OFFICE OF AGRICULTURE AND RURAL AFFAIRS
WASHINGTON, D.C. 20460

May 16, 2024

Jennifer Tucker, Ph.D.
Deputy Administrator
National Organic Program
1400 Independence Avenue, SW
Washington, DC 20250-0268

Dear Dr. Tucker,

Thank you for consulting with the U.S. Environmental Protection Agency (EPA) regarding ammonia products made from manure (i.e., ammonia extracts). We appreciate your patience as we evaluated your December 22, 2022, request and coordinated our response across multiple EPA program offices.

Let me begin my stating that we do not have determinative answers to the questions you posed in your letter; however, we hope our response can help inform the types of additional information that may be needed by the U.S. Department of Agriculture (USDA), including future data collection, peer reviewed research, and/or requests for public comment.

Background

In December 2022, the EPA Agriculture Advisor's office received a request from USDA's National Organic Program (NOP) seeking consultation regarding whether to include ammonia extracts (AE) on the National List of Prohibited Substances under the Organic Foods Production Act. In its letter, NOP raised two specific questions: Would the use of such substances be harmful to human health or the environment; and is the use inconsistent with organic farming or handling?

Over the course of 2023, the EPA Agriculture Advisor's office convened internal coordinating meetings with the Office of Chemical Safety and Pollution Prevention, Office of Water, Office of Air and Radiation, and Office of Research and Development to review the request from USDA. Subsequently, EPA staff gathered technical information regarding toxicological and hazard classification information on ammonia.

For example, an EPA Integrated Risk Information System (IRIS) assessment on ammonia inhalation (noncancer effects) was completed in 2016. Additionally, EPA's Office of Pesticide Programs published its Interim Registration Review Decision for Ammonia and Ammonium Sulfate in 2018. Both documents have been included as appendices to this letter.

However, if USDA believes that extracted ammonia may have a different toxicity profile than synthetic ammonia, it would be necessary to provide substantial details on synthesis and extraction methodologies, as well as chemical structure and degradation of each type. With this additional information, EPA would be willing to assist with conducting a cursory comparison of risk.

The following is a brief discussion of the two questions posed to EPA:

Question #1: Would the use of such substances be harmful to human health or the environment?

EPA has conducted numerous toxicological assessments of ammonia, which indicate the compound can be hazardous at certain levels of exposure. In addition, ammonia is listed as a hazardous substance under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Depending on how and where ammonia is used, there is a potential for it to cause harm to human health or the environment.

However, EPA's understanding of the hazardous properties of ammonia may not be determinative for purposes of excluding a substance from organic production. For example, there are other natural substances allowed in the National Organic Program that could present ecological or human health risks depending upon use.

EPA would benefit from understanding whether the ammonia extraction process could lead to reduced ammonia air emissions from animal feeding operations and any associated benefit to communities near the production areas. More data and research to better understand these effects would be of interest.

Regarding water quality impacts, it would be necessary to compare standard nutrient management practices in organic production (e.g., manure application) versus the use of AE fertilizer in a systems approach to determine if there is an increased or decreased risk to water quality. EPA has not been provided data to properly assess this; however, further research could be beneficial.

Question #2: Is the use inconsistent with organic farming or handling?

EPA does not have the same expertise as USDA regarding organic farming practices, so we would defer to the National Organic Program on this question.

However, USDA could explore whether requiring specific management techniques or limiting the nutrient concentration in AE products would sufficiently address soil health concerns. In other words, are there conditions of use that could enable AE application consistent with the principles

of organic farming? While this question was not directly posed to us, it seems relevant to the discussion about whether to add a natural substance to the prohibited list under OFPA.

We thank you for the opportunity to provide feedback into your decision-making process regarding AE products. Our technical experts remain available to provide additional support to NOP as you continue your deliberations.

Sincerely,

WelchWhite, Venus

Digitally signed by WelchWhite, Venus
Date: 2024.05.16 18:13:53 -04'00'

Venus Welch-White, Ph.D.
Acting Deputy Director
Office of Agriculture and Rural Affairs

Appendices:

- Request for consultation from USDA's National Organic Program to EPA regarding ammonia extracts (December 2022)
- Toxicological Review of Ammonia Noncancer Inhalation: Executive Summary (September 2016)
- Ammonia and Ammonium Sulfate Interim Registration Review Decision (December 2018)

USDA Agricultural Marketing Service

National Organic Program
1400 Independence Avenue, SW
Room 2642-South, STOP 0268
Washington, DC 20250-0268

December 22, 2022

Rodney Snyder
Senior Agricultural Advisor to the Administrator
Office of the Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Ave NW
Washington, DC 20460

Venus Welch-White
Senior Advisor
Office of the Agriculture Advisor
U.S. Environmental Protection Agency
1300 Pennsylvania Ave NW
Washington, DC 20460

Dear Mr. Snyder and Dr. Welch-White,

Thank you for taking the time to speak with us about our interest in consulting with the Environmental Protection Agency (EPA) about ammonia products made from manure (i.e., ammonia extracts). The USDA Agricultural Marketing Service (AMS) is following up on those meetings to request EPA's input regarding ammonia extracted from manure, specifically stripped and concentrated ammonia,[1] and its effect on the environment and human health. This consultation is part of our responsibilities under the Organic Foods Production Act of 1990 (OFPA).

Regulatory Overview

As background, in organic agriculture, the OFPA and the USDA organic regulations prohibit the use of any synthetic substance, unless explicitly allowed, and allow all natural substances, unless explicitly prohibited. The National List of Allowed and Prohibited Substances ("National List"), which is part of the USDA organic regulations, identifies the exceptions to this rule – i.e., allowed synthetic substances and prohibited natural substances for organic production.

[1] Stripped ammonia refers to products formed by isolating and separating ammonia from a natural source (usually manure). Concentrated ammonia refers to products formed by separating the liquid portion from solids, then concentrating the liquid portion to increase the nitrogen content.

To prohibit a natural substance from use in organic agriculture, OFPA requires, in part, that USDA consult with EPA and HHS to determine whether the substance would be harmful to human health or the environment and whether the use is inconsistent with organic farming or handling (7 U.S.C. 6517(c)(2)(A)).

The National Organic Standards Board (NOSB) is an advisory board under the Federal Advisory Committee Act (FACA) that provides recommendations to the Secretary of Agriculture on the National List and other aspects of the organic standards. The NOSB is made up of 15 public volunteer Board members that represent different organic sectors and interests. The Organic Foods Production Act of 1990 (OFPA) gives the NOSB authority to make rulemaking recommendations to the Secretary of Agriculture. AMS generally responds to these recommendations with rulemaking or other action, however, we do have regulatory discretion in this area.

Description of the Policy Question and Stakeholder Feedback

In Fall 2021, the NOSB made a recommendation to the USDA to prohibit two types of natural ammonia extracts (ammonia extracted from manure, specifically stripped and concentrated ammonia). In other words, the NOSB recommended that USDA add these materials to the National List's list of prohibited naturals in organic agriculture. In making their recommendation, the NOSB consulted the following key materials: a petition for rulemaking, a third-party technical report, and public comment.

Stakeholder feedback on prohibiting natural ammonia extracts has been split. Those in favor of prohibiting them emphasize that these products contain highly soluble, readily available nitrogen, which they believe is contrary to a core organic principle to "feed the soil, not the plant." They also note the potential for fraud, given that the nitrogen in these products is chemically similar, if not identical, to synthetic nitrogen. The concern is that adulteration would be commercially beneficial (as synthetic nitrogen is inexpensive) and difficult to identify.

On the other side, those wanting natural ammonia extracts to remain available argue that the products are a necessary tool for farmers, and that prohibiting this natural material would stifle innovation in the organic industry. They also argue that a prohibition is not consistent with the OFPA criteria for prohibiting a natural substance, namely that it is not harmful to human health and the environment. Further, they state these products can actually improve human health and the environment, by preventing manure runoff, lowering greenhouse gas emissions, and reducing water and fertilizer usage on farms.

Consultation to Date

In response to the NOSB recommendation prohibiting ammonia extracts, the USDA Agricultural Marketing Service (AMS) National Organic Program (NOP) began researching these substances and consulting with other agencies in February 2022.

To date, NOP has met with the following EPA offices: Office of Pesticide Programs, Biopesticides and Pollution Prevention Division; Office of Water, Science, and Technology, Ecological Criteria Division; Office of Radiation and Indoor Air; Integrated Risk Information System; Center for Public Health and Environmental Assessment; and the Exposure Analysis and Risk Characterization Group. This research has indicated that EPA does not currently regulate the use of ammonia extracts in agriculture.

Summary of Request

While these offices provided useful resources, we request your help to further evaluate this issue. OFPA notes that USDA can only list a natural product as prohibited in organic agriculture after consulting with EPA on the following questions: Would the use of such substances be harmful to human health or the environment; and is the use inconsistent with organic farming or handling? We request EPA to consider these questions and provide its input to support our regulatory process related to these substances.

Thank you for your help with this complex topic. Please reach out to me at Jennifer.Tucker@usda.gov or 202-317-0189 if you need additional information, have questions, or wish to discuss.

Sincerely,

Jennifer Tucker, Ph.D.
Deputy Administrator
National Organic Program

CC: Bruce Summers
AMS Administrator

Jenny Lester Moffitt, Under Secretary
USDA Marketing and Regulatory Programs

EPA/635/R-16/163Fc
www.epa.gov/iris

Toxicological Review of Ammonia
Noncancer Inhalation:
Executive Summary

[CASRN 7664-41-7]

September 2016

Integrated Risk Information System
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

EXECUTIVE SUMMARY

Occurrence and Health Effects

Ammonia occurs naturally in air, soil, and water. Ammonia is also produced by humans and other animals as part of normal biological processes.

Ammonia is used as an agricultural fertilizer and in many cleaning products. Exposure to ammonia occurs primarily through breathing air containing ammonia gas, and may also occur via diet, drinking water, or direct skin contact. Measured concentrations of ammonia range from 0.28 to 15 μg/m^3 in ambient outdoor air and from 0.09 to 166 μg/m^3 in indoor air.

Health effects of inhaled ammonia observed at levels exceeding naturally-occurring concentrations are generally limited to the respiratory tract, the site of direct contact with ammonia. Short-term inhalation exposure to high levels of ammonia in humans can cause irritation and serious burns in the mouth, lungs, and eyes. Chronic exposure to airborne ammonia can increase the risk of respiratory irritation, cough, wheezing, tightness in the chest, and impaired lung function in humans. Studies in experimental animals similarly indicate that breathing ammonia at sufficiently high concentrations can result in effects on the respiratory system. Animal studies also suggest that exposure to high levels of ammonia in air may adversely affect other organs, such as the liver, kidney, and spleen.

This assessment presents an evaluation of the noncancer health effects of ammonia by the inhalation route of exposure.

Chemical Properties

Ammonia (NH_3) is a colorless alkaline gas with a pungent odor. In solution, ammonia exists as ammonium hydroxide, a weak base that is only partially ionized in water according to the following equilibrium (ATSDR, 2004): $NH_3 + H_20 \rightleftarrows NH_4^+ + OH^-$. A decrease in pH results in an increase in the concentration of ammonium ion (NH_4^+) and a decrease in the concentration of the un-ionized form (NH_3). At physiological pH (7.4), this equilibrium favors the formation of NH_4^+.

Toxicokinetics

Inhaled ammonia is almost completely retained in the upper respiratory tract. Ammonia produced endogenously in the intestines through the use of amino acids as an energy source and by bacterial degradation of nitrogenous compounds from ingested food is largely absorbed. At physiological pH, 98.3% of ammonia is present in the blood as the ammonium ion (NH_4^+). Given its importance in amino acid metabolism, the urea cycle, and acid-base balance, ammonia is homeostatically regulated to remain at low concentrations in the blood. Ammonia is present in fetal circulation and in human breast milk as a source of nonprotein nitrogen. Ammonia production

occurs endogenously by catabolism of amino acids by glutamate dehydrogenase or glutaminase primarily in the liver, renal cortex, and intestines, but also in the brain and heart. Ammonia is metabolized to glutamine via glutamine synthetase in the glutamine cycle or incorporated into urea as part of the urea cycle. The principal means of excretion of ammonia is as urinary urea; lesser amounts are eliminated in the feces, through sweat production, and in expired air.

Effects Other Than Cancer Observed Following Inhalation Exposure

Respiratory effects have been identified as a human health hazard following inhalation exposure to ammonia. This hazard determination is based on findings from multiple epidemiology studies in human populations exposed to ammonia in different settings (workers in industrial, cleaning, and agricultural settings, volunteers exposed for up to 6 hours under controlled conditions, and case reports) and animals (short-term and subchronic studies in several species and across different exposure regimes).

Cross-sectional occupational studies involving chronic exposure to ammonia in industrial settings provide evidence of an increased prevalence of respiratory symptoms (Rahman et al., 2007; Ballal et al., 1998) and decreased lung function (Rahman et al., 2007; Ali et al., 2001; Ballal et al., 1998; Bhat and Ramaswamy, 1993). Other studies of exposure to ammonia when used as a disinfectant or cleaning product provide evidence of asthma, asthma symptoms, and impaired pulmonary function, using a variety of study designs (Casas et al., 2013; Arif and Delclos, 2012; Dumas et al., 2012; Lemiere et al., 2012; Vizcaya et al., 2011; Zock et al., 2007; Medina-Ramón et al., 2006; Medina-Ramón et al., 2005). Further evidence of respiratory effects of ammonia is seen in studies of pulmonary function in an agricultural setting, specifically in studies that accounted for effects of co-exposures to other agents such as endotoxin and dust (Donham et al., 2000; Reynolds et al., 1996; Donham et al., 1995; Preller et al., 1995; Heederik et al., 1990) and in one study that did not control for co-exposures (Loftus et al., 2015). Despite the variation in population characteristics, level and pattern of exposure, and potential confounders across these three settings of epidemiology studies, respiratory effects were consistently observed in these studies. Further, but more limited, support for the respiratory system as a target of ammonia toxicity comes from controlled human exposure studies of ammonia inhalation and case reports of injury in humans with inhalation exposure to ammonia. Additionally, respiratory effects were observed in several animal species following short-term and subchronic inhalation exposures to ammonia.

Overall, there are suggestions in experimental animals that ammonia exposure may be associated with effects on organs distal from the portal of entry, but there is inadequate information to draw conclusions about the liver, kidney, spleen, or heart as sensitive targets of ammonia toxicity.

Inhalation Reference Concentration (RfC) for Effects Other Than Cancer

Table ES-1. Summary of reference concentration (RfC) derivation

Critical effect	Point of departure[a]	UF	Chronic RfC
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)	$NOAEL_{ADJ}$: 4.9 mg/m^3	10	0.5 mg/m^3

[a]An estimate of the 95% lower confidence bound of the mean exposure concentration in the high-exposure group of the Holness et al. (1989) study was used as the NOAEL. Because the study involved workplace exposure conditions, the NOAEL of 13.6 mg/m^3 was adjusted for continuous exposure based on the ratio of VEho (human occupational default minute volume of 10 m^3 breathed during an 8-hour workday) to VEh (human ambient default minute volume of 20 m^3 breathed during the entire day) and an exposure of 5 days out of 7 days.

NOAEL = no-observed-adverse-effect level; UF = uncertainty factor

The study of ammonia exposure in workers in a soda ash plant by Holness et al. (1989), with support from three studies in urea fertilizer plants by Rahman et al. (2007), Ballal et al. (1998), and Ali et al. (2001), was identified as the principal study for RfC derivation. Respiratory effects, characterized as increased respiratory symptoms based on self-report (including cough, wheezing, and other asthma-related symptoms) and decreased lung function in workers exposed to ammonia, were selected as the critical effect. Rahman et al. (2007) observed an increased prevalence of respiratory symptoms and decreased lung function in workers exposed in a plant with a mean ammonia concentration of 18.5 mg/m^3, but not in workers in a second plant exposed to a mean concentration of 4.9 mg/m^3. Ballal et al. (1998) observed an increased prevalence of respiratory symptoms among workers in one factory with exposures ranging from 2 to 27.1 mg/m^3,[1] but no increase in another factory with exposures ranging from 0.02 to 7 mg/m^3. A companion study by Ali et al. (2001) also observed decreased lung function among workers exposed to higher cumulative ammonia levels (>50 mg/m^3-years), with an approximate 5–7% decrease in FVC% predicted and FEV_1% predicted (see definition of spirometry measures in Section 1.2.1). Holness et al. (1989), who investigated a plant with exposures generally lower than other studies, found no differences in the prevalence of respiratory symptoms or lung function between workers (mean exposure 6.5 mg/m^3) and the control group, and no differences when stratified by exposure level (highest exposure group, >8.8 mg/m^3).

These four studies addressed smoking by a variety of methods (e.g., adjustment for smoking, exclusion of smokers, stratification of the results by smoking status). Two of the

[1]This concentration range does not include exposures in the urea store (number of employees = 6; range of ammonia concentrations = 90–130.4 mg/m^3) because employees in this area were required to wear full protective clothing, thus minimizing potential exposure.

studies—Rahman et al. (2007) and Holness et al. (1989)—addressed other potential confounders as appropriate. In particular, a high level of control of exposures in the facility studied by Holness et al. (1989) was reported, suggesting a low potential for co-exposures. As discussed in more detail in the Literature Search Strategy | Study Selection and Evaluation section, confounding by other workplace exposures, although a potential concern, was unlikely to be a major limitation of these studies.

Considerations in selecting the principal study for RfC derivation include the higher confidence placed in the measures of ammonia exposure in Holness et al. (1989), evaluation of both respiratory symptoms and lung function parameters in this study, and the fact that the estimate of the no-observed-adverse-effect level (NOAEL) for respiratory effects of 13.6 mg/m^3 from Holness et al. (1989) was the highest of the studies with adequate exposure-response information. The synthesis of findings from the full body of evidence demonstrates that there is a relationship between ammonia exposure and respiratory effects. Although Holness et al. (1989) do not report associations between ammonia exposure and respiratory effects, it is included in the body of epidemiologic studies of industrial settings because it is informative of the levels above which ammonia causes effects. Other epidemiology studies include those with higher workplace ammonia concentrations associated with respiratory effects (i.e., higher concentrations relative to those reported by Holness et al. (1989)) and for which lowest-observed-adverse-effect levels (LOAELs) could be identified. The Holness et al. (1989) study is identified as the principal study for RfC derivation based on the quality of the exposure data and other factors, as stated above.

In summary, the study of ammonia exposure in workers in a soda ash plant by Holness et al. (1989) was identified as the principal study for RfC derivation, with support from Rahman et al. (2007), Ballal et al. (1998), and Ali et al. (2001), and respiratory effects were identified as the critical effect. The NOAEL, represented by an estimate of the 95% lower confidence bound of the mean exposure concentration in the high-exposure group from the Holness et al. (1989) study, or 13.6 mg/m^3, was used as the point of departure (POD) for RfC derivation. The NOAEL adjusted to continuous exposure (NOAEL$_{ADJ}$) was 4.9 mg/m^3.

An RfC of 0.5 (rounded) mg/m^3 was calculated by dividing the POD (adjusted for continuous exposure, i.e., NOAEL$_{ADJ}$) by a composite uncertainty factor (UF) of 10 to account for potentially susceptible individuals in the absence of data evaluating variability of response to inhaled ammonia in the human population.

Confidence in the Chronic Inhalation RfC

Study – medium
Database – medium
RfC – medium

Consistent with Environmental Protection Agency (EPA) *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994), the overall confidence in the RfC is medium and reflects medium confidence in the principal study (adequate design, conduct, and reporting of the principal study; limited by small sample size and identification of a NOAEL only) and medium confidence in the database, which includes occupational, cleaner, agricultural, and human exposure studies and studies in animals that are mostly of subchronic duration. There are no studies of developmental toxicity, and studies of reproductive and other systemic endpoints are limited; however, the likelihood of reproductive, developmental, and other systemic effects at the RfC is considered small because it is well documented that ammonia is endogenously produced in humans and animals, and any changes in blood ammonia levels at the POD would be small relative to normal blood ammonia levels. Further, EPA is not aware of any mechanisms by which ammonia can exert effects at the point of contact (i.e., respiratory system) that could directly or indirectly impact tissues or organs distal to the point of contact.

Susceptible Populations and Lifestages

Studies of the toxicity of ammonia in children that would support an evaluation of childhood susceptibility are limited. Casas et al. (2013) and Loftus et al. (2015) reported evidence of an association between ammonia exposure and decrements in lung function in children; however, these studies did not report information that would allow a comparison of children and adults.

A limited number of studies provides inconsistent evidence of greater respiratory sensitivity to ammonia exposure in asthmatics (Loftus et al., 2015; Petrova et al., 2008; Sigurdarson et al., 2004; Preller et al., 1995). Loftus et al. (2015) reported no increase in asthma symptoms and medication use in asthmatic children living near animal feeding operations; however, ammonia exposure was associated with lower FEV_1.

Hyperammonemia is a condition of elevated levels of circulating ammonia that can occur in individuals with severe diseases of the liver or kidney or with hereditary urea [$CO(NH_2)_2$] cycle disorders. These elevated ammonia levels can predispose an individual to encephalopathy due to the ability of ammonia to cross the blood-brain barrier; these effects are especially marked in newborn infants. Thus, individuals with disease conditions that lead to hyperammonemia may be more susceptible to the effects of ammonia from external sources, but there are no studies that specifically support this susceptibility.

Key Issues Addressed in This Assessment

Comparison of Exhaled Ammonia to the RfC

Ammonia is generated endogenously in multiple organs and plays central roles in nitrogen balance and acid-base homeostasis (Weiner et al., 2014; Weiner and Verlander, 2013). Given its

important metabolic role, free ammonia is homeostatically regulated to remain at low concentrations in blood (Souba, 1987). Elimination of ammonia occurs primarily in urine and exhaled breath. Consideration was given to the presence of ammonia in exhaled air because the range of ammonia concentrations in exhaled breath (0.009–2 mg/m^3) overlaps the ammonia RfC (0.5 mg/m^3).

In general, higher and more variable ammonia concentrations (0.03–2 mg/m^3) are reported in human breath exhaled from the mouth or oral cavity (Schmidt et al., 2013; Smith et al., 2008; Španěl et al., 2007a, b; Turner et al., 2006; Diskin et al., 2003; Smith et al., 1999; Norwood et al., 1992; Larson et al., 1977). Ammonia concentrations measured in breath derived from oral breathing largely reflect the production of ammonia via bacterial degradation of food protein in the oral cavity or gastrointestinal tract, and can be influenced by diet, oral hygiene, age, and saliva pH. In contrast, concentrations of ammonia in breath exhaled from the nose and trachea of humans (0.0092–0.1 mg/m^3) are lower than those in air exhaled from the mouth (Schmidt et al., 2013; Smith et al., 2008; Larson et al., 1977), and are generally lower than the RfC by a factor of five or more. Concentrations in breath exhaled from the nose appear to better represent levels at the alveolar interface of the lung and are more relevant to understanding systemic levels of ammonia than breath exhaled from the mouth (Schmidt et al., 2013; Smith et al., 2008); however, concentrations in breath from neither the mouth nor the nose can be used to predict blood ammonia concentration or previous exposure to environmental (ambient) concentrations of ammonia (see Appendix C, Section C.1.4).

Regardless of the source of expired ammonia (mouth or nose), the level of ammonia in breath, even at concentrations that exceed the RfC, does not necessarily raise questions about the appropriateness of the RfC. The exhalation of ammonia is a clearance mechanism for a product of metabolism that is otherwise toxic in the body at sufficiently high concentrations. Thus, ammonia concentrations in exhaled breath may be higher than inhaled concentrations. However, the presence of ammonia in exhaled breath is not considered an uncertainty in the RfC.

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Ammonia and Ammonium Sulfate
Interim Registration Review Decision
Case Numbers 7440 & 5073

December 2018

Approved by: _____

Anita Pease
Acting Director
Antimicrobials Division

Date: 12/17/2018

Docket Number: EPA-HQ-OPP-2012-0684
www.regulations.gov

Ammonia and Ammonium Sulfate
Registration Review Team

Human Health
Timothy Dole, Industrial Hygienist
Timothy F. McMahon, Ph.D., Physical Scientist

Environmental Fate and Effects
James Breithaupt, Agronomist
William Erickson, Biologist

Risk Management
Stephen Savage
Rick Fehir
Eric Miederhoff

Office of General Counsel
Philip Ross

Table of Contents

I. Introduction

This document is the Environmental Protection Agency's (EPA or the Agency) Interim Registration Review Decision (ID) for Ammonia (PC Code 005601, Case Number 7440) and Ammonium Sulfate (PC Code 005302, Case 5073) and is being issued pursuant to 40 CFR sections 155.56 and 155.58. A registration review decision is the Agency's determination whether a pesticide continues to meet, or does not meet, the standard for registration in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The Agency may issue, when it determines it to be appropriate, an interim registration review decision before completing a registration review. Among other things, the interim registration review decision may require new risk mitigation measures, impose interim risk mitigation measures, identify data or information required to complete the review, and include schedules for submitting the required data, conducting the new risk assessment and completing the registration review. Additional information on ammonia and ammonium sulfate can be found in the Agency's public docket (EPA-HQ-OPP-2012-0684) at www.regulations.gov.

FIFRA, as amended by the Food Quality Protection Act (FQPA) of 1996, mandates the continuous review of existing pesticides. All pesticides distributed or sold in the United States must be registered by the Agency based on scientific data showing that they will not cause unreasonable risks to human health or to the environment when used as directed on product labeling. The registration review program is intended to make sure that, as the ability to assess and reduce risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects. Changes in science, public policy, and pesticide use practices will occur over time. Through the registration review program, the Agency periodically re-evaluates pesticides to make sure that as these changes occur, products in the marketplace can continue to be used safely. Information on this program is provided at http://www.epa.gov/pesticide-reevaluation. In 2006, the Agency implemented the registration review program pursuant to FIFRA section 3(g) and will review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration.

The Agency is issuing an Interim Decision for ammonia and ammonium sulfate so that it can move forward with aspects of the registration review that are complete. EPA determined that no pollinator exposure and effects data are necessary to make a final registration review decision for ammonia and ammonium sulfate. The Agency has evaluated risks to listed species. The Agency is making a "no effects" finding for listed species and designated critical habitat. The Agency will complete endocrine screening for ammonia and ammonium sulfate, pursuant to the Federal Food, Drug, and Cosmetic Act (FFDCA) section 408(p), before completing registration review.

This document is organized in five sections: the *Introduction*, which includes this summary and a summary of any public comments received on the preliminary risk assessment and the Agency's responses; *Usage Information*, which describes how and why ammonia and ammonium sulfate are used; *Scientific Assessment*, which summarizes the Agency's risk assessments; the *Interim Registration Review Decision*, which describes the regulatory rationale for the Agency's interim registration review decision; and, lastly, the *Next Steps and Timeline* for completion of this registration review.

A. Summary of Ammonia and Ammonium Sulfate Registration Review

Pursuant to 40 CFR section 155.50, the Agency formally initiated registration review for ammonia and ammonium sulfate (PC Codes 005601 & 005302). The following summary highlights the docket opening and other significant milestones that have occurred thus far during the registration review of ammonia and ammonium sulfate:

- September 26, 2012 - The Ammonia and Ammonium Sulfate Preliminary Work Plan (PWP) was published to docket EPA-HQ-OPP-2012-0684 for a 60-day public comment. The public comment period closed November 26, 2012.

- February 20, 2013 - The Final Work Plan (FWP) for Ammonia and Ammonium Sulfate was published to docket EPA-HQ-OPP-2012-0684. During the PWP 60-day comment period, two comments were received from the public. The comments did not change the data needs, planned risk assessments, or the timeline for the registration review case; thus, the FWP did not modify the PWP.

- December 22, 2016 - The Amended Final Work Plan was completed and published to docket EPA-HQ-OPP-2012-0684. The amended FWP removed the previously anticipated 835.6200 aquatic field dissipation data requirement. All other elements of the Agency's Ammonia and Ammonium Sulfate FWP remained unchanged.

- December 29, 2016 - A Generic Data Call-In (GDCI) for ammonia and ammonium sulfate was issued for data needed to conduct the registration review risk assessments. All data have been waived and the GDCI is satisfied.

- February 27, 2018 - The Preliminary Risk Assessment for Ammonia and Ammonium Sulfate was published to docket EPA-HQ-OPP-2012-0684 for a 60-day public comment period. Several comments were received. The comments did not change the risk assessments or registration review timeline.

- June 25, 2018 - The Proposed Interim Decision was published to the docket EPA-HQ-OPP-2012-0684 for a 60-day public comment period. One comment was received, and the comment did not change the risk assessments or registration review timeline.

B. Public comments on the Proposed Interim Decision

During the 60-day public comment period on the Ammonia and Ammonium Sulfate Proposed Interim Decision, which opened June 25, 2018 and closed August 25, 2018, the Agency received one comment from the California Specialty Crops Council. The comment in its entirety can be found on the current docket for ammonia and ammonium sulfate (EPA-HQ-OPP-2012-0684). The comment was concerning insect pesticide resistance threatening crop yields and the need to rotate pesticides with differing modes of action. The comment does not specifically address risk from ammonia or ammonium sulfate uses or request any revision to the risk assessment or the registered use sites. The comment is associated with the non-pesticidal use of ammonia in

agricultural fields. Currently there are no registered uses of ammonia or ammonium sulfate in agricultural fields for the control of insects.

Agency Response: The Agency thanks the submitter for the comments. The comment did not affect the Agency's conclusions with respect to risk and did not alter the risk projections for ammonia and ammonium sulfate.

II. Usage Information

There are currently six registered pesticide products containing ammonia and ammonium sulfate. Four products incorrectly list ammonia (total) as the active ingredient when they contain ammonium sulfate (PC 005302) as the active ingredient. Two products are correctly listed as containing ammonium sulfate as the active ingredient. Therefore, the Agency assessed exposure and risk to the products in these cases as ammonium sulfate. The products are liquid soluble concentrates and contain 20% to 40% ammonium sulfate. As noted in the table in Appendix A, the Agency requires label amendments to correct the active ingredient listing.

Products containing ammonia and ammonium sulfate are registered for use to control algae, bacteria, fungi and mollusks in industrial systems (paper mills, recirculating cooling water systems, evaporative condensers, brewery and food pasteurizers, industrial fresh water systems, air washers, seawater desalination and reverse osmosis systems and paint spray booth sumps), non-fish containing decorative fountains and ponds used for cooling purposes, sewage and wastewater systems, and oil and gas systems. Ammonia and ammonium sulfate products are also registered for use to control algae, bacteria, fungi and mollusks in influent water systems (freshwater and seawater).

Products containing ammonia and ammonium sulfate are used in conjunction with sodium hypochlorite in a closed metered chemical feed system to produce monochloramine. The treatment can be administered using the slug, intermediate or continuous feed methods. The specified dose is 1 to 10 ppm available chlorine for both initial and subsequent treatments. Per the labels, prior to effluent release, the chloramine must be neutralized with sodium metabisulfite until chloramine is no longer detected. This neutralization results in the formation of ammonium and chloride ions, which are not of environmental or human health concern. Likewise, in aqueous media, ammonium sulfate dissociates into ammonium and sulfate ions, and under the heat of the paper finishing process, the chemical species likely to remain are ammonium ion, sulfate ion, nitrate ion, and chloride ion, for which there are no dietary concerns. Due to low potential for exposure and lack of toxicity from degradation products after ammonium sulfate use, a qualitative human health and environmental risk assessment was performed.

III. Scientific Assessment

A. Human Health Assessment

The most recent human health risk assessment for ammonium sulfate (D442473)[1] was completed in 2017 and nothing has changed since that assessment, therefore a qualitative assessment was done. The qualitative assessment did not include a quantitative human health risk assessment, based on the low potential for exposure and lack of toxicity in the database. The residues remaining in the finished paper have no dietary toxicity concerns. Even for products registered with ammonia as the active ingredient, the true active ingredient is believed to be ammonium sulfate; therefore, the exposure and risk assessment was conducted for ammonium sulfate only. For further information, please see, "Registration Review Preliminary Risk Assessment for Ammonia and Ammonium Sulfate" located in docket EPA-HQ-OPP-2012-0684 at www.regulations.gov.

1. Risk Summary and Characterization

The Agency has determined that risks to human health from the use of ammonia and ammonium sulfate are minimal based on no evidence of adverse effects and lack of exposure.

2. Human Incidents

No ammonia and ammonium sulfate related incidents have been reported in the Agency's Incident Data System (IDS) for the period from 1992 to September 13, 2017. IDS contain reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992.

3. Dietary Exposure/Tolerances

Since there are no food uses of ammonia and ammonium sulfate as an active ingredient, residues of ammonium sulfate are exempted from the requirement of a tolerance under the Federal Food, Drug, and Cosmetic Act (FFDCA) Section 408, when used as a solid diluent or carrier in accordance with good agricultural practices as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest (40 CFR 180.910), without limit. Under the FFDCA Section 409, ammonium sulfate is listed by Food and Drug Administration (FDA) as Generally Recognized as Safe (GRAS) when used as a direct food additive (21 CFR 184.1143).

Ammonia and ammonium sulfate produce no residues of potential toxicological concern that are expected to survive the paper manufacturing processes. Any chloramine not consumed in the water system is expected to degrade during the paper drying process. The remaining residues have no dietary toxicity concerns.

Further, very low levels of monochloramine may potentially be discharged from industrial water systems or paper mills; however, due to its rapid hydrolysis and biodegradation, it is not

[1] D442473. U.S. EPA. August 28, 2017. Qualitative Risk Assessment for New Ammonium Sulfate Product: Biosperse CX400.

expected to be stable in surface water. Therefore, no drinking water risks are expected from the registered uses of ammonia and ammonium sulfate.[2]

4. Food and Drinking Water

A dietary (food and drinking water) exposure assessment is not currently required for ammonia and ammonium sulfate. The FIFRA registered uses of ammonia and ammonium sulfate are not expected to result in direct or indirect dietary (food) exposure. The use of ammonia and ammonium sulfate products are not expected to pose a hazard to groundwater or surface waters; therefore, a drinking water assessment is not currently required.[3]

5. Occupational and Residential Exposures

No residential exposure scenarios are associated with use of ammonium sulfate. Therefore, there is no need to estimate residential risks.

The labels for the ammonia and ammonium sulfate products require the mixing of the product with sodium hypochlorite within an onsite feeder/delivery system which is a closed system. The ammonium sulfate is transferred from the shipping container to the feeder/delivery system via a closed loading system and therefore worker exposure to ammonium sulfate is not anticipated to be significant.[4]

6. Aggregate Risks

An aggregate exposure risk assessment was not conducted for this chemical because of a lack of dietary and residential exposure.[4]

7. Cumulative Risks

Unlike other pesticides for which the Agency has followed a cumulative risk approach based on a common mechanism of toxicity, the Agency has not made a common mechanism of toxicity finding as to ammonia and ammonium sulfate and any other substances and ammonia and ammonium sulfate does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, the Agency has not assumed that ammonia and ammonium sulfate have a common mechanism of toxicity with other substances.[4]

8. Human Health Data Needs

The Agency does not anticipate any further human health data needs for the ammonia and ammonium sulfate registration review.[4]

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[2] Registration Review of ammonium sulfate human health scoping document (D404903, D401474) conducted in 2012 and available in docket EPA-HQ-OPP-2012-0684 at www.regulations.gov.
[3] Ammonia and Ammonium Sulfate: Human Health Registration Review Scoping Document (D404903, D401474) conducted in 2012 and available in docket EPA-HQ-OPP-2012-0684 at www.regulations.gov.
[4] Ammonia and Ammonium Sulfate Draft Risk Assessment EPA-HQ-OPP-2012-0684 at www.regulations.gov.

B. Environmental Assessment

The Agency does not anticipate any significant risks to non-listed or listed species (aquatic, and terrestrial, including pollinators). Label restrictions prevent exposure into surface water, and the environmental fate data indicate strong sorption to sediment. Ammonia and ammonium sulfate have no outdoor registered uses. Due to lack of exposure, ammonia and ammonium sulfate pose no ecological risk to aquatic organisms or pollinators.

The only compounds of potential ecotoxicity concern from treated paper mill and industrial water systems are traces of chloramine and hypochlorous acid. These compounds are neutralized before being released into the environment. Therefore, only very low levels of these compounds would be discharged, and these would rapidly dissipate and biodegrade. Therefore, risks to non-target organisms are not expected from the ammonia and ammonium sulfate uses.

Based on ammonia and ammonium sulfate's physical and environmental fate properties, ammonia and ammonium sulfate are highly volatile substances and can easily transfer into the atmosphere; however, its half-life in air is short, and it is likely to rapidly degrade. Ammonia and ammonium sulfate are highly water soluble, and under aerobic conditions they undergo ready biodegradation. The available ecotoxicity data categorize ammonia and ammonium sulfate as being practically non-toxic to birds and aquatic organisms. For more information, please refer to "Ammonia and Ammonium Sulfate: Product Chemistry/Environmental Chemistry and Eco-Effects Scoping Document," located in docket EPA-HQ-OPP-2012-0684 at www.regulations.gov.

1. Environmental Fate and Exposures

When mixed with sodium hypochlorite in water systems, ammonia and ammonium sulfate turn into monochloramine (chloramine). All labels state "if chloramine is detected in the effluent, it can be neutralized by the addition of sodium metabisulfite until chloramine is no longer detected." Some labels also state that "residual levels of monochloramine in the effluent must be monitored and neutralized using on-line monitoring and control equipment." The neutralization results in the formation of ammonium and chloride ions, which are not of environmental concern.

The labels that do not currently require neutralization of monochloramine (chloramine) must be amended to make neutralization mandatory (see Section V). The Agency believes neutralization is already a common industry practice, therefore, the required label amendments will ensure that all registered labels are consistent with current processes.

If used as directed and neutralization is conducted, exposure of terrestrial receptors is not expected from the registered uses. Therefore, no terrestrial environmental fate data are required to estimate potential exposure of non-target organisms. In addition, the Agency determined that no pollinator exposure and effects data are necessary to make a final registration review decision for ammonia and ammonium sulfate.

2. Ecological Effects Assessment

An ecological effects risk assessment was not conducted for this chemical because of a lack of exposure to non-target organisms.

The Agency believes that ecological risks from the use of ammonia and ammonium sulfate are expected to be minimal based on the environmental fate of these chemicals once neutralized, which suggests negligible exposure to the environment.

3. Ecological Incidents

No ammonia and ammonium sulfate incidents have been reported in the Office of Pesticide Programs (OPP) Incident Data System (IDS) for the period spanning 2000 to September 13, 2017.

4. Ecological and Environmental Fate Data Needs

The Agency does not anticipate any further ecological and environmental fate data needs for the ammonia and ammonium sulfate registration review.

C. Endangered Species Assessment

The Agency has no expectation for the registered pesticide uses of ammonia and ammonium sulfate to cause direct or indirect adverse effects to threatened and endangered species. Due to label restrictions mandating the neutralization of effluent water until chloramine is no longer detected, environmental exposure is unlikely. No adverse modification of any designated critical habitat for such species is expected from the use of ammonia and ammonium sulfate. The Agency is making a "no effect" determination for ammonia and ammonium sulfate under the Endangered Species Act (ESA) for all listed species and designated critical habitat for such species and has therefore concluded that consultation with the Fish and Wildlife Service and the National Marine Fisheries Service under ESA section 7(a)(2) is not required.

D. Endocrine Disruptor Screening Program

As required by FIFRA and FFDCA, the Agency reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, the Agency evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent risk assessment for ammonia and ammonium sulfate, the Agency reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by

FFDCA Section 408(p), ammonia and ammonium sulfate are subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

The Agency has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife, similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where the Agency will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA Section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, the Agency issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[5] and includes some pesticides scheduled for registration review and chemicals found in water. Neither ammonia or ammonium sulfate are currently scheduled for screening. However, it should be noted that ammonia and ammonium sulfate will be screened for their potential to interact with the endocrine system. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[6]

In this interim decision, the Agency is making no human health or environmental safety findings associated with the EDSP screening of ammonia and ammonium sulfate. Before completing this Registration Review, the Agency will make an EDSP FFDCA section 408(p) determination.

IV. Interim Registration Review Decision

A. Risk Mitigation and Regulatory Rationale

In accordance with 40 CFR Sections 155.56 and 155.58, the Agency is issuing this Interim Registration Review Decision for ammonia and ammonium sulfate. The Agency's Interim Decision is (1) that no additional data are needed for the active ingredients, and (2) changes to the affected labels are needed at this time (see Appendix A). In addition, the Agency does not expect ammonia and ammonium sulfate to have direct or indirect adverse effects to non-listed and listed species or to adversely modify any designated critical habitat for such species and has made a "no effect" determination under the Endangered Species Act (ESA) for all listed species and designated critical habitat for such species. EPA determined that no pollinator exposure and

[5] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.
[6] http://www.epa.gov/endo/

effects data are necessary to make a final registration review decision for ammonia and ammonium sulfate. This Interim Decision does not cover the EDSP component of this registration review case and is being issued pending its evaluation.

V. Next Steps and Timeline

A. Interim Registration Review Decision

In accordance with 40 CFR Sections 155.56 and 155.58, the Agency is issuing the Interim Registration Review Decision for Ammonia and Ammonium Sulfate. A Federal Register Notice will announce the availability of this Interim Decision. EPA determined that no pollinator exposure and effects data are necessary to make a final registration review decision for ammonia and ammonium sulfate. A final decision on ammonia and ammonium sulfate registration review cases will occur after the EDSP FFDCA section 408(p) determination.

Label amendments for products formulated with ammonia and ammonium sulfate are required as discussed herein and set forth in Appendix A.

B. Implementation of Mitigation Measures

Once the Interim Registration Review Decision is published in the docket, ammonia and ammonium sulfate registrants will be required to submit amended labels that include the label changes described in Appendix A. The amended labels will be required to be submitted to the Agency for review within 60 days following publication of the Interim Registration Review Decision.

VI. Appendix

Appendix A: Required Labeling Changes for Ammonia and Ammonium Sulfate

Description	Amended Label Language for End-Use Products	Placement on Label
Addition of required neutralization of effluent water containing monochloramine (chloramine). EPA Registration Numbers: • 1448-432 • 1448-433 • 1448-442 • 1706-240 • 9386-49 • 74655-39	"If monochloramine (chloramine) is detected in the effluent, it must be neutralized by the addition of sodium meta-bisulfite until the monochloramine (chloramine) is no longer detected."	Directions for Use
Revise the active ingredient to list correct active ingredient. EPA Registration Numbers: • 1448-432 • 1448-433 • 1448-442 • 9386-49	Change ammonia to ammonium sulfate.	Ingredient Statement