Revisions to Limits for Toluene in Spacecraft Air

Cynthia M. Tapia; Shannon D. Langford; Valerie E. Ryder

INTRODUCTION: The original Spacecraft Maximal Allowable Concentrations (SMACs) for toluene (set for 1 h, 24 h, 7 d, 30 d, and 180 d) were first established by NASA in 1996 based on a human study in which no irritation or neurotoxicity was reported following 6-h exposure to 40 ppm toluene vapors. While the toluene SMACs were updated in 2008 to account for auditory, visual, and hormonal effects (for 7 d, 30 d, and 180 d) and to include a long-term SMAC (1000 d) in anticipation of longer spaceflight exploration missions, the short-term SMAC limits (1 h and 24 h) remained unchanged. Acute toluene exposure is reported to result in ocular and nasal irritation, although it is not a primary irritant, as well as central nervous system effects including headaches and dizziness. Long-term exposure to toluene can elicit hepatotoxicity, nephrotoxicity, neurotoxicity, and endocrine toxicity.

RESULTS AND DISCUSSION: Since publication of the original and revised toluene SMACs, the National Academy of Sciences developed interim Acute Exposure Guideline Limits reviewed by the National Research Council Committee. Based on these data, we have increased the limits for toluene in crewed spacecraft to 40 ppm for 1 h, 24 h, 7 d, and 30 d. SMACs for durations of 180 and 1000 d will remain unchanged.

KEYWORDS: toluene, SMACs, air quality.

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Toluene is a highly flammable substituted aromatic hydrocarbon and a benzene derivative.[1] It is present in scientific payloads and spacecraft systems including the Russian oxygen-generating system (unpublished NASA data, Toxicology of Spacecraft Air, https://www.nasa.gov/directorates/esdmd/hhp/toxicology-analysis-of-spacecraft-air/). The presence of toluene in spacecraft air has been detected in various missions at trace amounts (<0.013 ppm) and in rare off-nominal instances at higher levels (64 ppm).[1] NASA has established limits in spacecraft air for toluene following guidelines set by the National Research Council's (NRC) Committee on Toxicology.[2] These guidelines outline specific spaceflight considerations, including a population of only healthy adults and limited, but continuous, exposure durations.[2] The Spacecraft Maximum Allowable Concentrations (SMACs) provide guidance on allowable chemical exposures during normal operations and off-nominal situations in spaceflight.[2] Short-term (1-h and 24-h) and long-term (7-1000-d) SMACs serve slightly different purposes. Short-term SMACs aim to protect against irreversible harm and degradation in crew performance during rare off-nominal situations up to 24 h.[2] Long-term SMACs are to be protective against any adverse health effects or crew performance degradation for as long as 1000 d.[2]

SMACs for toluene were originally set by NASA in 1996 for 1 h, 24 h, 7 d, 30 d, and 180 d.[1] These SMACs were established based on a human volunteer study which reported a lack of central nervous system (CNS) and irritation effects for 16 subjects exposed to 40 ppm for 6 h.[3] All SMACs were based on this study with a final SMAC of 16 ppm.

NASA revisits SMACs as research on the effects of these chemicals evolves and spaceflight advances to ensure current SMACs are protective of crew health without hindering space exploration due to unnecessarily conservative limits. Revised SMACs are then used to provide guidance on acceptable air contaminant concentrations. NASA revised the 7-d, 30-d, and 180-d SMACs and added a long-term 1000-d SMAC in 2008.[4] This revision accounted for auditory, visual, and hormonal

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effects as well as adding the long-term SMAC in anticipation of longer spaceflight exploration missions. Several studies were used in the establishment of these new SMACs. A series of occupational exposure studies, in which 20 yr of 40–60-ppm toluene exposure resulted in changes to auditory and visual evoked potentials, was used to establish the 7-d and 30-d SMACs.[5–7] The 180-d and 1000-d SMACs were established using a human volunteer study wherein hormonal disruption (decreased luteinizing hormone, follicle-stimulating hormone, testosterone, and prolactin) was reported following 3 h of 50-ppm toluene exposure, as well as an occupational exposure study reporting the same hormonal disruptions at 36-ppm toluene exposure.[8,9] The final revised SMACs for 7-d, 30-d, and 180-d durations and the new 1000-d SMAC were set at 4 ppm.

Toluene is a widely used industrial thinner and solvent and a common gasoline component.[1,4,10] It has been measured in urban air at low levels (<0.05 ppm).[1,4,10] Toluene is highly volatile, with inhalation as the major route of exposure and absorption.[10] Absorption of toluene is greatly affected by exercise, and physical exertion can double total body burden.[10] Toluene is not a primary irritant, but slight irritation of the eyes, nose, and the upper respiratory tract have been reported in some clinical studies.[10] Toluene is relatively nontoxic and is mainly excreted unchanged through exhalation, but it is also metabolized and excreted via urine.[10] Acute toluene exposure primarily affects the central nervous system (CNS) and effects include dizziness, headaches, delirium, and unconsciousness.[1,4,10] Concentrations that produce unconsciousness have failed to produce residual organ damage.[10] While deaths following exposure to high concentrations of toluene have been reported, they are usually associated with intentional solvent abuse and are due to cardiac arrhythmias.[10] Long-term toluene exposure can induce hearing loss, decreased ability to discriminate between shades of color, cognitive deficits, and subtle changes in reproductive hormones.[1,4,10] An in-depth summary of toluene toxicity studies published prior to 1996 is provided in the original SMAC document, and a summary of toluene toxicity studies from 1996–2008 is provided in the updated SMAC document.[1,4]

RESULTS AND DISCUSSION

The original 1-h and 24-h toluene SMACs set by NASA in 1996 were based on a human volunteer study of 16 participants that identified a 6-h exposure to 40 ppm as the "No Observed Adverse Effect Level" (NOAEL) for CNS and irritant effects.[1,3] This study found no changes in nasal mucus flow, lung function, subjective response, and psychometric performance at 40 ppm for 6 h. At 100 ppm, irritation of eyes and nose was reported, and "borderline significance" was reported in a battery of eight psychometric tests for visual perception, vigilance, psychomotor functions, and higher cortical functions. A safety factor to account for the small sample size—a factor equal to one-tenth the square root of the number of subjects tested in the chosen study—was applied, which resulted in a 16-ppm SMAC. This approach is a well-established practice in risk assessment to account for the uncertainty added to a study due to small sample size, as outlined by the NRC, in conjunction with NASA, in the Guidelines for Developing SMACs.[2] No adjustment for duration between 1–24 h was made since irritation is not duration-dependent.

Original approach for 1-h and 24-h SMACs based on irritation:

$$= \text{NOAEL} \times 1/\text{small } n \text{ factor}$$

$$= 40 \text{ ppm} \times \left(\frac{\sqrt{16}}{10}\right) = 16 \text{ ppm}$$

Like short-term SMACs set by NASA to protect crews from unplanned chemical releases, the National Academy of Sciences sets acute exposure guideline limits (AEGLs) for the unexpected release of chemicals. There are three AEGL limits (AEGL-1, AEGL-2, and AEGL-3) set for five limited durations (10 min, 30 min, 1 h, 4 h, and 8 h). Concentrations above which the general population could experience transient but notable discomfort or irritation, which are not disabling and are reversible upon cessation of exposure, are defined as AEGL-1.

Since publication of the original 1996 toluene SMACs and revised 2008 toluene SMACs, the National Academy of Sciences developed interim AEGLs reviewed by the NRC for toluene.[10] AEGL-1 values were set based on the preponderance of data from clinical, occupational, and metabolism studies regarding CNS depression reported as neurobehavioral deficits. An 8-h exposure at 200 ppm was defined as the NOAEL for notable discomfort that elicited subjective, low-severity, non-sensory effects in some studies.[10] The clinical studies used to set the AEGL-1 included more than 300 participants and several thousand workers in the occupational monitoring studies. This broad spectrum of data likely captures different uptake rates of toluene based on different rates of physical exertion. While some studies identified slight respiratory irritation at 100 and 200 ppm, severity of irritation was below the AEGL-1 definition criteria. To account for differences in sensitivity to anesthetic gases, an uncertainty factor of 3 for human variability was applied to the 200-ppm NOAEL, as the minimum alveolar concentration for volatile anesthetics differs by no more than two- to threefold in the human population. This resulted in an AEGL-1 value of 67 ppm, which was applied for all AEGL durations as toluene rapidly reaches a steady-state in the blood.[5]

Similar to the AEGL-1 definition, NASA guidelines allow for minor, reversible effects that will not prevent a crewmember from responding to an emergency in off-nominal situations for the 1-h and 24-h SMACs.[2] When the original 1-h and 24-h SMACs were set based on a 40-ppm NOAEL with CNS depression and irritant endpoints, a small "n" safety factor was applied.[3] This safety factor was applied to account for any CNS depression or irritant symptoms not captured due to the small

Table I. Spacecraft Maximum Allowable Concentrations for Toluene Vapors.

DURATION	SMAC (PPM)	ENDPOINT	PRINCIPAL STUDY
1 h	40	CNS depression	Andersen et al.[3]
24 h	40	CNS depression	Andersen et al.[3]
7 d	40	CNS depression; auditory and ocular toxicity	Andersen et al.,[3] Vrca et al.,[5–7] & Schaper et al.[12]
30 d	40	CNS depression; auditory and ocular toxicity	Andersen et al.,[3] Vrca et al.,[5–7] & Schaper et al.[12]
180 d	4	Decreased hormones	Svensson et al.[9] & Luderer et al.[8]
1000 d	4	Decreased hormones	Svensson et al.[9] & Luderer et al.[8]

sample size. Reviewing data published since the development of these SMACs and the AEGL documentation, it is overly cautious to consider irritation as an endpoint at this exposure concentration. Toluene is not a primary irritant, many studies report irritation at concentrations above 100 ppm (some above 500 ppm), and NASA does allow for transient irritation for 1-h and 24-h SMACs.[2,10] Given the preponderance of evidence based on human data with CNS depression endpoints, the small "n" safety factor applied to the NOAEL is overly cautious and unnecessary. Many other studies have identified NOAELs for CNS depression endpoints as 100–200 ppm, and using a NOAEL of 40 ppm is extremely conservative.[2,10] It is important to remember that the study used to set this NOAEL only reported "borderline significance" for CNS depression effects at 100 ppm.[3] As toluene reaches steady-state in the blood rapidly, no adjustment for duration is necessary.[10] Given this reasoning, direct application of the NOAEL of 40 ppm is used as the new 1-h and 24-h SMAC limits, now closer in line to the AEGL-1 values set for all durations and the newly revised 1-h SMAC for benzene, a similar alkylbenzene that the AEGL committee has noted is less or equipotent to toluene for CNS effects.[11] A summary of proposed SMACs for toluene vapors is provided in **Table I**.

A series of occupational studies reported changes in auditory and visual evoked potentials in workers exposed to toluene concentrations of 40–60 ppm for an average of 20.3 yr.[5–7] While there is evidence that toluene exposure can induce hearing loss and impair color vision, the endpoint chosen from these studies is more indicative of CNS effects.[10] Furthermore, no ocular toxicity or ototoxicity was reported at these exposure levels in occupational studies.[10] It is also worth noting no other studies reported CNS depression effects at these exposure levels.[10] The 2008 revised SMAC documentation also highlighted an occupational study where 5-yr exposure to 45 ppm was identified as a NOAEL for ototoxicity and an occupational study where 35 ppm was identified as the NOAEL for impaired color vision.[12–14] It should be noted that the impaired color vision study did have age and alcohol consumption as confounding factors, so this NOAEL is likely overly conservative.[13,14] The AEGL documentation also outlined several animal studies which reported toluene-induced ototoxicity and ocular toxicity.[10] Given the long-term effects of auditory and visual decrements and the potential impairment of function in crew, the NOAEL of 45 ppm is determined to be protective of ocular toxicity and ototoxicity with no duration adjustment factors necessary. The new value for the 7-d and 30-d SMACs at 40 ppm will be protective against auditory and ocular toxicity but is based on CNS depression as outlined in Table I.

The current weight of evidence still supports the previous 180-d and 1000-d SMACs. While toluene is often considered dose- rather than duration-dependent, we think it is prudent to consider the subtle hormonal changes noted at 36 ppm in the occupational studies by Svensson et al.[5,8,9] This was considered a LOAEL to which a NOAEL to LOAEL safety factor of 10 was applied. The 180-d and 1000-d SMACs will remain at a rounded value of 4 ppm.

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