, diphosphate, sulfate, citrate*) where toxicity could reasonably be attributable to the ammonium ion. For epidemiologic studies, searches focused on occupations with potential exposure to ammonia (e.g., *brewers, janitors, cleaners, exterminators, cosmetologists, hairstylists, morticians, embalmers, agricultural workers, farmworkers, and fertilizer manufacture*). Eventually, the refined searches (see Appendix A) reduced the number of potentially pertinent studies to approximately 4,000. The refined searches did not target in-vitro studies of mechanisms of ammonia toxicity because the review of assessments by national and international health agencies or of comprehensive review articles did not identify any questions in which data on mechanisms would affect the identification of hazards or the modeling of dose-response for those hazards.

[6]Metabolic acidosis is a condition of excess acid in the body. It can arise from increased acid intake (e.g., ammonium chloride or sulfate), increased endogenous acid production, or decreased acid excretion. Metabolic acidosis is a serious medical condition that can lead to impaired growth of infants and children and loss of bone and muscle mass in adults. Metabolic acidosis is characterized by blood plasma pH <7.35, serum bicarbonate <22 mmol/L (Wingfield, 2001), or total carbon dioxide <22 mmol/L (Monsen, 1987).

[7]Hyperammonemia means an excess of ammonia in the blood. Hyperammonemia is a serious medical condition that can result in hepatic encephalopathy, characterized by altered mental state and potentially leading to brain edema, seizures, coma, or death.

The search results of approximately 4,000 studies include numerous studies in which an ammonium salt was administered at a single high dose level only as an established means to induce metabolic acidosis or hyperammonemia in experimental animals. These studies provide no information on lower dose levels that could induce these effects and, thus, have little utility for this assessment. As indicated above, these studies will only be surveyed in the assessment to describe the doses or durations of exposure that could induce these effects. Thus, these studies will be tagged as supplemental material during screening, except for those studies that are useful for setting an oral reference dose; that is, animal experiments that included multiple doses or exposure durations and studies of controlled human exposure will be fully evaluated. This restriction greatly reduces the number of studies considered most pertinent to this assessment.

Based on the literature searches and screening done to date, Table 2 presents the approximate number of primary studies likely to be cited for each broad health outcome to be addressed in the assessment.

Table 2. Approximate number of primary studies likely to be cited in the assessment

	Occupational cohort and case-control studies (in humans)	Population-based cohort and case-control studies (in humans)	Case reports of ingestion (by humans)	Intentional dosing studies in humans by ingestion	Multigenerational animal studies	Chronic animal studies	Subchronic animal studies	Short-term and acute animal studies
Gastric irritation			~20				1	3
Systemic toxicity						2	3	
Metabolic acidosis[a] (may be related to musculoskeletal toxicity)				5–10		1	1	3
Hyperammonemia[a] (may be related to neurotoxicity)				1		~5	~5	~5
Developmental toxicity			1		1			
Cancer (carcinogenicity studies)	1	1				4	N/A	N/A
Cancer (initiation-promotion studies)	N/A	N/A	N/A	N/A	N/A	3		N/A

N/A: Study design does not exist (e.g., there are never initiation-promotion studies in humans).

[a]Does not include studies described as supplemental, in which an ammonium compound was administered at a single high dose only to induce acidosis or hyperammonemia in animals.

Based on the literature searches and screening done to date, several health outcomes are likely to warrant inclusion in the assessment.

- Gastric irritation
- Systemic toxicity
- Metabolic acidosis (and potentially musculoskeletal toxicity)[8]
- Hyperammonemia (and potentially neurotoxicity)[8]
- Developmental toxicity

A preliminary reading of review articles and assessments by other health agencies suggests some potentially susceptible populations or life stages that are likely to warrant consideration in the assessment, to the extent that suitable data are available.

- **Individuals with impaired liver or kidney function:** The liver converts ammonia to urea, which enters the systemic circulation and is excreted by the kidneys. Individuals with impaired liver or kidney function (e.g., through liver cirrhosis or a urea-cycle disorder) would experience reduced clearance of ammonia, and hence, excess levels in the blood.
- **Individuals at risk for osteoporosis:** Metabolic acidosis can result in bone loss, potentially exacerbating this condition in individuals at risk for osteoporosis (IPCS, 1986).
- **Infants and children:** Ammonia can cross the blood-brain barrier, possibly inducing hepatic encephalopathy or other manifestations of neurotoxicity. The brain is not efficient at excreting ammonia. It is thought that infants and children may be more susceptible than adults to these effects (Braissant et al., 2013; Gropman et al., 2007). Experimental evidence in rats suggests that developing offspring are susceptible to exposure during pregnancy and lactation, providing further support (Miñana et al., 1995). In addition, bone loss resulting from metabolic acidosis can be of concern early in life, which is a crucial period for bone development.
- **Individuals infected with *Helicobacter pylori*:** *H. pylori*, a bacterium estimated to infect more than 30% of Americans (IARC, 2012), is a major cause of stomach ulcers and nearly 90% of noncardia stomach cancers (Plummer et al., 2012). *H. pylori* survives in the stomach by reducing acidity through the production of ammonia. Subsequent ingestion of ammonia

[8]As discussed in the main text of this section, metabolic acidosis and hyperammonemia are known hazards of ammonia exposure. The assessment will not review evidence to re-establish these hazards and will fully evaluate only the studies that are useful for setting an oral reference dose, that is, animal experiments that included multiple doses or exposure durations and studies of controlled human exposure.

could further increase stomach concentrations and potentially exacerbate the risk of stomach irritation or stomach cancer.

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.

It would be difficult to investigate effects of oral exposure in the intestines. Such studies have not been located, and the assessment will not evaluate the intestines as a target organ. On the other hand, studies have been able to investigate the effects of oral exposure in the mouth, esophagus, and stomach. These studies have reported clear dose-response relationships following oral exposure to ammonia and have not attributed any part of these effects to endogenous production. Similarly, numerous studies have investigated and shown a relationship between oral exposure and hyperammonemia or metabolic acidosis, with subsequent effects on neurotoxicity or bone loss, respectively.

Infection with *Helicobacter pylori* is a separate source of endogenous production of ammonia. Oral intake of ammonia would directly add to the burden of ammonia produced in the stomachs of infected individuals (see Section 2.3). The assessment will review studies that investigated the effect that oral intake could have on this potentially susceptible population.

3. OVERALL OBJECTIVE, SPECIFIC AIMS, AND DRAFT POPULATIONS, EXPOSURES, COMPARATORS, AND OUTCOMES (PECO) CRITERIA

The overall objective of this assessment is to identify adverse noncancer outcomes of oral exposure to ammonia and ammonium salts, to characterize exposure-response relationships, and to derive an oral reference dose. The assessment will use systematic review methods to evaluate the pertinent epidemiologic and experimental animal studies, including consideration of relevant mechanistic evidence. The evaluations conducted in the assessment will be consistent with relevant EPA guidance.[9] The systematic review protocol will be disseminated after review of the draft assessment plan and will reflect changes made to the specific aims and PECO criteria in response to public input.

3.1. SPECIFIC AIMS

- Identify epidemiologic and experimental animal studies pertinent to the health hazards of ammonia, as outlined in the PECO criteria. This will include noncancer effects of oral exposure to ammonia or ammonium salts. Identifying individual mechanistic studies is not considered critical for this assessment and therefore not included in the PECO criteria. Other published authoritative sources, such as public health agency reports and expert review articles, will be the primary basis for providing mechanistic context in the assessment.

- Conduct study evaluations (risk of bias and insensitivity) for individual epidemiologic and experimental animal studies. Studies with critical deficiencies will be considered uninformative and will not be considered further.

- Extract data on relevant health outcomes from epidemiological and experimental animal studies included based on the study evaluation.

- Synthesize the evidence across studies, assessing similar health outcomes using a narrative approach or quantitative analysis (if appropriate).

- For each health outcome, express confidence in conclusions across studies (or subsets of studies) within human and animal evidence streams, evaluating each evidence stream (human and animal) separately. Metabolic acidosis and hyperammonemia are known hazards of ammonia exposure (see Section 2.3); accordingly, the assessment will focus on

[9]EPA guidance documents: http://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance/

studies that provide information on doses or durations of exposure that could induce these effects.

- For each health outcome, integrate results across evidence streams (human and animal) to conclude whether a substance is hazardous to humans. Identify and discuss issues concerning potentially susceptible populations and life stages. Biological support from mechanistic studies will be summarized primarily by relying on other sources and targeted literature searches that might be conducted later, if warranted, to address specific topics that may arise when conducting the assessment.

- Derive oral reference doses as supported by the available data. If the data permit, also derive oral reference doses for less-than-lifetime exposure to better serve risk assessment needs at hazardous waste sites.

- Characterize uncertainties and identify key data gaps and research needs, such as limitations of the evidence base, limitations of the systematic review, and consideration of dose relevance and toxicokinetic differences when extrapolating findings from higher dose animal studies to lower levels of human exposure.

3.2. DRAFT PECO CRITERIA

A PECO will be used as an aid to focus the research questions, search terms, and inclusion/exclusion criteria in a systematic review. The draft PECO criteria for ammonia (see Table 3) was based on (1) nomination of the agent for assessment, (2) discussions with scientists in EPA program and regional offices to determine the scope of the assessment that will best meet Agency needs, and (3) a preliminary survey of the health effects literature (primarily health agency assessments and authoritative review articles). These served to identify the major health hazards and the key areas of scientific complexity.

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.

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Table 3. Draft Population, Exposure, Comparator, and Outcome criteria for the assessment of noncancer hazards of oral exposure to ammonia and ammonium salts (continued)

PECO element	Evidence
Outcomes	**Human and animal**: All noncancer health outcomes, or precursors. In general, endpoints related to clinical diagnostic criteria, disease outcomes, histopathological examination, or other apical/phenotypic outcomes will be prioritized for evidence synthesis over outcomes such as biochemical measures. Metabolic acidosis and hyperammonemia are established hazards of ammonia exposure. The assessment will not review evidence to re-establish these hazards and will fully evaluate only the studies that are useful for setting an oral reference dose, that is, animal experiments that included multiple doses or exposure durations and studies of controlled human exposure.

[a]Identifying individual mechanistic studies is not considered critical for this assessment and therefore not included in the PECO criteria. Other published authoritative sources, such as public health agency reports and expert review articles, will be the primary basis for providing mechanistic context in the assessment.

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APPENDICES

APPENDIX A. LITERATURE SEARCH TERMS

Table A-1. Summary of detailed search strategies for Ammonia (PubMed, Web of Science, Toxline)

Database	Terms	Date and Results
PUBMED	7664-41-7" OR ammonia "7783-18-8" OR ammonium thiosulfate OR ammonium thiosulfate OR ammonium thiosulphate OR "6484-52-2" OR ammonium nitrate OR ammonium salt OR "5421-46-5" OR ammonium thioglycolate OR "1111-78-0" OR ammonium carbamate OR "7773-06-0" OR ammonium sulfamate OR ammate OR ammonium sulphamate OR "7632-50-0" OR ammonium citrate OR "53956-04-0" OR ammonium glycyrrhizate OR ammonium glycyrrhizinate OR "12124-97-9" OR ammonium bromide OR "12125-02-9" OR ammonium chloride OR "7783-20-2" OR ammonium sulfate OR "12125-01-8" OR ammonium fluoride OR "12027-06-4" OR ammonium iodide	27 Apr 2017: 36,314
PUBMED	(("7664-41-7" OR ammonia "7783-18-8" OR ammonium thiosulfate OR ammonium thiosulfate OR ammonium thiosulphate OR "6484-52-2" OR ammonium nitrate OR ammonium salt OR "5421-46-5" OR ammonium thioglycolate OR "1111-78-0" OR ammonium carbamate OR "7773-06-0" OR ammonium sulfamate OR amate OR ammonium sulphamate OR "7632-50-0" OR ammonium citrate OR "53956-04-0" OR ammonium glycyrrhizate OR ammonium glycyrrhizinate OR "12124-97-9" OR ammonium bromide OR "12125-02-9" OR ammonium chloride OR "7783-20-2" OR ammonium sulfate OR "12125-01-8" OR ammonium fluoride OR "12027-06-4" OR ammonium iodide)) AND (live animal studies OR rats OR mice OR rabbits OR hamsters OR dogs OR monkeys OR pigs OR guinea pigs)	27 Apr 2017: 15,301 Batch# 21468
PUBMED	((("7664-41-7" OR ammonia "7783-18-8" OR ammonium thiosulfate OR ammonium thiosulfate OR ammonium thiosulphate OR "6484-52-2" OR ammonium nitrate OR ammonium salt OR "5421-46-5" OR ammonium thioglycolate OR "1111-78-0" OR ammonium carbamate OR "7773-06-0" OR ammonium sulfamate OR ammate OR ammonium sulphamate OR "7632-50-0" OR ammonium citrate OR "53956-04-0" OR ammonium glycyrrhizate OR ammonium glycyrrhizinate OR "12124-97-9" OR ammonium bromide OR "12125-02-9" OR ammonium chloride OR "7783-20-2" OR ammonium sulfate OR "12125-01-8" OR ammonium fluoride OR "12027-06-4" OR ammonium iodide)) AND (live animal studies OR rats OR mice OR rabbits OR hamsters OR dogs OR monkeys OR pigs OR guinea pigs)) AND (oral OR gavage OR ingestion OR inhal* OR diet OR food)	27 Apr 2017: 1898 Batch # 21470

Table A-1. Summary of detailed search strategies for Ammonia (PubMed, Web of Science, Toxline) (continued)

Database	Terms	Date and Results
PUBMED	(("7664-41-7" OR ammonia "7783-18-8" OR ammonium thiosulfate OR ammonium thiosulfate OR ammonium thiosulphate OR "6484-52-2" OR ammonium nitrate OR ammonium salt OR "5421-46-5" OR ammonium thioglycolate OR "1111-78-0" OR ammonium carbamate OR "7773-06-0" OR ammonium sulfamate OR ammate OR ammonium sulphamate OR "7632-50-0" OR ammonium citrate OR "53956-04-0" OR ammonium glycyrrhizate OR ammonium glycyrrhizinate OR "12124-97-9" OR ammonium bromide OR "12125-02-9" OR ammonium chloride OR "7783-20-2" OR ammonium sulfate OR "12125-01-8" OR ammonium fluoride OR "12027-06-4" OR ammonium iodide OR ammonium iodide)) AND (brewer OR brewery OR janitor OR housekeeper OR exterminator OR cosmetologist OR hairstylist OR mortician OR embalmer OR agricultural workers OR farm workers OR fertilizer manufacturers)	27 Apr 2017: 40 batch# 21471
PUBMED	(((("7664-41-7" OR ammonia "7783-18-8" OR ammonium thiosulfate OR ammonium thiosulfate OR ammonium thiosulphate OR "6484-52-2" OR ammonium nitrate OR ammonium salt OR "5421-46-5" OR ammonium thioglycolate OR "1111-78-0" OR ammonium carbamate OR "7773-06-0" OR ammonium sulfamate OR ammate OR ammonium sulphamate OR "7632-50-0" OR ammonium citrate OR "53956-04-0" OR ammonium glycyrrhizate OR ammonium glycyrrhizinate OR "12124-97-9" OR ammonium bromide OR "12125-02-9" OR ammonium chloride OR "7783-20-2" OR ammonium sulfate OR "12125-01-8" OR ammonium fluoride OR "12027-06-4" OR ammonium iodide OR ammonium iodide)) AND (brewer OR brewery OR janitor OR housekeeper OR exterminator OR cosmetologist OR hairstylist OR mortician OR embalmer OR agricultural workers OR farm workers OR fertilizer manufacturers)) AND (cancer OR neoplasm OR malignancy OR tumor*)	27 Apr 2017: 1 Batch# 21472
WEB OF SCIENCE	(TS=("7764-41-7") OR TS="ammonia" OR TS=("7783-18-8") OR TS="ammonium thiosulfate" OR TS="ammonium thiosulfate" OR TS="ammonium thiosulphate" OR TS=("6484-52-2") OR TS="ammonium nitrate" OR TS="ammonium salt" OR TS=("5421-46-5") OR TS="ammonium thioglycolate" OR TS=("1111-78-0") OR TS="ammonium carbamate" OR TS=("7773-06-0") OR TS="ammonium sulfamate" OR TS="ammate" OR TS="ammonium sulphamate" OR TS=("7632-50-0") OR TS="ammonium citrate" OR TS=("53956-04-0") OR TS="ammonium glycyrrhizate" OR TS="ammonium glycyrrhizinate" OR TS=("12124-97-9") OR TS="ammonium bromide" OR TS=("12125-02-9") OR TS="ammonium chloride" OR TS=("7783-20-2") OR TS="ammonium sulfate" OR TS=("12125-01-8") OR TS="ammonium fluoride" OR TS=("12027-06-4") OR TS="ammonium iodide")	27 Apr 2017: 151,702

Table A-1. Summary of detailed search strategies for Ammonia (PubMed, Web of Science, Toxline) (continued)

Database	Terms	Date and Results
WEB OF SCIENCE	(TS=("7764-41-7") OR TS="ammonia" OR TS=("7783-18-8") OR TS="ammonium thiosulfate" OR TS="ammonium thiosulfate" OR TS="ammonium thiosulphate" OR TS=("6484-52-2") OR TS="ammonium nitrate" OR TS="ammonium salt" OR TS=("5421-46-5") OR TS="ammonium thioglycolate" OR TS=("1111-78-0") OR TS="ammonium carbamate" OR TS=("7773-06-0") OR TS="ammonium sulfamate" OR TS="ammate" OR TS="ammonium sulphamate" OR TS=("7632-50-0") OR TS="ammonium citrate" OR TS=("53956-04-0") OR TS="ammonium glycyrrhizate" OR TS="ammonium glycyrrhizinate" OR TS=("12124-97-9") OR TS="ammonium bromide" OR TS=("12125-02-9") OR TS="ammonium chloride" OR TS=("7783-20-2") OR TS="ammonium sulfate" OR TS=("12125-01-8") OR TS="ammonium fluoride" OR TS=("12027-06-4") OR TS="ammonium iodide") AND (TS="live animal studies" OR TS="rats" OR TS="mice" OR TS="rabbits" OR TS="hamsters" OR TS="dogs" OR TS="monkeys" OR TS="pigs" OR TS="guinea pigs"))	27 Apr 2017: 4885 Batch# 21476
WEB OF SCIENCE	((((TS=("7764-41-7") OR TS="ammonia" OR TS=("7783-18-8") OR TS="ammonium thiosulfate" OR TS="ammonium thiosulfate" OR TS="ammonium thiosulphate" OR TS=("6484-52-2") OR TS="ammonium nitrate" OR TS="ammonium salt" OR TS=("5421-46-5") OR TS="ammonium thioglycolate" OR TS=("1111-78-0") OR TS="ammonium carbamate" OR TS=("7773-06-0") OR TS="ammonium sulfamate" OR TS="ammate" OR TS="ammonium sulphamate" OR TS=("7632-50-0") OR TS="ammonium citrate" OR TS=("53956-04-0") OR TS="ammonium glycyrrhizate" OR TS="ammonium glycyrrhizinate" OR TS=("12124-97-9") OR TS="ammonium bromide" OR TS=("12125-02-9") OR TS="ammonium chloride" OR TS=("7783-20-2") OR TS="ammonium sulfate" OR TS=("12125-01-8") OR TS="ammonium fluoride" OR TS=("12027-06-4") OR TS="ammonium iodide") AND (TS="live animal studies" OR TS="rats" OR TS="mice" OR TS="rabbits" OR TS="hamsters" OR TS="dogs" OR TS="monkeys" OR TS="pigs" OR TS="guinea pigs") AND (TS="oral" OR TS="gavage" OR TS="ingestion" OR TS="inhal*" OR TS="diet" OR TS="food"))))	27 Apr 2017: 1301 Batch # 21478
WEB OF SCIENCE	((TS=("7764-41-7") OR TS="ammonia" OR TS=("7783-18-8") OR TS="ammonium thiosulfate" OR TS="ammonium thiosulfate" OR TS="ammonium thiosulphate" OR TS=("6484-52-2") OR TS="ammonium nitrate" OR TS="ammonium salt" OR TS=("5421-46-5") OR TS="ammonium thioglycolate" OR TS=("1111-78-0") OR TS="ammonium carbamate" OR TS=("7773-06-0") OR TS="ammonium sulfamate" OR TS="ammate" OR TS="ammonium sulphamate" OR TS=("7632-50-0") OR TS="ammonium citrate" OR TS=("53956-04-0") OR TS="ammonium glycyrrhizate" OR TS="ammonium glycyrrhizinate" OR TS=("12124-97-9") OR TS="ammonium bromide" OR TS=("12125-02-9") OR TS="ammonium chloride" OR TS=("7783-20-2") OR TS="ammonium sulfate" OR TS=("12125-01-8") OR TS="ammonium fluoride" OR TS=("12027-06-4") OR TS="ammonium iodide") AND (TS="brewer" OR TS="brewery" OR TS="janitor" OR TS="housekeeper" OR TS="exterminator" OR TS="cosmetologist" OR TS="hairstylist" OR TS="mortician" OR TS="embalmer" OR TS="agricultural workers" OR TS="farm workers" OR TS="fertilizer manufacturers"))	27 Apr 2017: 88 Batch# 21480

Table A-1. Summary of detailed search strategies for Ammonia (PubMed, Web of Science, Toxline) (continued)

Database	Terms	Date and Results
WEB OF SCIENCE	((TS=("7764-41-7") OR TS="ammonia" OR TS=("7783-18-8") OR TS="ammonium thiosulfate" OR TS="ammonium thiosulfate" OR TS="ammonium thiosulphate" OR TS=("6484-52-2") OR TS="ammonium nitrate" OR TS="ammonium salt" OR TS=("5421-46-5") OR TS="ammonium thioglycolate" OR TS=("1111-78-0") OR TS="ammonium carbamate" OR TS=("7773-06-0") OR TS="ammonium sulfamate" OR TS="ammate" OR TS="ammonium sulphamate" OR TS=("7632-50-0") OR TS="ammonium citrate" OR TS=("53956-04-0") OR TS="ammonium glycyrrhizate" OR TS="ammonium glycyrrhizinate" OR TS=("12124-97-9") OR TS="ammonium bromide" OR TS=("12125-02-9") OR TS="ammonium chloride" OR TS=("7783-20-2") OR TS="ammonium sulfate" OR TS=("12125-01-8") OR TS="ammonium fluoride" OR TS=("12027-06-4") OR TS="ammonium iodide") AND (TS="brewer" OR TS="brewery" OR TS="janitor" OR TS="housekeeper" OR TS="exterminator" OR TS="cosmetologist" OR TS="hairstylist" OR TS="mortician" OR TS="embalmer" OR TS="agricultural workers" OR TS="farm workers" OR TS="fertilizer manufacturers") AND TS="cancer" OR TS="neoplasm" OR TS="malignancy" OR Ts="tumor")	27 Apr 2017: 1 Batch# 21481
TOXLINE	@OR+("ammonium+salt"+@TERM+@rn+7664-41-7+"ammonia"+@TERM+@rn+7783-18-8+"ammonium+ thiosulfate"+"ammonium+ thiosulfate"+"ammonium+ thiosulphate"+@TERM+@rn+6484-52-2+"ammonium+ nitrate"+@TERM+@rn+5421-46-5+"ammonium+ thioglycolate"+@TERM+@rn+1111-78-0+"ammonium+ carbamate"+@TERM+@rn+7773-06-0+"ammonium+ sulfamate"+"ammate"+"ammonium+ sulphamate"+@TERM+@rn+7632-50-0+"ammonium+citrate"+@TERM+@rn+53956-04-0+"ammonium+ glycyrrhizate"+"ammonium+ glycyrrhizinate"+@TERM+@rn+12124-97-9+"ammonium+ bromide"+@TERM+@rn+12125-02-9+"ammonium+ chloride"+"ammonium+hydrochloride"+@TERM+@rn+7783-20-2+"ammonium+ sulfate"+@TERM+@rn+12125-01-8+"ammonium+ fluoride"+@TERM+@rn+12027-06-4"+"ammonium+ iodide")	27 Apr 2017: 73 Batch# 21482
TOXLINE	@AND+@OR+("ammonium+salt"+@TERM+@rn+7664-41-7+"ammonia"+@TERM+@rn+7783-18-8+"ammonium+ thiosulfate"+"ammonium+ thiosulfate"+"ammonium+ thiosulphate"+@TERM+@rn+6484-52-2+"ammonium+ nitrate"+@TERM+@rn+5421-46-5+"ammonium+ thioglycolate"+@TERM+@rn+1111-78-0+"ammonium+ carbamate"+@TERM+@rn+7773-06-0+"ammonium+ sulfamate"+"ammate"+"ammonium+ sulphamate"+@TERM+@rn+7632-50-0+"ammonium+citrate"+@TERM+@rn+53956-04-0+"ammonium+ glycyrrhizate"+"ammonium+ glycyrrhizinate"+@TERM+@rn+12124-97-9+"ammonium+ bromide"+@TERM+@rn+12125-02-9+"ammonium+ chloride"+"ammonium+hydrochloride"+@TERM+@rn+7783-20-2+"ammonium+ sulfate"+@TERM+@rn+12125-01-8+"ammonium+ fluoride"+@TERM+@rn+12027-06-4"+"ammonium+ iodide")+@AND+@OR+("live+animal+studies"+"rats"+"mice"+"rabbits" +"hamsters"+"dogs"+"monkeys"+"pigs"+"guinea+pigs")+@SYN+@OR+("oral"+"gavage"+"ingestion"+"inhal*"+"food "+"diet")	27 Apr 2017: 13 Batch# 21483

Table A-1. Summary of detailed search strategies for Ammonia (PubMed, Web of Science, Toxline) (continued)

Database	Terms	Date and Results
TOXLINE	@OR+("ammonium+salt"+@TERM+@rn+7664-41-7+"ammonia"+@TERM+@rn+7783-18-8+"ammonium+ thiosulfate"+"ammonium+ thiosulfate"+"ammonium+ thiosulphate"+@TERM+@rn+6484-52-2+"ammonium+ nitrate"+@TERM+@rn+5421-46-5+"ammonium+ thioglycolate"+@TERM+@rn+1111-78-0+"ammonium+ carbamate"+@TERM+@rn+7773-06-0+"ammonium+ sulfamate"+"ammate"+"ammonium+ sulphamate"+@TERM+@rn+7632-50-0+"ammonium+citrate"+@TERM+@rn+53956-04-0+"ammonium+ glycyrrhizate"+"ammonium+ glycyrrhizinate"+@TERM+@rn+12124-97-9+"ammonium+ bromide"+@TERM+@rn+12125-02-9+"ammonium+ chloride"+"ammonium+hydrochloride"+@TERM+@rn+7783-20-2+"ammonium+ sulfate"+@TERM+@rn+12125-01-8+"ammonium+ fluoride"+@TERM+@rn+12027-06-4"+"ammonium+ iodide")+@AND+@OR+("cancer"+"neoplasm"+"malignancy"+"tumors")	27 Apr 2017: 2
TOXLINE	@OR+("ammonium+salt"+@TERM+@rn+7664-41-7+"ammonia"+@TERM+@rn+7783-18-8+"ammonium+ thiosulfate"+"ammonium+ thiosulfate"+"ammonium+ thiosulphate"+@TERM+@rn+6484-52-2+"ammonium+ nitrate"+@TERM+@rn+5421-46-5+"ammonium+ thioglycolate"+@TERM+@rn+1111-78-0+"ammonium+ carbamate"+@TERM+@rn+7773-06-0+"ammonium+ sulfamate"+"ammate"+"ammonium+ sulphamate"+@TERM+@rn+7632-50-0+"ammonium+citrate"+@TERM+@rn+53956-04-0+"ammonium+ glycyrrhizate"+"ammonium+ glycyrrhizinate"+@TERM+@rn+12124-97-9+"ammonium+ bromide"+@TERM+@rn+12125-02-9+"ammonium+ chloride"+"ammonium+hydrochloride"+@TERM+@rn+7783-20-2+"ammonium+ sulfate"+@TERM+@rn+12125-01-8+"ammonium+ fluoride"+@TERM+@rn+12027-06-4"+"ammonium+ iodide")+@AND+@OR+("brewer"+"brewery"+"janitor"+"housekeeper"+"exterminator"+ "cosmetologist"+"hairstylist"+"mortician"+"embalmer"+"agricultural workers"+"farm workers"+"fertilizer manufacturers")	27 Apr 2017: 0 Batch # 21484
TOXLINE	@OR+("ammonium+salt"+@TERM+@rn+7664-41-7+"ammonia"+@TERM+@rn+7783-18-8+"ammonium+ thiosulfate"+"ammonium+ thiosulfate"+"ammonium+ thiosulphate"+@TERM+@rn+6484-52-2+"ammonium+ nitrate"+@TERM+@rn+5421-46-5+"ammonium+ thioglycolate"+@TERM+@rn+1111-78-0+"ammonium+ carbamate"+@TERM+@rn+7773-06-0+"ammonium+ sulfamate"+"ammate"+"ammonium+ sulphamate"+@TERM+@rn+7632-50-0+"ammonium+citrate"+@TERM+@rn+53956-04-0+"ammonium+ glycyrrhizate"+"ammonium+ glycyrrhizinate"+@TERM+@rn+12124-97-9+"ammonium+ bromide"+@TERM+@rn+12125-02-9+"ammonium+ chloride"+"ammonium+hydrochloride"+@TERM+@rn+7783-20-2+"ammonium+ sulfate"+@TERM+@rn+12125-01-8+"ammonium+ fluoride"+@TERM+@rn+12027-06-4"+"ammonium+ iodide")+@AND+@OR+("brewer"+"brewery"+"janitor"+"housekeeper"+"exterminator"+ "cosmetologist"+"hairstylist"+"mortician"+"embalmer"+"agricultural workers"+"farm workers"+"fertilizer manufacturers")+@AND+@OR+("cancer"+"neoplasm"+"malignancy"+"tumors")	27 Apr 2017: 0 Batch# 21485