Before a Decision-Making Committee
Of the Environmental Protection Authority

APP203660

Under	the Hazardous Substances and New Organisms Act 1996
In the matter of	the modified reassessment of methyl bromide
By	**Stakeholders in Methyl Bromide Reduction Inc** Applicant

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STATEMENT OF EVIDENCE OF MARK ALAN PEMBERTON

27 JULY 2020

Counsel Acting
M J Slyfield
Stout Street Chambers

(04) 915 9277
morgan.slyfield@stoutstreet.co.nz
PO Box 117, Wellington

INTRODUCTION

1. My full name is Mark Alan Pemberton.

Qualifications and Experience

2. I have a a B.Sc. (Honours) in Biology from Manchester University and a Ph.D. in Toxicology from Bradford University, UK.

3. I am the owner and principal toxicologist of Systox Ltd, and for more than 40 years I have worked as a regulatory toxicologist. I am a member of the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Scientific Committee and have worked on, chaired and stewarded several past and current task forces on chemicals and regulatory issues.

4. Before starting my consultancy in 2011, I worked for ICI in Pharmaceutical research, as a study director and facility manager at the Central Toxicology Laboratory and latterly as a business toxicologist with responsibility for several of ICI's businesses. I was the founder of the European Chemical Industry Council (CEFIC) Methacrylates Sector Group Methacrylates Toxicology Committee and chaired this between 1992 and 2002. I am the current chairman of the US Methacrylate Producers Association (MPA), Science Committee and the US Cyanide Council Toxicology Committee, the US Cyanide Counsel and a member of the US Acylonitrile Association.

5. I have over 20 years of setting company occupational exposure standards, stewarded the ECETOC Guidance on assessment factors to derive a DNEL (Derived No Effect levels) and the primary author ECETOC's second guidance document on this topic that is in preparation.

6. I provided evidence to another Decision-making Committee of the EPA, in relation to the setting of a TEL for ethanedinitrile (EDN).

Scope of Evidence

7. Sullivan Environmental Consulting Ltd (SEC) has undertaken air dispersion modelling to predict exposures to methyl bromide, based on timber

fumigations at the Port of Tauranga.[1]

8. I have been contracted by STIMBR to provide an analysis of the human health effects that are likely to occur as a result of persons being exposed to MeB at levels predicted by SEC's modelling.

9. I have been instructed to base my analysis on predicted exposures up to (and including) concentrations at the 99.99th percentile values from the distributions produced by the modelling.

Code of Conduct

10. I understand this reassessment is to be determined by a Decision-making Committee of the Environmental Protection Authority. However, I have read the Code of Conduct for expert witnesses in the Environment Court Practice Note 2014 and I have complied with it when preparing this evidence. Other than when I state that I am relying on the advice of another person, this evidence is within my area of expertise. I have not omitted to consider material facts known to me that might alter or detract from the opinions that I express.

Executive Summary

11. In my assessment there is low confidence in any prediction of likely health effects based upon the existing TEL values. Since the setting of the TEL values there have been more recent and reliable reviews that provide a more appropriate basis for assessing likely health effects. Utilising that data, there can be moderate to high confidence that no adverse health effects would occur for the exposures predicted by the air dispersion modelling.

ASSESSMENT OF HUMAN HEALTH EFFECTS

Preamble

12. TELair values are air quality controls set by ERMA to manage the risks posed by toxic substances to human health and are intended to protect the general population from involuntary and accidental exposure to a chemical.

[1] "Modelling Report for Methyl Bromide Exposures for Timber Fumigation at the Port of Tauranga, New Zealand" (25 June 2020).

TELair values are set for 1hr, 24hr and annual exposure periods. TELair 1hr values are protective against immediate effects from acute exposure while TELair annual values are protective against adverse effects that may occur during continuous lifetime exposure. TELair 24hr values are protective against adverse effects that may occur within a 24-hr timeframe and can be "effects-based" or "derived" from an annual-based TEL protective of long-term exposure, and converted to 24-hr by application of a standard factor.

13. When predicting adverse health effects that may occur when TELair values are exceeded it is important to understand the basis upon which the values were established, and the "Window of Susceptibility" for the toxicity endpoint being considered. Immediate effects, e.g. acute toxicity and irritation, are more relevant toxicities for TELair 1hr predictions and chronic effects, e.g. cancer etc., for TELair annual predictions. In the case of TELair 24hr predictions these can be made with relatively high confidence if the value is "effects-based" but there will be low confidence if it is "derived" from a TELair annual since it is unlikely that the "Window of Susceptibility" required for these toxicities to develop will be expressed within this short timeframe.

14. Accordingly, in order to develop predictions of sufficiently high confidence I have considered the basis for the existing TELair values, the toxicities that they are protecting against and their "Window of Susceptibility" based upon their recognised mode of action. Since the existing TELair values are in some cases based upon health-based standards established in the USA decades ago, I have researched the background to these standards and critically reviewed their relevance in light of the current state-of-knowledge on the toxicity of MeB.

15. This differs from the approach taken by the Institute of Environmental Science and Research Limited (ESR), who have assessed health risks to bystanders from MeB fumigations at the Port of Tauranga in two reports: a July 2019 report based on air dispersion modelling by Golder, and a July 2020 addendum based on SEC's most recent modelling. ESR's assessments rely on current TELair values set by ERMA in 2010 as the most relevant reference concentrations for assessing human health risks, whereas I consider there are more recent and reliable reviews that provide a more appropriate basis for the assessment. Despite these differences of approach, we reach a

common conclusion, namely that there will be no adverse health effects at the exposures to MeB predicted in SEC's latest modelling.

Basis of the current TELs

16. The existing TELair values are based upon prior established health-based standards in the USA.

17. The TELair (1hour) is based on the Permissible Exposure Limit (PEL) set by the Office of Environmental Health Hazard Assessment (OEHHA) of California in 2008 (Cal EPA OEHHA, 2000).

18. The TELair (24hour) and TELair (chronic, annual average) are based on the reference concentration (RfC) established by the US EPA (US EPA, 2008; RfC last updated in 1992)(U.S. EPA, 1992).

19. Since the setting of the PEL by the OEHHA of California, and the RfC by the US EPA, there has been other more recent, and more informative reviews on the toxicity of methyl bromide including the US NAC AEGL review of 2012 (NAC, 2012), the North Carolina DAQ review of 2019 (US North Carolina DAQ, 2019), and the ATSDR Toxicological Profile of March 2020 (ATSDR, 2020). These reviews significantly advance our understanding of the relevance of the available human health and animal toxicology data on methyl bromide for human risk assessment and provide a more appropriate basis than the PEL and RfC for the assessment of likely health effects of exposures to methyl bromide.

TELair (1 hour)

Basis for the existing standard

20. As stated previously, the 1 hour TEL is based on the PEL set by the California OEHHA. The OEHHA, 2008 assessment cites the paper by Watrous, 1942 as its key study. The OEHHA documentation contains a brief description of the key findings:

> During a two-week manufacturing operation, 90 persons were exposed to concentrations of methyl bromide generally less than 35 ppm (136 mg/m3)). Toxic symptoms developed sometime during the workshift, for example, following a few hours of exposure. In others, the symptoms were delayed and did not develop until several hours following the shift. The symptoms occurred in 33 of the 90 workers and were described as mild systemic symptoms primarily of anorexia, nausea and headache. Anorexia (reported by 25 of the 90 workers) was a

> common symptom and in some cases lasted for a week or more post-exposure, but without marked weight-loss. In some cases, the symptoms progressed to vomiting. Headache was a fairly common symptom (16 of 90) which disappeared when exposure ceased. While exposure was measured in a crude fashion using a "Frigidaire Leak Detector" (measures halides by color of flame), extensive monitoring was conducted throughout the manufacturing operation. In general, concentrations were at or below the limit of detection of 35 ppm.

21. OEHHA went on to describe the basis for their setting of the REL as follows:

> Study Watrous, 1942 Study population humans, 90 workers Exposure method acute inhalation of 35 ppm Critical effects anorexia, nausea, headache LOAEL 35 ppm NOAEL not available Exposure duration 2 hours Extrapolated 1 hour concentration 59 ppm C1.33 (2 hr) = C1.33 (1 hr) LOAEL uncertainty factor 6 Interspecies uncertainty factor 1 Intraspecies uncertainty factor 10 Cumulative uncertainty factor 60 Reference Exposure Level 1 ppm (3.9 mg/m³; 3,900 µg/m³)
>
> The evaluation by Watrous (1942) of 90 workers indicated that symptoms developed during the workshift. We thus assumed a 2 hour exposure was sufficient to cause the symptoms to occur. Using the value for the exponent "n" in the modified Haber's Law equation Cn x T = K of 1.33, derived by Zwart et al. (1992) from the data of Irish et al. (1940), we extrapolated to a one-hour LOAEL of 59 ppm. Applying an uncertainty factor of 6 for extrapolation of a LOAEL to a NOAEL for mild adverse effects, and an additional uncertainty factor of 10 for intraindividual variability yields an acute REL of 1 ppm."

22. The original article by Watrous could not be obtained. However, the NAC AEGL committee in 2012 also cited the Watrous study, but in this case as an example of the use of imprecise measurement of exposure, stating:

> Measurements of methyl bromide were generally less than 35 ppm, but exposures were based on a color detection method (methanol torch) with a lower detection limit of 35 ppm. Analytic methods for detecting higher concentrations involved flame colorimetry, an imprecise method. The exposures were complicated by accidents and routine dermal contact with the cooled liquid.

23. The US North Carolina (DAQ) review of 2019 not only criticised the Watrous study, but also the way that it had been used by the California OEHHA, stating:

> DAQ was not able to locate a copy of the original 1942 study, but did locate a 1981 paper (Anger et al., 1981) that discussed the original study. The Anger et al. paper identified the 1940 exposure estimate was based on a non-specific detector, a "gross measuring device, the halide detector". This indicates that the estimated exposure concentration that induced the described "mild" effects did not provide a level of contaminant specificity or quantitation accuracy required to meet current levels of data quality. This inaccuracy was compounded by the extrapolation of an estimation that a 2-hour exposure resulted in the observed effects and was used to estimate a 1-hour exposure concentration. Additionally, DAQ noted that current risk assessment methods apply a default UF of 10 to adjust a LOAEL to a NOAEL when a NOAEL is not defined by the study data. An UF of 6 used to derive the 1 ppm level is less health protective than an UF of 10.

24. DAQ concluded:

> Because of the uncertainty of the exposure concentration measurement, the small number of subjects, the severity of the adverse effects utilized as the critical effects for the LOAEL, the extrapolation methods and the lack of documentation available, the DAQ does not judge this as an appropriate reference for an acute inhalation level protective of public health.

25. In summary, the AEGL and DAQ identify the following concerns that question the suitability of the Watrous study for setting a health-based standard and the way in which OEHHA made the derivation:

(a) Original 1942 article cannot be obtained so it is not possible to verify all details, though some further details were obtained from the Anger et al., 1981 paper.

(b) It appears that only area measurements or time weighted average exposure data are available (limit of detection 35ppm). AEGL and DAQ reviewers' note that the exposures were complicated by "accidents and routine dermal contact with the cooled liquid". Exposure data on peak exposures that would have occurred during accidents, and that would have likely been responsible for the reported effects, were not available. Also this measure of exposure does not account for dermal contact and absorption.

(c) The Anger et al. paper identified the 1940 exposure estimate was based on a non-specific detector, a "gross measuring device, the halide detector" so specificity or quantitation accuracy do not meet current levels of data quality.

(d) The duration of exposure was reported as being up to 2 weeks. OEHHA reported the symptoms as having "developed sometime during the workshift, for example, following a few hours of exposure. In others, the symptoms were delayed and did not develop until several hours following the shift" so the claim that it was "assumed a 2 hour exposure was sufficient to cause the symptoms to occur" was without any rational explanation or justification.

(e) OEHHA cited the 35ppm as a LOAEL based upon reported mild effects and applied an UF of 6 opposed to a conventional UF of 10 without justification.

(f) It is also noted that OEHHA used the value of n of 1.33 for time scaling (Cn × t = k) derived by Zwart et al. (1992) from the data of Irish et al. (1940), whereas the NAC AEGL ctee used 1.2, based on lethality data in the rat. While it is not clear which factor is more or less appropriate there is an apparent difference that makes a significant impact on the time adjusted outcome.

(g) Effects were only observed in a proportion of workers and were described as mild systemic symptoms primarily of anorexia, nausea and headache (33/90); anorexia that in some cases lasted for a week or more post-exposure, but without marked weight-loss but did progressed to vomiting in some cases (25/90) and headache (16/90).

26. Since exposures were based on an insensitive colour detection method (methanol torch) with a lower detection limit of 35 ppm and there were concerns that peak exposures and dermal contact were not recorded, nor necessarily reflected in these measurements, in my opinion the value of 35ppm is not a robust point of departure upon which to set a health-based exposure standard. Furthermore, the scaling to a 1hour exposure period and the use of a factor of 6 to extrapolate from a presumed LOEL to a NOEL is completely arbitrary. With all these now recognised weaknesses the basing of a 1hr TEL solely on the study of Watrous is associated with a low degree of confidence.

A more robust POD

27. Controlled laboratory studies using animal models provide a more comprehensive review of health effects associated with inhalation exposures to methyl bromide.

28. NAC AEGL (2012) committee established health based values for methyl bromide based upon animal data. AEGL-1 values[2] were not established as methyl bromide has no odour or irritation properties at concentrations below those that cause adverse health effects.

[2] AEGL-1 is the airborne concentration (expressed as ppm [parts per million] or mg/m3 [milligrams per cubic meter]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

29. The NAC AEGL documentation, 2012 states:

> The primary target of toxicity in humans accidentally or occupationally exposed to methyl bromide is the CNS (Alexeeff and Kilgore 1983; O'Neil et al. 2014). Symptoms of overexposure by inhalation to methyl bromide are headache, visual disturbance, vertigo, nausea, vomiting, anorexia, irritation of the respiratory system, abdominal pain, malaise, muscle weakness, incoordination, slurring of speech, staggering gait, hand tremor, convulsions, mental confusion, dyspnea, pulmonary edema, coma, and death from respiratory or circulatory collapse (O'Neil et al. 2014).

30. As this is the lead health effect in humans they established the AEGL-2 values[3] based on the no-observed-adverse-effect level (NOAEL) for neurotoxicity, as evidenced by a lack of clinical signs in studies with rats and dogs. The weight-of-evidence from those studies indicates that 200 ppm of methyl bromide for 4 hours is the threshold concentration for neurotoxicity (Hurtt et al. 1988; Hastings 1990; Japanese Ministry of Labour 1992; Newton 1994). Key short duration studies include:

(a) Rats:

(i) No clinical or neurotoxic signs were observed in rats exposed at 90 or 100 ppm for 6 h (Hurtt et al. 1988; Driscoll and Hurley 1993).

(ii) No clinical or neurotoxic signs were observed in rats exposed at 63 ppm for 8 h (Honma et al. 1985).

(iii) No clinical signs were observed in rats (species not specified, N=30) at 200 ppm for 4 hr (Hastings, L. 1990).

(iv) No clinical or neurotoxic signs were observed in F-344rats exposed at 150 ppm for 4 h (Japanese MOL, 1992).

(v) A NOAEL of 90 ppm for damage to the olfactory epithelium* was observed after 6-h exposure of rats to methyl bromide (Hurtt et al. 1988).

(vi) No olfactory epithelium lesions were found after a 6-h exposure at 350 ppm (Driscoll and Hurley 1993).

[3] AEGL-2 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

(vii) No clinical signs and reversible olfactory epithelium degeneration* was observed in F-344 rats (N=15 male) at 200 ppm for 6 h (Newton, 1994).

(viii) Reversible metaplasia of the olfactory epithelium* was observed in F-344rats exposed at 225 ppm for 4 hr (Japanese MOL, 1992).

(ix) Transient changes in standard neurobehavioral tests were observed in rats after a 6-h exposure at 350 ppm (Driscoll and Hurley 1993).

(b) Mice:

(i) No clinical or neurotoxic signs were observed in mice exposed at 566 ppm for 1 h, although there was a transient weight loss in the mice (Alexeeff et al. 1985).

(ii) No clinical or neurotoxic signs were observed in mice exposed at 225 ppm for 4 h (Japanese MOL, 1992).

(iii) A NOAEL of 150 ppm for damage to the olfactory epithelium* was observed after 4-h exposure of mice to methyl bromide (Japanese MOL, 1992).

(c) Dogs:

(i) No toxic signs or brain lesions were observed in a beagle dog (N=1) at 233 ppm for 5 hr (Hurtt et al., 1988).

(ii) Dogs exhibited clinical signs of tremors, hunched appearance, and laboured breathing during the last 2 h of a 7-h exposure at 233 ppm (Newton 1994).

31. As recognised by the NAC AEGL committee:

> Reversible impairment of olfactory function (lesions of the olfactory epithelium) was observed in the rat (Hurtt et al. 1988; Hastings 1990; Japanese Ministry of Labour 1992). These lesions are specific to the nasal olfactory epithelium of the rat, based on nasal air flow patterns (Bush et al. 1998; Frederick et al. 1998), so it is unlikely that such lesions would occur in primates at the same exposure concentration and duration.

32. The same considerations would apply to the similar findings in mice (MOL, 1992).

33. The two 90-day inhalation studies in mice reported by Drew, 1984 and Cockerham et al, 1992 were not included since the NAC AEGL committee had recognised that:

> Because of differences in methyl-halide metabolism between mice and other rodents and the greater sensitivity of mice to the structurally-similar chemical methyl chloride (metabolism is also by the glutathione [GHS] pathway), the mouse was not considered an appropriate model from which to derive AEGL values for methyl bromide.

On this basis greater weight should be given to the findings in rats over mice.

34. The assertion that neurotoxicity is the lead health effect for acute exposure in humans is consistent with the data from all studies in animals that confirm that short term (less than 4 hrs) inhalation exposures in animals of up to approximately 200ppm do not result in any adverse clinical effects (see Appendix c of the NAC AEGL (2012) documentation and figure C-1 below).

APPENDIX C

CATEGORY GRAPH OF TOXICITY DATA AND AEGL VALUES FOR METHYL BROMIDE

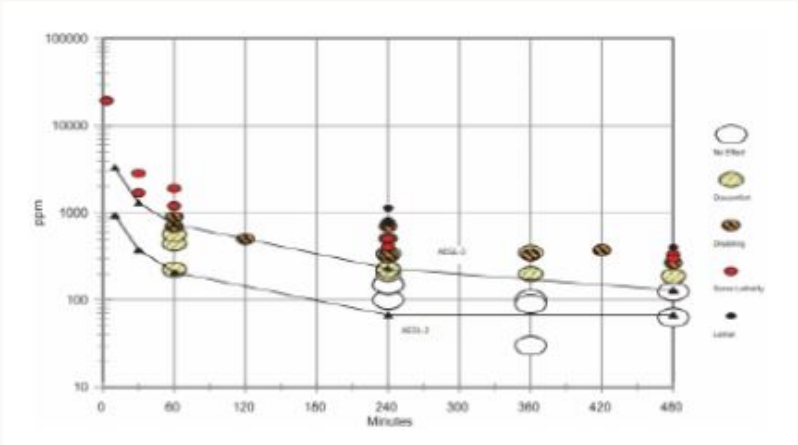

FIGURE C-1 Category graph of toxicity data on methyl bromide compared with AEGL values. All of the toxicity data pertain to laboratory animals; no clinical data were available.

35. Changes in neurotransmitter levels in rat brains following 8-hour exposure to 31 ppm MeB resulted in significant decreases in norepinephrine levels in the hypothalamus and 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 (Honma 1987; Honma et al. 1987).

36. Honma et al. (1985) reported the effects of 8-hr exposure to MeB in rats at concentrations approaching the 8-hr LC50 value of 302 ppm (95% confidence limits 267–340) ppm. Decreased body temperature was observed at 125 ppm and decreased locomotor activity including reduced activity levels, muscular coordination and muscle strength in a rats exposed at 188 ppm, but not 125ppm, and that reversed by 24 hr after the exposure.

37. Continuous exposure at 10 ppm for 3 weeks resulted in decreases in norepinephrine levels in the hypothalamus (Honma et al. 1982). The authors suggested that the results suggest that MeB might have enhanced the stimulation of DA receptors and weakened the stimulation of ACh receptors in the brain.

38. Gotoh et al. (1994) reported slight atrophy in the cerebellum in a 2-year study exposing mice at 64 ppm. However, it should be noted that mice are very sensitive to MeB toxicity, "because of differences in methyl-halide metabolism between mice and other rodents and the greater sensitivity of mice to the structurally-similar chemical methyl chloride (metabolism is also by the glutathione [GHS] pathway" (NAC, 2012).

39. In summary, the dose response curve for MeB toxicity is extremely steep going from subtle changes in neurotransmitter levels in the brain in the low tens of ppm range to functional deficit and clinical adverse effects as it approached the acute LC50 over an order of magnitude higher.

40. The most sensitive measure of acute neurotoxicity appears to be changes in neurotransmitter levels in rat brains after single 8-hour exposures to 31 ppm. While this is an effect level, functional deficits are apparent close to the threshold for clinical effects, around 200ppm.

Modification of POD to account for differences in exposure duration

41. An 8hr exposure at 31ppm MeB corrected for time scaling according to Haber's rule ($C^n \times t = k$) (ten Berg et al., 1986) corresponds to a 1 hour exposure of 153.5ppm or 175.4ppm for ^{n}=1.3 or 1.2 respectively.

42. It would not be appropriate to calculate the equivalent 1hr exposure level for functional deficit observed following 8hrs since the data is too limited and currently indistinguishable from the 200ppm threshold for clinical effects observed in toxicology studies. 200ppm MeB corrected for time scaling ($C^n \times t = k$) (ten Berg et al., 1986) to a 1 hour exposure equals 581ppm or 635ppm for ^{n}=1.3 or 1.2 respectively.

43. The lower value of the range 154ppm for changes in neurotransmitter levels in the absence of functional effects and 581ppm for functional effects can be taken as corrected PODs for the assessment of health effects.

Application of Uncertainty Factors in deriving a TELair (1 hour)

44. In terms of inter-species uncertainty the use of standard allometric scaling factors are not applicable for extrapolation of inhalation studies to human inhalation exposure. In this regard it is noteworthy that the NAC AEGL committee in setting the AEGL-2 and -3 values in 2012 recognised that "*Because uptake of methyl bromide is greater in rodents than in humans (based on comparative respiratory rates and comparisons with methyl chloride) and because GST concentrations in rodents are higher than in humans (resulting in more rapid production of toxic metabolites), an interspecies uncertainty factor of 1 was considered sufficient*".

45. In terms of intra-species uncertainty the NAC AEGL committee again recognised that "Humans differ in their capacity to metabolize methyl bromide, but toxicologically the difference is not thought to be greater than 3-fold (Nolan et al. 1985). An intraspecies uncertainty factor of 3 is supported by the steep dose-response curve for lethality by methyl bromide, which indicates that there might be little intraspecies variation". Indeed, human polymorphism with respect to GST levels and differences in sensitivity of humans would favour individuals being of lesser not greater susceptibility. Notwithstanding this and considering the steep dose response curve, the use of the default factor of 10 would provide a greater level of protection for more susceptible individuals.

46. Considering the POD is set based upon sensitive changes in neurotransmitter levels in the absence of clinical relevance and the use of a factor of 10 compared with 3 for intra-species uncertainty, no other uncertainty factors, for example to compensate for the adequacy of the database, are considered necessary.

47. Applying this overall UF of 10 to the PODs of 580.9ppm for functional deficits/clinical effects and 153.5ppm for changes in neurotransmitter levels in the absence of functional effects produces TELs of 58ppm and 15ppm, respectively.

48. There is moderate to high confidence in the derived TEL (1 hour) of 15ppm for changes in neurotransmitter levels in the absence of functional effects considering the strength of the database, the margin of safety between this and the TEL for the functional deficits/clinical effects and the fact that no reports of adverse effects in human have been reported below this exposure level.

TELair (24 hour)

49. The basis of the current TELair (24 hour) is the adoption of the acute (24 hour) reference concentration (RfC) established by the US EPA (US EPA, 2008; last updated in 1992). US EPA claims that the acute reference value was derived based on the need to protect humans from developmental toxicity.

50. However, studies cited in the EU registration of methyl bromide under REACH provide reliable evidence that methyl bromide is not reproductive toxicant and there is no concern for developmental toxicity. Methyl Bromide was non-toxic to the reproductive system in a Two-Generation Reproduction Toxicity Test (EU Method B.35). Methyl Bromide was also not a selective developmental toxicant at exposure levels that do not produce overt maternal toxicity in rats and rabbits (EEC B30 Teratogenicity Study).

51. Overview of reproduction toxicity studies with Methyl Bromide:

Parameter	Species	Result	Reference
NOEL (Multi generation study)	Rat	32 mg/kg bw	Enloe et al, 1986
NOEL (Developmental study)	Rat	74 mg/kg bw	Sikov et al, 1981
NOEL (Developmental study)	Rabbit	20 ppm	Sikov et al, 1981
NOEL (Developmental study)	Rabbit	40 ppm	Breslin et al, 1990

52. The documentation for the IRIS chronic RfC states that it is based on the LOAEL: 11.7 mg/m^3 (3 ppm) for nasal lesions described as "very slight basal cell hyperplasia of the olfactory epithelium" in rats from a 2-year study (Reuzel et al., 1987, 1991). The IRIS reviewers adjusted the 6-hour/day and 5-day/week animal study LOAEL to a 24hour/day and 7-day/week LOAEL concentration, followed by extrapolation of the rodent LOAEL ($LOAEL_{rat}$) to a human-equivalent concentration (HEC) LOAEL ($LOAEL_{HEC}$). The RfC derivation includes an uncertainty factor (UF) of 3 for use of a LOAEL (UFL) for "mild effects" and an UF of 3 for intraspecies extrapolation (UFA) because dosimetric adjustments had been applied (the RGDR-based model), and an UF of 10 for intraspecies (UFH, human population) variability, resulting in an overall UF = 100. This derived a 0.001 ppm (5 µg/m^3).

53. ATSDR also set a chronic inhalation exposure provisional Minimal Risk Level (MRL) for methyl bromide in 2018. ATSDR's chronic MRL was derived from the same studies as the IRIS chronic RfC (U.S. EPA. 1992) i.e. 0.001 ppm (5 µg/m^3) based on nasal lesions described as "very slight basal cell hyperplasia of the olfactory epithelium" in rats from a 2-year study (Reuzel et al., 1987, 1991). The chronic MRL was derived from a $LOAEL_{rat}$ of 3.1 ppm adjusted to a $LOAEL_{HEC}$ of 0.13 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; the 3 UFs are calculated as the square root of 10).

54. However, as noted by the NAC AEGL committee:

> these lesions are specific to the nasal olfactory epithelium of the rat, based on nasal air flow patterns (Bush et al. 1998; Frederick et al. 1998), so it is unlikely that such lesions would occur in primates at the same exposure concentration and duration.

Accordingly nasal lesions, while being the most sensitive endpoint in rodent inhalation studies, is unlikely to be the lead health effect in humans following chronic exposure.

55. ATSDR (2018) identifies neurotoxicity as the most sensitive effect of acute exposures to animals and set a provisional Minimal Risk Level (MRL) for methyl bromide intermediate-duration inhalation exposures (15-364 days) of 0.02 ppm (78 µg/m^3). The intermediate inhalation MRL is based on a 10 ppm LOAEL for neurobehavioral effects from the NTP (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 an $LOAEL_{HEC}$ 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).

56. While neurotoxicity is evidently the most sensitive endpoint relevant to humans the ATSDR assessment failed to recognise the limitations of relying on a study of mice, as expressed by NAC AEGL, 2012:

> Because of differences in methyl-halide metabolism between mice and other rodents and the greater sensitivity of mice to the structurally-similar chemical methyl chloride (metabolism is also by the glutathione [GHS] pathway), the mouse was not considered an appropriate model from which to derive AEGL values for methyl bromide.

57. The TEL (24 hour) can more appropriately be extrapolated from the most sensitive measure of acute changes in neurotransmitter levels in rat brains after single 8-hour exposures to 31 ppm MeB. Corrected for time scaling according to Haber's rule ($C^n \times t = k$) to a 24 hour exposure leads to a conservative corrected POD of 13.3ppm or 12.4ppm for ^{n}=1.3 or 1.2 respectively. As the overall uncertainty factor of 10 used for deriving the 1 hour TEL equally applies to the 24 hr TEL this would result in a TEL(24hrs) of 1.3ppm or 1.2ppm.

58. A conservative approach would be to take the lowest value of 1.2ppm as the 24hr TEL.

TELair (chronic, annual average)

Basis for the existing standard

59. The TELair (chronic, annual average) is based on the reference concentration (RfC) established by the US EPA (US EPA, 2008; RfC last updated in 1992). The basis of these standards was a LOAEL of 11.7 mg/m^3 (3 ppm)/LOAEL (HEC): 1.7ppm (0.48 mg/m^3) for degenerative and proliferative lesions of the olfactory epithelium of the nasal cavity of rats. A total uncertainty factor (UF) of 100 was applied.

60. However, as mentioned previously the NAC AEGL committee noted:

> these lesions are specific to the nasal olfactory epithelium of the rat, based on nasal air flow patterns (Bush et al. 1998; Frederick et al. 1998), so it is unlikely that such lesions would occur in primates at the same exposure concentration and duration.

Accordingly nasal lesions while being the most sensitive endpoint in rodent inhalation studies is unlikely to be the lead health effect in humans following chronic exposure.

A more robust POD

61. There are several repeat dose inhalation studies available to assess the chronic toxicity of methyl bromide, some of which are well conducted guideline, or comparable to guideline and provide a robust basis for setting a long-term health based standard.

62. The longer duration inhalation studies on methyl bromide include:

(a) The NOEL for any effects in rabbits was < 65 ppm and for rats 55ppm for 28 days (Anger et al, 1981).

(b) The NOEL for any effects in rats was 160 ppm for 28 days (Eustis et al, 1988).

(c) The NOEL for any effects in rats was 150 ppm for 28 days (Kato et al, 1986).

(d) The NOEL for any effects in dogs was 55 ppm for 28 days (Newton, 1994).

(e) No neurotoxic signs or tissue lesions were observed in dogs at 20 ppm (the highest concentration tested), 7 h/day, 5 days/week for 6 weeks (Schaeffer 2002).

(f) The NOEL for decreased body weight, decreased serum creatine kinase, and increased chloride and decreased activity in dogs was 25 ppm for 28 days (McMahon, 1977).

(g) No neurobehavioral effects were observed in rabbits at 27 ppm for 8-months (Russo et al. 1984).

(h) Survival was unaffected in F-344.DuCrj rats exposed to MeB at 0, 4, 20, or 100 ppm for 104 weeks. (Gotoh et al. 1994).

(i) The NOAEL for decreases in body weight and absolute and relative brain weight was 3 ppm and LOEL 30ppm in Wistar rats exposed for 29 months. 90 ppm MeB resulted in reduced body weights, increases in cartilaginous metaplasia (males), moderate to severe myocardial degeneration (females), and thrombi (males and females) and early deaths. Basal-cell hyperplasia of the olfactory epithelium was observed in MeB exposed and control animals with higher incidence in exposed animals. (Reuzel et al. 1987, 1991).

(j) The LOAEL for cerebellar and cerebral degeneration, myocardial degeneration and chronic cardiopathy, sternal dysplasia and olfactory metaplasia/necrosis was 100 ppm and the NOAEL 33 ppm. No olfactory lesions were found in the 3-ppm group at the end of 24 months (NTP 1992).

(k) The NOAEL for both maternal toxicity and developmental effects in rats and rabbits was 20 ppm (Breslin et al. 1990; Hardin et al. 1981, Sikov et al, 1981).

(l) The NOEL in a Multi generation study in rats was 32 mg/kg bw (Enloe et al, 1986).

63. The available studies suggest the presence of a threshold c.a. 25ppm below which adverse effects are not observed, irrespective of the study duration. The slight but statistically significant decreases in body weight and absolute and relative brain weight observed by Reuzel et al. (1987, 1991) at 30 ppm is balanced by the NOAEL of 33 ppm for all effects observed by NTP (1992). On

balance, 25ppm can therefore be used as a POD for deriving a TELair (chronic, annual average). This value is sufficiently protective for acute neurotoxicity, as reflected in sensitive changes in neurotransmitter levels in rat brains after single 8-hour exposures to 31 ppm.

Modification of POD to account for differences in exposure duration

64. Since the threshold c.a. 25ppm was observed in experimental studies in animals that would typically have employed 6 h/day, 5 days/week exposure schedule it is necessary to convert this to a 24h/day, 7 days/week for the consumer/general public by multiplication by a factor of 6/24 x 5/7 i.e. 0.179. This results in a modified POD of 4.29ppm.

Application of Uncertainty Factors in deriving a TELair (chronic, annual average)

65. In terms of inter-species uncertainty the use of standard allometric scaling factors are not applicable for extrapolation of inhalation studies to human inhalation exposure.

66. The NAC AEGL committee in setting the AEGL-2 and -3 values recognised that:

> Because uptake of methyl bromide is greater in rodents than in humans (based on comparative respiratory rates and comparisons with methyl chloride) and because GST concentrations in rodents are higher than in humans (resulting in more rapid production of toxic metabolites), an interspecies uncertainty factor of 1 was considered sufficient.

67. It is noted that the mechanism of methyl-bromide-induced CNS toxicity has not been established, although it is known that methyl-bromide methylation of sulfhydryl containing enzymes and proteins in mammalian tissues and that CNS toxicity might be mediated by CNS glutathione depletion and inhibition of GST activity (Davenport et al. 1992). However, the possibility that systemic toxicity could occur through some other mechanism cannot be excluded, so an additional uncertainty factor of 2.5 to account for toxicodynamic differences between animals and humans is recommended.

68. In terms of intra-species uncertainty the NAC AEGL committee again recognised that:

> Humans differ in their capacity to metabolize methyl bromide, but toxicologically the difference is not thought to be greater than 3-fold (Nolan et al. 1985). An intraspecies uncertainty factor of 3 is supported by the steep dose-response curve

for lethality by methyl bromide, which indicates that there might be little intraspecies variation.

69. Again, a more conservative approach would be to apply the default factor of 10 thereby affording a higher level of protection with respect to the potential for human polymorphism and differences in sensitivity of humans with respect to GST levels.

70. Considering the already conservative assumptions of using a UF of 10 compared with 3 for intra-species uncertainty no other uncertainty factors, for example to compensate for the adequacy of the database, are considered necessary.

71. This derives an overall UF of 25 and when applied to the modified POD of 4.29ppm derives a TELair (chronic, annual average) of 0.17 ppm.

72. There is a high degree of confidence in the TELair (chronic, annual average) of 0.17ppm derived from studies in animals as it is consistent with the observation of no reports of adverse effects observed in exposed individuals at or below this level.

CONCLUSIONS

73. I have low confidence in any prediction of likely human health effects based upon the existing TEL values. Since the TEL values were set there have been more recent and reliable reviews that provide a more appropriate basis for assessing likely health effects. Utilising that information, I have derived alternate TELs. The existing TEL values and my derived alternate TEL values are set out below:

Exposure Period	**NZ EPA**	**Systox, 2020**
TEL 1h	1ppm (3.9mg/m^3)	15ppm (58.5mg/m^3)
TEL 24h	0.333ppm (1.3mg/m^3)	1.2ppm (4.68mg/m^3)
TEL Chronic annual average	0.0013ppm (0.005 mg/m^3)	0.17ppm (0.663 mg/m^3)

In my opinion, the derived alternate TELs can be used to predict likely human health effects from exposure to methyl bromide with a moderate to high confidence.

74. The maximum exposures predicted in the air dispersion modelling conducted by Sullivan Environmental Consulting (excluding the 100th percentiles from distributions) are all well below the derived alternate TELs.

75. In my opinion persons exposed to methyl bromide at the levels predicted by the air dispersion modelling would not experience adverse health effects.

MARK ALAN PEMBERTON

27 July 2020

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