**Updates to Spacecraft Maximum Allowable Concentrations for 2-Butanone**

**Suggested short title:** 2-Butanone SMACs

Manuscript metrics

Word count for abstract: 354

Word count for main text: 2027

Number of references: 25

Number of tables: 3

Number of figures: 0

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**Abstract:**

Introduction

Spacecraft Maximal Allowable Concentrations for 2-butanone were established by NASA in 1996. 2-butanone is an irritant that may also cause central nervous system effects at high concentrations. Limits for short-duration, off-nominal scenarios were set at 50 ppm based on human exposure data from the 1940s. Limits for 7, 30, and 180 days were set at 10 ppm using the same data but further accounting for the small number of volunteers and extrapolation from mild effects to no effects for nominal operations. Limits were not established for missions of 1000 days.

Methods

A literature search was conducted using keywords ‘methyl ethyl ketone’ and further narrowed with ‘acute toxicity’ or ‘irritation’ for short-term SMAC development and ‘sub-chronic toxicity’, ‘chronic toxicity’, ‘CNS effects’, or ‘reproductive effects’ for SMAC durations of 7 days or more. Additionally, studies cited in the development of existing occupational limits, acute exposure guidelines, and state permitting and monitoring limits, were assessed.

Results

Several toxicity studies were published after the original SMACs were set and are summarized here. Acute SMACs were increased from 50 ppm to 200 ppm. The SMAC for 7 days was increased from 10 ppm to 67 ppm, and the SMACs for 30 and 180 days were increased from 10 ppm to 22 ppm. A SMAC for 1000-d has now been set at 22 ppm.

Discussion

As part of a periodic review of historical limits, SMACs were revised for all durations for 2-butanone. Limits based on the most recent evidence and risk assessment methodologies will ensure the appropriate degree of conservatism in future spacecraft design.

**Keywords:** 2-butanone, methyl ethyl ketone, SMACs, air quality

**Introduction**

2-butanone, also known as methyl ethyl ketone or MEK, is a colorless flammable liquid that evaporates fairly quickly due to high vapor pressure (~71 mmHg) at room temperature. The physical and chemical properties are provided in Table I. 2-Butanone is widely produced industrially but occurs at very low levels naturally. It is primarily used as a solvent in a wide variety of industries to manufacture numerous products and is usually found in mixtures with other solvents. It has an odor threshold of ~5-10 ppm1. Occupational limits are provided in Table II.

Following inhalation, 2-butanone is rapidly absorbed (uptake estimated at 70%) and easily distributed (highly soluble in blood) throughout the body2. It has a short half-life (40-80 min) and is excreted in exhaled breath and urine as the compound itself or as the metabolite 3-hydroxy-2-butanone (acetylmethylcarbinol)3. As a result, it does not accumulate in the body4. It can also be absorbed dermally5.

Nominal concentrations on ISS are at very low levels (< 0.5 ppm), and levels have dropped over time (< 0.07 ppm in only 6 samples since 2015). The drop corresponds to the installation of charcoal filters6 in Node 1 in May 2015 and later installation across the ISS stack of combined charcoal/HEPA filters in 2019. MEK is often detected when crew open the hatch of an arriving vehicle, but concentrations are consistent with background (0.02 – 0.5 ppm).

**Toxicity Summary**

*Acute Inhalation Toxicity*

The original acute SMACs (1 h and 24 h) values of 50 ppm were based on reports of slight nose and throat irritation following short exposures (3-5 min) of 10 human volunteers to 100 ppm MEK. That concentration was then divided by a safety factor of 2 to ensure only mild irritation since 3-5 min exposures to 300 ppm were not tolerable to these subjects7. As noted in the original SMAC document, the authors did not indicate whether or not they analytically determined exposure concentrations.

Several studies in human volunteers were published after the SMACs were established in 1996. Twenty-four healthy male volunteers (aged 26 ± 4.6 years) were exposed to solvents in a climate-controlled exposure chamber for 4 hours8. Exposure concentrations were set at or near odor thresholds for low exposures (9.6 ppm for MEK) and a time-weighted average at or near occupational limits (189 ppm for MEK) for high exposures. Each subject completed four exposure sessions in a cross-over study design with 2 days between each session. Annoyance ratings for MEK (3.6 on a scale of 1-7) at the high concentration were higher than all other solvents tested except ethyl benzene, and suggest the current occupational limits are unlikely to preclude effects. Physiological measures of air flow and nasal lavage did not demonstrate any association with subjective measures of annoyance or irritation.

In a separate but related study, 24 healthy male students (12 with self-identified multiple chemical sensitivity and 12 without) were exposed to MEK at similar concentrations of approximately 10 ppm or a time-weighted average of 200 ppm for 4 hours9. Reports of nasal irritation were higher in the chemically sensitive group at the high concentration, and while variability in reports of nasal irritation in the non-chemically sensitive group increased at the high concentration, the median did not differ from the low concentration exposure for this group. Measured biomarkers of irritation were not increased in either exposure group.

Another group exposed 19 healthy, non-smoking men to 0 or 200 ppm MEK for 4 h in a cross-over study design with one week between exposure sessions10. The study was not blind since participants noted odors at the start of exposures to MEK. Subjects reported no irritation symptoms during the exposure. Mucocilliary transport time was impaired (increased) following exposure to MEK at the occupational limit (200 ppm) in contrast to other industrial solvents which did not impair this endpoint at their occupational limits. Markers of inflammation were also increased with MEK exposure, though not statistically significantly so. The authors suggest the results are a pre-clinical indication of solvent-induced rhinitis.

Another study investigated chemosensory irritation to solvents, including exposure of 24 human volunteers to an increasing concentration from 10-380 ppm MEK for 4 hours. Odor was noted and annoyance ratings increased with increasing concentrations of MEK, but irritation scores were low11.

Though published at the time, some, but not all, of a series of studies by Dick et al.12-15 were considered in the original SMAC development. One (Dick et al. 1992) was used by other agencies in setting permitting and monitoring limits in Texas16 and for accidental exposures of the general public17. Psychomotor function (measures of visual-vigilance, choice reaction time, and pattern recognition) was assessed in human volunteers exposed to toluene and MEK in combination and individually. Ethanol ingestion was used as a positive control. There was no statistically significant impairment in volunteers exposed to an average concentration of 189 ppm MEK for 4 hours; however, the authors noted that post-exposure performance was not measured for the MEK exposure group, and the positive control group’s performance was notably worse than any other control group15. In a separate study reported twice, neurobehavioral effects were assessed in 25 subjects exposed to an average of 186 ppm MEK for 4 hours12, 14. Pre-exposure scores served as a baseline for each subject. Ethanol ingestion (95% at 0.84 mL/kg) was again used as a positive control. While mild effects were seen in some measures following exposure to acetone (also tested), there were no statistically significant effects noted following exposure to MEK12, 14.

*Subchronic Inhalation Toxicity*

To investigate subchronic effects of solvent exposure, including MEK, on immune cell function, a T cell line (Jurkat) was exposed in a gas-tight glass exposure system to various solvent concentrations for 5 days18. Cell membrane damage was assessed by measuring LDH in the culture media. The NOAEL for MEK-induced cell membrane damage was ~13 mM, and the LOAEL was ~40 mM. Intracellular free calcium, reduced GSH, oxidized glutathione, and MAP kinase phosphorylation were also assessed. The lowest NOAEL for these changes was ~4 mM for intracellular free calcium, and the LOAEL was ~13 mM. Glutathione redox status was impacted at higher concentrations and there was no impact of exposure on MAP kinase phosphorylation. These results were compared to blood concentrations of humans exposed to 25 – 200 ppm MEK which ranged from 0.3 – 5.8 μg/ml (4.16 – 80.4 μM) and suggest that cellular effects may occur at levels below the current occupational limit of 200 ppm.

A 90-d vapor inhalation study was conducted in Fischer 344 rats exposed to target concentrations of 0, 1250, 2500, or 5000 ppm (actual avg = 1254, 2518, and 5041 ppm) MEK for 6 h/d, 5 d/wk (total exposure = 390 hours)19. Animals were observed following exposure, including food intake and weight measures. Eye exams were conducted prior to necropsy, and urine and blood samples were collected for clinical pathology. Gross pathology and standard histopathology along with specialized neuropathology were conducted. There were no signs of nasal irritation and no ocular effects in exposed rats. There were no exposure related effects on food consumption, but body weights were elevated in rats exposed to 1250 and 2500 ppm and transiently decreased in rats exposed to 5000 ppm. Liver weight and size was increased in rats exposed to 5000 ppm. Some serum chemistry markers were elevated in female rats (only) in the 5000 ppm exposure group. There were no signs of upper airway irritation nor pathological changes, including neurological pathology, associated with exposure in any dose group. The liver changes were considered an exposure-related adaptive effect and the NOAEL was 5000 ppm.

*Chronic Inhalation Toxicity*

There remains debate about whether MEK alone can cause neurotoxicity or if it only potentiates neurotoxicity from concurrent exposure to other solvents like hexane. Neurotoxicity from chronic exposure to solvents was assessed in 41 exposed and 63 control workers (aged 36 ± 9.2 years) with a mean exposure of 14 ± 7.5 years20. Exposure levels of MEK over an 8-h shift in workers applying an MEK containing lacquer to cables ranged from 149 – 342 mg/m3 (50 – 116 ppm). Symptoms including memory difficulties and sleep disturbances were reported at higher rates in exposed individuals than controls, and headache was reported in nearly half of exposed individuals. Irritation symptoms, particularly ocular irritation, were also reported at notably higher levels in exposed individuals compared to controls. Muscular, bone, and joint pains were also reported at higher rates by exposed individuals. Statistically significant changes were also noted in several parameters across different nerves in motor never conduction velocity tests in exposed individuals. Taken together, these results suggest that exposures below the occupational limit of 200 ppm may be associated with adverse effects; however, these results are inconsistent with other data and significant concerns were noted by Graham in a letter to the editor21. One of the Mitran study authors also noted these effects (central and peripheral nervous system impairment, fatigue, chronic headache, memory issues, etc.) in a case study22, but the exposure concentrations and co-exposures in that case are not fully defined.

*Reproductive Toxicity*

While MEK exposure does impact fetal development at high exposures (3000 ppm), there are no major adverse maternal effects reported23. Since pregnancy is not anticipated in flight, developmental effects are not currently used to establish spaceflight limits for chemicals.

*Genotoxicity and Carcinogenicity*

The National Toxicology Program reported negative results in CHO chromosome aberrations, CHO sister chromatid exchange, and the Ames test24.

**RESULTS AND DISCUSSION**

*SMAC Development*

A summary of the recommended SMAC values is provided in Table III. Short-term SMAC limits (1 h and 24 h) are intended for off-nominal or contingency situations and allow for minor, reversible health effects. While more recent human volunteer studies do indicate that the current occupational limit of 200 ppm may not be completely without effect, particularly for sensitive individuals, the reported odors and annoyance were tolerable in 4 h exposure studies8-9. Additionally, the study by Dick et al. 1992 used as the key study for limits set by the Texas Commission on Environmental Quality and the acute exposure guidelines limit (AEGL) committee reported no adverse neurobehavioral or sensory irritation effects in male and female human volunteers exposed to 200 ppm for 4 h13. We therefore believe it is reasonable and appropriate to set the 1 h limit at 200 ppm.

As noted in the original SMAC document, there is no expectation that irritation at a constant concentration would increase over time. The acute exposure guidelines limits (AEGL), which are similarly set for short-term exposure to accidental chemical release, are also set at 200 ppm across all durations (10 min – 8 h). As such, we have elected to also increase the 24 h SMAC limit to 200 ppm. This is supported by studies in rodents that indicate a sharp reduction in respiratory rate (correlated with perceived sensory irritation in humans) almost immediately upon exposure to concentrations of ~3000 – 30,000 ppm MEK that plateaued or dropped only slightly over the remaining 30 min of exposure and recovered fully for the 3000 ppm exposure or partially for all other exposures within an hour of recovery post-exposure25.

 While acceptable for short periods where minor, reversible effects are allowed, the weight of evidence suggests that the current occupational limit of 200 ppm may not fully preclude all adverse effects, including irritation and neurobehavioral effects. Additionally, astronauts are exposed continuously for 6-12 months rather than intermittently 8 h/d, 5 d/wk. As such, we have applied a safety factor of 3 to reduce a mild LOAEL (200 ppm) to a NOAEL, resulting in a recommended 7-d SMAC limit of 67 ppm. Although developmental effects are not considered for spaceflight, this value is similar to the recently revised occupational threshold limit value of 75 ppm set by the American Conference of Governmental Industrial Hygienists to protect against adverse effects on fetal development.

 While there is controversy surrounding MEK-related chronic neuropathy, we applied an additional safety factor of 3 for lack of chronic toxicity studies for exposures of 30, 180, and 1000 days. This results in a conservative limit of 22 ppm that is still double the prior limits of 10 ppm for 30 and 180 days and is expected to be protective of irritation and neurological effects.

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**Table I.** Physical and chemical properties of 2-butanone

|  |  |
| --- | --- |
| **Property** | **Value** |
| Synonyms | 2-butanone, methyl ethyl ketone (MEK), methyl acetone |
| Formula | C4H8O |
| CAS number | 78-93-3 |
| Molecular weight | 72 g/mol |
| Boiling point | 80°C |
| Melting point | -86°C |
| Flash Point | -9°C |
| Density | 0.8 g/mL at 25°C |
| Vapor Pressure | 10.3 kPa at 20°C |
| Solubility | Miscible (completely soluble) |
| Conversion factors at 25°C and 1 atm | 1 ppm = 3 mg/m31 mg/m3 = 0.3 ppm |

**Table II.** Exposure Limits Set by Other Organizations

|  |  |
| --- | --- |
| Organization | Concentration, ppm |
| OSHA's PEL | 200 (TWA) |
| NIOSH's REL | 200 (TWA) |
| NIOSH's STEL | 300 |
| NIOSH's IDLH | 3000 |
| ACGIH TLV | 75 (TWA) |
| ACGIH TLV | 150 (STEL) |

PEL = permissible exposure limit. TWA = time-weighted average. REL = recommended exposure limit. STEL = short-term exposure limit. IDLH = immediately dangerous to life and death.

**TABLE III. Spacecraft Maximum Allowable Concentrations**

|  |  |  |  |
| --- | --- | --- | --- |
| Duration | ppm | mg/m3 | Target Toxicity |
| 1 h | 200 |  | Neurobehavioral, Irritation |
| 24 h | 200 |  | Neurobehavioral, Irritation |
| 7 d | 67 |  | Neurobehavioral, Irritation |
| 30 d | 22 |  | Neurological, Irritation |
| 180 d | 22 |  | Neurological, Irritation |
| 1000 d | 22 |  | Neurological, Irritation |