Acceptable Ambient Level (AAL) Recommendation for Methyl Bromide

Prepared by the

Division of Air Quality
North Carolina Department of Environmental Quality

Submitted to

The Secretaries' Science Advisory Board

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North Carolina Department of Environmental Quality (DEQ)
Division of Air Quality (DAQ)
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DAQ's Charge to the Secretaries' Science Advisory Board for Methyl Bromide

Methyl bromide is a Clean Air Act federally listed Hazardous Air Pollutant (HAP) used in North Carolina as a pesticide to fumigate whole logs. The log export market primarily requires either methyl bromide fumigation or debarking. Recently there has been an increase in the number of permit applications and inquiries from entities interested in using methyl bromide for log fumigation. The fumigation process is done in sealed containers generally with a treatment period of 60 to 72 hours, followed by degassing the container to the atmosphere. None of the current log fumigation operations in North Carolina capture the fumigant. All existing facilities are limited via their air quality permit to using ten tons per year of methyl bromide, but some may use all 10 tons in a matter of a few months if demand and logistics allow. Additionally, DAQ has received recent permit applications requesting up to 140 tons per year of emissions. Some of the facilities are within a few hundred feet of residential communities. Although listed as a HAP, there is no specific federal regulation to protect the public from log fumigation related methyl bromide releases. Similarly, since methyl bromide is not listed as a North Carolina Toxic Air Pollutant (TAP), there are no state air quality regulations.

The respiratory tract and the nervous system are the most sensitive targets to methyl bromide inhalation exposures, and adverse effects may not be evident until several hours after exposure. Chronic exposures in humans are associated with headache, weakness and neurological effects including muscle ache, fatigue and dizziness. Similar effects have been observed in chronic inhalation exposures to laboratory animals. Acute inhalation exposure effects reported in humans include olfactory and respiratory tissue irritation and damage, lung edema, tremors, seizures, neurotoxicity, kidney and liver damage and death.

The DEQ Division of Air Quality has identified the U.S. EPA IRIS program chronic inhalation reference concentration (RfC) as the appropriate value to serve as the basis for developing an Acceptable Ambient Level (AAL) to protect the health of all persons that may live or work in areas subject to airborne releases of methyl bromide from log fumigation operations. DAQ is proposing a 24-hour averaging time for the methyl bromide AAL to reflect potential chronic effects, the rapid adsorption and distribution of methyl bromide throughout the body including to sensitive target organs following inhalation exposures, the potential for large segments of the human population to have increased sensitivity to neurotoxic effects that was not captured by animal studies used to develop the RfC, and due to the potential for delayed onset of adverse effects following exposures.

DAQ is requesting the Secretaries' Science Advisory Board review and affirm the IRIS RfC as the appropriate basis for the AAL and the 24-hour chronic toxicant averaging time. The following text summarizes the current health-related science to support DAQ's proposal for the methyl bromide AAL.

Introduction

Methyl bromide (also known as bromomethane or monobromomethane) is a fumigant that has historically been widely used to control pests in soil, fresh and dry agricultural products, and exports including logs. Due to restrictions, it is now limited to quarantine and pre-shipment uses and minimal critical use exemptions as approved through EPA rulemaking and by parties to the Montreal Protocol[1]. The acute and chronic health effects associated with methyl bromide inhalation exposure have been well documented (IRIS 1992, PPRTC 2007, ATSDR 1992, ATSDR 2018). Inhalation of low levels of methyl bromide causes headaches, weakness and nausea (ATSDR 1995). Breathing higher concentrations or over longer periods may cause lung edema, muscle tremors, kidney and liver damage and potentially mortality. Neurological and respiratory effects are of greatest concern.

To reduce potential harmful exposures to residents and bystanders near adjacent log fumigation operations, the DAQ is proposing 5 µg/m^3 methyl bromide (0.005 mg/m^3 or 1 ppbv) in air as the 24-hour N.C. Acceptable Ambient Level (AAL). The proposed AAL is set at the chronic reference concentration (RfC) established by the United States Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) program. Persons living adjacent to log fumigation operations may be exposed to fumigants released to the ambient air under exposure frequency and duration conditions that reflect the EPA chronic exposure definition.

The DAQ identifies the IRIS chronic RfC as the most appropriate and scientifically valid human health value to provide protection for the long-term health of persons in North Carolina, including sensitive subpopulations that may live adjacent to a log fumigation facility that repeatedly releases methyl bromide to the ambient air during operations. Sensitive subpopulations to methyl bromide exposures include infants, children, the elderly and those persons with pre-existing health conditions that may pre-dispose them to the adverse health effects associated with the inhalation of methyl bromide. This document addresses only human health concerns associated with the potential exposure to methyl bromide in the ambient air and does not address concerns associated with the potential for ecological receptors.

Physical and Chemical Properties of Methyl Bromide

Chemical name: Methyl bromide (MeBr), Bromomethane, Monobromomethane
CAS Registry Number: 74-83-9
Molecular formula: CH_3Br
Molecular weight: 94.94 g/mole
Boling Point: 3.5 °C
Water solubility: 15,200 mg/L

[1] Information available at: *https://www.state.gov/e/oes/eqt/chemicalpollution/83007.htm*

Solubility in other solvents: Soluble in alcohol, chloroform, ether, carbon disulfide, carbon tetrachloride, benzene
Vapor pressure: 1620 mm Hg (20 °C)
Octanol/Water partition coefficient: 1.19 log K_{ow}
Conversion factor: 1 ppbv = 3.9 µg/m^3
1 µg/m^3 = 0.26 ppbv

Under normal environmental temperatures and pressures methyl bromide is a colorless odorless gas. The degradation half-life of methyl bromide is estimated at approximately 11 months in air and 1-month in groundwater (ATSDR 1992).

USEPA IRIS Program Review of Human Health Effects Associated with the Inhalation of Methyl Bromide

Derivation of the IRIS Chronic Reference Concentration for Methyl Bromide

The EPA Integrated Risk Information System (IRIS)[2] program characterizes the health hazards of chemicals found in the environment. IRIS assessments are the preferred source of toxicity information used by the EPA and are an important source of toxicity information used by state and local health agencies, other federal agencies, and international health organizations (IRIS 2018). The EPA IRIS health values undergo extensive internal EPA and external technical and public peer review. IRIS health values are developed following a comprehensive review of all validated human and animal studies and are calculated using the most current human health risk assessment methods. The N.C. Department of Environmental Quality references the IRIS program as its initial source of health-based toxicity values for human health risk assessment.

The IRIS program set a human population chronic inhalation reference concentration (RfC) for methyl bromide in their 1992 (IRIS) assessment (Appendix A) based on laboratory animal inhalation exposure studies. The EPA defines a human chronic exposure as a repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans (IRIS 2011). IRIS chronic reference concentrations are set at exposure levels to protect the most sensitive subpopulation from daily exposures that may result in an adverse health effects. Sensitive populations may include infants, children, the elderly, or persons with pre-existing conditions that may result in increased susceptibility to inhalation hazards.

The EPA defines a reference concentration (RfC) as "*an estimate with uncertainty spanning perhaps an order of magnitude of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime*" (IRIS 1992). The IRIS program methyl bromide chronic inhalation RfC is 5 µg/m^3 (0.005 mg/m^3 or 1 ppbv). EPA defines a chronic human exposure as a repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans.

The non-cancer critical effect that is the basis of the IRIS methyl bromide chronic RfC is degenerative and proliferative lesions of the olfactory epithelium in the nasal cavity observed in a 29-month rat study

[2] Accessible at: *https://www.epa.gov/iris*

performed by the National Institute of Public Health and Environmental Hygiene of the Netherlands (Reuzel et al., 1987, 1991). The chronic RfC was calculated from the rat study inhalation concentration that exhibited statistically-significant adverse effects to the study animals at the lowest-observed adverse effect level (LOAEL). Adverse effects were observed at all exposure concentrations, therefore a no-observed adverse effect level (NOAEL) was not available in this study. When available, a NOAEL is preferred to a LOAEL as the basis for calculation of IRIS RfCs. The principle study parameters are provided in Table 1. Adverse health effects observed in the principle rat study are listed in Table 2.

To better define inhalation concentrations that are expected to not pose adverse health hazards to humans, the IRIS reviewers adjusted the 6-hour/day and 5-day/week animal study LOAEL to 24-hour/day and 7-day/week LOAEL concentration, followed by extrapolation of the rodent LOAEL ($LOAEL_{rat}$) to a human-equivalent concentration (HEC) LOAEL ($LOAEL_{HEC}$). In translating animal toxicity studies to health values protective of humans, humans are assumed to be more sensitive than animals. It is recognized that there is always a degree of scientific uncertainty in risk assessment. To acknowledge this, risk assessment errs on the side of protection. To set a margin-of-safety intended to be protective of sensitive human subpopulations the adverse health effect concentration identified in the animal study was translated to a human exposure concentration (the RfC) after application of uncertainty factors. The methyl bromide RfC includes default EPA uncertainty factors (UF) of 10 for a LOAEL to NOAEL adjustment (UF_L) and 10 for human population sensitivity variability (UF_H) ($\sum UF = 10 \times 10 = 100$). The IRIS assessment notes "high" confidence in the RfC. The RfC calculation, including the HEC adjustment and the applied UFs, followed standard IRIS and EPA protocols.

$$5\ \mu g/m^3 \text{ Human Chronic Inhalation RfC} = 480\ \mu g/m^3\ LOAEL_{HEC} / (10\ UF_L \times 10\ UF_H)$$

Studies Evaluating Effects Associated with the Inhalation of Methyl Bromide

Human Health Effects Reported for Methyl Bromide Inhalation Exposures

There are limited studies evaluating long-term methyl bromide inhalation exposures to humans. Most reports are of accidental or intentional acute exposures, or occupational exposures involving a healthy worker population. Studies evaluating occupational exposures suffer from a number of limitations and uncertainties. Occupational studies relate effects observed in a healthy adult working population and may not be representative of the effects and effect-levels that would be observed for the general population that includes potentially-sensitive subpopulations. It is also difficult to define the exposure concentrations and eliminate confounding exposures in occupational studies. ATSDR (1992) suggested that while there were no studies at the time to evaluate the increased susceptibility of human subpopulations to adverse effects associated with the inhalation of methyl bromide, it would be expected that the young, the elderly, and people with lung, kidney, or neurological disease might be more readily affected than healthy adults. ATSDR also noted that animal studies indicate species differences in sensitivity and for some species gender-related sensitivity differences.

Methyl bromide is acutely toxic to humans (ATSDR 1992). IRIS (1992) identifies the most common signs of acute methyl bromide exposures in humans are neurotoxic in nature and include headache, dizziness, fainting, apathy, weakness, tiredness, giddiness, delirium, stupor, psychosis, loss of memory, mental

confusion, speech impairment, visual effects, limb numbness, tremors, muscle twitching, paralysis, ataxia[3], seizures, convulsions, and unconscious.

Reports of neurological effects from occupational inhalation exposures reported in IRIS (1992) include the Anger et al. (1986) study that evaluated a fumigator population using both methyl bromide and sulfuryl fluoride. The study included workers exposed for at least 1 year and that had fumigated a field within the last 50 days. Indications of mild neurological effects associated with methyl bromide in the fumigant-exposed group were reported. Workers in the exposed group did not perform as well as the control group (control group = no exposure within the last 50 days) on behavioral tests including tests of cognitive function, reflexes, and sensory and visual effects. Another study (Herzstein and Cullen, 1990) reported in IRIS (1992) noted delayed on-set of some effects after four unprotected nursery workers were exposed to 98% methyl bromide and 2% chloropicrin following removal of polyethylene sheets covering fumigated soil. The following day all noted fatigue and lightheadedness. Three of the four workers reported severe coughing, chest tightness, nausea, vomiting, headaches, and tremulousness[4] during the night, along with ataxia and tremor. At 3-weeks post exposure two of the workers continued to experience reduced manual dexterity and paresthesia[5].

Studies Indicating Increased Neurotoxic Susceptibility in Segments of the Human Population

The EPA Superfund Program's 2007 *Provisional Peer Reviewed Toxicity Values for Bromomethane* (PPRTV 2007) includes an updated literature review (1989 through July 2001) relative to the IRIS (1992) methyl bromide assessment. The PPRTV review summarizes studies that identify a potentially sensitive human subpopulation (Schröder et al., 1992; Garnier et al., 1996). The human subpopulation sensitivity was associated with the Phase II glutathione (GSH) metabolism system and the glutathione-S-transferase (GST) enzyme that conjugates methyl bromide with GSH. The GSH pathway generates methyl bromide metabolites reported to have more severe neurotoxic effects than the parent compound. These studies report the GST conjugating enzymes may be inactive in some human subpopulations, while other subpopulations will have lower or higher levels of the enzyme. An investigation of two accidently exposed fumigation workers (Garnier et al., 1996) reported a delayed onset of more severe neurotoxic symptoms in a worker identified with normal GST conjugating enzyme activity, while the enzyme was not detectable in the worker with the less severe effects. Both workers experienced nausea, vomiting, headaches, and dizziness at the time of the exposure. Two hours post exposure one of the workers that was later identified as having normal GST conjugating enzyme activity, experienced severe myoclonic seizures[6] and later developed "very severe poisoning". The other worker was reported to have developed only "mild neurotoxic symptoms". No detectable GST conjugating enzyme activity was identified in the worker with the mild symptoms. The authors suggested the severity of neurotoxic

[3] Ataxia is the loss of muscle control or coordination of voluntary movements, potentially affecting speech, eye movement and swallowing. Source: https://www.mayoclinic.org/

[4] Tremulousness is characterized by trembling or tremors. Source: *https://www.merriam-webster.com/dictionary/tremulous*

[5] Paresthesia is defined as a sensation of pricking, tingling, or creeping on the skin usually associated with injury or irritation of a sensory nerve or nerve root. Source: *https://www.merriam-webster.com/dictionary/paresthesia*

[6] A myoclonic seizure is a seizure characterized by jerking (myoclonic) movements of a muscle or muscle group, without loss of consciousness. Source: *https://www.medicinenet.com/script/main/art.asp?articlekey=32955*

effects associated with exposure to methyl bromide was related to the level of the GST conjugating enzyme.

Another study summarized in the PPRTV (2007) assessment noted "marked differences in the severity of reaction" of nine greenhouse workers accidentally exposed to similar levels of methyl bromide (>200 ppm) over 6 hours (Hustinx et al., 1993). The authors reported that seven of the workers were discharged after overnight observation and had few residual symptoms while the other two required intensive care for several weeks due to severe muscle contractions and convulsions. The wide variation in effects observed in persons exposed in this incident may reflect variation associated with the GST conjugating enzyme.

These human-specific Phase II GSH-based metabolism differences, which appear to be prevalent normal population genetic variations, suggest that large segments of the human population have enhanced susceptibility to methyl bromide induced neurotoxic effects that would not be captured in rodent toxicity assays. Human-health toxicity values developed from rodent toxicity studies and applying the default EPA uncertainty factors without specific consideration of this genetic variability would not have captured this risk component. The potential for human subpopulations with enhanced sensitivity to neurological effects associated with methyl bromide inhalation, along with the concern for the exposure to infants and children, support a 24-hour averaging time and the application of the IRIS chronic RfC as the basis of the proposed North Carolina AAL.

Adverse Effects Identified in Animal Inhalation Exposure Studies

Controlled laboratory studies using animal models provide a more comprehensive review of health effects associated with inhalation exposures to methyl bromide. The 1992 IRIS methyl bromide assessment calculated the RfC for the most sensitive adverse health effect observed in the Reuzel et al., (1987, 1991) chronic inhalation rat studies. Other animal chronic exposure inhalation studies summarized in the IRIS assessment include a 1990 National Toxicology Program study (NTP 1992) which exposed mice to 0, 10, 33 and 100 ppm methyl bromide for 6 hours per day, 5 days per week for up to 103 weeks. This study included neurobehavioral assessments and neuropathological examinations at 20-weeks and 6, 15 and 24 months. Target organs of toxicity identified in the study were the brain, bone (sternum), heart, and nose, with lesions in these organs occurring more frequently in the males. Concentration-related effects included an increased incidence of neurotoxic effects identified as cerebellar degeneration[7] in the brain of both sexes at the 100 ppm exposures that was statistically significant only in males. Other statistically-significant effects reported for both sexes of the 100 ppm-exposed animals included dysplasia[8] of the sternal bone marrow, myocardial degeneration and chronic

[7] Cerebellar degeneration is a process in which neurons (nerve cells) in the cerebellum - the area of the brain that controls coordination and balance - deteriorate and die. Source: *https://www.ninds.nih.gov/Disorders/All-Disorders/Cerebellar-Degeneration-Information-Page*

[8] Dysplasia is abnormal growth or development (as of organs or cells) or an abnormal anatomical structure due to such growth. May develop into cancer. Source: *https://www.merriam-webster.com/dictionary/dysplasia* *and* *https://www.cancer.gov/publications/dictionaries*

cardiomyopathy[9], nasal cavity olfactory epithelial necrosis[10] and metaplasia[11]. A NOAEL of 33 ppm (HEC = 4.4 mg/m^3 for respiratory effects and 23 mg/m^3 for extra-respiratory effects) and a LOAEL of 100 ppm (HEC = 13 mg/m^3 for respiratory effects and 69 mg/m^3 for extra-respiratory effects) were identified by NTP based on toxicity in multiple organs. Significant mortality was also reported in the study at 20 weeks, 47% in the males and 10% in the females.

IRIS (1992) reviewed several animal studies that included short-term repeated exposures to study acute effects to the olfactory epithelium. In Hurtt et al. (1988), male rats were exposed to 0, 90 and 200 ppm methyl bromide for 6 hours/day for 1 to 5 days. After a single 6-hour exposure at 90 and 200 ppm extensive destruction of the olfactory epithelium, characterized by epithelial disruption, fragmentation, and exfoliation[12] was observed, with the most severe effects observed in the structural and mature sensory cells. Impaired olfactory function was reported in the 200-ppm exposed animals. Other studies report similar observations of extensive damage to the olfactory epithelium after single exposures in repeated exposure studies of 4 to 6-hours/day over 2 weeks or less (Hastings 1990).

The Hurtt et al. (1988) study also exposed male rats at 0, 90, 175, 250 and 325 ppm methyl bromide for 6 hours/day for 5 days. Partial mortality was reported in the 325 ppm treatment. In the 175 ppm treatment, observations included cellular degeneration of the adrenal gland[13] and the cerebellar cortex[14]. Degeneration of the nasal olfactory sensory cells affecting 50-80% of the olfactory mucosa characterized by complete or partial destruction of the olfactory epithelium was reported at 175 ppm and higher concentration groups. Diarrhea, hemoglobinuria[15], gait disturbances, convulsions and hepatocellular degeneration were observed in the 250 ppm treatment groups. Minor alterations in testicular histology and cerebral cortex degeneration were observed in the 350 ppm exposure group.

IRIS (1992) also summarizes several animal studies evaluating neurological effects associated with methyl bromide exposures. Kato et al. (1986) exposed male rats to 0, 200, 300, or 400 ppm bromomethane for 4 hours/day, 5-days/week for 6 weeks. Neurological dysfunction (ataxia[16] and paralysis) was reported beginning at the 300 ppm exposures and cerebral hemisphere cortex necrosis was reported at 400 ppm. Other effects reported included testicular atrophy and suppression of

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[9] Myocardial degeneration is the deterioration of the heart muscle. Chronic cardiomyopathy is diseases of the heart characterized by the heart muscle becoming enlarged, thick, or rigid and the heart becoming weaker over time. In severe cases the muscle may be replaced by scar tissue. Source: *https://www.nhlbi.nih.gov/health-topics/cardiomyopathy*

[10] Necrosis is a form of cell injury which results in the premature death of cells in living tissue as opposed to the spontaneous natural death or wearing out of tissue. Source: *https://www.britannica.com/science/necrosis*

[11] Metaplasia is a change of cells to a form that does not normally occur in the tissue in which it is found. Source: *https://www.cancer.gov/publications/dictionaries/cancer-terms/def/metaplasia*

[12] Epithelial fragmentation and exfoliation is described as an irreversible process in which the two-dimensional epithelial tissue layer tends to break up forming smaller fragments, followed by exfoliation characterized by the complete detachment of single epithelial cells or groups of cells from an epithelial layer. Source: *http://rsif.royalsocietypublishing.org/content/14/128/20170032* and *https://link.springer.com/content/pdf/10.1007%2F978-3-642-27841-9_2056-2.pdf*

[13] The adrenal glands produce hormones that help regulate metabolism, the immune system, blood pressure and stress response. Source: https://www.hopkinsmedicine.org/

[14] The cerebellar cortex is part of the hindbrain that functions in motor commands, balance, coordination of movement and cognitive functions. Source: https://nba.uth.tmc.edu/neuroscience/

[15] Hemoglobinuria is the excretion of hemoglobin in the urine. Source: *https://www.medicinenet.com/script/main/art.asp?articlekey=3693*

[16] Ataxia is the lack of muscle control or coordination of voluntary movements. Source: *https://www.mayoclinic.org/diseases-conditions/ataxia/symptoms-causes/syc-20355652*

spermatogenesis at 400 ppm. Focal necrosis and fibrosis[17] of coronary ventricles and muscle were noted at all treatment levels. Neurobehavioral effects to rabbits were observed in studies by Anger et al. (1981), reported as decreased eye reflex and nerve conduction velocity at 65 ppm exposures for 7.5 hours/day, 4 days/week for 4 weeks. Signs of limb paralysis and decreased body weight gain were also reported.

Studies indicate that methyl bromide is rapidly taken up following inhalation exposures and rapidly distributed throughout the body. In animal studies methyl bromide is quickly distributed throughout the body following inhalation exposure, with the highest concentrations observed in the nasal passages, lungs, brain, adrenal gland, kidneys, liver, muscle and adipose tissue (IRIS 1992, ATSDR 2008).

Some animal studies have indicated slower elimination of methyl bromide from the brain and liver compared to other compartments (ATSDR 2008). Inhalation exposure elimination studies report excretion is mainly by expiration of carbon dioxide or by urinary excretion of nonvolatile metabolites, with little excretion of the parent chemical (Bond et al. 1985, Jaskot et al. 1988; Medinsky et al. 1985). Half-lives reported for the parent chemical are 15-30 minutes, and 2-10 hours in most tissues for metabolites (Honma et al. 1985; Jaskot et al. 1988). A significant proportion (25-35%) of inhaled methyl bromide was reported to remain in the tissues after 24-72 hours and is excreted more slowly, likely a result of turnover of intercellular metabolites or adducts. Honma et al. (1985) reported a half-life of 5 days for bromine from the blood, kidneys and liver in rats exposed to methyl bromide.

The higher accumulation levels and slower elimination rates are associated with target organ sensitivity in the nasal passages and lungs, as well as the liver and the brain. de Souza et al. (1985) reported the relative hydrophobicity of methyl bromide suggests it may cross the blood-brain barrier. There are no studies relating distribution of methyl bromide in humans following inhalation exposure (ATSDR 2008).

Developmental and Reproduction Studies in Animals

IRIS (1992) summarized effects observed in developmental and reproduction laboratory studies exposing animals during gestational development. Maternal effects reported in rabbits exposed to 0, 20, 40, or 80 ppm treatments for 6 hours/day on gestational days 6-19 included reduced body weight and body weight gain, and signs of central nervous system (CNS) toxicity observed at 80 ppm (Breslin et al., 1990). Deficits in embryonic development of the gall bladder and sternum were reported in the young, along with reduced fetal body weights. A 2-generation reproduction study in rats exposed at 0, 3, 30, or 90 ppm during pre-mating, gestation and lactation reported decreased body weight and body weight gain in the parent animals (F0 generation) and decreased body weight in the second generation (F2) young.

[17] Fibrosis is the thickening and scarring of connective tissue, usually due to injury. Source: *https://www.dictionary.com/*

Cancer-Effect Studies

The IRIS (1992) methyl bromide cancer classification is "Classification D; not classifiable as to human carcinogenicity" because of inadequate human and animal data to quantitatively assess the carcinogenicity. The human and animal cancer studies included in IRIS (1992) are summarized below.

- Human occupational exposures – An increased mortality for testicular cancer was reported in a study of >3500 male chemical workers exposed to a mixture of brominated chemicals in which methyl bromide was the only common brominated organic chemical exposure over the 21-year exposure period.
- *In vitro* and *in vivo* mutagenicity studies – Positive mutagenicity reported in –
    - *Salmonella* strains and in modified *Salmonella* strains following vapor phase exposures
    - *Escherichia coli* with and without metabolic activation
    - *Drosophilia* (fruit flies)
    - Mouse lymphoma cells

The PPRTV (2007) review includes summaries of additional studies evaluating the mutagenicity and genotoxic potential of methyl bromide, including a Vogel and Nivard (1994) study that identifies methyl bromide as a "very reactive methylating agent" that readily methylates biomolecules critical to a wide range of physiological functions, including thiols, thioether sulfurs, nitrogen in amino groups and rings, and oxygen atoms in carboxylate ions and hydroxy groups. PPRTV references a study that involved 4-hour oral and inhalation exposures of male and female rats. The study reported methyl bromide was widely distributed throughout the body of the study animals with clear indications of DNA methylation (Gansewendt et al., 1991). Detection of DNA adducts in the liver and lung were reported, with the highest activity noted in the stomach and forestomach for both the inhalation and oral exposure routes.

In 1992 the National Toxicology Program (NTP) summarized a study by Bolt and Gansewendt (1993) that NTP stated clearly indicated methyl bromide exposure can cause genotoxic and/or mutagenic changes. NTP reported methyl bromide was positive for reverse mutation, with and without S9 activation, in two *Salmonella typhimurium* strains. It was also positive for mutation induction in two *Escherichia coli* strain assays and in the *Klebsiella pneumoniae* fluctuation test. It was negative in three other bacterial strains. Methyl bromide tested positive for mutagenicity in the *Drosophila melanogaster* sex-linked recessive lethal test, in the somatic recombination assay, and induced sister chromatid exchange (SCE) in human lymphocytes *in vitro* and in rats and mice *in vivo*. It tested positive for induction of 6-thioguanine and bromodeoxyuridine resistance in L5178Y mouse lymphoma cells, but negative in an assay in primary rat hepatocytes and for transformation by SA7 adenovirus in Syrian hamster embryo cells.

The EPA (EPA 2005) notes carcinogenesis involves a complex series and interplay of events that alter the signals a cell receives from its extracellular environment, promoting uncontrolled growth. The EPA identifies multiple modes of carcinogenic action include mutagenicity, mitogenesis[18], inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression. Evidence that a parent substance or its metabolite is DNA-reactive and/or has the ability to bind to DNA (a DNA adduct) is also evidence supportive of a mutagenic mode-of-action. Different carcinogenesis modes-of-action can

[18] Mitogenesis is the induction of mitosis. A mitogen is a chemical substance that encourages a cell to commence cell division, triggering mitosis. Source: *https://biology.stackexchange.com/questions/42819/growth-factors-vs-mitogens*

operate in different dose ranges, with an agent acting predominantly by a cytotoxic mechanism at high doses and by a mutagenic mechanism at lower doses where cytotoxicity is not induced.

Discussion of Occupational Health Values for Methyl Bromide

While occupational exposure limits are available for methyl bromide and similar values have been used historically to develop AALs for the protection of the general public, DAQ considers the IRIS RfC as a more appropriate health-based value for protection of public health. The EPA IRIS RfC has gone through extensive EPA internal technical team review, external-to-the EPA technical peer review, and public comment. Additionally, as defined above the RfC is intended to be health-protective for the general population, including subpopulations that may have increased sensitivity to development of adverse health effects associated with specific exposures. Occupational exposure limits are intended to be protective of a healthy adult working population which may have different sensitivity to exposures than does the general public. In the context of public health, the "general public" encompasses subpopulations, such as infants, children, the elderly and persons with pre-existing conditions or a genetic predisposition that may manifest as increased susceptibility to the adverse effects associated with inhalation to methyl bromide and other toxicants. For these reasons, DAQ identifies the EPA IRIS RfC as the most appropriate health-based value protective of inhalation exposures for all persons that may be repeatedly exposed to methyl bromide at locations adjacent to log fumigation operations.

ATSDR Toxicological Profile for Bromomethane - Draft for Public Comment, April 2018

In late June 2018 the ATSDR released their *Toxicological Profile for Bromomethane* (methyl bromide) *Draft for Public Comment*, dated April 2018. Following is a summary of information in this most-recent review of the human health implications of methyl bromide exposure not presented previously, with relevance to the proposed North Carolina AAL.

ATSDR-Derived Provisional Inhalation Health Values

ATSDR (2018) identifies neurotoxicity as the most sensitive effect of acute exposures to animals. Neurological effects observed in laboratory animals included overt signs of neurotoxicity such as trembling, ataxia, lethargy, paralysis, and hyperactivity; decreases in brain neurotransmitter levels; impaired olfactory function; and histopathological damage in the cerebrum, cerebellum, and olfactory bulb. ATSDR's provisional Minimal Risk Level (MRL) for methyl bromide intermediate-duration inhalation exposures is 0.02 ppm (78 µg/m^3). ATSDR defines an intermediate exposure as 15-364 days, and an MRL is defined an estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse non-cancer health effects over a specified route and duration of exposure, with exceedances of an MRL indicating the need for further evaluation of the potential exposure conditions of frequency and duration, as well as the characteristics of the receptor population[19].

[19] Minimal Risk Levels (MRLs) – For Professionals. Toxic Substances Portal. Agency for Toxic Substances & Disease Registry (ATSDR). Accessed at: *https://www.atsdr.cdc.gov/mrls/index.asp*

The intermediate inhalation MRL is based on a 10 ppm LOAEL for neurobehavioral effects from the NTP (1992) study that reported decreased locomotor activity in male mice at the 6-month evaluation period in the 2-year cancer bioassay. The LOAEL was adjusted to a Human Equivalent Concentration (HEC) of 1.8 ppm and divided by a composite uncertainty factor (UF) of 90 (UF 3 for LOAEL to NOAEL extrapolation, UF 3 for animal to human extrapolation with dosimetric adjustment, and UF 10 for human variability).

ATSDR's chronic inhalation exposure provisional MRL for methyl bromide is 0.001 ppm (3.9 µg/m^3) based on nasal lesions described as "very slight basal cell hyperplasia of the olfactory epithelium" in female rats from a 2-year study (Reuzel et al., 1991). The chronic MRL was derived from a rat LOAEL of 3.1 ppm adjusted to a HEC LOAEL of 0.108 ppm and a composite UF of 90 (UF 3 for LOAEL to NOAEL extrapolation, UF 3 for animal to human extrapolation with dosimetric adjustment, and UF 10 for human variability). ATSDR defines chronic exposures as 365 days or longer. The ATSDR provisional chronic inhalation MRL is lower than the IRIS chronic inhalation RfC (5.0 µg/m^3).

Discussion of Neurological Effects

ATSDR (2018) states inhalation exposures to methyl bromide frequently lead to a spectrum of neurological effects in humans, with initial symptoms typically including headache, dizziness, nausea/vomiting, confusion, weakness, numbness, slurred speech, visual disturbances, lack of inhibition, agitation and confusion. ATSDR further notes severe exposures may progress to ataxia, tremor, seizures and coma. ATSDR also confirms that in most acute exposures, there is a lag period of several hours before effects occur, and in some cases effects may not develop for several weeks after the exposure ceases (Herzstein and Cullen 1990).

ATSDR (2018) notes neurotoxicity in animal studies characterized as changes to neurotransmitter levels in rat brains after single 8-hour exposures (Honma 1987; Honma et al. 1987). An 8-hour exposure to 31 ppm methyl bromide resulted in significant decreases in norepinephrine levels in the hypothalamus and the 100 ppm exposure resulted in decreases in dopamine and serotonin in the striatum and decreased norepinephrine levels in the striatum, hypothalamus, frontal cortex and midbrain. Continuous exposure to 10 ppm for 3 weeks resulted in decreases in norepinephrine levels in the hypothalamus (Honma et al. 1982). Honma et al. (1985) reported decreased locomotor activity in a rat 8-hour exposure at 188 ppm and decreased motor activity and changes in performance on a suite of neurobehavioral assessment tests (Functional Observational Battery (FOB) tests) following a 6-hour exposure at 350 ppm. An FOB assessment evaluates neurotoxic effects measured as gross functional deficits in rats. Changes were observed in measurements of activity levels, muscular coordination and muscle strength.

An 8-hour exposure to methyl bromide resulted in decreased locomotor activity at 188 ppm, decreased body temperature at 125 ppm, and increased sleep potency of thiopental at 63 ppm in rats exposed at 350 ppm for 6 hours, a decrease in motor activity and a number of alterations in FOB test performance, including inactivity, decreased rearing, uncoordinated righting response and decreased hind limb grip strength (EPA 1993). Gotoh et al. (1994) reported slight atrophy in the cerebellum in a 2-year study exposing mice at 64 ppm.

ATSDR (2018) also reports more recent studies with observed effects to the olfactory system, including olfactory bulb neuron damage. Death in 90-98% of olfactory bulb neurons were reported by Schwob et al. (1999) and Youngentob and Schwob (2006) following 6-hour exposures at 330 ppm methyl bromide.

Developmental Effects

Developmental effect studies not included in the 1992 ATSDR review included an epidemiological study by Gemmill et al. (2013) which reported an association between residential proximity to methyl bromide application and developmental outcomes. Moderate or high methyl bromide use during the second trimester was associated with decreased birth weight, birth length and head circumference for women living within 3-, 5-, or 8-km radius from the source. Decreased pup weights were also reported in a multi-generation rat study exposed to 30 ppm methyl bromide for 5 days per week for 6 hours per day (Enloe et al., 1986). The NOAEL for the pup weight effect was 3 ppm and the LOAEL was 30 ppm.

Cancer-Effect Studies

Several new reports of cancer-effect studies were included in ATSDR (2018). Alavanja et al. (2003) found elevated odds ratios[20] (ORs) for prostate cancer among applicators with the two highest cumulative exposure quintiles in the Agricultural Health Study[21] cohort of male pesticide applicators (OR 2.73, 95% CI 1.18–6.33 and OR 3.47, 95% CI 1.37–8.76, respectively). A later analysis of data in the Agricultural Health Study cohort reported an increased risk of stomach cancer among applicators with high use (RR 3.13; 95% CI 1.25–7.80; RR 3.33, 95% CI 1.30–8.51 with a 15-year lag)[22] compared to those with no use (Barry et al. 2012). Mills and Yang (2003) reported an increased risk of prostate cancer in the highest use group in a nested case-control study when farm workers were categorized by estimated methyl bromide use amounts (OR 1.59; 95% CI 0.77–3.30). Cockburn et al. (2011) reported an increased risk of prostate cancer in a case-control study of exposed residents living near agricultural uses of methyl bromide in California (OR 1.62; 95% CI 1.02–2.59). ATSDR summarizes the epidemiological cancer studies by stating that the occupational studies provide some suggestive associations of an increased cancer risk and methyl bromide exposure, but the studies are not adequate for establishing causality. None of the studies measured exposure concentrations and possible exposure to other pesticides contributed to their conclusion. The lack of positive cancer studies in animals contributes to the lack of weight-of-evidence to adequately support a human cancer association with methyl bromide exposure.

[20] An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. Source: *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2938757/*

[21] The Agricultural Health Study began in 1993 and is a prospective study of cancer and other health outcomes in a cohort of licensed pesticide applicators and their spouses from Iowa and North Carolina. https://aghealth.nih.gov/

[22] The risk ratio (RR) is the ratio of incidence rates in the exposed and unexposed groups. Source: http://sphweb.bumc.bu.edu/otlt/MPH-Modules/EP/EP713_Association/EP713_Association3.html

SUMMARY

DAQ has identified the U.S. EPA IRIS program chronic inhalation reference concentration (RfC) as the appropriate value for the Acceptable Ambient Level (AAL) to protect all persons that may live or work in areas subject to repeated airborne releases of methyl bromide from fumigation operations. Protecting public health includes protecting segments of the population that may have greater sensitivity to the adverse effects associated with toxicant exposures, including infants, children, the elderly and persons with pre-existing health conditions that may result in increased susceptibility to toxicants, such as persons with asthma or chronic cardiac or lung disease. Protecting public health also includes protection of subpopulations that may have genetic or physiological variations that influence their susceptibility, such as is the case with persons that possess the Phase II glutathione (GSH) metabolism system that increases the sensitivity and severity of neurotoxic effects in persons exposed to methyl bromide. DAQ is proposing a 24-hour averaging time for the methyl bromide AAL to reflect the rapid adsorption and distribution of methyl bromide following inhalation exposures, the slower elimination from target organs, the potential for large segments of the human population to possess a genetic variation that leads to increased sensitivity to neurotoxic effects that was not captured by animal studies used to develop the RfC, and due to the potential for delayed onset of adverse effects following exposures. DAQ is requesting the Secretaries' Science Advisory Board review and affirm the IRIS RfC as the appropriate basis for the AAL and the 24-hour chronic toxicant averaging time.

Table 1. Study parameters for the critical effect study used by IRIS for the chronic RfC.

Assay Parameters	Assay Detail
Study reference	Reuzel et al., 1987, 1991 National Institute of Public Health and Environmental Hygiene of the Netherlands
Test animals	50 male and 60 female Wistar rats
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)
Exposure scenario	Inhalation, 6 hours per day, 5 days per week
Study length	29 months, 10 animal sacrifices per exposure concentrations at 14, 53 and 105 weeks
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
Study results	$LOAEL_{rat}$ 11.7 mg/m^3 $LOAEL_{rat}$ adjusted to continuous exposure 2.08 mg/m^3 $LOAEL_{human}$ 0.48 mg/m^3 (120 ppbv)
RfC calculation components	Uncertainty Factors: 10 LOAEL to NOEL extrapolation 10 Human population variability

Table 2. Adverse health effects identified in the Reuzel et al. (1991) methyl bromide rat inhalation study that was the IRIS reference concentration (RfC) principle study. Inhalation exposures concentrations were 0, 3, 30, 90 ppm methyl bromide.

Statistically Significant Concentration-Related Adverse Health Effect	**Exposure Duration**	**Methyl Bromide Inhalation Effect Concentration**
Degenerative and proliferative lesions of the olfactory epithelium in the nasal cavity (Critical effect)	29 months	3 ppm ($LOAEL_{rat}$)
Decrease in relative kidney weight	29 months	30 ppm, males
Decrease in mean absolute brain weight	53 weeks	90 ppm, females
Hyperplastic changes in basal cells with degeneration of olfactory epithelium of the nasal cavity	29 months	3 ppm
Heart lesions, metaplasia and thrombus	29 months	90 ppm, males
Heart lesions, myocardial degeneration and thrombus	29 months	90 ppm, females
Hyperkeratosis of the esophagus	29 months	90 ppm, males
Non-Statistically Significant Concentration-Related Adverse Health Effect	**Exposure Duration**	**Methyl Bromide Inhalation Effect Concentration**
Basal cell hyperplasia	53 weeks	30 ppm
Decreased body weight gains	29 months	90 ppm
Mortality	29 months	90 ppm
Forestomach lesions	29 months	Not indicated

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Appendix A

Chemical Assessment Summary – Bromomethane (CASN 74-83-9)

Integrated Risk Information System (IRIS)
U.S. Environmental Protection Agency National Center for Environmental Assessment

Last Revised April 1, 1992

Bromomethane; CASRN 74-83-9

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Bromomethane

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/26/1988
Inhalation RfC (I.B.)	yes	04/01/1992
Carcinogenicity Assessment (II.)	yes	06/01/1989

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Bromomethane
CASRN — 74-83-9
Primary Synonym — Methyl bromide
Last Revised — 09/26/1988

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an

elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Epithelial hyperplasia of the forestomach **Rat Subchronic Gavage Study** **Danse et al., 1984**	NOAEL: 1.4 mg/kg/day LOAEL: 7.1 mg/kg/day	1000	1	1.4E-3 mg/kg/day

*Conversion Factors and Assumptions — doses adjusted for gavage schedule (5 days/week)

I.A.2. Principal and Supporting Studies (Oral RfD)

Danse, L.H.J.C., F.L. van Velsen and C.A. van der Heijden. 1984. Methylbromide: Carcinogenic effects in the rat forestomach. Toxicol. Appl. Pharmacol. 72: 262-271.

Treatment of groups of 10 male and 10 female Wistar rats by gavage 5 days/week for 13 weeks with bromomethane at 0, 0.4, 2, 10, or 50 mg/kg resulted in severe hyperplasia of the stratified squamous epithelium in the forestomach at a dose of 50 mg/kg/day and slight epithelial hyperplasia in the forestomach at a dose of 10 mg/kg/day (Danse et al., 1984). At the 50 mg/kg/day dose level, decreased food consumption, body weight gain and anemia were observed in the male rats. Slight pulmonary atelectasis was observed, at the two higher dose levels, in both male and female rats; however, the investigators stated that the possible inhalation of bromomethane-containing oil during the gastric intubation procedure might have been responsible for this effect. No neurotoxic effects were observed at any dose level tested. Renal histopathology was not evaluated. Adverse effects were not observed at 0.4 or 2 mg/kg.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The UF includes the standard uncertainty factors for interspecies and intrahuman variability and a factor of 10 for extrapolation to lifetime exposure from an intermediate exposure duration.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

The current RfD is based on the Danse et al. (1984) study, which uses the preferred oral route of exposure for deriving an oral RfD. The previous oral RfD (4E-4 mg/kg/day) was based on the inhalation studies by Irish et al. (1940). Inhalation studies are inappropriate for oral risk assessment extrapolation for bromomethane because portal-of-entry effects are observed for both the inhalation route (lung pathology) and oral route (stomach hyperplasia). In addition, neurological effects reported after inhalation exposures have not been reported after oral exposures.

Beagle dogs of either sex were fed methyl bromide fumigated food ad libitum for 1 year so that groups of four dogs each ingested approximately 35, 75, or 150 mg/kg/day of bromide, or adjusting for molecular weight, 41.6, 89.1, or 178.2 mg/kg/day of methyl bromide, assuming all the bromide was present as methyl bromide (Rosenblum et al., 1960). The control group consisted of three male and three female dogs fed only dog chow, ad libitum. The dogs ingesting 178.2 mg/kg/day methyl bromide gained more weight than the controls or the two lower treatment groups; they also became lethargic and displayed excessive salivation and occasional diarrhea. Methyl bromide was reported to have no effect on hematological values, urinalysis, blood chemistry (including BUN levels) or mortality rate. Mild chronic renal inflammation was reported in two dogs in the high-dose group and in one dog in the control group. Mild hepatic focal inflammation was reported in three dogs in the high-dose group, two dogs in the low-dose group and one dog in the control group. No other histological lesions were reported.

No adverse developmental effects were observed in the fetuses of Wistar rats exposed to 20 ppm (78 mg/cu.m) or 70 ppm (272 mg/cu.m) of bromomethane for 7 hours/day on days 1-19 of gestation (Hardin et al., 1981; Sikov et al., 1980). Exposure to 20 ppm (78 mg/cu.m) or 70 ppm (272 mg/cu.m) for 7 hours/day, 5 days/week for 3 weeks prior to mating, and gestation, did not result in developmental toxicity in the offspring. No maternal toxic effects were observed.

Bromomethane was highly toxic to pregnant New Zealand White rabbits exposed to 70 ppm (272 mg/cu.m) for 7 hours/day, 5 days/week on days 1 to 15 of gestation; 24/25 rabbits died by day 30 of gestation (Hardin et al., 1981; Sikov et al., 1980). No adverse developmental effects were

observed in the one remaining litter or in a group of rabbits exposed to 20 ppm (78 mg/cu.m) of bromomethane for 7 hours/day, 5 days/week on days 1 to 30 of gestation.

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

The study by Danse et al. (1984) used the preferred route of administration for derivation of an oral RfD. The study was adequately conducted, and the determination of epithelial hyperplasia of the forestomach was independently confirmed.

I.A.6. EPA Documentation and Review of the Oral RfD

U.S. EPA. 1986. Health and Environmental Effects Profile for Methyl Bromide. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington DC.

U.S. EPA. 1987. Drinking Water Health Advisory for Bromomethane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington DC.

Agency Work Group Review — 12/02/1985, 02/05/1986, 09/29/1986, 04/15/1987, 05/26/1988

Verification Date — 05/26/1988

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Bromomethane conducted in November 2001 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Bromomethane
CASRN — 74-83-9
Primary Synonym — Methyl bromide
Last Revised — 04/01/1992

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. 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). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Degenerative and proliferative lesions of the olfactory epithelium of the nasal cavity **Rat 29-month Inhalation Study** **Reuzel et al., 1987, 1991**	NOAEL: None LOAEL: 11.7 mg/cu.m (3 ppm) LOAEL (ADJ): 2.08 mg/cu.m LOAEL (HEC): 0.48 mg/cu.m	100	1	5E-3 mg/cu.m

*Conversion Factors: MW = 94.95. Assuming 25 degrees C and 760 mmHg, LOAEL(mg/cu.m) = 3 ppm x 94.95/24.45 = 11.7 mg/cu.m. LOAEL(ADJ) = 11.7 x 6 hours/24 hours x 5 days/7 days = 2.08 mg/cu.m. The LOAEL(HEC) was calculated for a gas:respiratory effect in the extrathoracic region. MVa (chronic, female Wistar rats) = 0.30 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 11.6 sq. cm., Sh(ET) = 177 sq. cm. RGDR(ET) = (MVa/Sa)/(MVh/Sh) = 0.23. LOAEL(HEC) = LOAEL(ADJ) x RGDR = 0.48 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

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, P.G.J., H.C. Dreef-van der Meulen, V.M.H. Hollanders, C.F. Kuper, V.J. Feron and C.A. van der Heijden. 1991. Chronic inhalation toxicity and carcinogenicity study of methyl bromide in Wistar rats. Fd. Chem. Toxic. 29(1): 31-39.

A series of inhalation toxicity studies of bromomethane were conducted under the sponsorship of the National Institute of Public Health and Environmental Hygiene of the Netherlands. In a chronic inhalation study conducted by Reuzel et al. (1987, 1991), 50 male and 60 female Wistar rats were exposed to 0, 3, 30, or 90 ppm (0, 11.7, 117, or 350 mg/cu.m, respectively) 98.8 % pure bromomethane 6 hours/day, 5 days/week (duration- adjusted concentrations are 0, 2.08, 20.9, or 62.5 mg/cu.m, respectively) for up to 29 months. Three satellite groups of 10 animals/sex/exposure level were sacrificed at 14, 53, and 105 weeks of exposure. Animals were observed daily, and body weight was recorded weekly for the first 12 weeks and monthly thereafter. Hematology, clinical chemistry, and urinalyses were conducted at 12-14 weeks and 52-53 weeks in the satellite groups. Eleven organs were weighed at necropsy, and approximately 36 tissues, including the lungs with trachea and larynx; 6 cross-sections of the nose; heart; brain; and adrenal glands were examined histopathologically. The test atmosphere was measured by gas chromatography every 30 minutes during exposure.

Males and females exposed to 90 ppm exhibited decreased body weight gains; no treatment-related changes in hematological, biochemical, or urine parameters were observed. A significant concentration-related decrease in relative kidney weights was reported in the 30- and 90-ppm males. A decrease in mean absolute brain weight was reported to occur in the 90-ppm females at weeks 53 and 105, but there was no change in relative brain weight or in brain histology. Microscopic evaluation revealed that the nose, the heart, and the esophagus and forestomach were the principle targets of bromomethane toxicity in this study. Very slight to moderate

hyperplastic changes in the basal cells accompanied by degeneration in the olfactory epithelium in the dorso- medial part of the nasal cavity were observed in all exposed groups of both sexes at 29 months of exposure. At the lowest concentration, the lesion is described as very slight. These changes were concentration-related in both incidence and severity and were statistically significant at 29 months. Incidence of basal cell hyperplasia in control, 3-, 30-, and 90-ppm groups were 4/46, 13/48, 23/49, and 31/48 in males and 9/58, 19/58, 25/59, and 42/59 in females, respectively. Slight increases in incidence of basal cell hyperplasia in the 30- and 90-ppm groups (n=7-10) at 53 and 105 weeks were not statistically significant. Lesions in the heart were statistically significant in the males (cartilaginous metaplasia and thrombus), and the females (myocardial degeneration and thrombus) exposed to 90 ppm. The authors attributed part of the increased mortality in the high-concentration animals to the cardiac lesions. A statistically significant increase in hyperkeratosis of the esophagus was observed in the 90-ppm males after 29 months of exposure. Slight increases in forestomach lesions were not statistically significant. No effects were observed in the tracheobronchial or pulmonary regions of the respiratory tract. No other exposure-related effects were noted. Based on these results, a LOAEL of 3 ppm (HEC = 0.48 mg/cu.m) for nasal effects is established.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — The uncertainty factor of 100 reflects a factor of 10 for intraspecies uncertainty, a factor of 3 for the use of a LOAEL for a mild effects and a factor of 3 for interspecies extrapolation because dosimetric adjustments have been applied. The factors of 3 represent operational application of a geometric half of the standard factor of 10, rounded to a single significant figure. As a result, multiplication of two factors of 3 results in a composite factor of 10.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

NTP conducted a 13-week subchronic study in B6C3F1 mice and F344 rats and a 6-week target organ study (Eustis et al., 1988; NTP, 1990). A chronic study on the toxicology and carcinogenesis of bromomethane following inhalation exposure to B6C3F1 mice was also conducted (NTP, 1990).

In the 13-week study, 18 rats/sex/group were exposed to target concentrations of 0, 30, 60, or 120 ppm (0, 117, 233, or 466 mg/cu.m, respectively) bromomethane 6 hours/day, 5 days/week (duration-adjusted concentrations are 0, 20.9, 41.6, and 83.2 mg/cu.m, respectively). Mice (18-27/sex/group) were exposed to 0, 10, 20, 40, 80, or 120 ppm (0, 38.8, 77.6, 155, 311, or 466 mg/cu.m, respectively) bromomethane 6 hours/day, 5 days/week (duration-adjusted concentrations are 0, 6.93, 13.9, 27.7, 55.5, or 83.2 mg/cu.m, respectively). Hematological

parameters were measured and organ weights were determined for the adrenals (rats only), brain, heart, kidney, lung, spleen (rats only), testis, and thymus (mice only). Pseudocholinesterase activity was measured in the mice only. Neurobehavioral testing was conducted on 8 rats and 8 mice/sex/group at weeks 0, 6, and 12, and neuromorphological studies were conducted on 4 rats/sex from the control and 120-ppm group and on 4 mice/sex for each concentration. Histopathological examination of approximately 40 tissues from control and 120-ppm animals were carried out, including lungs, bronchi, and nasal turbinates. Exposure-related changes seen in the mice were a significant (58%) body weight gain reduction and a 17% increase in mortality in mice exposed to 120 ppm bromomethane. Mice exposed to this level exhibited severe curling and crossing of the hindlimbs and twitching of the forelimbs; these effects were more severe in the males. Hematological parameters that were found to be statistically significantly different from control values in mice included decreased mean cell hemoglobin, decreased mean cell count, and increased erythrocyte count in males exposed to 40, 80, and 120 ppm; and increased hemoglobin in males exposed to 120 ppm. No exposure-related effects were seen upon histopathological examination. In the rats there was no increase in mortality, but the males exposed to 120 ppm and the females exposed to 60 and 120 ppm bromomethane exhibited significant decreases in body weight gain. Mild neurobehavioral effects were noted in the high-concentration rats of both sexes. Females exposed to 120 ppm were found to have significantly lower hematocrit, hemoglobin, and erythrocytes counts, but the males did not exhibit these changes. The only exposure-related effect noted at histopathological examination was an increase in the incidence of olfactory epithelial dysplasia and cysts in the rats of both sexes exposed to 120 ppm [LOAEL(HEC) = 12 mg/cu.m]. Based on these results a NOAEL of 80 ppm [NOAEL(HEC) = 8 mg/cu.m] for nasal olfactory epithelial changes in rats is established.

Because no significant target organ toxicity was noted in the 14-day or 13-week studies, a special 6-week target organ toxicity study at a near lethal concentration was conducted in F344 rats and B6C3F1 mice (Eustis et al., 1988; NTP, 1990). Groups of 5 animals/sex were exposed to 0 or 160 ppm (621 mg/cu.m) bromomethane 6 hours/day for either 3 consecutive days (rats), or 5 days/week over 2 weeks (rats and mice) or 6 weeks (rats). Fifteen mice/sex/dose were exposed to 0 or 160 ppm (621 mg/cu.m) 6 hours/day, 5 days/week, for 6 weeks. Endpoints studied included clinical observations, mortality, body and organ weights, hematology, clinical chemistry, urinalysis, gross pathology, and histopathology of a standard set of tissues, including the lungs and nasal turbinates. The female rats were the only group to demonstrate more than 50% survival, with mice being more sensitive than rats (mortality exceeded 50% after 6-8 exposures in both the male and female mice and after 14 exposures in the male rats). Because of the high mortality, the male and female mice and male rats were killed after 10, 8, or 14 exposures, respectively. Neurological signs exhibited by both rats and mice, but to a lesser extent in the rats, included lethargy and curling and crossing of hindlimbs, forelimb twitching, and tremors. Decreases in body weight gain were observed in the exposed animals as compared to controls (18% in the mice and 32% in the rats). The mean organ weights of most organs were

significantly reduced in both species. Notable hematological effects were seen mostly in the female mice and included decreased RBC and increased WBC counts. Target organs affected by exposure to 160 ppm bromomethane were the brain, kidney, nasal cavity, heart, adrenal gland, liver, and testes. Species differences were noted in the responses of these organs. For example, neuronal necrosis in the cerebral cortex, hippocampus, and thalamus of the brain were seen in the rats whereas neuronal necrosis was seen predominantly in the internal granular layer of the cerebellum of the mice. Nephrosis, characterized by degeneration, necrosis, and sloughing of the epithelium of the cortical convoluted tubules was seen in all of the exposed mice and was considered by the authors to be partially responsible for the increase in mortality, but these lesions were not observed in the rats. Degeneration and atrophy of the seminiferous tubules was observed in several of the exposed rats and mice, but was less severe in the mice. Olfactory epithelial degeneration was observed in the rats of both sexes, and this was seen to a lesser degree in the male mice, with only one female mouse exhibiting this lesion. Myocardial degeneration was seen in rats of both sexes, and to a lesser degree in the male mice. Atrophy of the inner zone of the adrenal cortex was observed in the female mice, and cytoplasmic vacuolation of the adrenal cortex was seen in rats.

In the chronic study (NTP, 1990), a total of 86 mice/sex/concentration were exposed to 0, 10, 33, or 100 ppm (0, 38.8, 128, or 388 mg/cu.m, respectively) bromomethane 6 hours/day, 5 days/week (duration-adjusted concentrations are 0, 6.93, 22.9, or 69.3 mg/cu.m, respectively). Exposures to 10 and 33 ppm were for 103 weeks, with interim sacrifices at 6 and 11 months. Exposure to 100 ppm produced 47% mortality in the males and 10% mortality in the females by 20 weeks, so exposure was discontinued in this group at this time and the surviving animals were observed for an additional 84 weeks, except for the females scheduled for the 15-month sacrifice. The endpoints studied were the same as those described for the 6-week target organ toxicity study in addition to neurobehavioral assessments in 16 mice/sex/group and neuropathological examination on 3-8 animals/sex/group at 20 weeks and 6, 15, and 24 months. Body weights were significantly depressed in the animals exposed to 100 ppm (33% in the males and 31% in the females) beginning at week 11 and persisting until study termination. Significant body weight changes were not observed in the lower exposure groups. Because of the reduced body weight in the 100-ppm animals, organ weight changes were difficult to interpret, but reduced absolute and relative thymus weights were observed in both the males and females exposed to 100 ppm bromomethane. Clinical signs of toxicity observed almost exclusively in the 100-ppm animals that persisted throughout the 103 weeks included tremors, abnormal posture, and limb paralysis. Functional neurobehavioral changes consisting of hypoactivity, a heightened startle response, and higher hindlimb grip scores and hot plate latency were observed in both sexes exposed to 100 ppm at various times during exposure, but were more pronounced in the males. The target organs of toxicity identified in this study were the brain, bone (sternum), heart, and nose, with lesions in these organs occurring more frequently in the males. In the brain, there was a statistically significant increase in the incidence of cerebellar degeneration in the animals

exposed to 100 ppm. Cerebral degeneration was also observed in these animals, but the incidence of this lesion was statistically significant in the males only. Because this lesion was observed more frequently in the animals that died prior to study termination, it may have contributed to the early mortality in this group. Dysplasia of the sternal bone marrow was observed at a statistically significantly increased rate in both the males and the females exposed to 100 ppm, but because it was observed more frequently in the animals that survived to study termination than in those that died early, it was not considered to be a contributing factor to the death of these animals. Myocardial degeneration and chronic cardiomyopathy were also observed at a statistically higher incidence in both males and females exposed to 100 ppm bromomethane, and occurred at a higher incidence in those animals dying early. Finally, a statistically significant increase in the incidence of olfactory epithelial necrosis and metaplasia was seen in the nasal cavities of both the male and female mice exposed to 100 ppm. Necrosis was seen only in the animals dying early, whereas metaplasia was exhibited mainly in those animals surviving until study termination. Histopathological changes in other organs were observed and considered to be secondary to stress and weight loss rather than a direct toxic effect of bromomethane. Animals exposed to lower concentrations did not exhibit significant increases in any of the lesions described above. Based on the results of this study, a NOAEL of 33 ppm (HEC = 4.4 mg/cu.m for respiratory effects and 23 mg/cu.m for extrarespiratory effects) and a LOAEL of 100 ppm (HEC = 13 mg/cu.m for respiratory effects and 69 mg/cu.m for extrarespiratory effects) are established based on toxicity in multiple organs.

Male Fischer 344 rats (10/group) were exposed to 0, 90, 175, 250, or 325 ppm (0, 350, 680, 971, or 1,262 mg/cu.m, respectively) bromomethane (99.9% pure) 6 hours/day for 5 days (Hurtt et al., 1987). The brain, nasal cavity, liver, kidney, adrenal glands, testes, and epididymides were examined histopathologically. The lungs were not examined. Three animals exposed to 325 ppm died after the fourth exposure. Diarrhea, hemoglobinuria, gait disturbances, convulsions and hepatocellular degeneration were observed in animals exposed to 250 ppm or greater; vacuolar degeneration of the zona fasciculata of the adrenal gland and cerebellar granule cell degeneration were observed in rats exposed at 175 ppm and greater. Minor alterations in testicular histology and cerebrocortical degeneration were observed in the 350-ppm exposure group. A concentration-dependent degeneration of the nasal olfactory sensory cells was observed in rats exposed to 175 ppm bromomethane or greater. This degeneration affected 50-80% of the olfactory mucosa, and was characterized by complete or partial destruction of the olfactory epithelium at the higher concentrations. Small foci of hepatocellular coagulative necrosis were observed in animals exposed to the two highest concentrations. No exposure-related lesions were noted in the kidneys.

In a subsequent study, Hurtt et al. (1988) investigated the ability and time-course of the olfactory epithelium to regenerate following acute exposure to bromomethane. Male Fischer 344 rats were exposed to 0 (n=5) or 200 ppm (n=40) 99.9% pure bromomethane (777 mg/cu.m) 6 hours/day

for 1-5 days. Five animals/group were killed after 1, 3, or 5 days of exposure and 1, 2, 3, 5, or 10 weeks after cessation of treatment. In a companion study, 6 animals/group were exposed to 0, 90, or 200 ppm (0, 350, or 777 mg/cu.m) bromomethane for 6 hours and olfactory function was studied by determining the effects of bromomethane on the ability of food-deprived animals to locate buried food pellets. Additional animals similarly exposed were killed at various times following the single 6-hour exposure to assess the state of morphological regeneration at the time of functional recovery. Only the nasal cavities were examined histopathologically in these studies. No clinical signs of toxicity were observed in the exposed animals. Extensive destruction of the olfactory epithelium, characterized by epithelial disruption, fragmentation, and exfoliation, was evident after a single 6-hour exposure to 90 or 200 ppm, with the most severe effects observed in the sustentacular and mature sensory cells, and the basal cell remaining intact. Regeneration of the olfactory epithelium, characterized at first by replacement with a squamous cell layer that increased in thickness, began by the third day of exposure and was essentially complete by 10 weeks after the last exposure. It is important to note that regeneration began even though exposure to bromomethane was still ongoing. Olfactory function was impaired in animals exposed to 200 ppm bromomethane, but not 90 ppm. Recovery of this function was evident by 4-6 days after exposure, which preceded morphological regeneration.

Similar results were obtained by Hastings (1990). In this study, rats were exposed to 200 ppm (777 mg/cu.m) bromomethane 4 hours/day 2 days/week for 2 weeks. Prior to exposure, rats were food-deprived and trained to find buried food pellets. Morphological as well as biochemical (carnosine content in the olfactory bulb, which is an indication of the integrity of the olfactory primary sensory neurons) studies were performed as well to assess the integrity of the olfactory epithelium. Extensive damage to the olfactory epithelium was seen, as evidenced by both morphological analysis and decreased carnosine content after a single 4-hour exposure. Olfactory function was also impaired after 4 hours, as evidenced by the inability of the rats to find the buried food pellets. However, olfactory function began to return after the second week of exposure and the animals performed as well as their controls by the end of the exposure period whereas regeneration of the olfactory epithelium, as indicated by morphological and biochemical analysis was not complete until 30 days from the start of exposure.

The most common signs of acute intoxication with bromomethane in humans are neurotoxic in nature and include headache, dizziness, fainting, apathy, weakness, tiredness, giddiness, delirium, stupor, psychosis, loss of memory, mental confusion, speech impairment, visual effects, limb numbness, tremors, muscle twitching, paralysis, ataxia, seizures, convulsions, and unconscious. Several studies have been conducted on the longer-term effects of occupational exposure to bromomethane. None of these studies can serve as the basis for the derivation of an RfC for bromomethane because of concurrent exposures to other chemicals, inadequate quantitation of exposure levels and/or durations, and other deficits in study design.

In a cross-sectional occupational study conducted by Anger et al. (1986), soil and structural fumigators underwent a neurological examination. The exposure group was blinded to the physician giving the examination. Most of the structural fumigators used both bromomethane (MB) and sulfuryl fluoride (SF). The formation of the study groups was based on the estimated time devoted to bromomethane and sulfuryl fluoride fumigation activities, and estimated length of time in the occupation. Four groups were formed: the MB group (n=32) consisted of structural fumigators using MB 80% or more of the time and soil fumigators using the mixture MB and chloropicrin; the SF group (n=24) consisted of structural fumigators who used SF 80% or more of the time; group COMB (n=18) consisted of workers using both MB and SF 40-60% of the time, the reference group (Group R, n=29) consisted of those workers who were not directly exposed to fumigants, but worked in the fumigation industry. The workers in the exposed groups had been in the profession for 1 or more years and had fumigated a house or field within the last 50 days. More symptoms were reported in the exposed groups than in the reference population: 78-83% and 41% respectively showed symptoms. The difference was significant for the MB and COMB groups when compared to Group R. The MB group did not perform as well as referents on several behavioral tests, including tests of cognitive function, reflexes, sensory and visual effects. Although this study suggests mild neurological effects of exposure to methyl bromide, it is difficult to draw any conclusions between exposure and effect because of the confounding factors. The exposed and reference groups were not well matched for age; use of prescription medication, alcohol, or illegal drugs within 2 days of the testing; education; or ethnic group. In addition, participation in the study was voluntary and no information is provided on the use of personal protective equipment in these groups.

Herzstein and Cullen (1990) reported on 4 cases of bromomethane toxicity at a nursery following the removal of polyethylene sheets covering soil fumigated with 98% bromomethane and 2% chloropicrin. Four workers involved in removing the tarp wore no respiratory protection, and had no training in the handling or Hazards of bromomethane. On the second day, all four workers noted fatigue and lightheadedness. After arriving home, three of the workers developed severe coughing, chest tightness, nausea, vomiting, headaches, and tremulousness during the night. Three workers were found to have either ataxia, tremor, or both. Blood bromide levels were not performed. The symptoms continued to improve without treatment. Upper- and lower-extremity paresthesias and reduced hand dexterity were reported in two workers at 3 weeks post-exposure. There were no long-term adverse effects after 18 months of follow-up.

The first reported study on the effects of short-term and repeated exposure to bromomethane in experimental animals was conducted by Irish et al. (1940). In the first set of experiments, rats and rabbits were exposed once to 420-50,000 mg/cu.m bromomethane for varying lengths of time. Concentrations of bromomethane greater than or equal to 10,000 mg/cu.m were lethal to 100% of the animals within 6-132 minutes. Deaths also occurred at 6-36 hours after exposure to concentrations less than 10,000 mg/cu.m. Clinical signs observed in rats exposed to less than

10,000 mg/cu.m included roughening of the fur, hunching of the back, drowsiness, heavy breathing, and lacrimation. Nasal irritation and lacrimation were observed, in addition to the signs mentioned above, at higher concentrations. Rabbits did not exhibit these signs. However, in rats exposed to greater than 1000 mg/cu.m for 20 hours, a hyperexcitable state was observed, whereas rabbits exposed to the same concentration exhibited paralysis. Evidence of pulmonary irritation (congestion and edema) was found (predominantly in the rat) following exposures to 1,000-20,000 mg/cu.m.

In subsequent studies, rats (n=135), rabbits (n=104), guinea pigs (n=98) and female rhesus monkeys (n=13) were exposed to 0, 17, 33, 66, 100, or 220 ppm (0, 66, 128, 256, 388, or 853 mg/cu.m, respectively) 7-8 hours/day, 5 days/week for 6 months or until the majority exhibited severe reactions or died. The frank-effect-levels (increased mortality) were 100 ppm for rats, guinea pigs, and monkeys and 133 ppm for rabbits (Irish et al., 1940). Rabbits and monkeys exhibited paralysis after exposure to 66 ppm whereas rats and guinea pigs exhibited no adverse effects. Pulmonary damage was still seen in rabbits exposed to 33 ppm, but the monkeys appeared normal. None of the species exhibited adverse effects following repeated exposure to 17 ppm (66 mg/cu.m; Irish et al. 1940).

The brain and heart also appeared to be target organs following inhalation exposure to bromomethane in a study conducted by Kato et al. (1986). Male Sprague-Dawley rats (10-12/group) were exposed to 150 ppm (583 mg/cu.m) bromomethane (purity unspecified) 4 hours/day, 5 days/week for 11 weeks (duration-adjusted to 69.3 mg/cu.m). Focal necrosis and fibrosis of coronary ventricles and papillary muscle disorders were observed in the exposed animals. In the same study, male Sprague-Dawley rats (10-12/group) were exposed to 0, 200, 300, or 400 ppm (0, 777, 1,165, or 1,553 mg/cu.m) 4 hours/day, 5 days/week for 6 weeks (duration-adjusted concentrations are 0, 92.5, 139, and 185 mg/cu.m, respectively). Focal necrosis and fibrosis of coronary ventricles and papillary muscle were observed in all exposed animals. Neurological dysfunction (ataxia, paralysis) were reported at levels at and exceeding 300 ppm; necrosis in the bilateral regions of the dorso-external cortex of the cerebral hemisphere was observed in animals exposed at 400 ppm. Testicular atrophy with suppression of spermatogenesis was apparent in 6 of the 8 the animals exposed to 400 ppm. Although the lungs appeared to be one of the tissues examined histopathologically, respiratory effects were not addressed in the descriptions of either experiment.

Neurobehavioral effects of bromomethane inhalation were studied in rats and rabbits by Anger et al. (1981). In one set of experiments, Sprague-Dawley rats and New Zealand white rabbits were exposed to 0 (n=2) or 65 ppm (252 mg/cu.m, n=6) 7.5 hours/day, 4 days/week for 4 weeks. Neurobehavioral testing, consisting of conduction velocity in the sciatic and ulnar nerves (rats and rabbits), eye-blink reflex (rabbits), open field activity (rats), and grip/coordination (rats) were conducted weekly. Exposed rabbits exhibited depressed body weight gain as compared

with the controls, and signs of hind limb paralysis were evident during the last week of exposure. Statistically significant decreases in the eyeblink reflex magnitude and in nerve conduction velocity were also observed in the exposed rabbits. In contrast, no effects on weight gain, grip/coordination, or nerve conduction velocity were observed in the rats exposed to 65 ppm for 4 weeks. The LOAEL for neurological effects in rabbits and the NOAEL for rats is 65 ppm. In another experiment that was performed as part of this study, Sprague-Dawley rats were exposed to 0 or 55 ppm (214 mg/cu.m) bromomethane 6 hour/day, 5 day/week for 36 weeks. Neurobehavioral tests (conduction velocity in the sciatic and ulnar nerves, open-field activity, and grip/coordination) conducted at 25- to 30-day intervals did not reveal any exposure-related effects.

In a subsequent study performed by this group (Russo et al., 1984) that was designed to assess the neurotoxic effects of bromomethane in rabbits following longer-term exposure at lower concentration, male New Zealand white rabbits were exposed to 0 (n=2) or 26.6 ppm (103 mg/cu.m, n=6) 99% pure bromomethane 7.5 hours/day, 4 days/week for 8 months (Russo et al., 1984). Exposure concentrations were monitored every 12 minutes by an infrared analyzer. Neurobehavioral tests examined the latency rates of the sciatic and ulnar nerves and the amplitude of the eyeblink reflex of the orbicularis oculi muscle. No other parameters, including respiratory effects, were monitored. No exposure-related neurological effects were observed [NOAEL(HEC) = 23 mg/cu.m]. As part of this study, the animals exposed to 252 mg/cu.m bromomethane for 4 weeks (previously discussed; Anger et al., 1981) were allowed to recover for 6-8 weeks and the neurological tests were repeated. The animals demonstrated partial, but not complete recovery within the 6-week period. Therefore rabbits, which are sensitive to the neurotoxic effects of high-level exposure to bromomethane, can tolerate long-term low-level exposure to bromomethane, and appear to be able to recover from severe neurological effects after cessation of exposure.

Morrissey et al. (1988), using data obtained from the 13-week NTP (1990) study in rats and mice, evaluated testis, epididymis, and cauda epididymis weights; caudal sperm motility and count; sperm head morphology; average estrous cycle length; and relative frequency of different estrous stages to assess the potential reproductive effects of bromomethane. In mice, they found that inhalation exposure to bromomethane resulted in an increase in the relative weights of the epididymis and testis, a decrease in sperm density, and an increase in the percentage of abnormal sperm. In the rats, a decrease in absolute cauda epididymis and absolute and relative epididymis weights, an increase in relative testis weight, and a decrease in sperm motility occurred as a result of subchronic inhalation exposure to bromomethane. No effects on estrous cycle length were noted. This study is an evaluation of a screening method for reproductive toxicants and was applied to 50 subchronic studies carried out by the NTP. The exposure levels at which these effects were found were not specified.

Male Fischer 344 rats (75/group) were exposed to 0 or 200 ppm bromomethane (777 mg/cu.m) 6 hours/day for 5 consecutive days and sacrificed on various days beginning on day 1 of exposure through 68 days after termination of exposure. Plasma testosterone and testicular glutathione levels were depressed, but returned to control levels within 3 days after exposure had ended. No effects on spermatogenesis, sperm quality, or testicular weight or histology were noted (Hurtt and Working, 1988).

Female Wistar rats (n=39-45) were exposed to 0, 20, or 70 ppm (0, 78, or 272 mg/cu.m, respectively) bromomethane 7 hours/day, 5 days/ week for 3 weeks, mated and exposed during gestational days 1-19. The study design included groups at each exposure level exposed pregestationally, during gestation, and both, as well as a control. At gestational day 21, litters were evaluated for fetotoxicity and live fetuses were examined for external, visceral (about 1/2 of fetuses), and skeletal abnormalities. Maternal organ weights for liver, kidney, and lung, and histopathology on 8 animals/group on ovaries, uterus, kidney, lung, and trachea were performed. No mortality or change in organ weights were observed and body weight was decreased during gestation but was not different than controls at full term. Histological effects observed in the lung and kidney were not clearly exposure-related due to the small sample size and high control incidence. There was no effect on pregnancy rate or fetal size. There were 31-38 litters/group examined and no effect on embryotoxicity, fetal viability, or fecundity measures was observed. There was no increase in malformations. The NOAEL for reproductive toxicity (changes in fertility rate) and maternal and fetal toxicity in rats is 70 ppm (Sikov et al., 1981; Hardin et al., 1981).

Female New Zealand white rabbits (25/group) were exposed to 0, 20, or 70 ppm (0, 78, or 272 mg/cu.m, respectively) bromomethane 7 hours/day, 5 days/week for 3 weeks during gestational days 1-24. Evaluation of developmental effects was the same as in the rat study except that all fetuses were evaluated for visceral abnormalities. In the 70-ppm group, severe neurotoxic effects occurred and 24/25 animals died. No effects on body weight, organ weight, or histology were observed in maternal animals exposed to 20 ppm. There was no effect on pregnancy rate or fetal size. There were 13 litters in the group exposed to 20 ppm examined and no effect on embryotoxicity, fetal viability, or fecundity measures was observed. There was no increase in malformations. The NOAEL for maternal and fetal toxicity in rabbits is 20 ppm (Sikov et al., 1981; Hardin et al., 1981).

Breslin et al. (1990) performed a developmental study in rabbits in which New Zealand rabbits (26/group) were exposed to 0, 20, 40, or 80 ppm (0, 78, 155, or 311 mg/cu.m, respectively) methyl bromide 6 hours/day on gestation days 6-19. Maternal toxicity at 80 ppm included reduced body weight and weight gain. Clinical signs of central nervous system toxicity were observed at 80 ppm. There was no effect on pre- or postimplantation loss, litter size, or fetal body weights. There was an increase in agenesis of the gall bladder and fused sternebrae at 80

ppm. The NOAEL for maternal toxicity and developmental effects in this study is 40 ppm [NOAEL(HEC) = 155 mg/cu.m].

American Biogenics Corporation (1986) conducted a two-generation reproduction study in Sprague-Dawley rats. Groups of 25 rats/sex/dose were exposed by inhalation to methyl bromide vapor at 0, 3, 30, or 90 ppm (0, 12, 117, or 350 mg/cu.m) 6 hours/day, 5 days/week during the premating, gestation, and lactation periods for 2 generations. In F0 male rats, exposure at 90 ppm caused statistically significant decreases in body weight gain during the premating period, final body weight, and total weight gain. No treatment- related changes in reproductive organs were noted. Also, no adverse effects were found on the progeny and reproductive parameters examined. In second generation (F1) animals, no adverse effects were found on body weights, histopathology of reproductive organs, or reproductive parameters measured. However, a statistically significant concentration-related reduction in body weights at 28 days was noted in F2 males and females at 30 ppm and 90 ppm. Although significant changes were seen in some of the mean organ weights and organ-to-body weight ratios in F0, F1, and F2 generation animals, no histopathology changes were seen in these organs. Therefore, the biological significance of these findings if any is not clear. Under the conditions of the study, exposure to methyl bromide did not affect fertility in rats but decreased the body weights of parental rats and reduced the growth of neonatal rats. The NOAEL and LOAEL for these effects were 30 and 90 ppm for adult rats and 3 and 30 ppm for neonates, respectively.

Medinsky et al. (1985) and Bond et al. (1985) conducted a series of experiments to assess the uptake, distribution, and excretion of bromomethane in rats following inhalation exposure. In one experiment, F344 rats were exposed to 1.6, 9, 170, or 310 ppm (6, 35, 660, or 1,203 mg/cu.m) radiolabeled bromomethane (nose-only) for 6 hours (Medinsky et al., 1985), and in the other, F344 rats were exposed to 9 ppm radiolabeled bromomethane for 6 hours (Bond et al., 1985). The percentage of total volume of inhaled radiolabeled bromomethane that was absorbed decreased in a concentration-related manner from 48+/-2% at the two lower concentrations to 27+/-4% at the highest concentration, which indicates that uptake of bromomethane is a saturable process. In both studies, inhaled bromomethane was distributed quickly throughout the body, and the highest concentrations were found in the lung, adrenal, kidney, liver, and nasal turbinates. By 65-66 hours after exposure, 75% of the radiolabel had been eliminated. The amount of bromomethane eliminated was linearly related to the amount absorbed (Medinsky et al., 1985). Excretion of bromomethane and its metabolites does not appear to be a concentration dependent (i.e., saturable) process, once absorbed.

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — High
RfC -- High

The Reuzel et al. (1987, 1991) chronic study was well conducted, used an appropriate number of animals and exposure levels, and included thorough histopathological examination of the respiratory tract; however, it is given a medium confidence rating because it did not identify a NOAEL. The LOAEL identified in this study is supported by the effects seen in rats in the subchronic NTP (1990) study and mice in the chronic NTP (1990) study, as well as in subacute and subchronic studies in rats (Hastings, 1990; Hurtt et al., 1987, 1988). The database is given a high confidence rating because there is a chronic inhalation study in two species supported by subchronic inhalation studies in several species, and because data are available on the developmental and reproductive effects of bromomethane as well as its pharmacokinetics following inhalation exposure. Based on the confidence in the database and study, high confidence in the RfC follows.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in an existing U.S. EPA document.

Other EPA Documentation — U.S. EPA, 1986, 1987

Agency Work Group Review — 10/13/1988, 09/19/1989, 08/15/1991, 12/10/1991

Verification Date — 12/10/1991

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Bromomethane conducted in November 2001 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address)

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Bromomethane
CASRN — 74-83-9
Primary Synonym — Methyl bromide
Last Revised — 06/01/1989

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — D; not classifiable as to human carcinogenicity

Basis — Inadequate human and animal data: a single mortality study from which direct exposure associations could not be deduced and studies in several animal species with too few animals, too brief exposure or observation time for adequate power. Bromomethane has shown genotoxicity.

II.A.2. Human Carcinogenicity Data

Inadequate. A prospective mortality study was reported for a population of 3579 white male chemical workers. The men, employed between 1935 and 1976, were potentially exposed to 1,2-dibromo-3-chloropropane, 2,3-dibromopropyl phosphate, polybrominated biphenyls, DDT, and several brominated organic and inorganic compounds (Wong et al., 1984). Overall mortality for the cohort, as well as for several subgroups, was less than expected. Of the 665 men exposed to methyl bromides (the only common exposure to organic bromides), two died from testicular

cancer, as compared with 0.11 expected. This finding may be noteworthy as testicular cancer is usually associated with a low mortality rate. Therefore, there could be more cancer cases than there appear to be based on mortality. The authors noted that it was difficult to draw definitive conclusions as to causality because of the lack of exposure information and the likelihood that exposure was to many brominated compounds.

II.A.3. Animal Carcinogenicity Data

Inadequate. Bromomethane was administered by gavage to groups of 10 male and female Wistar rats (Danse et al., 1984). Animals were administered doses of 0, 0.4, 2, 10, or 50 mg/kg/day bromomethane in arachis oil 5 days/week for 13 weeks, at which time the experiment was terminated. There was an apparent dose-related increase in diffuse hyperplasia of the forestomach. The authors reported a forestomach papilloma incidence of 2/10 in the high-dose males and forestomach carcinoma incidences of 7/10 and 6/10 in the high-dose males and females, respectively. These results were subsequently questioned (U.S. EPA, 1985; Schatzow, 1984). A panel of NTP scientists reevaluated the histological slides and concluded that the lesions were hyperplasia and inflammation rather than neoplasia.

Rosenblum et al. (1960) reported a 1-year study in which beagle dogs (4/treatment group, 6/control) were provided diets fumigated to residue levels of 0, 35, 75, or 150 ppm bromomethane. No tumors were observed at any dose level; however, there was no indication that the dogs were examined for tumors. In addition, 1-year observation is considered to be inadequate by the EPA for tumor induction in dogs.

In an earlier study (Irish et al., 1940) small numbers of rats, guinea pigs, rabbits and monkeys were exposed by inhalation to bromomethane at doses ranging from 0.065 to 0.85 mg/L air. Exposures were for 7.5 to 8 hours/day, 5 days/week for up to 6 months. The authors reported that the highest dose produced acutely toxic effects in all species, but no tumors were observed at any dose level. The short duration of exposure and observation are considered inadequate by the EPA.

Bromomethane is currently on test at NTP.

II.A.4. Supporting Data for Carcinogenicity

Bromomethane has been shown to produce mutations in Salmonella strains sensitive to alkylating agents and to E. coli both with and without the addition of a metabolic activation system (Voogd et al., 1982; Moriya et al., 1983; Kramers et al.,1985; Djalali-Behzad et al., 1981). Bromomethane was also mutagenic in a modification of the standard Salmonella assay employing vapor phase exposure (Simmon and Tardiff, 1978; Simmon, 1978, 1981; Simmon et

al., 1977). Bromomethane was observed to be mutagenic for Drosophila and for mouse lymphoma cells (Voogd et al., 1982; Kramers et al., 1985).

Bromomethane is structurally related to bromoethane which, when tested in mice and rats of both sexes, has shown clear evidence of carcinogenicity in some cases and equivocal in others. NTP (1988) conducted an inhalation bioassay on bromoethane, and the results were recently released in a draft report. Groups of F344/N rats (50/sex) and B6C3F1 mice (50/sex) were exposed to 0, 100, 200 or 400 ppm bromoethane 6 hours/day for 5 days/week. A statistically significant increase in uterine adenomas, adenocarcinomas, or squamous cell carcinomas was observed in female mice exposed to 200 and 400 ppm, indicating clear evidence of carcinogenic activity. Equivocal evidence of carcinogenic activity was reported for male and female rats and male mice. While alveolar/bronchiolar adenomas or carcinomas and pheochromocytomas were observed in male rats, the incidences were not dose-related and were within the historical ranges for NTP studies. Granular cell tumors of the brain were also observed in male rats and, although not statistically significant, the incidence was higher than historical incidence in either the study lab or NTP studies. The incidence of alveolar/bronchiolar neoplasms in exposed male mice was marginally greater than control or historical incidence. An increased incidence of gliomas in exposed female rats was significant by the trend test; however, the incidence was not significantly greater when compared with the controls in the study and the controls used in NTP studies.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1985, 1986, 1987

The Health and Environmental Effects Profile for Methyl Bromide and the Health Effects Assessment for Bromoethane received Agency Review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 02/01/1989, 03/01/1989

Verification Date — 03/01/1989

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Bromomethane conducted in November 2001(revised May 2003) identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Bromomethane
CASRN — 74-83-9
Primary Synonym — Methyl bromide

VI.A. Oral RfD References

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VI.C. Carcinogenicity Assessment References

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VII. Revision History

Substance Name — Bromomethane
CASRN — 74-83-9
Primary Synonym — Methyl bromide

Date	Section	Description
06/30/1988	I.A.	Withdrawn; new RfD verified (in preparation)

Date	Section	Description
09/26/1988	I.A.	Oral RfD summary replaced
06/01/1989	II.	Carcinogen summary on-line
04/01/1992	I.B.	Inhalation RfC summary on-line
12/03/2002	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Bromomethane
CASRN — 74-83-9
Primary Synonym — Methyl bromide
Last Revised — 01/31/1987

- 74-83-9
- Brom-o-gas
- Bromomethane
- Curafume
- Dowfume MC-2 Soil Fumigant
- Dowfume MC-33
- Edco
- Embafume
- Halon 1001
- Haltox
- Iscobrome
- Kayafume
- MB
- MBX
- MEBR
- Metafume
- Methane, Bromo-
- Methogas

- Methyl bromide
- Monobromomethane
- Pestmaster
- Profume
- R40B1
- Rotox
- Terabol
- Terr-o-gas 100
- Zytox