MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Ammonium hydroxide (CAS# 1336-21-6)

FROM: Keisha Williams, Air Quality Division

DATE: January 31, 2017

SUBJECT: Screening level update for ammonium hydroxide

The initial threshold screening level (ITSL) for ammonium hydroxide is 720 µg/m^3 (1-hr averaging time) based on the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) Rule 336.1229 (2) (b) and 336.1232 (1) (a). The ITSL for ammonium hydroxide is based on the ITSL for ammonia (CAS#7664-41-7), with molecular weight adjustment, because these chemicals are expected to act via the same mechanism of action (ATSDR, 2004; MDEQ, 2017; see attached memo to file).

Using the ammonia acute ITSL, the ammonium hydroxide acute ITSL is derived as follows:

$$acute\ ITSL = 350\,\frac{\mu g}{m^3}\ x\,\frac{molecular\ weight\ of\ ammonium\ hydroxide}{molecular\ weight\ of\ ammonia}$$

$$acute\ ITSL = 350\,\frac{\mu g}{m^3}\ x\,\frac{35.06}{17.03} = 720.55\,\frac{\mu g}{m^3} \approx \mathbf{720}\,\frac{\boldsymbol{\mu g}}{\boldsymbol{m^3}}$$

References

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control
Rules, Michigan Department of Environmental Quality.

ATSDR. 2004. Toxicological Profile for Ammonia. Accessed on July 7, 2015. http://www.atsdr.cdc.gov/toxprofiles/tp126.pdf

MDEQ. *Memo from Keisha Williams to File for Ammonia (*CAS# 7664-41-7*).* January 31, 2017. Michigan Department of Environmental Quality, Air Quality Division.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Ammonia (CAS # 7664-41-7)

FROM: Keisha Williams, Air Quality Division (AQD)

DATE: January 31, 2017

SUBJECT: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for ammonia is 350 µg/m^3 (1-hour averaging time), and it is based on a controlled human study (Sundblad et al., 2004). The acute ITSL is being changed at this time, based on an updated review of the toxicological literature.

A chronic ITSL at 100 µg/m^3 (annual averaging time) was established for ammonia on February 20, 1990. This ITSL was based on the U.S. Environmental Protection Agency's (EPA's) reference concentration (RfC) for ammonia. The EPA RfC was recently re-evaluated and changed to 500 µg/m^3 (annual averaging time) (EPA, 2016a). A review of the toxicological literature showed that the recently changed EPA RfC is still the most appropriate basis for a chronic ITSL. However, the EPA RfC-derived chronic ITSL is being removed at this time, because the acute ITSL is restrictive enough to be health-protective for the effects protected the recently updated EPA RfC.

The following references or databases were searched to identify data to determine the screening level: United States (EPA's) Integrated Risk Information System (IRIS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels, International Agency for Research on Cancer (IARC) Monographs, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Status Report, EPA Superfund Provisional Peer Reviewed Toxicity Values, EPA Acute Exposure Guideline Levels (AEGLs) for Airborne Chemicals, EPA High Production Volume Database, United States Department of Labor Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs), Spacecraft Maximum Allowable Concentrations (SMACs), California Office of Environmental Health Hazard Assessments Reference Exposure Levels, Chemical Safety Program Protective Action Criteria (PAC), Texas Commission on Environmental Quality (TCEQ) Effects Screening Levels (ESLs), and European Chemicals Agency Registered Substances Dossiers.

Chronic ITSL derivation

The EPA's RfC is based on a free standing no observable adverse effect level (NOAEL) of 13.6 mg/m^3 from an occupational exposure study, and further supported by 3 other occupational exposure studies where a lowest observable adverse effect level (LOAEL) was identified (Ali, 2001; Ballal, 1998; EPA, 2016a; Holness et al., 1989; Rahman, 2007). In the Holness et al. (1989) study, workers (N=52) in the exposed group had been exposed for an average of 12.2 years. The control group consisted of 31 office and store workers. All of the participants in the study were male. The critical effects were decreased lung function and increased respiratory symptoms. The NOAEL was adjusted for exposure duration as shown in Equation 1 and an uncertainty factor (UF) of 10 was applied for intraspecies extrapolation as shown in Equation 2.

Equation 1.

$$NOAEL_{ADJ} = NOAEL\ x \frac{VE_{ho}}{VE_h}\ x \frac{days\ of\ exposure}{7\ days}$$

Where:

NOAEL = 13.6 mg/m^3

VE_{ho} = human occupational default minute volume during an 8-hr. workday = 10 m^3

VE_h = human ambient default minute volume breathed during a 24-hr. day = 20 m^3

Days of exposure = 5 days

$$NOAEL_{ADJ} = 13.6 \frac{mg}{m^3}\ x \frac{10\ m^3}{20\ m^3}\ x \frac{5\ days}{7\ days} = 4.9 \frac{mg}{m^3}$$

Equation 2.

$$RfC = \frac{NOAEL_{ADJ}}{Uncertainty\ Factors}$$

Where:

Uncertainty Factor=10 for human variability

$$RfC = \frac{4.9 \frac{mg}{m^3}}{10} = 0.49 \frac{mg}{m^3} \approx 0.5 \frac{mg}{m^3}$$

$$0.5 \frac{mg}{m^3} x\ 10^3 \frac{\mu g}{mg} = 500\ \frac{\mu g}{m^3}$$

While a number of agencies have derived health benchmarks for chronic exposure to ammonia, the Holness et al. (1989) study is often identified as the key study (Table 1). Differences in benchmark values reside within the point of departure (POD), application of different uncertainty factors, modifying factors and exposure duration adjustment factors (Table 1).

Table 1. Health Benchmark Values for Chronic Exposure to Ammonia based on the Holness (1989) et al. study

Agency Reference	Benchmark Value and Corresponding Derivation Factors
ATSDR, 2004	MRL=70 µg/m^3 POD=6.4 mg/m^3 POD is the time weighted average (TWA) of the overall exposed group ADJ=8 hours/24 hours x 5 days/7days UF=10 for intraspecies variation Modifying Factor=3 for lack of reproduction and development studies
EPA, 2016	RfC=500 µg/m^3 POD=13.6 mg/m^3 POD is the estimate of 95% lower confidence bound of the mean exposure concentration in the high exposure group Duration Adjustment Factor (ADJ)=10 m^3/20 m^3 x 5 days/7 days Uncertainty Factor (UF)=10 for intraspecies variation
OEHHA, 2008a*	REL=200 µg/m^3 POD=6.4 mg/m^3 POD is the TWA of the overall exposed group ADJ=10 m^3/20 m^3 x 5 days/7 days UFs=10 for intraspecies variation
TCEQ, 2016**	Chronic Reference Value (ReV)=320 µg/m^3 POD=8.7 mg/m^3 POD is the TWA immediately below the high exposure group ADJ=10 m^3/20 m^3 x 5 days/7 days UF=10 for intraspecies variation

*The last chronic REL revision occurred in 2000.

**The original derivation appears to have occurred in 2014 based on the “Revision History” section in the Development Support Document.

The current EPA RfC value would be utilized by MDEQ-AQD for setting a chronic ITSL for the following reasons:

1) It is the most recent peer-reviewed health benchmark evaluation for ammonia. With this, it has a comprehensive review of the toxicological literature.

2) Although ATSDR (2004) applied a modifying factor of 3, THE EPA (2016a) provides adequate reasoning for why a modifying factor was not used for the lack of reproductive and developmental studies. Their justification for not using an uncertainty factor for the lack of reproductive and developmental studies is as follows:

"The inhalation ammonia database includes one limited study of reproductive and developmental toxicity in pigs that did not examine a complete set of reproductive or developmental endpoints. Normally, confidence in a database lacking reproductive and developmental toxicity studies is considered to be lower… 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 effects at the point of contact (i.e., respiratory system) could directly or indirectly impact tissues or organs distal to the point of contact."

3) The EPA provided justifiable reasoning for the POD value it used. Some agencies use the time weighted average of the overall exposed group, but more recent derivation methods use an exposure concentration estimate that is specific to the NOAEL for the high exposure group from the study (EPA, 2016a; TCEQ, 2016). In the supplemental information for the IRIS toxicological profile review, the appropriateness of the POD was further addressed (EPA, 2016b), in which the EPA stated,

"…the frequency distribution information provided in Holness et al. (1989) was used to estimate the parameters of the lognormal distribution that best fit the data…Assuming a lognormal distribution for the measured concentrations, EPA estimated the mean concentration for the high-exposure group (17.9 mg/m^3). The 95% lower confidence bound on the mean exposure concentration, or 13.6 mg/m^3, was used as the POD for deriving the RfC to reflect the statistical uncertainty around the estimate of the mean."

Given the attempt to use a more conservative estimate of the mean for the high exposure group, the POD used by EPA is appropriate.

Acute ITSL derivation

As shown in Table 2, there are several acute health benchmarks for ammonia. The majority of these health benchmarks are derived from key studies that are controlled human studies. However the lowest LOAEL (and resulting POD) has been identified in the Sundblad et al. (2004) study.

Table 2. Health Benchmarks for Acute Exposure to Ammonia

Agency Reference	Benchmark Value, and Point of Departure
ACGIH, 2001	TLV=35 ppm (24 mg/m^3), 15 minute averaging and 25 ppm (17 mg/m^3), 8-hr averaging POD=unknown
ATSDR, 2004	MRL=1.7 ppm (≈1200 µg/m^3), 24-hr averaging POD=LOAEL of 50 ppm (≈35 mg/m^3) (Verberk, 1977)
DOE, 2016	PAC-1=30 ppm (≈21 mg/m^3), 1 hr averaging POD=LOAEL of 21 mg/m^3 (MacEwen et al., 1970) NOTE: values adopted from AGEL values for 1 hr averaging
NIOSH, 2016	REL=27 mg/m^3, 15 minute averaging and 18 mg/m^3, 8-hr averaging POD=unknown
National Research Council (NRC), 2007	AEGL=30 ppm (≈21 mg/m^3), for both 1-hr and 8-hr averaging* POD=LOAEL of 21 mg/m^3 (MacEwen et al., 1970)
NRC, 2008	SMACs=30 ppm (≈21 mg/m^3), 1-hr averaging and 20 ppm (≈14 mg/m^3), 24-hr averaging POD for 1-hr averaging time SMAC=LOAEL of 30 ppm (MacEwen et al., 1970) POD for 8-hr averaging time SMAC=LOAEL of 20 ppm (Vigliani and Zurlo 1955; Furguson et al. 1977)
OEHHA, 2008b**	REL=3200 µg/m^3, 1-hr averaging POD=BC05** of 13.6 ppm (≈9.5 mg/m^3) (Industrial Biotest Laboratories, 1973; MacEwen et al., 1970; Silverman et al., 1949; Verberk, 1977)
OSHA, 2012	PEL=35 mg/m^3 POD=unknown
TCEQ, 2016***	Acute ReV=590 µg/m^3 POD=LOAEL of 5 ppm (≈3.5 mg/m^3) (Sundblad et al., 2004)

*The AEGL derivation documentation states that “The same value is proposed for 5, 30, 60, 240, and 480 min, because any effects that occur are not expected to become more severe with duration of exposure because adaptation occurs during prolonged exposure.”

**The last acute REL revision occurred in 1999.

***BC_{05}=the 95% lower confidence limit of the concentration expected to produce a response rate of 5%.

Since the TCEQ identified the study with the LOAEL (Table 2; Sundblad et al., 2004), this was the primary study considered for ITSL derivation. TCEQ utilized a total uncertainty factor of 6, 3 for intraspecies extrapolation and 2 for LOAEL to NOAEL extrapolation (TCEQ, 2016).

In the Sundblad et al. (2004) study, twelve healthy volunteers (7 women and 5 men) were randomly exposed to sham or ammonia on 3 separate occasions for 3 hours each time. The ammonia group was exposed to 5 and 25 ppm ammonia. For half of the

3-hour exposure, the volunteers exercised on a stationary bicycle. Lung spirometry, methacholine challenge provocation testing, inflammatory cell count and complement factor C3 and C3b in peripheral blood, cytokines in nasal lavage, exhaled nitric oxide, and self-reported respiratory symptoms were evaluated. Statistical analysis was performed, and significant differences were considered when "a p-value was < 0.05 (or <0.01 when multiple comparisons were performed." A dose-dependent relationship was identified for respiratory irritation. The low exposure group (5 ppm) is regarded as a LOAEL for slight severity. No other significant differences were observed based on the ammonia exposure as compared to the sham exposure.

This was a well conducted human study, and is suitable for application to ITSL derivation. An acute ITSL is derived as shown in Equation 3.

Equation 3.

$$Acute\ ITSL = \frac{LOAEL}{UFs}$$

Where:

LOAEL=3.5 mg/m^3
UFs=10 from a combination of 3 for human variability (OEHHA, 2008) and 3 for a LOAEL to NOAEL extrapolation for minimal adverse effects of irritation.

$$Acute\ ITSL = \frac{3.5\,\frac{mg}{m^3}}{10}\ x\ 10^3\,\frac{\mu g}{mg} = 350\,\frac{\mu g}{m^3}, 1\ hour\ averaging$$

A factor of 3 was used for human variability based on guidance that indicates "for direct-acting chemicals whose site of action is the point of first contact…√10 may be sufficient" (OEHHA, 2008c). Similarly, for their derivation of an acute health benchmark for ammonia, an UF of 3 for human variability was used by both the TCEQ and OEHHA (OEHHA, 2008b; TCEQ, 2016).

It may be noted that an alternative, similar acute ITSL could be derived utilizing MDEQ-AQD Rule 336.1232 (1) (c) based on the ACGIH (2001) TLV-short-term exposure limit of 24 mg/m^3, which would result in a potential ITSL equal to 240 µg/m^3 (1 hour averaging). The chosen approach using the Sundblad et al. (2004) study has a more clear basis and was therefore preferred.

Again, it should be noted that this acute ITSL is more stringent than the most appropriate potential chronic ITSL (500 µg/m^3, annual averaging). Furthermore, both EPA (NRC, 2007) and ACGIH (2001) have noted that adaption may occur with prolonged exposure. This may explain the unusual situation of a lower POD and benchmark for acute exposure than for chronic.

The ITSL for ammonia is 350 µg/m^3 (1-hour averaging time).

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