Revisions to Limits for Methanol in the Air of Spacecraft

Robert R. Scully; Hector Garcia; James T. McCoy; Valerie E. Ryder

INTRODUCTION: The previous Spacecraft Maximal Allowable Concentrations (SMACs) for methanol were established by characterizing minor effects upon cognitive functions as a no-observable adverse effects level (NOAEL). However, an increasing awareness of the risk posed by Space-Associated Neuro-ocular Syndrome (SANS) has caused NASA Toxicology to reexamine SMACs for methanol because exposure to it can also adversely affect ocular health. An updated review of the literature indicates that no adjustments to the SMACs due to SANS complications were required, while confirming that effects upon the central nervous system remain the appropriate basis for the SMACs for methanol. Our review, however, identified several issues that provide justification for modest SMAC reductions. It has recently been recognized that inhaled methanol may reach the brain via the olfactory system and be absorbed there into the highly toxic metabolite formaldehyde. A benchmark dose (BMD) for an extra risk of 10%, derived from an analysis of the incidences of neurological lesions in monkeys chronically exposed to methanol, is an order of magnitude less than the Environmental Protection Agency's (EPA's) reference concentration for chronic inhalation of methanol. Reports calling attention to the relative insensitivity of traditional methods of assessing cognitive function erode confidence that adverse effects at the concentration reported as a NOAEL would have been recognizable. Therefore, an additional modest safety factor of three is applied to SMACs for methanol.

KEYWORDS: inhalation toxicity, benchmark dose, exposure limit.

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NASA uses Spacecraft Maximum Allowable Concentrations (SMACs) to provide guidance on acceptable exposures to airborne contaminants during both nominal and off-nominal situations. Short-term concentration limits are intended to prevent irreversible harm and degraded crew performance during off-nominal conditions lasting up to 24 h. Longer term SMACs are intended to prevent adverse health effects (either immediate or delayed) that could degrade crew performance as a consequence of continuous exposure in a spacecraft for up to 1000 d.[41]

SMACs for methanol were originally set by Wong,[46] based upon a no-observable adverse effect level (NOAEL) that was estimated from a lowest observable adverse effect level (LOAEL) derived from findings of impaired vision among teachers who were exposed to methanol vapors while using duplicating machines.[16] These SMACs, ranging from 7 ppm for 180-d exposure to 30 ppm for a 1-h exposure, were later revised by Garcia,[17] who used a NOAEL that was based upon mild cognitive effects experienced by human subjects exposed to low methanol concentrations to revise the SMACs. The revised, less stringent SMACs ranged from 70 ppm for 180 d to 200 ppm for 1 h. A new SMAC for 1000 d was set at 23 ppm.

It is possible for spaceflight crews to be exposed to methanol. A high concentration of methanol was found in a sample of air from the Functional Cargo Block of the International Space Station (ISS), although the exact source was never determined.[23] An increasing awareness of the risk posed by Spaceflight Associated Neuro-ocular Syndrome (SANS)[21,25] has provided an impetus for NASA to reexamine SMACs for methanol because this toxicant also produces adverse effects on ocular health, which can include permanent blindness. With longer duration missions, the risk of permanent decrements to ocular health has been recognized in a subset of crewmembers who have flown aboard the ISS.[1] Ocular changes that include optic-disc edema, cotton wool spots, choroidal folds, optic nerve sheath distention, and/or posterior globe flattening have been observed

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in these crewmembers. These changes have varied in severity and duration among those afflicted.[1] This document examines the toxicity of methanol in view of relevant literature published since these limits were last revised,[17] and reexamines older literature (see **Appendix A** online, https://doi.org/10.3357/AMHP.5378sd.2019 for methods of literature review) in light of recent reconsiderations of the mechanisms responsible for methanol's adverse effects. Literature concerning exposure by ingestion is considered, as it provides the bulk of the evidence for the mechanisms responsible for the production of adverse effects by methanol. However, a reexamination of limits for exposure via ingestion (Spacecraft Water Exposure Guidelines) will be presented elsewhere.

Methanol Toxicity

Ocular effects. In mammals, methanol is metabolized primarily in the liver. In a sequence of oxidative steps metabolites formaldehyde, formate, and carbon dioxide are produced.[13] Studies and case reports show that the first signs of visual toxicity following exposure to methanol are associated with blood formate concentrations greater than 3.7 mmol $\cdot$ L^{-1}.[49] These are observed only after a latent, symptom-free period that usually ranges from 6 to 30 h after exposure. During that interval methanol is metabolized to formaldehyde, formate, and CO_2 until the body's stores of tetrahydrofolate are depleted and blood formate concentrations increase, causing acidosis,[20] inhibition of mitochondrial cytochrome C oxidase (COX),[26,27,33] increasing reactive oxygen species (ROS) and oxidative stress. ROS damages cell membranes,[5] endogenous DNA,[31] and promotes apoptosis.[45]

Methanol-induced depression of ATP production impairs active transport processes that are essential to the regulation of cell volume, resulting in cell swelling. In the case of oligodendroglial cells, their swelling produces "cuffs" around the axons. These compressive forces may be expected to exacerbate adverse effects induced by factors associated with SANS, if, as hypothesized, SANS elevates pressure within the optic nerve sheath.[21,25]

Neurological effects. Although many of the symptoms of methanol poisoning are common to those resulting from metabolic acidosis produced by other causes,[2] several of the outcomes of methanol toxicity, such as irreversible blindness and Parkinsonian effects, are not associated with metabolic acidosis arising from other causes.[44] It was postulated that formaldehyde might be responsible for some of the symptoms of methanol poisoning that are not common to those of acidotic symptoms.[18] This proposition was difficult to reconcile with the well-established findings that methanol is metabolized slowly relative to formaldehyde, and formaldehyde is rapidly converted to formic acid, with a half-life of a few minutes.[29] Therefore, it was thought improbable that formaldehyde produced from orally administered methanol, which is metabolized in the liver, could be distributed from the liver to increase the intracellular level of formaldehyde in the eye or brain sufficiently to account for the damage in those organs.[9] Indeed, the possibility that formaldehyde contributes substantially to the toxicity of methanol has been extensively investigated, but elevated concentrations of formaldehyde have not been found in body fluids of animals after oral administration of methanol[26,27] or in humans after methanol poisoning.[40] However, inhaled alcohol initially bypasses the metabolism in the liver and rapidly reaches the arterial circulation and the brain,[24] and alcohol dehydrogenase, which converts methanol to formaldehyde, is present in the brain.[50] Recently, evidence for conversion of methanol to formaldehyde in the brains of nonhuman primates coupled with detection of formaldehyde in the cerebral spinal fluid after 18 h raises the possibility that formaldehyde may contribute significantly in methanol neurotoxicity.[50] Although McMartin[29] is routinely cited as discounting a role for formaldehyde in the toxicity of methanol, the reports of Tulpe and Dringen[42] and Zhai[50] appear to provide good reasons to take greater notice of the caution given by McMartin[29] that "it is not possible to completely eliminate formaldehyde as a toxic intermediate because formaldehyde could be formed slowly within cells and interfere with normal cellular function without ever obtaining levels that were detectable in body fluids."

Exposures to methanol via inhalation (see **Appendix B**, online, https://doi.org/10.3357/AMHP.5378sd.2019 for a summary) at levels that are without adverse effects upon the optic system can produce significant consequences in the central nervous system (CNS). Case reports describe Parkinsonian effects after chronic exposure to methanol vapors which were not accompanied by adverse effects to the optic system.[15,19] In these cases, the effects developed several weeks[19] to 6 yr[15] after the exposures to methanol vapor had ended. In the latter case, the patient had been exposed for 5 yr at unknown concentrations.[15] The latency was explained as arising from a long-term acceleration of the normal rate of neuronal loss by the toxicant during the period of exposure, which was followed by a continuation of the normal rate of neuronal loss due to aging so that eventually the accumulated loss crossed the threshold for symptoms.[15] In the cases noted,[15] the absence of ocular effects indicates that formate had not accumulated sufficiently to produce detectable decrements in the ocular system. This suggests either that the Parkinsonian effects were more sensitive than ocular effects to formate and/or the Parkinsonian effects were the result of other metabolites of methanol.

Effects of chronic inhalation of methanol were assessed in female long-tailed macaques exposed for 21 h/d for up to 29 mo to 10, 100, and 1000-ppm methanol.[32] This study, conducted by the New Energy Development Organization (NEDO) in Japan, was reported in Japanese. A review of this NEDO[32] study, which was commissioned by the U.S. Environmental Protection Agency (EPA) and conducted by the Eastern Research Group[12] (ERG), reported that the NEDO investigators considered the NOAEL and LOAEL to be 10 and 100 ppm, respectively.

However, a member of the ERG review[12] panel, David Gaylor, proposed calculation of benchmark concentrations for use in noncancer and cancer risk assessments[12] as an appropriate alternative to the traditional use of a NOAEL to estimate a permissible chronic exposure limit. We found no account of the

recommended analysis. Therefore, we used the compilation of the incidence of the degeneration, hyperplasia, and fibrogenesis of stellate cells as a function of methanol concentration, which were provided in Gaylor's assessment of the NEDO study, to conduct the benchmark dose analysis proposed by Gaylor[12] (see **Appendix C** online; https://doi.org/10.3357/AMHP.5378sd.2019). An extra risk of 10% was used as the benchmark response because this is recommended as a standard reporting level for dichotomous data.[10,43] The BMD/BMDLs of the two variables (out of six tested), which met all of the U.S. EPA's recommended criteria for modeling, were 3.7/1.1 ppm for cerebral white matter lesions and 3.3/1.3 ppm for lesions of the Pons tegmentum.

Cognitive effects. Memory tasks[7] and Symbol Digit tests[6] of human subjects were slightly affected by exposures of 1.25 h at 191 ppm and 4 h at 200 ppm, respectively. These exposure conditions would not have caused tetrahydrofolate to become exhausted or formate levels to increase above background levels.[22] The cause of the slight neurocognitive effects, therefore, may be one of methanol's other metabolites. It has been well established that there is a direct correlation between elevated levels of formaldehyde in the brain and memory impairment.[11]

No studies of the effects of methanol on human cognition more recent than those described above[6,7] were identified. However, examinations of chronic methanol exposure effects in animals have been motivated by the recent establishment of a link between the methanol metabolite formaldehyde and the pathology of Alzheimer's disease.[47,48] In a study in which mice were given a solution of 2 or 3.8% methanol in drinking water over 6 wk, impaired spatial recognition and olfactory memory in a Y-maze and olfactory memory paradigms were evident.[47] In vitro experiments with mouse embryonic cerebral cortex neurons and mouse neuroblastoma N2a cells demonstrated that formaldehyde, but not methanol or formic acid, induced microtubule disintegration and tau protein hyperphosphorylation.[47] The in-vitro experiments suggested that formaldehyde was most likely responsible for tau phosphorylation and the subsequent impaired memory in the mice.[47] In studies with Rhesus macaques allowed chronic, ad libitum access to 3% methanol for 2.5 yr, performances on Variable Spatial Delay Response Tasks indicated memory decline,[48] which persisted 6 mo beyond termination of the feeding regimen, the latest time at which the animals were assessed. This change coincided with increases in tau protein phosphorylation in the cerebrospinal fluid during feeding as well as with increases in tau phosphorylated aggregates and amyloid plaques in the frontal, parietal, and temporal lobes, and the hippocampus. These findings are consistent with a role of methanol and its metabolite formaldehyde in neuropathology similar to that of Alzheimer's disease.

SMACs Development

Current SMACs limit exposures to methanol to levels well below those at which formate would accumulate. Therefore, they protect against any exacerbation of SANS-associated effects on the optic nerve and other effects on the ocular system by methanol. Although our review indicates that no adjustments to the SMACs due to SANS complications were required, it confirmed that effects upon the central nervous system remain the appropriate basis for the methanol SMACs and identified several issues that provide justification for modest SMAC reductions. In the last revision to the SMACs for methanol,[17] a 1-h value was derived from a NOAEL of 200 ppm that was based upon studies that identified only minor effects of methanol on memory tasks[7] and Symbol Digit tests.[6] However, after brief exposures to low concentrations of methanol, the demonstration of mild effects with neurobehavioral tests that are capable of detecting effects of severe trauma to the CNS[34,36] which may not be sensitive to less profound effects[8,38] raises concern that tests that are more sensitive could detect effects on performance with exposures below 200 ppm. Although findings that formate, the metabolite long considered responsible for methanol toxicity, did not accumulate after exposures of 200 ppm[14,22,35] appear to support the use of 200 ppm as a NOAEL. A number of recent studies suggest that methanol metabolites other than formate[18,50] contribute to its toxicity. Inhaled alcohol rapidly reaches the brain;[24] it is converted in the brain to formaldehyde.[4,30] Very small increases in formaldehyde could strongly affect energy metabolism of the brain.[42] It has been well established that there is a direct correlation between elevated levels of formaldehyde in the brain and memory impairment.[11] These recent findings, together with the demonstration of minor neurocognitive effects associated with methanol exposure,[6,7] lessen confidence in the NOAEL of 200 ppm derived from those studies.[17] Thus, a minor database uncertainty factor of 3 is applied to the 200 ppm NOAEL derived from studies of neurocognitive effects of methanol.[6,7] Therefore:

$$\text{1- and 24-h SMACs} = 200 \text{ ppm (NOAEL)} \div 3 \text{ (uncertainty factor)} = 70 \text{ ppm}$$

The mathematical model developed by Bouchard[3] predicts that about 20 h of continuous inhalation exposure is needed for blood methanol concentrations to achieve near steady state at an atmospheric concentration of 200 ppm of methanol. The model predicts that 5 d of continuous exposure to methanol at 200 ppm would result in blood formate concentrations in humans of 0.16 $mg \cdot L^{-1}$, a value well below experimental mean background concentrations in unexposed subjects (4.9–10.3 $mg \cdot L^{-1}$) reported by various authors. The finding that blood methanol concentrations should be near steady state but formate concentrations remain near background after the first 20 h implies that continuous exposure to methanol vapors at 200 ppm could be maintained indefinitely without risk of toxicity being produced by formate. However, the Bouchard model explicitly assumes that folate has not been depleted because no saturation of formate metabolism was apparent in the experimental data used to validate the model. It is unknown, however, whether tetrahydrofolate concentrations would continue to decrease at exposure durations >20 h. As a result, an additional safety factor of 3 was applied to SMACs for durations greater than 24 h. Therefore:

7-d, 30-d, 180-d SMACs = 200 ppm (NOAEL)
÷ 3 (uncertainty factor-modeling)
÷ 3 (uncertainty factor)
= 22.2 ppm, rounded to 20 ppm

Because of concern that folate deficiency could develop in long-duration ISS crewmembers, Garcia applied a safety factor of 3 in formulating the SMAC for missions of 1000 d.[17] However, the studies that demonstrated the risks associated with folate deficiency, and that provided the basis for this safety factor, were conducted prior to 1999 when average serum folate values for U.S. men and women were 15.8 ± 0.5 and 17.7 ± 0.5 nmol · L^{-1}, respectively, and red blood cell (RBC) folate was 734 ± 9 nmol · L^{-1} for men and 759 ± 12 nmol · L^{-1} for women.[37] In contrast, average serum folate concentrations for ISS crews, among a subpopulation with the lowest levels of serum folate, was not below 24 ± 8 nmol · L^{-1} during flights of 48–215 d.[51] RBC folate in ISS crews was 1549 ± 403 nmol · L^{-1} before flight and 1260 ± 423 nmol · L^{-1} after flights of 128–195 d.[39] Because serum and blood folate concentrations in a subpopulation of ISS crews having the lowest levels after flight greatly exceeds the average values of the population from which subjects were drawn for studies that assessed effects of folate deficiency, an additional safety factor for folate deficiency may not be necessary for ISS crews. However, with the increased radiation exposure that will be experienced with travel beyond low Earth orbit, together with genetics of some crew that may affect their folate and vitamin B-12 dependent 1-carbon transfer metabolism, and their dietary intake choices, the possibility that folate levels will not fall to levels lower than those of ISS crewmembers cannot be excluded[51] during exploration missions (lunar surface missions, Mars, etc.). Therefore, acknowledging both a risk of deterioration of folate with missions extending well beyond the duration and proximity of ISS missions and the much improved status of folate in ISS crewmembers relative to the general population, we have retained a safety factor for risk of folate deficiency, but have reduced it from a factor of 3 to a factor of 2.

Experimental assessment of effects in monkeys resulting from chronic exposures to methanol via inhalation for 7 to 29 mo was performed by NEDO.[32] We have used an extra risk of 10% as the benchmark response in a benchmark dose analysis of the incidence of neurological lesions reported in this study.[32] The BMDLs of the two variables, which met all of the U.S. EPA's recommended criteria for modeling, were 1.1 ppm for effects in the cerebral white matter and 1.3 ppm for effects in the Pons tegmentum. However, identifications of inconsistencies and uncertainties in the details of the NEDO study identified in the U.S. EPA-sponsored review[12] of the study precludes the attainment of a level of confidence in that study that would justify the direct application of the BMDL derived from this single study to produce SMACs that would differ by an order of magnitude from the current inhalation Reference Concentration for chronic exposure to methanol of 20 mg/m^3 (15 ppm),[44] which is based upon reduced brain weights in rat pups (a gestational effect irrelevant to spaceflight crews). However, the findings of the BMD analysis of data from the NEDO study is viewed as providing additional support for retention of a safety factor. Therefore:

1000-d SMACs = 200 ppm (NOAEL) ÷ 3 (uncertainty)
÷ 3 (uncertainty-modeling)
÷ 2 (uncertainty-folate)
= 11.1 ppm, rounded to 10 ppm

A compilation of the revised SMACs for methanol vapors is provided in **Table I**.

Table I. Proposed Spacecraft Maximum Allowable Concentrations (SMACs) for Methanol Vapors.

DURATION	ppm	mg/m^3	TARGET TOXICITY
1 h	70	92	CNS effects
24 h	70	92	CNS effects
7 d	20	26	CNS effects
30 d	20	26	CNS effects
180 d	20	26	CNS effects
1000 d	10	13	CNS effects

Table II. Exposure Limits Set or Recommended by Other Organizations.

ORGANIZATION & LIMIT	EXPOSURE LIMIT, ppm
ACGIH TLV	200 ppm (262 mg/m^3) TWA
	250 ppm (328 mg/m^3) STEL BEI, Skin
OSHA PEL	200 ppm (260 mg/m^3) TWA
NIOSH REL	200 ppm (260 mg/m^3) ST 250 ppm (325 mg/m^3) [skin] (TWA)
EPA AEGL 1	670 ppm (to 30 min)
EPA RfC for chronic inhalation	15 ppm (20 mg/m^3)

ACGIH, American Conference of Governmental Industrial Hygienists; AEGL, Acute Exposure Guide Limits established by the National Research Council (NRC; 2004) for the Environmental Protection Agency (EPA) to protect the general public, including sensitive individuals; NIOSH, National Institute for Occupational Safety and Health; PEL, permissible exposure limit; REL, recommended exposure limit; RfC, chronic inhalation Reference Concentration, which is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime; TLV, Threshold Limit Value; TWA, time-weighted average.

Comparison with other air quality limits. The values proposed here for the SMACs for methanol are based upon effects to the CNS. As noted, several lines of evidence suggest that some of these effects may result from the conversion of methanol to formaldehyde in the CNS. This possibility draws attention to a comparison of the SMACs for methanol to those for formaldehyde. For all durations of exposures, the values of the SMACs for formaldehyde are substantially lower than those for methanol. SMACs for formaldehyde for 1 h and 1000 d are 0.8 and 0.1 ppm, respectively, whereas for methanol these are 70 and 10 ppm, respectively. The SMACs for formaldehyde acknowledge a potential for neurotoxicity, but a review of evidence from animal studies, controlled humans exposures, and occupational and community health findings indicated that irritation in the

upper respiratory tract, where exposure to the toxicant is direct, is the more sensitive endpoint for formaldehyde.[28] The higher SMACs for acute exposure to methanol are based on localized metabolism in the brain, where endogenous alcohol dehydrogenase converts methanol to formaldehyde,[4,30] rather than a direct point of entry effect. These values are also consistent with recommended occupational limits summarized in **Table II**.

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