Revisions to Acute/Off-Nominal Limits for Benzene in Spacecraft Air

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BACKGROUND: The previous short-term (1-h and 24-h) Spacecraft Maximal Allowable Concentrations (SMACs) for benzene were established at 10 and 3 ppm by NASA in 1996, based on a study of mice in which no hematological effects were noted following two 6-h exposures to benzene. When the benzene SMACs were updated in 2008, there was no revision to the short-term SMAC limits. Rather, that effort developed a long-term SMAC (1000-d) for Exploration mission scenarios.

Acute benzene exposures can cause numerous neurological effects, and long-term exposure to low levels is well-known to cause acute myeloid leukemia. Since publication of the original benzene SMACs, the National Academy of Sciences developed interim Acute Exposure Guideline Limits (AEGLs) for unintentional releases of benzene into the air. Based on the data used to establish the AEGLs, we have increased our short-term, off-nominal limits for benzene in crewed spacecraft to 40 ppm and 6.7 ppm for 1-h and 24-h, respectively.

KEYWORDS: benzene, SMACs, air quality.

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Benzene is an aromatic hydrocarbon that is not generally detected in spacecraft atmospheres. However, it is a potential product of combustion and NASA has therefore established limits to support crew response to an off-nominal contamination of the habitable spacecraft volume. NASA utilizes Spacecraft Maximum Allowable Concentrations (SMACs) to provide guidance on acceptable exposures to airborne contaminants during spaceflight. Short-term (1-h and 24-h) SMACs for benzene were originally set by James and Kaplan,[3] based a lack of hematological effects in mice after two 6-h exposures to benzene at 100 ppm. A safety factor of 3 was applied to adjust from animals to humans due to similarities in metabolism between mice and humans, an additional spaceflight specific safety factor of 3 was applied due to evidence of immunological effects of microgravity in the absence of benzene, and a duration adjustment factor was applied for the 24-h value. The resulting values were 11 ppm (rounded to 10 ppm) for the 1-h SMAC and 3 ppm for the 24-h SMAC.

Benzene Toxicity

Benzene is widely used and ubiquitously present in the Earth's atmosphere. It is a component of gasoline, present in cigarettes, used as a solvent, and used in the production of plastics, synthetic rubbers, and many other products. A summary of effects in studies published prior to 2008 is provided in the original SMAC documents.[3,4] Benzene is best known for its association with the development of leukemia; although shorter-term exposures (days to weeks) can cause hematological abnormalities, only prolonged exposures over "several months to several years" have the potential to cause permanent changes in pluripotent stem cells in bone marrow, which can lead to the development of leukemias. Acute benzene exposures can cause numerous neurological effects, including drowsiness, dizziness, headache, tremor, nausea, convulsions, delirium, and loss of consciousness.[6] Given the potential impact of such symptoms on crew performance, these symptoms are most relevant for establishing short-term off-nominal limits for benzene exposure.

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SMAC Development

In the original development of SMACs, a 1-h value was derived from a No Observable Adverse Effects level (NOAEL) for hematological effects in mice exposed twice to 100 ppm benzene for 6 h.[3] The same study/endpoint was used to derive the 24-h SMAC by applying an additional duration adjustment factor.

Per NASA guidelines, 1-h and 24-h SMACs apply to off-nominal situations and allow minor, reversible symptoms that will not prevent a crewmember from responding to an emergency.[2] Similarly, acute exposure guideline limits (AEGLs) are set for limited duration to address unexpected releases of chemicals. There are three AEGL levels (AEGL-1, AEGL-2, and AEGL-3) set for 5 durations (10 min, 30 min, 1 h, 4 h, and 8 h). Concentrations at or below AEGL-1 limits are not expected to result in any adverse effects in the general population, including sensitive individuals. Concentrations between the AEGL-1 and AEGL-2 limits may result in some adverse effects, but are not expected to result in serious, long-lasting, or irreversible effects, nor are they expected to impair ability to escape. Concentrations above AEGL-2 limits may result in serious adverse effects, and concentrations above AEGL-3 limits may be life-threatening.

As noted above, neurological effects are the appropriate endpoint for establishing short-term limits for single, unexpected benzene exposures. AEGL-1 values are based on benzene inhalation exposures in 23 volunteers in which no symptoms were reported to the investigators following exposures up to 110 ppm for 2 h.[7] For AEGL-2 values, the committee selected a rodent study for the point of departure because there are no adequate dose-response studies in which humans experienced effects consistent with AEGL-2 levels (serious, long-lasting effects or impaired ability to escape).[5,6] The highest reported concentration with no AEGL-2 effects was 4000 ppm in rats exposed for 4 h. Both the SMAC and AEGL committees agreed that an interspecies adjustment factor of 3 is acceptable due to limited variability in response to benzene across species.[3,6] If the spaceflight factor of 3 intended to protect against hematological effects in microgravity is applied, the resulting 1-h SMAC would be 400 ppm since guidelines for establishing SMACs do not recommend adjustment from longer to shorter durations. In contrast, a duration adjustment would apply to extrapolate from the 4-h study to a 24-h exposure. The resulting 24-h SMAC would be 67 ppm.[1] While these values (400 and 67 ppm) are likely appropriate based on current NASA guidelines, the AEGL committee noted that benzene is less or equally potent to other alkylbenzenes, particularly toluene, for CNS effects. The published 1-h and 24-h SMACs for toluene are 16 ppm based on a lack of CNS and irritation effects in 16 human volunteers exposed to 40 ppm for 6 h, adjusted by a "small n" factor ($\sqrt{16}/10$). Based on similar potency and the use of human data to establish short-term SMACs for toluene, which is preferred per NASA guidelines, an additional safety factor of 10 was applied to establish a new 1-h SMAC limit of 40 ppm and a new 24-h SMAC limit of 6.7 ppm for benzene. These values are well below the exposure levels documented by Srbova et al.[7] as resulting in no reported effects in volunteers, and thus we expect these safety limits to be strongly conservative in the spaceflight environment.

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