The Fertilizer Institute
Nourish, Replenish, Grow
Wade Foster
Manager, Regulatory and Scientific Affairs

July 9, 2014

VIA ELECTRONIC SUBMISSION

Dr. Sue Shallal
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Re: Comments on revised external review draft human health assessment titled "Toxicological Review of Ammonia: In Support of Summary Information on the Integrated Risk Information System (IRIS)" (EPA/635/R-13/139a).

Dear Dr. Shallal:

The Fertilizer Institute ("TFI"), on behalf of its member companies, submits these comments in response to the U.S. Environmental Protection Agency's ("EPA" or "Agency") March 25, 2014 *Federal Register* notice announcing two meetings of the Chemical Assessment Advisory Committee Augmented for the Review of the Draft Ammonia Assessment ("CAAC-Ammonia Panel") to review the revised external human health assessment entitled *Toxicological Review of Ammonia: In Support of Summary Information on the Integrated Risk Information System (IRIS)* (hereinafter "Revised Toxicological Review").[1] 79 *Fed. Reg*. at 16,326.

Statement of Interest

TFI represents the nation's fertilizer industry including producers, importers, retailers, wholesalers and companies that provide services to the fertilizer industry. TFI members provide nutrients that nourish the nation's crops, helping to ensure a stable and reliable food supply. TFI's full-time staff, based in Washington, D.C., serves its members through legislative, educational, technical, economic information and public communication programs.

TFI members produced 11.5 million tons[2] of ammonia (CAS # 7664-41-7) in 2012 which represents virtually all of the ammonia commercially produced in the United States. TFI members also use ammonia to produce other nitrogenous fertilizer products. TFI and its members have specific technical expertise in the chemical, physical, and toxicological properties of ammonia. Because of

[1] US EPA. *Toxicological Review of Ammonia: In Support of Summary Information on the Integrated Risk Information System (IRIS)*. EPA/635/R-13/139A. August 2013.
[2] International Fertilizer Industry Association, 2012 Ammonia Statistics, 2012 report released Oct. 2013

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the aforementioned reasons, TFI and its members have an interest in EPA's review of the scientific literature and risk assessment procedures used to potentially make revisions to the *Toxicological Review of Ammonia*.

TFI Comments

TFI appreciates EPA's efforts to critically review the publically available studies on ammonia in order to identify its adverse health effects and to characterize exposure-response relationships. However, TFI is concerned that the Revised Toxicological Review is not consistent with EPA guidance on setting RfCs [3] and relies on the lowest No Observed Adverse Effect Level (NOAEL) in a single study, without regard to confounding chemicals, to derive an overly conservative reference concentration for ammonia. TFI offers the following specific comments on the Toxicological Review.

A. EPA Should Revisit Specific Comments as Submitted by TFI

TFI, on behalf of its member companies, previously submitted comments in response to the EPA's June 08, 2012 *Federal Register* notice announcing a 60-day external review draft human health assessment entitled *Toxicological Review of Ammonia: In Support of Summary Information on the Integrated Risk Information System* (hereinafter "Toxicological Review").[4] 77 *Fed. Reg*, at 34,039.

In reviewing the appendices[5] for the Revised Toxicological Review (hereinafter "Supplemental Information"), TFI believes that specific comments, which were based on additional referenced scientific literature and technical expertise, were not fully addressed and should be further evaluated.

First, TFI requested some discussion from EPA of how potentially confounding variables should be addressed in determining the Confidence Statement and in selection of the Point of Departure (POD) for derivation of the Inhalation Reference Concentration.

In response, EPA stated:

> "EPA appreciates this comment. Consideration of potential confounding was addressed more fully in Tables D-2, D-3, and D-4 on the evaluation of epidemiology studies (see Appendix D), and in text in the Literature Search Strategy | Study Selection and Evaluation section of the external review draft. Consideration of co-exposure to other agents in the livestock farmer studies was also addressed in Appendix E and Tables E-7 and E-8. Section 2.2.1 was revised to clarify the rationale for selection of the NOAEL from Holness et al. (1989) as the POD for the ammonia RfC." Supplemental Information, p. G-6.

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[3] EPA Risk Assessment Forum. *A Review of the Reference Dose and Reference Concentration Processes. EPA/630/P-02/002F. December 2002.*
[4] US EPA. *Toxicological Review of Ammonia: In Support of Summary Information on the Integrated Risk Information System (IRIS)*. EPA/635/R-11/013A. June 2012.
[5] US EPA. *Toxicological Review of Ammonia: In Support of Summary Information on the Integrated Risk Information System (IRIS) – Supplemental Information*. EPA/635/R-13/139b. August 2013.

Second, TFI remains concerned that concurrent exposure to similar alkaline substances in the four cross-sectional occupational epidemiology studies results in an underestimation of the NOAEL from ammonia inhalation exposure alone. TFI understands that confounding exposures from formaldehyde-based additives and soda ash are not addressed in the four studies. However, the policy issue of how the lack of data on these confounding variables should be addressed in expressing confidence in the assigned to the study used to derive the RfC, the overall database and the RfC itself remains.

Finally, and of critical importance, TFI comments regarding a valid, defensible selection of a point of departure for derivation of the Reference Inhalation Concentration should be revisited. The selection of the POD value of 8.8 mg/m^3 (12.5 ppm) is not supported by existing EPA guidance nor is it the NOAEL cited by the referenced study (Holness et al., 1989). Additional regulatory values, such as the Threshold Limit Value (TLV), Reference Exposure Level (REL), and Permissible Exposure Level (PEL) can be used to support a higher POD value which is justified and verified by results of the the primary reference study.

B. Consideration of Respiratory Hazard Studies Should Include Discussion of Potential Confounding Variables

The Toxicological Review relies on four cross-sectional occupational epidemiology studies (Rahman et al., 2007; Ali et al., 2001; Holness et al., 1989; Ballal et al., 1998) as the primary references to examine the association between inhaled ammonia and prevalence of respiratory symptoms and changes in lung function. None of the studies adequately controls for concurrent exposure to ambient levels of chemicals whose exposures cause health effects similar to those of ammonia.

In three of the studies (Rahman et al., 2007; Ali et al., 2001; Ballal et al., 1998), exposure assessments were conducted in urea plants. Because urea is produced with formaldehyde-based additives, urea plant workers can reasonably be anticipated to be exposed to formaldehyde. Formaldehyde is considered a sensory irritant, upper respiratory tract irritant, asthma and allergen trigger as well as a causative agent in reduced lung function.[6] While these studies indicate that higher ammonia levels were associated with urea production portions of studied production facilities and that higher ammonia levels were associated with exposure endpoints, none quantitatively or qualitatively examined the role of ambient formaldehyde or particulate dust as a potential confounding variable in study results. While confounding variables including dust are cited as limiting the utility of studies examining ammonia exposures in farm settings, no qualitative limitations are noted for exposures in urea plants.

TFI argues that this distinction is important, especially given differences in exposures between workers exposed to gaseous ammonia and those workers exposed to ammonia in urea production areas, which include gaseous ammonia, formaldehyde and particulate constituents from solid urea production.

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[6] US EPA. *Toxicological Review of Formaldehyde – Inhalation Assessment (CAS No. 50-00-0): In Support of Summary Information on the Integrated Risk Information System (IRIS) EPA/635/R-10/002A*. June 2, 2010.

TFI requests that the Confidence Section of the Toxicological Review include a qualitative discussion regarding potential confounding factors associated with ammonia exposure assessments in solid urea production areas and the potential for derived NOAELs to underestimate a NOAEL for ammonia alone. Further, TFI requests that potential confounding from concurrent exposure to formaldehyde be factored into the selection of a defensible POD from which the Inhalation Reference Concentration is derived.

The fourth cited study, Holness et al., 1989, examines ammonia exposures in the production of sodium carbonate (soda ash) via the Solvay process. Sodium carbonate particulate exposure may cause mechanical irritation to the eyes, nose, throat and lungs. Inhalation may lead to pulmonary fibrosis, chronic bronchitis, emphysema and bronchial asthma. Dermatitis and asthma may result from short contact periods. However, potential confounding effects from sodium carbonate exposure are not discussed in the Holness et al. study.

The Organization for Economic Co-operation and Development's SIDS dossier for sodium carbonate[7] discusses relevant studies in its Inhalation Toxicity section. The SIDS dossier states:

> A repeated dose inhalation study has been reported by Reshetyuk and Shevchenko (1966) but this study was not reported in sufficient detail. Male rats were exposed to a 2% aqueous sodium carbonate aerosol for 4 h/day, 5 days/week for 3.5 months. The final concentration was reported to be 70 ± 2.9 mg/m^3, whereas particle size was reported not to exceed 5 µm (no further details given). When compared to controls there were no changes in body weight gain, organ weights, body temperature, or several blood parameters. Pulmonary ascorbic acid levels were decreased.
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> Deviations in lungs were found in control and experimental animals but only experimental animals displayed hyperplasia and desquamination of bronchiolar epithelium, and perivascular oedema. The upper respiratory tract was not examined. Other pulmonary changes included thickening of alveolar walls, hyperaemia and lymphoid infiltration but these changes were also observed in about 50% of the controls. A preliminary study of unknown duration at a concentration of 10-20 mg/m3, did not induce toxic effects (Reshetyuk and Shevchenko, 1966).
>
> Although this was a limited reported study, the histopathological changes observed in the lungs are not unexpected, in view of the alkaline nature of the solution (0.1 M (ca. 1%), pH = 11.6). However, in view of the histopathological lesions observed in animals exposed during a single 2 h period, which were almost exclusively confined to the upper respiratory tract (pharynx and larynx; Busch *et al.*, 1983), it may be concluded that changes, likely to be present in the upper respiratory tract, would have been more severe than those observed at the pulmonary level in the above described study of 3.5 months.

From these studies, it is clear that soda ash is a respiratory irritant with toxicological endpoints consistent with those found in ammonia exposure. While no quantitative relationship between soda ash exposure and lung function results have been conclusively demonstrated, concurrent exposure

[7] OECD. SIDS Dossier for Sodium Carbonate, CAS N°: 497-19-8. October 2002. p. 15.

to soda ash can be reasonably expected to be a confounding variable in assessing toxicological endpoints from ammonia exposure. Thus, the selection of a POD should qualitatively account for the fact that the no observed adverse effect level (NOAEL) derived from the Holness et al. study most likely underestimates the NOAEL from ammonia inhalation exposure alone.
TFI requests that the Hazard Identification section of the Toxicological Review include some qualitative discussion regarding potential confounding factors associated with ammonia exposure assessments in sodium carbonate production areas, including a qualitative statement that these exposures and derived NOAEL are expected to be underestimated or a conservative estimate of ammonia inhalation exposure alone.

TFI also requests that potential confounding from concurrent exposure to urea and/or sodium carbonate be factored into the selection of a defensible POD from which the Inhalation Reference Concentration is derived.

C. Inhalation Reference Concentration Is not Based on EPA Guidance and Should be Revised Upwards

The Toxicological Review incorrectly references the highest occupational exposure in the Holness et al. (1989) study, a NOAEL of 8.8 mg/m^3 (12.5 ppm)[8], as POD for RfC derivation. This NOAEL is based on presentation of data in the study of exposed workers grouped into three exposure categories – high => 12.5 ppm (8.8 mg/m^3), medium = 6.25 – 12.5 ppm (4.4 – 8.8 mg/m^3, and low = < 6.25 ppm (4.4 mg/m^3). However, a review of the actual study shows that the selection of 12.5 ppm (8.8 mg/m^3) does not reflect the "highest occupational exposure" in the Holness et al. study, but rather the lower bound estimate of exposure in the high exposure category. In the Discussion section of the study, the authors conclude that:

> "In this group of workers with airborne ***ammonia exposure levels below 50 ppm (35.4 mg/m^3), and with most exposures below 25 ppm (17.7 mg/m^3)***, no differences in symptoms, sense of smell, acute changes in lung function during exposure, or changes in baseline lung function were evident when the group of exposed workers was compared to the control workers. No relationship was demonstrated between the level of exposure to ammonia at these low levels of exposure and acute changes in lung function over the work shift. No chronic effects on lung function which could be related to the length of exposure were demonstrated."[9] (emphasis added)

The selection of a NOAEL of 8.8 mg/m^3 (12.5 ppm) does not seem to meet EPA's IRIS definition of a NOAEL:

> Definition: The highest level at which there are no biologically significant increases in the frequency severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects.

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[8] 1 ppm of ammonia is equivalent to 0.707 mg/m^3; likewise, 1 mg/m^3 of ammonia is equivalent to 1.414 ppm.
[9] Holness, DL; Purdham, JT; Nethercott, JR. (1989) Acute and chronic respiratory effects of occupational exposure to ammonia. AIHA J 50: 646-650. pp 649-650.

The rationale provided in Revised Toxicity Assessment does not conform to EPA guidance found in *A Review of the Reference Dose and Reference Concentration Processes* (hereinafter, "Review").[10] In the Review, the Technical Panel recommends that 'the data for the point of departure (POD) be evaluated on the basis of a comparison of all relevant endpoints carried through the derivation of sample reference values, with selection of the limiting value(s) as the final step rather than on the basis of selection of a single "critical study" and "critical effect."' Review, p. xvii. The Review also defines the POD in concurrence with the current IRIS definition of POD as:

> **Point of Departure**: The dose-response point that marks the beginning of a low-dose extrapolation. ***This point is most often the upper bound on an observed incidence or on an estimated incidence from a dose-response model***. Review, p. G-6 (emphasis added).

In contrast, the Revised Toxicological Assessment appears to select the POD based on an inverse logic, stating:

> The NOAEL of 8.8 mg/m^3 (12.5 ppm) from the Holness et al. (1989) study represents the low end of the high-exposure group (defined as those exposed to >8.8 mg/m^3 (12.5 ppm)) from this study. The authors state that 3 of the 12 workers in the high-exposure group were exposed to concentrations >17.7 mg/m^3 (25 ppm); therefore, the majority of workers in the high-exposure group (9 of 12) would have been exposed to ammonia concentrations in the range of 8.8–17.7 mg/m^3 (12.5 – 25 ppm). ***In the absence of more detailed exposure information, the low-end of the range was considered a reasonable estimate of the NOAEL from the Holness et al. (1989) study.*** Revised Toxicological Review, pp. 2-3 – 2-4.

Selecting the lowest exposure value from the Holness et al, study as the NOAEL value eliminates the concept of a threshold value in determining an RfC for ammonia. The study authors clearly delineate a NOAEL value of 50 ppm (35.4 mg/m^3) and an upper-bound exposure value of 25 ppm (17.7 mg/m^3). Selection of a value below 25ppm based on the Holness et al. study is not supported by the paper itself or by EPA policy for selection of a NOAEL or POD.

Utilizing EPA guidance for defining a POD provides a higher POD value for deriving the Inhalation Reference Concentration. Using the exposure values provided by the study authors gives a POD of approximately 34.8 mg/m^3 at 50 ppm ammonia and 17.4 mg/m^3 at 25 ppm. Using the calculations provided in the Revised Toxicological Review, the adjusted NOAELs ($NOAEL_{ADJ}$) for these PODs would be 12.4 mg/m^3 (17.5 ppm) and 6.21 mg/m^3 (8.8 ppm), respectively. Thus, the derived reference concentration (RfC) should be set at 1.24 mg/m^3 (1.75 ppm) or 0.62 mg/m^3 (0.88 ppm), depending on the actual value selected as the "highest occupational exposure" in the Holness et al. study and thus representing the "upper bound on an observed incidence or on an estimated incidence." Regardless, the RfC of 0.31mg/m^3 (0.44 ppm) should be revised as it is not supported by EPA guidance or the Holness et al. study.

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[10] EPA Risk Assessment Forum. *A Review of the Reference Dose and Reference Concentration Processes. EPA/630/P-02/002F. December 2002.*

TFI also recommends that the POD based on a NOAEL consistent with EPA guidance be supported by other health agencies, such as the American Conference of Governmental Industrial Hygienists (ACGIH), the National Institute for Occupational Safety and Health (NIOSH), and the Occupational Safety and Health Administration (OSHA). These agencies have set workplace exposure limits of 25 ppm (17.7 mg/m^3), 25 ppm (17.7 mg/m^3, and 50 ppm (35 mg/m^3), respectively, based on protection from irritation to the eye and respiratory tract.[11] The value of 25 ppm (17.7 mg/m3) supports the NOAEL obtained from the Holness et al study.

*TFI requests that the final Toxicity Assessment select 25 ppm (17.7 mg/m^3) as the POD for derivation of the RfC. The concentration of 25 ppm (*17.7 mg/m^3*) is justified because it is consistent with the Holness et al. study and health agency derived safe levels.*

Conclusion

TFI appreciates the opportunity to submit comments regarding the Toxicological Review of Ammonia. TFI requests that proper qualitative language be included in the final Toxicological Review reflecting the potential for confounding variables in the health effects studies considered in the inhalation hazard assessment. TFI also requests that the final Toxicological Review utilizes the NOAEL POD from the Holness et al. study that is consistent with EPA guidance to derive the RfC. Should you have any questions regarding our comments, please call me at (202) 515-2701, or email me at wfoster@tfi.org.

Sincerely yours,

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[11] ACGIH, 2001; NIOSH, 2010; OSHA, 2006)