Revisions to Limits for Propylene Glycol in Spacecraft Air

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INTRODUCTION: The previous Spacecraft Maximal Allowable Concentrations (SMACs) for propylene glycol were established based on a study of rodents exposed to propylene glycol (PG) aerosol for 6 h/d, 5 d/wk for 90 d. This study has been used as the basis for the few existing limits, but all exposure concentrations were well above the saturated vapor concentration of ~100 ppm for pure propylene glycol at room temperature. For this reason, the Environmental Protection Agency and the Agency for Toxic Substances and Disease Registry noted that the method used to generate the aerosols for the two published studies of animal exposures are not relevant to exposure conditions for the general public, and most regulatory agencies have not established inhalation limits for propylene glycol, citing lack of data. Since publication of the PG SMACs in 2008, an acute inhalation study was conducted in healthy human subjects which allows us to revise our assessment. This manuscript provides the rationale for increasing the prior limits for PG in spacecraft air from 32 and 17 ppm to 64 and 32 ppm for off-nominal scenarios/releases (1-h and 24-h limits) and from 9, 3, and 1.5 ppm to 32 ppm for all nominal timeframes (7, 30, and 180 d). Due to a lack of longer-term exposure data, NASA has elected to eliminate the 1000-d SMAC limit at this time.

KEYWORDS: propylene glycol, SMACs, health limits.

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For several decades, NASA has developed limits for chemical contaminants in spacecraft air and water per guidelines set forth by the National Research Council's Committee on Toxicology.[2] These guidelines are predicated on standard toxicology risk assessment practices, but capture spaceflight-specific considerations, such as a healthy adult population and limited but continuous exposure durations. Human studies are preferred over animal studies where available, and studies with total exposure durations equivalent or similar to the durations of interest for nominal spaceflight (7, 30, 180, and 1000 d) are primary resources for establishing Spacecraft Maximum Allowable Concentrations (SMACs) in air.

Propylene glycol is a coolant that is being used in a mixture with water for exploration spacecraft thermal control systems. Therefore, NASA must provide occupational exposure limits to support appropriate system design and to evaluate crew exposures in the event of off-nominal contamination of the habitable spacecraft volume. NASA uses SMACs to provide guidance on acceptable exposures to airborne contaminants during spaceflight. SMACs for propylene glycol (PG) were originally set by Ramanathan,[4] based upon eye, nose, and throat irritation in human subjects exposed acutely (1 min) to PG mist[7] for the 1-h SMAC, nasal hemorrhaging and ocular discharge in rodents[6] for the 24-h, 7-d, and 30-d SMACs, and increased goblet cells, increased mucin production, and thickening of the respiratory epithelium[6] for the 180-d and 1000-d SMACs. These SMACs range from 32 to 1.5 ppm.

Propylene Glycol Toxicity

Propylene glycol is generally considered as safe and is frequently used in oral suspensions and cosmetic applications. It is not highly volatile and, as such, very few inhalation exposure studies have been published. A summary of effects in studies

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published prior to 2008 is provided in the original SMAC document.[4] Since then, Dalton et al.[1] published a study in which human volunteers (10 men/10 women) were exposed to PG aerosol. Subjects were exposed for 4 h to a total concentration (droplets + gas) of 95.6 and 442.4 mg · m^{-3} and a vapor concentration of 20 and 100 mg · m^{-3} (6 and 32 ppm) and for 30 min to a total concentration of 871 mg · m^{-3} and vapor concentration of 200 mg · m^{-3} (64 ppm). There were no exposure-related changes in pulmonary function as measured by spirometry and no measurable ocular irritation based on blink response. Subjective measures of nose, throat, eye, skin, and miscellaneous (fatigue, headache, nausea, etc.) health endpoints provided by subjects were exposure-related, but were never reported above 'slight' on a 5-point scale of: 1) Not at all; 2) Slightly; 3) Moderately; 4) Very; and 5) Extremely.

SMAC Development

In the original development of SMACs, a 1-h value was derived from a mild lowest observable adverse effect level (LOAEL) in humans exposed for 1 min to PG mist.[5] Reported symptoms in human volunteers (described above)[1] were consistent with minor, reversible effects, which are allowable in short-term, off-nominal spaceflight scenarios.[2] Additionally, these exposures were not limited to PG vapor only, but to a higher total concentration of vapor + aerosol. We have therefore revised the 1-h SMAC from 32 ppm to 64 ppm. Similarly, there were no more than mild effects reported by subjects exposed to 32 ppm (100 mg · m^{-3}) for 4 h.[1] Again, because 1-h and 24-h SMACs are intended to apply to off-nominal scenarios and allow for minor adverse effects that will not compromise crew ability to respond to the release, we expect exposure to 32 ppm (100 mg · m^{-3}) to be acceptable beyond 4 h and have revised the 24-h SMAC from 17 ppm to 32 ppm. This value is supported by the lack of nasal dryness/bleeding for the first 30 h of exposure (6 h/d for this first week) to 50 ppm in the study by Suber et al. described below.[6] These values are further supported by analysis of PG in both aerosols and vapor phase in Dalton et al.,[1] which were markedly higher than the nominal droplet concentrations. At the highest dose level, the combined (droplet + vapor) concentration was 280 ppm (870 mg · m^{-3}).

Existing SMACs for 7 and 30 d were derived from a LOAEL for nasal hemorrhaging in rodents exposed to PG aerosol for 6 h/d, 5 d/wk for 90 d.[4] This endpoint was attributed to dehydration of the nasal passages at concentrations well above the saturated vapor concentration for PG and did not appear until the second week of exposure. Other effects reported were nonsevere LOAELs for increased hemoglobin in monkeys exposed to supersaturated PG (110 ppm) continuously for 13 mo and increased body weight at the same concentration in rats exposed continuously to PG for 18 mo.[5] Because these were limited subchronic/chronic effects in two species, application of the 24-h SMAC value of 32 ppm for irritation, which is duration independent, provides a threefold margin of safety for long-term exposure and is recommended as the SMAC for 7, 30, and 180 d. Importantly, this value (32 ppm) for pure propylene glycol exceeds the saturated vapor concentration for most propylene glycol/water mixtures being considered as thermal control fluids in exploration spacecraft. At this time, there are insufficient data to establish a 1000-d limit and we are, therefore, eliminating the prior SMAC limit of 1.5 ppm. A summary of the revised SMACs for PG vapors is provided in **Table I**.

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

DURATION	ppm	mg · m^{-3}	ENDPOINT
1 h	64	200	Irritation
24 h	32	100	Irritation
7 d	32	100	Irritation
30 d	32	100	Irritation
180 d	32	100	Irritation
1000 d	–	–	

Comparison with Other Air Quality Limits

Because propylene glycol is generally considered safe, there are limited occupational or environmental limits for exposure. Limits that do exist generally address injection or ingestion from drug and food products. Because propylene glycol has a low vapor pressure, inhalation exposure to concentrations of concern for human health are generally not expected to occur and, therefore, occupational limits have not been developed by the American Conference of Governmental Industrial Hygienists, Occupational Safety and Health Administration, or National Institute for Occupational Safety and Health. In 2009, the New Jersey Department of Health reported a workplace environmental exposure limit of 3.2 ppm (10 mg · m^{-3}) set by the American Industrial Hygiene Association.[3] While 10 times lower than our recommended SMACs, this limit is intended to protect workers over a working lifetime (40 yr) for 8 h/d, 5 d/wk and accounts for individual variability, which is not generally considered by NASA per our guidelines based on a healthy adult astronaut cohort.[2]

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