RESEARCH ARTICLE

Safe human exposure limits for airborne linear siloxanes during spaceflight

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Abstract

Background: Low molecular weight siloxanes are used in industrial processes and consumer products, and their vapors have been detected in the atmospheres of the Space Shuttle and International Space Station. Therefore, the National Aeronautics and Space Administration (NASA) developed spacecraft maximum allowable concentrations (SMACs) for siloxane vapors to protect astronaut health. Since publication of these original SMACs, new studies and new risk assessment approaches have been published that warrant re-examination of the SMACs.
Objective: To reevaluate SMACs published for octamethyltrisiloxane (L3) for exposures ranging from 1 hour to 180 days, to develop a 1000-day SMAC, and to expand the applicability of those values to the family of linear siloxanes.
Methods: A literature review was conducted to identify studies conducted since the SMACs for L3 were set in 1994. The updated data were reviewed to determine the sensitive toxicity endpoints, and current risk assessment approaches and methods for dosimetric adjustments were evaluated.
Results: Recent data were used to update the original 1-hour, 24-hour, 30-day, and 180-day SMACs for L3, and a 1000-day SMAC was developed to protect crewmembers during future exploration beyond Earth orbit. Group SMACs for the linear siloxane family, including hexamethyldisiloxane (L2), L3, decamethyltetrasiloxane (L4), and dodecamethylpentasiloxane (L5), were set for exposures of 1-hour to 1000 days.
Conclusion: New SMACs, based on acute pulmonary and neurotoxicity at high doses only achievable with L2 and potential liver effects following longer-term exposures to L2 and L3, were established to protect crewmembers from the adverse effects of exposure to linear siloxanes.

Introduction

Siloxanes are polymeric compounds containing a linear or cyclic backbone of alternating silicon and oxygen atoms bound to hydrogen or hydrocarbon side chains. These high-production volume chemicals are used in a wide variety of industrial and consumer products, including hydraulic fluids, adhesives, textiles, detergents, antiperspirants and cosmetic products (Horii & Kannan, 2008; HSDB, 2006). Although many siloxanes can be synthesized, low molecular weight siloxanes present the highest potential risk for exposure in air, since vapor pressures quickly drop as chain length (molecular weight) increases. Physical and chemical properties for some common low molecular weight linear siloxanes used as chemical intermediates in the production of silicone fluids are presented in Table 1. These compounds are highly lipophilic liquids and will generate appreciable amounts of vapors at standard temperature and pressure. The widespread use of these compounds began during World War II and evaluation of their toxicity dates back to that period (Rowe et al., 1948). The acute oral and inhalation toxicities of silicone fluids, including the linear siloxane, hexamethyldisiloxane (L2), were found to be low. As a result, relatively few toxicity studies were undertaken to evaluate these compounds until concerns began to arise regarding an association between silicone breast implants and autoimmune diseases (Baldwin & Kaplan, 1983; Varga et al., 1989; Yoshida et al., 1993). Additional studies resulted from Industry Product Stewardship initiatives focused on siloxanes found in consumer products.

Octamethyltrisiloxane (L3) vapor was first detected in the Skylab 4 atmosphere at concentrations of 105 to 138 ppb (Liebich et al., 1975). NASA is interested in the toxicity of low molecular weight siloxanes because these compounds have routinely been found in air samples collected from the Space Shuttle (James et al., 1994) and International Space Station (ISS) (James et al., 2003) and may be emitted from hardware, lubricants, and personal care products carried onboard (Figure 1). In addition, silicone oils are now being

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Table 1. Chemical and physical properties of linear siloxanes.

	Hexamethyl-disiloxane (L2)	Octamethyl-trisiloxane (L3)	Decamethyl-tetrasiloxane (L4)	Dodecamethyl-pentasiloxane (L5)
Structure				
Formula	$C_6–H_{18}–O–Si_2$	$C_8–H_{24}–O_2–Si_3$	$C_{10}–H_{30}–O_3–Si_4$	$C_{12}–H_{36}–O_4–Si_5$
CAS Registry #	107-46-0	107-51-7	141-62-8	141-63-9
Molecular Weight	162.38	236.53	310.69	384.84
Physical State	Clear, colorless liquid	Clear, colorless liquid	Clear, colorless liquid	Clear, colorless liquid
Boiling Point (°C)	99	152	194	232
Melting Point (°C)	−66	−82	−68	−80
log K_{ow}	4.2	4.8	5.4	6
Vapor pressure at 25°C (torr)	42	3.9	0.4	0.1
Saturated vapor concentration (ppm)[a]	55 300	5131	530	130

Information obtained from NCBI PubChem: http://pubchem.ncbi.nlm.nih.gov/.
[a]Saturated vapor concentration = $(VP/760) \times 10^6$.

Figure 1. Astronaut Jerry Linenger with personal hygiene items onboard the Russian Space Station MIR.

used in experimental payloads onboard the ISS. Measured concentrations have consistently been well below the spacecraft maximum allowable concentrations (SMACs) for L3. These SMACs were developed using the *Guidelines for Developing Spacecraft Maximum Allowable Concentrations for Space Station Contaminants* (NRC, 1992), which were described in detail in a subsequent publication (James & Gardner, 1996). These exposure limits are intended to prevent adverse effects in healthy adult men and women and therefore do not consider susceptible populations, such as pregnant women, unborn children, infants, adolescents, the elderly, or individuals with preexisting conditions. However, SMACs do incorporate appropriate safety factors for spaceflight-associated physiological changes, such as suppression of immune function, loss of red cell mass or heightened risk of cardiac arrhythmia that may render astronauts uniquely susceptible to certain toxic effects.

Because of its common use and detection in the atmosphere of spacecraft, NASA decided to establish an SMAC for L3 in the early 1990s. A literature search at the time yielded no toxicity data for this compound. However, oral toxicity data for structurally similar linear siloxanes, L2, decamethyltetrasiloxane (L4) and dodecamethylpentasiloxane (L5), as well as inhalation toxicity data for L2 were identified and examined (Henderson & James, 1994). It was assumed that the inhalation toxicity of L3 was similar to that of L2. Since the adverse effects on liver and kidney produced by L2 vapor were assumed to have a threshold, a traditional

Table 2. Summary of previously published octamethyltrisiloxane (L3) SMAC values and the critical adverse effect (Henderson & James, 1994).

Octamethyltrisiloxane				
1-hour SMAC	24-hour SMAC	7-day SMAC	30-day SMAC	180-day SMAC
400 ppm Lethality	200 ppm Hepatotoxicity Nephrotoxicity	100 ppm Hepatotoxicity Nephrotoxicity	20 ppm Hepatotoxicity Nephrotoxicity	4 ppm Hepatotoxicity Nephrotoxicity

no-observed-adverse-effect level (NOAEL) approach, in which the highest dose that produces no observed adverse effects was divided by uncertainty factors (UFs) to account for unknown or missing information and inherent variability, was used to establish SMACs for L3 using the L2 inhalation data (Appendix).

The present publication presents the results of a reassessment of the toxicological profile of linear siloxane compounds and the development of generic group SMACs to replace the previously published SMACs for L3 shown in Table 2 (Henderson & James, 1994). This reassessment evaluates new data to determine whether the previously established SMACs remain the most appropriate limits for astronaut exposure to L3 and other linear siloxanes. In addition to new data, various approaches, such as benchmark dose modeling and dosimetric adjustments, were also considered. Ultimately, SMACs for linear siloxanes were changed after uncertainties were reduced by additional information. This update also establishes a 1000-day SMAC, which is important for assessing the longer-term crew exposures expected during exploration beyond Earth orbit.

To our knowledge, no recent systematic review on the toxicological literature of these compounds has been published, and the only limits for human exposure to linear siloxanes are the previously published SMACs and Dow Corning internal health guidelines (IHGs) and worker do not exceed levels (DNELs) established for the European REACH program. It is our hope that the data summarized herein and applied to risk assessment for astronauts will be useful to those who set out to establish an exposure limit for ground-based populations.

Methods

A literature review was conducted to identify relevant studies of all short chain linear siloxanes performed since the SMACs for L3 were set in 1994. The most sensitive and relevant toxicity endpoints were determined using both old and new data. Methods for dosimetric adjustments and newer risk assessment approaches were evaluated for use with each data set in calculating acceptable concentrations for each toxicological endpoint and exposure duration. Updated SMACs for various exposure times were derived and expanded to include all linear siloxanes encountered during the spaceflight.

Results

Summary of new data

Studies performed since 1994 are summarized in Table 3 and are described in more detail further.

Acute effects

Dow Corning Corporation (DCC) completed acute exposure studies of L2 and L3, which were documented by internal reports. In a 1996 study of L2, three groups of five male and five female F-344 rats were exposed at target concentrations of 11 000, 14 000 or 18 000 ppm for 4 hours (DCC, 1996). Average measured exposure concentrations were 10 067, 14 050 and 16 659 ppm. All rats were observed for treatment-related signs of toxicity, including evidence of respiratory, dermal, behavioral, nasal or ocular changes, for 14 days post-exposure and were then sacrificed for gross pathological examination. One female and one male rat in the 14 000 ppm exposure group died 3 and 4 days post-exposure, respectively. An additional female rat in the mid-dose group was sacrificed for humane reasons 4 days post-exposure. In the high-exposure group, three male rats died 3 days post-exposure, and three female rats died 2 days post-exposure. No deaths were observed in any of the animals exposed to 11 000 ppm L2. Signs of neurological dysfunction were reported during exposure in the mid- and high-dose groups, but did not occur in animals exposed to 11 000 ppm L2. Adverse pulmonary effects, including congestion and hemorrhage, were noted in animals exposed to 14 000 and 16 000 ppm L2 but not in animals exposed to 11 000 ppm. Based on these results, 11 000 ppm was considered a no-observable adverse effect level (NOAEL) (DCC, 1996).

In the study of L3, five female and five male albino Sprague Dawley (SD) rats were exposed to 2350 ppm (the highest achievable vapor concentration under exposure conditions used) for 4 hours (DCC, 2004a). No adverse clinical or macroscopic effects were noted immediately following exposure through 14 days post-exposure.

Sub-acute effects

More recently, a combined repeated-exposure toxicity study that included reproductive/developmental toxicity screening was conducted (DCC, 2007b). Male and female SD rats were exposed daily to 0, 800, 1600 or 3200 ppm L3 for 6 hours/day for 28-29 days. Clinical examinations were performed daily following exposure, and detailed physical examinations and body weight measurements were recorded weekly. Neurological evaluations using the functional observational battery and motor activity tests were performed prior to exposure and during the fourth week of exposure. Blood samples were collected for hematology and serum chemistry immediately prior to necropsy, and microscopic evaluations were performed on the kidney, liver and thyroid of male rats and the liver and thyroid of female rats. This study reported that male animals exposed to 3200 ppm L3 and female animals at all concentrations of L3 experienced a dose-related increase in liver weights that correlated with centrilobular hepatocellular hypertrophy (DCC, 2007b). However, the study authors considered this an adaptive, rather than an adverse effect, because it is a common finding with xenobiotic exposure associated with the induction of hepatic metabolic enzymes. Male-specific protein droplet nephropathy was also noted in SD rats exposed to 800, 1600 or 3200 ppm L3 for 6 hours/day lasting for 29 days; however, this effect is generally considered irrelevant to human risk

Table 3. Summary of new studies.

Test article	Strain; number of animals	Exposure duration	Target exposure levels (ppm)	Results	NOAEL/BMDL	Reference
Acute						
L2	F-344 rats 5/sex/dose	Single 4 hr	11 000, 14 000, 18 000	Death: 6/10 at 18 000 ppm, 2/10 at 14 000 ppm, 0/10 at 11 000 ppm; Local respiratory effects and neurological dysfunction at 18 000 and 14 000 ppm	11 000 ppm	DCC (1996)
L3	SD rats 5/sex/dose	Single 4 hr	2350	No adverse treatment-related effects	2350 ppm	DCC (2004a)
Subacute						
L3	SD rats 10/sex/dose	6 hr/day 5 day/week 28 days (females) 29 days (males)	0, 800, 1600, 3200	Hepatic porphyrins in males at 1600 and 3200 ppm; Increased liver weights in males at 3200 ppm and in females at 800, 1600, and 3200 ppm[a]	594 ppm (BMDL)	DCC (2007a)
L4	SD rats 10/sex/dose	6 hr/day 5 day/week 28 days (females) 29 days (males)	0, 400	No adverse treatment-related effects	400 ppm[e]	DCC (2007b)
Subchronic						
L2	F-344 rats 20/sex/dose	6 hr/day 5 day/week 13 weeks	0, 50, 200, 600, 1500, 5000	Male-specific hyaline casts at 600, 1500, and 5000 ppm[b]	5000 ppm	DCC (1998, Cassidy (2001)
L2	SD rats 30/sex/dose	6 hr/day 7 day/week 146 days (F_0 males) 138 days (F_1 males)[c] 163 days (F_0 females) 159 days (F_1 females)[c]	0, 100, 400, 1600, 5000	Subtle neurological endpoints noted in offspring[c]; Male-specific hyaline casts at 5000 ppm[b]; Hepatic porphyrins, periportal inflammation, and bile duct hyperplasia at 5000 ppm in the F_0 generation	1600 ppm	DCC (2006, DCC (2008)
L3	SD rats 10/sex/dose	6 hr/day 7 day/week 90 days	0, 95, 400, 3200	Hepatic porphyrins in males at 3200 ppm; Increased liver weight in males at 400 and 3200 ppm[a]; Periportal inflammation in 10 males/1 female at 3200 ppm, 1 male/1 female at 400 ppm, 1 female at 95 ppm, and 1 male/1 female control[d]	400 ppm	DCC (2010a)
L4	SD rats 10/sex/dose	6 hr/day 7 day/week 90 days	0, 70, 400	No adverse treatment-related effects	400 ppm[e]	DCC (2010b)
Chronic						
L2	F-344 rats 20/sex/dose	6 hr/day 5 day/week 24 months	0, 100, 400, 1600, 5000	Male-specific hyaline casts at 5000 ppm[b]; Increased liver weights in males at 1500 and 5000 ppm[a]; Leydig cell tumors in all males (including controls)[d]	5000 ppm	DCC (2004b)

[a]Considered adaptive metabolic response, rather than adverse effect, due to lack of histopathological findings.
[b]Considered irrelevant to human risk assessment.
[c]NASA does not consider developmental endpoints since astronauts are screened for pregnancy prior to flight, and conception is not expected during flight.
[d]Considered irrelevant to human risk assessment and not test article related.
[e]Highest achievable vapor concentration.

assessment (Swenberg, 1993). Hepatic porphyrins were noted in male animals exposed to 1600 and 3200 ppm L3 (DCC, 2007b). This study reported no adverse reproductive and development effects of the offspring (DCC, 2007b).

Inhalation exposure of SD rats to 400 ppm L4 (the highest achievable vapor concentration) for 28 days (females) or 29 days (males) was evaluated in a combined repeated-exposure toxicity study that included reproductive/developmental toxicity screening endpoints (DCC, 2007a).

Clinical examinations were performed daily and were immediately followed by exposure and detailed physical examinations. Body weight measurements and food consumption assessments were performed at least weekly. Neurological endpoints were assessed using the functional observational battery and motor activity evaluations prior to initiation of exposures and during the fourth week of exposure. Blood samples for hematology and serum chemistry evaluations were collected at the scheduled necropsy

from males and toxicity group females. Complete necropsies were performed on the males and the toxicity group females and selected organs were weighed. Microscopic examination was performed on selected tissues from the control and 400 ppm exposure groups. L4 did not produce any treatment-related systemic or reproductive effects in either sex at 400 ppm. There were no clinical signs or effects on body weights and food consumption. No treatment-related changes were observed in neurological parameters, hematology and serum chemistry parameters, organ weights or histopathology (DCC, 2007a).

Sub-chronic effects

Male and female albino Fischer 344 rats were exposed to 0, 50, 200, 600, 1500 or 5000 ppm L2 for 6 hours/day, 5 days/week for 13 consecutive weeks (DCC, 1998; Cassidy et al., 2001). The high dose of 5000 ppm was set at approximately half the lower explosive limit (LEL) and represented a safe level for working with vapor concentrations in the laboratory. All animals were observed daily for mortality and clinical signs, including changes in behavior, somatomotor activity, body position, respiration and alterations of the skin, nose or eyes. Body weight measurements were taken weekly. Ocular examinations were performed prior to exposure and at week 11. Blood and urine samples were collected for hematology, serum chemistry and urinalysis immediately prior to necropsy. Weights of adrenal glands, brain, heart, kidneys, liver, lungs, ovaries, spleen, testes and thymus were recorded at necropsy for all dose groups. Histopathology was performed on paraffin embedded sections of all major organs in the control and high-dose groups and on the lungs, kidneys, nasal cavities and testes of the other dose groups. The only test article-related effects reported were renal tubular changes, including increased hyaline casts, in male animals exposed to 600, 1500 and 5000 ppm L2. Mechanistic studies conducted to evaluate these effects indicated that α-2-μ-globulin accumulation in tubular epithelial cells produced the observed kidney nephropathy (DCC, 2002). This effect is well established as a male rat-specific phenomenon and therefore, it was deemed not relevant to humans.

In a 90-day study of L3, groups of 10 male and 10 female SD rats were exposed to 0, 95, 400 or 3200 ppm for 6 hours/day, 7 days/week for 90 days (DCC, 2010b). Another set of 10 animals of each sex were exposed to 0 or 3200 ppm, followed by a 28-day exposure-free recovery period. All animals were observed daily for mortality and clinical signs followed immediately by exposure and weekly acclimation. Body weight measurements were recorded weekly. Ocular examinations were performed prior to exposure and again after 3 months, just before study completion. Blood and urine samples were collected for hematology, serum chemistry and urinalysis at the end of the exposure or recovery periods. Weights of adrenal glands, brain, heart, kidneys, liver, lungs, ovaries, spleen, testes, thymus and uterus were recorded at necropsy following exposure or recovery. Histopathology was performed on paraffin-embedded sections of all major organs, and liver slides were peer-reviewed. No adverse clinical or macroscopic effects were noted immediately after exposure or

28 days post-exposure. Increased liver weights, with corresponding centrilobular hepatocellular hypertrophy, were noted in males exposed to 400 and 3200 ppm and females exposed to 3200 ppm. A transient increase in relative kidney weights (resolved during recovery period) was also noted in male rats exposed to 3200 ppm. These effects were considered adaptive, rather than adverse. Hyaline droplets observed in the kidney represented α-2-μ-globulin accumulation, which is a common response observed in male rats and not relevant to human risk. Brownish-red pigment deposits were noted in the livers of all male animals exposed to 3200 ppm. Additional studies determined these pigment deposits to be due to altered protopophyrin accumulation (DCC, 2012). Chronic periportal inflammation, believed to be associated with porphyrin accumulation, was noted in all 10 males and 1 female exposed to 3200 ppm. However, this inflammation was also noted in one control animal of each sex. The incidence was then increased to 4 of 10 male control animals following the recovery period. Therefore, the relationship to the test article is unclear.

L4 was evaluated for the potential to cause systemic toxicity following whole body inhalation exposure to SD rats (10/sex/group) at 0, 70 and 400 ppm (highest achievable vapor concentration) for 6 hours/day, 7 days/week for 90 days followed by a 28-day exposure-free recovery period (DCC, 2010a). Body weight measurements were recorded weekly. Ocular examinations were performed prior to exposure and again after 3 months, just before study completion. Blood and urine samples were collected for hematology, serum chemistry and urinalysis at the end of the exposure or recovery periods. Organ weights were recorded at necropsy following exposure or recovery. Histopathology was performed on paraffin-embedded sections of all major organs of the 400 ppm exposure group. L4 did not produce any adverse effects in male and female SD rats. No target organs were identified and no adverse clinical or macroscopic effects were noted immediately following exposure or 28 days post-exposure (DCC, 2010a).

In addition to the 90-day studies described above, a two-generation reproductive toxicity study on L2 exposure was conducted (DCC, 2006). Groups of male and female SD rats (30/sex/group) were exposed via whole-body vapor inhalation to L2 for 6 hours/day, 7 days/week for at least 70 consecutive days prior to mating. Target concentrations of L2 were 0, 100, 400, 1600 or 5000 ppm. First (F_0) and second (F_1) generation male rats were exposed through mating until the day prior to sacrifice (146 days total for F_0 males and 138 days total for F_1 males). F_0 female rats were exposed through gestation day 20 (163 days total), and exposure of F_1 female rats began on postnatal day 22 (159 days total). Endpoints evaluated include clinical observations, evaluation of reproductive performance, parturition in females and spermatogenic endpoints in males, collection of litter data, sensory function and neurobehavioral testing, anatomical pathology and organ weight changes, histopathology of the liver of all animals and the central nervous system tissues of the offspring. No reproductive effects were noted in the F_0 or F_1 rats tested. A functional observational battery (FOB) neurobehavioral screen was performed on a sub-group of the F_0 female SD rats. FOB, surface-righting, air-righting, auditory startle response,

locomotor activity, and learning and memory assessments were also performed on F_1 female rats. No adverse effects were noted in any of the neurological assessment sub-groups of animals. In addition, no microscopic evidence of neuropathology was observed in the cerebrum, cerebellum and pons. No test article-related clinical findings or effects on gestation, lactation, body weight, or food consumption were noted in either parental generation. Systemic effects in this study included hepatic porphyrins in 6/30 F_0 male rats exposed to the highest dose of L2 tested (5000 ppm) and in F_1 male and female SD rats exposed to 1600 (24/30 males and 7/30 females) and 5000 ppm (29/29 males and 26/28 females) L2. In addition, periportal, subacute inflammation of the liver and bile duct hyperplasia were reported, although bile duct hyperplasia was noted only in F_1 male and female rats exposed to the highest dose. These effects correspond to higher mean relative liver weights only for F1 males (1600 and 5000 ppm). A follow-up report, released by DCC in 2008, identified an NOAEL of 400 ppm based on pigment accumulation in the liver (DCC, 2008); however, this was based on effects noted in the F_1 generation, which are not relevant to NASA SMACs. Test article-related kidney weight increases were noted for F0 and F1 males in the 1600 and 5000 ppm groups. Corresponding histopathological effects of L2 in this study included hyaline droplets (5000 ppm) and increased incidence and severity of basophilic tubules in the kidneys (5000 ppm) associated with male rat-specific hyaline droplet (consistent with α-2 urinary globulin) nephropathy. Therefore the kidney effects were not deemed relevant to humans.

Chronic effects

Dow Corning conducted a 24-month combined chronic toxicity/oncogencity study of L2 in Fischer 344 rats (DCC, 2004b). Three groups of animals (20/sex/group) were exposed to 0, 100, 400, 1600 or 5000 ppm L2 via whole body inhalation for 6 hours/day, 5 days/week. The first group was sacrificed after 1 year of exposure, the second group after 1 year of exposure and 1 year of recovery, and the third group after 2 years of exposure. Animals were observed twice daily for mortality and twice per week for clinical signs during exposure and weekly during acclimation and recovery. Body weight measurements were recorded weekly for the first 14 weeks and every other week thereafter. Blood and urine samples were collected for hematology, serum chemistry and urinalysis following 3, 6 and 12 months of exposure. Weights of adrenal glands, brain, heart, kidneys, liver, lungs, ovaries, pituitary gland, spleen, testes and thymus were recorded at necropsy following exposure or recovery. Histopathology was performed on paraffin-embedded sections of all major organs. Following 1 year of exposure, increased relative liver weights (relative to body weight) were reported in male rats exposed to 1600 ppm L2, and increased relative and absolute liver weights occurred in males exposed to 5000 ppm L2 for the same duration. No associated histological lesions were noted in these animals, and this phenomenon was attributed to transient metabolic adaptation (DCC, 2004b). The same study reported increased relative testes weights in male animals exposed to 5000 ppm L2 for 12 months; however, Leydig cell hyperplasia occurred in all male animals at all exposure levels, including

controls. Leydig cell tumors (LCTs) were noted in 4/20, 13/20, 13/20, 15/20 or 18/20 male rats in the 0, 100, 400, 1600 or 5000 ppm exposure groups, respectively. After 2 years of exposure, 62/65, 64/65, 62/65, 63/65 and 64/64 rats developed LCTs. In animals exposed for 1 year and then allowed to recover for 1 year, the animals in the control and low-dose exposure groups and 19 out of 20 animals in the remaining exposure groups developed LCTs. Finally, this study reported renal tubular adenomas in 2/20 and 4/20 male rats and renal tubular carcinomas in 1/20 and 2/20 males following 2 years of exposure to the highest doses of L2 (1600 and 5000 ppm). However, a follow-up mechanistic study indicated that these tumors were caused by a male rat-specific α-2-μ-globulin mechanism that is not relevant to humans (DCC, 2002).

Summary of the development of updated SMACs

Reported data indicate similar endpoints across exposure durations for L2 and L3 (male rat-specific α-2-μ-globulin effects in the kidneys, liver enlargement and hepatic porphyrins with associated periportal, subacute inflammation and bile duct hyperplasia). L4 did not cause any adverse effects following both 28-day and 90-day inhalation exposures up to the highest achievable vapor concentration of 400 ppm. Due to the significant decrease in vapor pressure and associated achievable vapor concentrations with increasing molecular weight, the JSC Toxicology Office determined that vapor concentrations of no concern for L2 and L3 would also pose no concern for L4 and L5, as it is unlikely that those concentrations could even be reached (Table 1). Therefore, group SMACs were developed for the family of linear siloxanes L2-L5, rather than attempting to develop individual SMACs.

1-Hour SMAC

The key study used to set the previous 1-hour SMAC for L3 (Rowe et al., 1948) was the only acute study available at the time. Since then, Dow Corning completed 4-hour acute exposure studies of L2 and L3, which reported NOAELs of 11 000 and 2350 ppm. As there was no effect at a saturated concentration of L3 and they were considered as a family, the highest NOAEL of 11 000 ppm was selected as the point of departure (POD) for development of the updated acute SMACs.

One of the criticisms of the NOAEL approach is that it uses only a single dose and does not account for the slope of the dose–response curve at doses above the NOAEL (Farland & Dourson, 1992). Benchmark dose modeling is an alternative approach that results in a model-derived lower confidence limit on the dose that causes a specific increase in response over controls (Farland & Dourson, 1992). However, benchmark dose modeling was not possible, due to the lack of unexposed controls (DCC, 1996). Therefore, the use of the traditional NOAEL approach remains appropriate.

Calculation of a human equivalent concentration (HEC) following the USEPA reference concentration guidelines (USEPA, 1994) was also considered. Ideally, use of a physiologically-based pharmacokinetic (PBPK) model is recommended to describe chemical-specific kinetic

disposition in rodents and humans and derive an internal dose metric. A preliminary rodent PBPK model for L2 has been developed (Dobrev et al., 2003; McMullin et al., 2013). This current model, however, is not sufficiently parameterized for extrapolation to humans and is limited to describing the kinetic disposition of L2, not L3. When PBPK models are not available, the USEPA (1994) recommends default dosimetry adjustments for gases (vapors) and particles (mists) to obtain an HEC. Based on the known saturated vapor concentrations of the linear siloxanes, all concentration levels tested are considered to represent vapor exposures. Therefore, L3 was considered to be a vapor and default dosimetry adjustments for gases/vapors were applied. Since L3 is poorly soluble in water and produces systemic effects, it was considered a Category 3 vapor, as defined by the USEPA (1994). For these vapors, movement from the respiratory tract into the blood, as defined by the blood–gas partition coefficient, is most relevant. Although the blood–gas partition coefficient for L2 was estimated to be 0.8 *in vitro* using rat blood in a sealed container with a saturated atmosphere of L2 at 37 °C (Dobrev et al., 2003), we were unable to locate a blood–gas partition coefficient for L2 in humans. Therefore, a default ratio of 1 was used to account for potential differences in the blood–gas partition coefficient between animals and humans and to calculate the HEC.

Finally, the application of UFs in the original risk assessment was reconsidered. Intraspecies and interspecies uncertainty is typically divided equally between toxicodynamic and toxicokinetic processes, although there is evidence to suggest that toxicokinetic differences are larger than toxicodynamic differences (Dourson et al., 1996). Application of the default dosimetry adjustment described earlier accounts for potential toxicokinetic differences between animals and humans, which therefore reduced the interspecies UF from 10 to 3 (the geometric half of 10, rounded to one significant figure). As SMACs are developed for well-screened, healthy adults, the JSC Space Toxicology Office does not include an intraspecies UF unless there is a defined susceptible population (e.g. a genetic variant) that is not screened out. The UF of 3 that was originally included to account for a potential difference in the structure–activity relationship between L2 and L3 has been reduced to 2, since the overall database now includes information on L2, L3 and L4. The similar toxicities noted for these compounds reduce uncertainty regarding potential variability in the toxicity of other linear siloxanes. Finally, an UF of 3 was incorporated to account for the severity of the endpoint (death). The resulting rounded value for the 1-hour SMAC is 600 ppm (Equation 1). As the 1-hour SMAC is based on a 4-hour exposure, this value is conservative. However, given the severity of the effects noted in the higher doses, we determined that this conservatism was appropriate.

$$\frac{10\,067\,\text{ppm}}{3 \times 3 \times 2} = 560\,\text{ppm} \qquad (1)$$

- NOAEL: 10 067 ppm [measured concentration]
- UF for interspecies differences: 3
- UF for structure–activity extrapolation: 2
- UF for severity of endpoint (death): 3

24-Hour SMAC

Applying a duration adjustment factor to the data from the same 4-hour study used for calculating the 1-hour SMAC results in an SMAC of 93 ppm.

$$\frac{10\,067\,\text{ppm}}{3 \times 3 \times 2} \times \frac{4\,\text{h}}{24\,\text{h}} = 93\,\text{ppm} \qquad (2)$$

- NOAEL: 10 067 ppm [measured concentration]
- UF for interspecies differences: 3
- UF for structure–activity extrapolation: 2

UF for severity of endpoint (death): 3A rounded value of 100 ppm was selected for the 24-hour SMAC, as this is in line with the 7-day SMAC calculated below.

7-Day SMAC

The existing 7-day SMAC for L3 was based on an NOAEL of 4400 ppm in rats exposed for 105 hours to L2 (Rowe et al., 1948). It is the policy of the JSC Space Toxicology Office to ''...begin with data based on exposures having a cumulative duration as close as possible to the potential human exposure period in question'' (James & Gardner, 1996). For the 7-day SMAC, the most relevant exposure is the 28-29 day Dow Corning study of L3, which reported cumulative exposure durations of 174 and 168 hours (DCC, 2007b). This study reported hepatic porphyrin, accompanied by bile duct proliferation and chronic inflammation in male animals exposed to 1600 and 3200 ppm L3 and centrilobular hypertrophy in females at every exposure level (800, 1600 and 3200 ppm) and males exposed to the highest dose (DCC, 2007b).

As no other adverse effects were reported, we evaluated the human relevance of hepatic porphyrins. In rats, protoporphyria is believed to involve enzymes mediating the heme biosynthesis pathway, including the male rat-specific enzyme P450 2C11. The human relevance of enzymatic alterations leading to hepatic porphyrin accumulation is still uncertain due to differences in cytochrome P450 enzymes between species (Lavigne et al., 2002). In addition, clinical porphyrias in humans are generally due to a genetic disorder in specific enzymes involved in heme biosynthesis (Bloomer, 1997). However, porphyrins are known to be a chemically reactive material that, in excess, can lead to various strain, species and sex specific pathological liver effects in animal models (Anstey & Hift, 2007; Knasmuller et al., 1997) Therefore, the JSC Space Toxicology Office conservatively chose to protect against porphyrin deposits. Based on this approach, 800 ppm was considered a NOAEL and was selected as the POD for the 7-day SMAC. No duration adjustment was applied because the cumulative exposure durations of 174 and 168 hours are sufficiently similar to 7 days of continuous exposure (168 hours).

Benchmark dose modeling was again considered, and in this instance it was found to be applicable. We utilized the freely available USEPA benchmark dose modeling software (version 2.2) (Research Triangle Park, NC) to evaluate the data and followed their recommendations for performing and evaluating benchmark dose modeling. The initial step is to select the appropriate benchmark response. For dichotomous data, such as the presence or absence of porphyrin, an extra
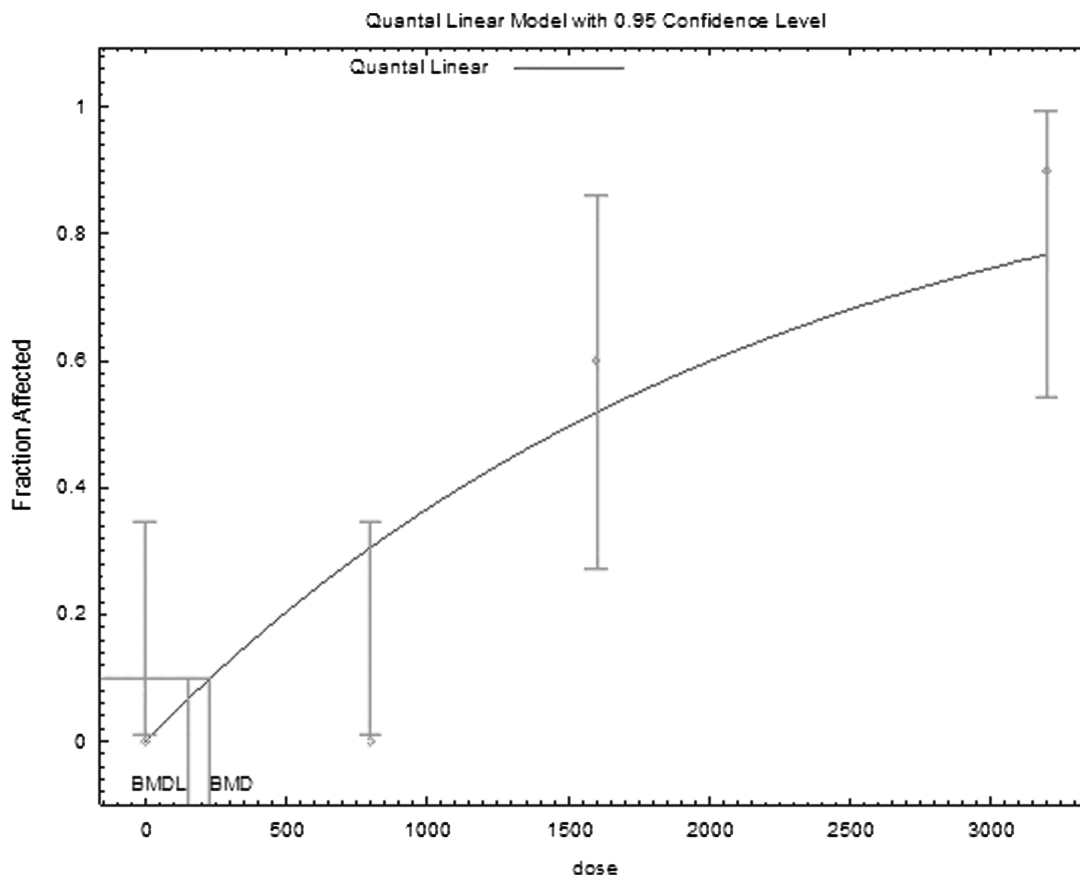
Figure 2. Quantal-linear model rejected due to poor fit for 7-day SMAC endpoint (porphyrin).

Table 4. Summary of benchmark dose modeling output for 7-day SMAC development.

Model	Gamma	Logistic	Log-logistic	Log-probit	Multistage (2)	Multistage (3)	Probit	Weibull	Quantal-linear
p Value	0.3548	0.1298	0.4837	0.4854	0.4770	0.2683	0.1418	0.2667	0.1298
Scaled residual	−0.822	−1.054	−0.725	−0.677	−1.286	−1.189	−1.043	−1.09	0
AIC	26.562	28.704	25.804	25.773	25.857	27.801	28.690	27.610	30.708
BMDL	479.43	538.22	572.00	**593.68**	303.04	281.91	514.32	364.56	150.42

The value in bold is the value that resulted from the best-fitting model and selected for derivation of the SMAC.

risk of 10% is recommended as the standard reporting level, because it is generally near the limit of sensitivity for most assays. We selected 10% extra risk and plotted the porphyrin incidence in male rats, without regard to severity using all available dichotomous models. All models were restricted to ensure that polynomial coefficients were positive and power and slope terms were 1 or greater. The model outputs were then evaluated for goodness of fit. The goodness of fit *p* values and scaled residuals met the criteria of $p > 0.1$ and absolute value <2.0 for all models; however, visual inspection of the quantal-linear model indicated that it was not a good fit in the low-dose region (Figure 2), and it was therefore not considered relevant. All remaining models predicted a lower statistical limit on the benchmark response (BMDL) within a 2-fold range of one another (Table 4). The Akaike's Information Criteria (AIC) was therefore used to identify the best fitting model, the log-probit model (Figure 3). The BMDL calculated from this model was 594 ppm, which was used as the POD for derivation of the 7-day SMAC.

Calculation of an HEC following the USEPA reference concentration guidelines (USEPA, 1994) was also considered.

As stated previously, PBPK models were not identified for L3. Therefore, the USEPA recommended default dosimetry adjustment for gases (vapors) was applied (USEPA, 1994). As before, L3 was considered a Category 3 vapor, and the default blood–gas partition coefficient of 1 was used to calculate the HEC.

Application of the default dosimetry adjustment described earlier accounts for potential toxicokinetic differences between animals and humans, which therefore reduced the interspecies UF from 10 to 3 (the geometric half of 10, rounded to one significant figure). It was observed that wherever comparable data exist on linear siloxane compounds, the potency differences were not large. Therefore, a final UF of 2 was applied to account for potential structure-activity differences between linear siloxane family members. Although the core studies were not published in peer-reviewed journals, they come from a respected company and were submitted to a federal agency; thus, a factor to compensate for database insufficiency is not necessary. The default dosimetry adjustment for a Category 3 vapor and application of UFs resulted in a value of 99 ppm
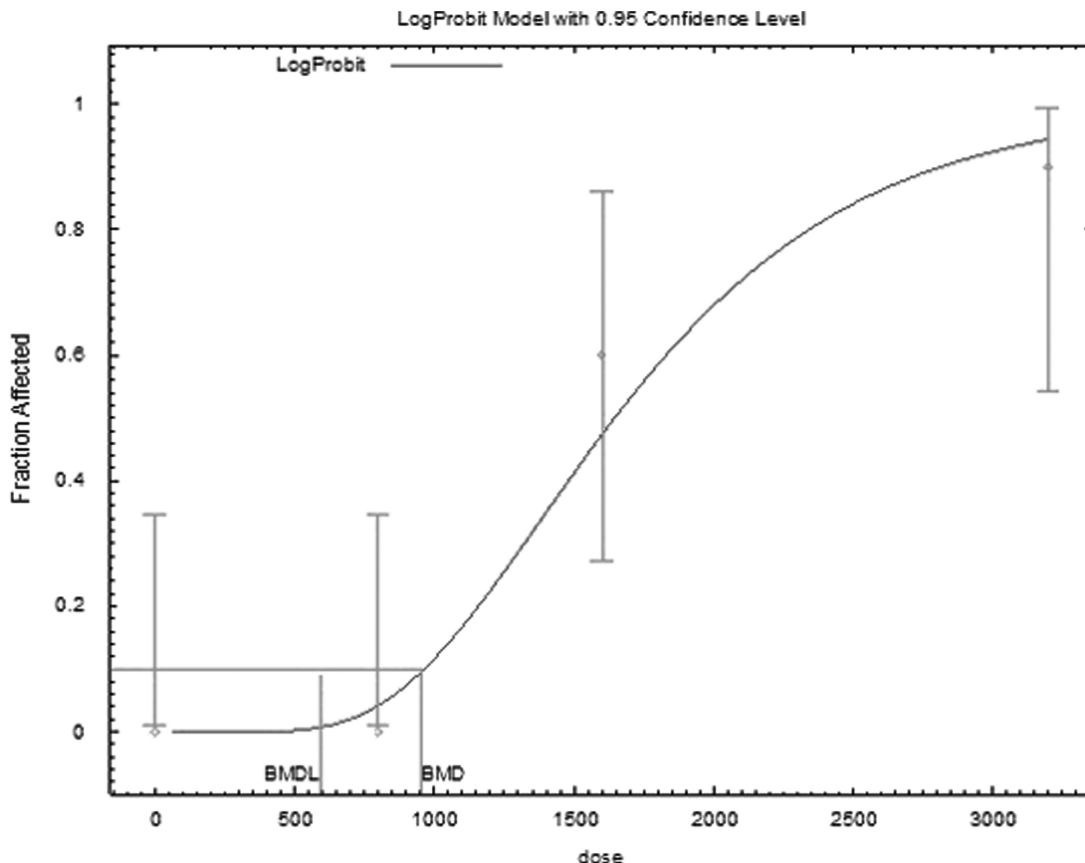
Figure 3. Log-probit model selected as the best fit for potential hepatotoxicity due to porphyrin deposits for 7-day SMAC development.

(Equation 2). A rounded value of 100 ppm was adopted as the 7-day SMAC.

$$\frac{594 \text{ ppm} \times 1}{3 \times 2} = 99 \text{ ppm} \tag{3}$$

- BMDL: 594 ppm [log-probit model result]
- Ratio of animal to human blood partition coefficient: 1 [dosimetric adjustment]
- UF for interspecies differences: 3
- UF for structure–activity extrapolation: 2

30-Day SMAC

A 90-day study (total exposure duration = 540 hours) most closely matches the exposure duration of interest (720 hours). This study reported increased liver weights in male SD rats exposed to 400 and 3200 ppm and females exposed to 3200 ppm L3 and hepatic porphyrins in all 10 male animals exposed to 3200 ppm (DCC, 2010b). Although the lack of hepatic porphyrins in a study of similar duration conducted in Fischer-344 rats using L2 suggests that porphyrin development may be strain-specific (Cassidy et al., 2001; DCC, 1998), the JSC Space Toxicology Office again chose to conservatively protect against porphyrin deposits and potential hepatotoxicity.

For this study, benchmark dose modeling could not be used, because only one test dose (the highest) produced an

effect, and that effect was present in all male animals. The NOAEL of 400 ppm was chosen for the 30-day SMAC. This value was adjusted from the total study exposure duration (540 hours) to 720 hours that is approximately equal to a continuous 30-day exposure. Default dosimetric adjustment for a Category 3 vapor (default value of 1) was applied, and application of an interspecies UF of 3 and a structure–activity UF of 2 resulted in a value of 50 ppm (Equation 3). The value of 50 ppm was adopted as the new 30-day SMAC.

$$\frac{400 \text{ ppm} \times 1 \times \frac{540 \text{ hours}}{720 \text{ hours}}}{3 \times 2} = 50 \text{ ppm} \tag{4}$$

- NOAEL: 400 ppm
- Ratio of animal to human blood partition coefficient: 1
- Duration adjustment: 540 hours/720 hours
- UF for interspecies differences: 3
- UF for structure–activity extrapolation: 2

180-Day SMAC

A 90-day study evaluating exposure to 0, 95, 400 or 3200 ppm L3 reported hepatic porphyrins in males (DCC, 2010b). Similarly, a 2-generation reproductive toxicity study reported hepatic porphyrins in 6/30 F_0 male SD rats exposed to 5000 ppm L2 for 6 hours/day for 146 days and in F_1 rats exposed to 1600 (24/30 males and 7/30 females) or 5000 ppm (29/29 males and 26/28 females) (DCC, 2006, 2008). As before, the JSC Space Toxicology Office chose to

conservatively protect against porphryin deposits and potential hepatotoxicity; however, effects were only considered in the F_0 generation, as NASA does not consider developmental endpoints for the derivation of SMACs since astronauts are screened for pregnancy prior to launch and conception is not expected during flight. The highest NOAEL of 1600 ppm noted in the F_0 generation of the 2-generation study was used as the POD.

Benchmark dose modeling was not applicable because effects were only seen at the highest dose in the F_0 generation. The NOAEL of 1600 ppm was therefore extrapolated from intermittent to continuous exposure (6 hours/24 hours), and the default dosimetric adjustment factor of 1 for the blood–gas coefficient difference between animals and humans for a Category 3 vapor was applied to account for potential interspecies toxicokinetic differences (USEPA, 1994). The resulting HEC is 400 ppm. A UF of 3 was applied to account for interspecies toxicodynamic differences, and a UF of 2 was applied to account for potential structure–activity differences. These calculations (Equation 5) result in a value of *67* ppm.

$$\frac{1600\,\text{ppm} \times 1 \times \frac{6\,\text{hours}}{24\,\text{hours}}}{3 \times 2} = 67\,\text{ppm} \tag{5}$$

This value is slightly higher than the value calculated for the 30-day SMAC. Therefore, the value of 50 ppm used for the 30-day SMAC was set for the 180-day SMAC as well.

Development of an extended-duration (1000-day) SMAC

Since publication of the previous SMACs for siloxanes, NASA has begun to develop 1000-day SMACs for extended duration flights associated with sending humans beyond Earth orbit. The JSC Space Toxicology Office identified only one study of chronic exposure to linear siloxanes. Groups of 20 male and 20 female Fischer-344 rats were exposed to L2 for 6 hours/day, 5 days/week and sacrificed after one year of exposure, after 1 year of exposure and 1 year of recovery, or after 2 years of exposure (DCC, 2004b). The study reported adaptive liver response (increased liver weights due to liver hypertrophy) and Leydig cell tumor formation in exposed animals. This tumor type is common in Fischer 344 rats and occurred spontaneously in all control animals by the end of the study; however, the study authors also observed that exposure may have accelerated LCT progression, based on the data collected 1 year after exposure (DCC, 2004b). Reported human incidence of LCTs (0.00004%) is nearly 2 million-fold lower than the spontaneous tumor formation rate in Fischer 344 rats (~80%) (Clegg et al., 1997; Cook et al., 1999). The true incidence in humans may be somewhat higher, as small, non-palpable tumors may escape detection; however, human incidence is significantly lower than in rats (Cook et al., 1999).

The primary non-DNA-reactive mechanisms of LCT formation involve disruption of the hypothalamic–pituitary–testicular (HPT) axis and a resulting increase in luteinizing hormone (LH) (Clegg et al., 1997). Rats appear to be more sensitive to increases in LH hormone levels, in part because rodent Leydig cells have a greater number of receptors compared to human cells (Cook et al., 1999). Greater sensitivity in rats may also be due to a lack of sex hormone binding protein, (which allows greater testosterone blood level fluctuations in rats), enhanced sensitivity to human chorionic gonadotropin and prolactin, and the presence of gonadotropin releasing hormone receptors (Cook et al., 1999). In addition, L2 did not elicit a positive mutagenic response in the Ames test, with or without S9 activation (Isquith et al., 1988; Wagner, 2008). Therefore, the mode of action for tumor development is likely non-mutagenic. Since rats are much more susceptible than humans to the non-mutagenic modes of action described earlier, LCT formation was not considered a relevant endpoint for human risk assessment and was therefore not considered for use in setting the 1000-day SMAC.

As no adverse effects were reported, the highest exposure dose, 5000 ppm, is considered a NOAEL. However, this study was conducted in Fischer-344 rats, which appear to be less sensitive than SD rats to the adverse effects of siloxanes. Data from the sub-chronic studies in the SD rats are consistent and the fact that the NOAEL for 180 days is not lower than the NOAEL for 30 days suggests a threshold mechanism for the development of liver porphyrins. Therefore, based on the data from the most sensitive strain of rats studied (SD rats), the JSC Space Toxicology Office chose to protect against potential long-term effects associated with chronic deposition of hepatic porphyrins by electing to set the 1000-day SMAC at 50 ppm, the value for the 30-day and 180-day SMACs set to prevent development of porphyrins, inflammation and bile duct hyperplasia.

Spaceflight factors

There is no evidence that linear siloxanes elicit toxic effects that would be potentiated by spaceflight-induced physiological changes.

Linear siloxane group SMACs

We have relied on data from L2 and L3 toxicity studies to set SMACs that we intend to apply to the group of linear siloxanes. We expect these to be the most toxic compounds in the family via inhalation exposure, due to the rapid decline in volatility with increasing molecular weight, as shown in Table 1. The final SMACs for the group of linear siloxanes are given in Table 5. These values will be applied on a ppm basis (adjusted for molecular weight) to the family of linear siloxanes.

Table 5. Summary of updated SMAC values for linear siloxanes and the critical adverse effect.

Linear siloxanes					
1-hour SMAC	24-hour SMAC	7-day SMAC	30-day SMAC	180-day SMAC	1000-day SMAC
600 ppm	100 ppm	100 ppm	50 ppm	50 ppm	50 ppm
Pulmonary/neurotoxcity	Pulmonary/neurotoxcity	Hepatotoxicity	Hepatotoxicity	Hepatotoxicity	Hepatotoxicity

Limitations

The 1-hour SMAC value is likely to be overly conservative. Data on the acute toxicity of linear siloxanes are limited to a single, dated study that evaluated limited endpoints. Because the exposure concentrations in this study were high, the proportions of vapor and aerosol to which the animals were exposed is unknown, resulting in high uncertainty in extrapolating the results from animals to humans. Despite the uncertainty, the JSC Space Toxicology Office deemed it necessary to set short-term SMACs for linear siloxanes due to the recent utilization of silicone oil in experiments aboard ISS.

Conclusion

SMACs for linear siloxanes were changed after uncertainties were reduced by additional information. Most values were updated by the application of the default dosimetric adjustment factors recommended by the USEPA, resulting in the application of a less conservative interspecies UF and group SMAC values that are somewhat higher than previous SMACs for L3 alone. The critical adverse effects for the 1-hour and 24-hour SMACs are neurotoxicity and pulmonary toxicity. 7-Day, 30-day and 180-day SMACs were set to protect against liver effects, including hepatic porphyrins, inflammation and bile duct hyperplasia. New data from chronic toxicity studies were used to establish a 1000-day SMAC to protect crewmembers during future extended-duration flights beyond Earth orbit. This value was conservatively set to protect against potential long-term effects associated with chronic hepatic porphyrins, including the possibility of liver cancer. Adherence to the final values summarized in Table 5 will ensure safe exposures to linear siloxanes during human spaceflight.

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Declaration of interest

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Appendix: Summary of the development of the original SMACs for L3

Single, whole-body exposure of guinea pigs to 25 000 ppm L2 for 30 minutes did not result in adverse clinical effects or lethality; whereas death occurred within 15–20 minutes at a saturated atmosphere of 40 000 ppm (Rowe et al., 1948). The NOAEL of 25 000 ppm was used as the POD for the 1-hour SMAC. A duration adjustment from 30 to 60 minutes and UFs (10 for interspecies differences and 3 for structure–activity uncertainty) were then applied to the NOAEL to calculate a value of 420 ppm (Equation A1). A rounded value of 400 ppm was set as the 1-hour SMAC.

$$\frac{25\,000\,\text{ppm} \times \frac{30\,\text{min}}{60\,\text{min}}}{10 \times 3} = 420\,\text{ppm} \qquad (A1)$$

The same authors reported that rats exposed to 4400 ppm L2 by inhalation during 15 separate 7-hour exposure sessions over 18 days experienced a 10% decrease in liver and kidney weights. In the absence of other changes, the small organ weight decrease was not considered an adverse effect, and 4400 ppm was considered an NOAEL. In the absence of pharmacokinetic data, the JSC Space Toxicology Office selects studies in which the cumulative exposure duration most closely matches the exposure duration for the SMAC being set (James & Gardner, 1996). Although this approach often requires the use of data from intermittent exposures to derive continuous exposure limits, it was accepted by the National Research Council's subcommittee on spacecraft exposure guidelines and has been consistently applied to the derivations of SMACs. In this case, fifteen 7-hour sessions resulted in a total exposure time of 105 hours. This cumulative exposure period was considered sufficiently similar in duration to a 7-day continuous exposure (168 hours) to develop an SMAC, but a time adjustment factor (105 hours/168 hours) was applied. In addition, a structure–activity factor of 3 was applied because the key study examined L2; whereas, the compound of interest was L3. Finally, an interspecies UF of 10 was also applied to obtain the calculated value of 92 ppm (Equation A2). A rounded value of 100 ppm was adopted as the 7-day SMAC.

$$\frac{4400\,\text{ppm} \times \frac{105\,\text{hours}}{168\,\text{hours}}}{10 \times 3} = 92\,\text{ppm} \qquad (A2)$$

SMACs for spaceflight-relevant exposure durations that could not be directly derived from experimental data were developed using Haber's rule, which assumes that concentration (C) and exposure time (T) play equal roles and may be reciprocally adjusted to maintain a cumulative exposure constant (K) that results in a given toxic effect (C × T = K). Haber's Rule is typically used to extrapolate from short- to long-term durations. Haber's Rule was applied to the calculated 7-day SMAC value of 92 ppm to establish the resulting 30-day and 180-day SMACs of 21 and 3.6 ppm (Equations A3 and A4). The SMAC values for L3 were rounded to 400, 100, 20 and 4 ppm (4000, 1000, 200 and 40 mg/m^3) for the final 1-hour, 7-day 30-day, and 180-day SMACs, respectively.

$$\frac{92\,\text{ppm} \times 7\,\text{days}}{30\,\text{days}} = 21\,\text{ppm} \qquad (A3)$$

$$\frac{92\,\text{ppm} \times 7\,\text{days}}{180\,\text{days}} = 3.6\,\text{ppm} \qquad (A4)$$

Haber's rule was not used to develop a 24-hour SMAC. Rather, a decision was made to assume that a 24-hour SMAC of 200 ppm (2000 mg/m^3) was appropriate, since it lies between the data-derived for 1-hour (400 ppm) and 7-day (100 ppm) SMACs. Table 2 summarizes the original SMACs for L3, and additional information on the basis of the original SMACs for L3 can be found in Volume 1 of *Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants* (Henderson & James, 1994).