Addendum to the
Acceptable Ambient Level (AAL) Recommendation for Methyl Bromide

Prepared by the

Division of Air Quality
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Submitted to

The Secretaries' Science Advisory Board

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North Carolina Department of Environmental Quality (DEQ)
Division of Air Quality (DAQ)
November 30, 2018, Revised December 5, 2018

DAQ's Charge to the Secretaries' Science Advisory Board for Methyl Bromide

The Division of Air Quality (DAQ) is requesting the Secretaries' Science Advisory Board (SAB) review and affirm the IRIS chronic RfC as the appropriate basis for the Acceptable Ambient Level (AAL) and the 24-hour chronic toxicant averaging time to protect the general public from inhalation exposures at the property line and beyond from methyl bromide released from a log fumigation operation.

Additional Information Requested by the Secretaries' Science Advisory Board

Following the DAQ methyl bromide AAL presentation on October 22, 2018 the SAB requested additional information to complete their review and finalize their recommendations. Those requests included additional information on the following:

- Occupational exposure levels and health values
- Acute exposure health values
- Methods utilized by the U.S. EPA IRIS program and the ATSDR to extrapolate rodent to human inhalation exposure levels in their critical studies that served as the basis of each agencies' chronic inhalation health values

Occupational Exposure Levels and Health Values

The NC DEQ does not have purview over occupational exposure levels. The DAQ is requesting input on inhalation exposure health values to protect the general public at the property line of log fumigation operations. The DEQ has requested Industrial Hygiene specialists with the N.C. DHHS Division of Public Health (DPH) to provide to the SAB a review occupational health values. Although the USDA guidelines for the use of methyl bromide requires fumigation operators to monitor methyl bromide onsite during fumigation and aeration processes, no specific datasets have been provided to DEQ.

Acute Inhalation Exposure Levels for Methyl Bromide

The DAQ has confirmed that neither the U.S. Environmental Protection Agency (EPA), the EPA's Integrated Risk Information System (IRIS) program or the Agency for Toxic Substances and Disease Registry (ATSDR) provide acute health values protective of the general public for methyl bromide inhalation exposures. Acute inhalation values that may exist for occupational exposures are developed for a healthy adult working population and are not developed to be protective of the general population which includes infants, children, the elderly and persons that may have pre-existing health conditions that increase their susceptibility to adverse inhalation exposures associated with specific contaminants (ATSDR 1992).

ATSDR had previously provided an acute inhalation Minimal Risk Level (MRL)[1] for methyl bromide[2] in their 1992 review (ATSDR 1992), but the acute MRL was removed with the release of their 2018 draft methyl bromide review update (ATSDR 2018). In their 2018 draft review update ATSDR noted they considered the available toxicity database for methyl bromide to be inadequate to develop an acute inhalation point of departure (POD) and an acute-duration inhalation MRL. ATSDR defines an acute exposure duration as that occurring up to 14 days[3]. They reference the NTP 1992 study as having identified the lowest duration-adjusted LOAEL, but suggest there is considerable uncertainty with this value. ATSDR noted the NTP study (1992) reported "*neurological signs including trembling, jumpiness, and paralysis were observed in all groups but were most pronounced in the three highest dose groups (50, 100, 200 ppm)*", but noted NTP did not include incidence data for these effects and it is unclear whether any or all of the effects were observed at the lowest concentration tested. ATSDR does affirm that neurotoxicity is the most sensitive effect observed in animal studies.

In addition to the uncertainty noted above, ATSDR (2018) also notes acute inhalation health values may not be protective when the adverse effects of an exposure may be delayed or are or result from repeated exposures, such as hypersensitivity reactions, asthma, or chronic bronchitis. This is certainly relevant to the adverse effects associated with the inhalation of methyl bromide since it is odorless, colorless and tasteless, and it is well documented that there may be a delay in the development of the negative effects associated with both low-level and acute inhalation exposures (ATSDR 1992, ATSDR 2018, Garnier et al., 1996, IRIS 1992). The steep dose-response curve noted for methyl bromide inhalation effects also likely contributes to the uncertainty in developing an acute inhalation exposure level protective for the general public (ASTDR 2018).

In developing their recommendations for the methyl bromide AAL the DAQ applied the most health-protective inhalation exposure level intended to be protective of the general public including sensitive sub-groups, the IRIS chronic RfC, and a 24-hour averaging time. The scientific basis for DAQ's AAL recommendation includes:

- The IRIS chronic RfC[4] is the most health-protective final value intended to be protective of the general public.
- The 24-hour averaging time reflects the application of the chronic RfC as the daily continuous exposure concentration that over a lifetime of exposure is expected to not result in deleterious health effects.
- The 24-hour averaging time reflects the concerns associated with the:
    - rapid uptake and distribution of methyl bromide following inhalation exposures,
    - lack of odor, taste or color to alert persons to a methyl bromide exposure, and

[1] A Minimal Risk Level (MRL) is an ATSDR estimate of daily human exposure to a hazardous substance at or below which that substance is unlikely to pose a measurable risk of harmful (adverse), noncancerous effects. MRLs are calculated for a route of exposure (inhalation or oral) over a specified time period (acute, intermediate, or chronic). Source: https://www.atsdr.cdc.gov/glossary.html

[2] The removed ATSDR acute inhalation MRL was 0.05 ppm methyl bromide, based on a neurological endpoint (ATSDR 1992). 0.05 ppm = 190 µg/m^3. This value was not included with the 2018 draft update.

[3] ATSDR acute exposure duration definition source: https://www.atsdr.cdc.gov/glossary.html

[4] The EPA defines a chronic reference concentration (RfC) as an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure for a chronic duration (up to a lifetime) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Source: https://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/home.do

- concerns associated with segments of the human population to have increased susceptibility to neurotoxic effects due to genetic polymorphisms that do not exist in the critical study test species (rats) and thus was not captured in the RfC development, and the lack of data to quantify this increased human sensitivity.

Method of Extrapolation of Animal-to-Human Inhalation Exposures in the Derivation of the IRIS Chronic RfC and the ATSDR Chronic MRL

Both the current IRIS chronic inhalation RfC and the ATSDR chronic MRL were developed from the same National Institute of Public Health and Environmental Hygiene of the Netherlands rat studies (Reuzel et al., 1987, 1991) and identified the same critical effect, degenerative effects to the olfactory epithelium. Table 1 provides parameter details of the critical studies and the data analysis and extrapolations intrinsic in the development of the IRIS and ATSDR chronic inhalation health values. The following address the SAB's questions regarding the development of the IRIS and ATSDR chronic health values:

- Both IRIS (1992) and ATSDR (2018) mathematically converted the rodent exposure scenarios (6-hours per day for 5-days per week) to continuous exposure levels (24-hour per day, 7-day per week)
- Both ultimately used a LOAEL for the point of departure (POD). ATSDR initially applied Benchmark Dose (BMD) modeling to the data, but the resulting benchmark response level was greater than the POD using the LOAEL approach.
- Both used the Regional Gas Dose Ration (RGDR) approach to extrapolate animal exposure levels to human-equivalent concentrations (HEC) and both referenced the current U.S. EPA documents describing the RGDR methodology at the time of their reviews.
- Differences in the RGDR extrapolation parameters utilized are indicated, likely a result of the modifications resulting from the length of time between the two reviews. The RGDR parameters and references are noted in the Table supplemental information.
- Both reviews applied the same uncertainty factors (UFs) to the POD, while IRIS rounded their calculated composite UF = 90 to 100 and ATSDR did not, using the calculated composite UF = 90.

Both IRIS and ATSDR rounded the final chronic inhalation value to one significant figure. If carried to two significant figures, the calculated $LOAEL_{HEC}$ for the two studies are 0.48 mg/m^3 (IRIS) and 0.54 mg/m^3 (ATSDR), with the difference attributable to slight differences in the RGDR values and the composite Uncertainty Factors.

References

ATSDR 1992. Toxicological Profile for Bromomethane. September 1992. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service, U.S. Department of Health & Human Services, Atlanta, GA. Accessed at: https://www.atsdr.cdc.gov/substances/index.asp

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Garnier, R., M. Rambourg-Schepens, A. Müller and E. Hallier. 1996. Glutathione transferase activity and formation of macromolecular adducts in two cases of acute methyl bromide poisoning. Occup. Environ. Med. 53: 211-215.

IRIS 1992. Bromomethane Integrated Risk Information System (IRIS) Chemical Assessment Summary. U.S. Environmental Protection Agency, National Center for Environmental Assessment, Washington, D.C. Last updated: April 1, 1992. Accessed at: https://www.epa.gov/iris

Reuzel, P.G.J., C.F. Kuper, H.C. Dreef-van der Meulen and V.M.H. Hollanders. 1987. Chronic (29-month) inhalation toxicity and carcinogenicity study of methyl bromide in rats. Report No. V86.469/221044. Netherlands Organization for Applied Scientific Research, Division for Nutrition and Food Research, TNO. EPA/OTS Document No. 86-8700001202.

Reuzel PG, Dreef-van der Meulen HC, Hollanders VM, et al. 1991. Chronic inhalation toxicity and carcinogenicity study of methyl bromide in Wistar rats. Food Chem Toxicol 29(1):31-39.

Table 1. Summary of Critical Study Specifications, Methyl Bromide Chronic RfC (IRIS 1992) and ATSDR Draft Chronic MRL (2018)

Parameter	**IRIS Chronic RfC (1992)**	**ATSDR Chronic MRL (Draft 2018)**
Study reference	Reuzel et al., 1987, 1991 - National Institute of Public Health and Environmental Hygiene of the Netherlands	Reuzel et al., 1987, 1991 - National Institute of Public Health and Environmental Hygiene of the Netherlands
Test species	50 male, 60 female Wistar rats per treatment	50 male, 60 female Wistar rats per treatment
Test concentrations, as 98.8% methyl bromide	0, 11.7, 117, 350 mg/m^3 (= **3, 30, 90 ppm**) (verified every 30 minutes by GC)	0, 11.7, 117, 350 mg/m^3 (= **3.1, 29.6, 89.1 ppm**) (verified every 30 minutes by GC)
Study exposure scenario	Inhalation, 6 hours per day, 5 days per week	Inhalation, 6 hours per day, 5 days per week
Study length	29 months	29 months
Observations	Body Weight, Hematology, Clinical Chemistry, Urinalyses, 11 Organ Weights and Necropsy, Histological exam of 36 tissues, including the nose, trachea, lungs, heart, brain, and adrenal glands	Body Weight, Hematology, Clinical Chemistry, Urinalyses, 11 Organ Weights and Necropsy, Histological exam of 36 tissues, including the nose, trachea, lungs, heart, brain, and adrenal glands
Identified target organs	Nose, heart, esophagus, forestomach	Not noted
Critical effect description	Degenerative and proliferative lesions of the olfactory epithelium; **Males and Females**	Basal cell hyperplasia the olfactory epithelium; **Males and Females**
$LOAEL_{rat}$	11.7 mg/m^3 "for nasal effects" (3.01 ppm)	12.0 mg/m^3 (3.1 ppm)
Continuous exposure adjustment	$LOAEL_{rat}$(Adjusted) = 2.08 mg/m^3 (Adjusted exposure concentrations: 2.08, 20.9, 62.5 mg/m^3)	$LOAEL_{rat}$(Adjusted) = 0.55 ppm (2.1 mg/m3)
BMD modeling	Not applied	Calculated $BMCL_{10}$ = Male, 14.2 mg/m^3 (3.65 ppm) Female, 16.0 mg/m^3 (4.13 ppm); **$BMCL_{10}$ value not used - Higher than empirical 3.1 ppm LOAEL**
Human Equivalent Concentration (HEC) extrapolation method	Regional Gas Dose Ratio (RGDR), Extrathoracic region **RGDR = 0.23 F**	Regional Gas Dose Ratio (RGDR), Extrathoracic region **RGDR = 0.280 M, 0.200 F**
$LOAEL_{HEC}$	$LOAEL_{HEC}$ = 0.48 mg/m^3 (0.12 ppm)	**Mean $LOAEL_{HEC}$ = 0.512 mg/m^3** (Mean = 0.132 ppm) (0.598 M, 0.427 mg/m^3 F; or, 0.154 M, 0.110 F ppm)
Uncertainty Factors	**Composite UF = 100**; UF 3 - LOAEL for mild effects, UF 3 - interspecies extrapolation w/ dosimetric adjustments, UF 10 – human variability UF (100 = √10 x √10 x 10)	**Composite UF = 90**; UF 3 – minimal LOAEL, UF 3 - interspecies extrapolation w/ dosimetric adjustments, UF 10 – human variability (UF 90 = 3 x 3 x 10)
Chronic Inhalation Value	**RfC = 0.005 mg/m^3** (0.0048 mg/m^3; or, 0.0012 ppm rounded)	**Calculated MRL = 0.005 mg/m^3** (0.0014 ppm; or, 0.0054 mg/m^3 rounded) **Presented as 0.001 ppm Provisional MRL**
Confidence in toxicity value	Study – Medium (no NOAEL) Database – High RfC - High	Not noted

UF = Uncertainty Factor

RGDR = Regional gas dose ratio is the ratio of the inhalation volume to surface area for animals and humans used to convert animal exposure concentrations to human-equivalent concentrations (HECs).

$$RGDR_r = (V_E / SA_r)_A / (V_E / SA_r)_H$$

where:

r = specific respiratory tract region
V_E = ventilation rate (L/min)
SA_r = surface area of exposed respiratory tract region (cm^2)
A = animal
H = human

Reference: 2012 EPA, *Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment, EPA/600/R-12/044*RGDR calculation, IRIS (1992) –

IRIS (1992) – Rat LOAEL extrapolation to Human LOAEL using RGDR model -

$$RGDR(ET) = (MV_a/S_a)/(MV_h/S_h) = 0.23$$
$$LOAEL(HEC) = LOAEL(ADJ) \times RGDR = 0.48\ mg/m^3$$

where:

MV_a (chronic, Wistar rats) = 0.30 m^3/day
MV_h = 20 m^3/day
S_a(ET) = 11.6 cm^2
S_h(ET) = 177 cm^2
ET = extrathoracic region

IRIS (1992) reference: "*Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994)."*

ATSDR (Draft 2018) - RGDR(ET) male rats = 0.280; female rats = 0.200

$$RGDR_{ET} = (V_E/SA_{ET})_{Rat} / (V_E/SA_{ET})_{Human}$$

where:

V_E = ventilation rate, m^3/day: humans 20; male Wistar rats 0.42; female Wistar rats 0.30 (Reference: EPA 1988b)

SA_{ET} = surface area of extrathoracic region of the respiratory tract, cm^2: humans 200; male and female rats 15 (Reference: EPA 1994b)

References:

EPA 1988b. Recommendations for and documentations of biological values for use in risk assessment. Cincinnati, OH: U.S. Environmental Protection Agency.

EPA 1994b. Methods for derivation of inhalation reference concentrations and applications of inhalation dosimetry. Washington, DC: U.S. Environmental Protection Agency. EPA600890066F.

Table 1 notes:

LOAEL = lowest observed adverse effect level (the lowest exposure concentration indicating a statistically-significant adverse effect)
NOAEL = no observed adverse effect level (highest exposure concentration with no statistically-significant observed adverse effect level)
MRL = Minimal Risk Level
RfC = reference concentration
UF = uncertainty factor

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