Spacecraft Maximum Allowable Concentrations (SMACs) for C3 to C8 Aliphatic Saturated Aldehydes

Dr. Shannon D. Langford
Johnson Space Center Toxicology Group
National Aeronautics and Space Administration
Houston, Texas

BACKGROUND

Spacecraft maximum allowable concentrations (SMACs) for C3 to C8, straight-chain, aliphatic aldehydes have been previously assessed and have been documented in volume 4 of *Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants* (James, 2000). These aldehydes as well as associated physical properties are shown in Table 1. The C3 to C8 aliphatic aldehydes can enter the habitable compartments and contaminate breathing air of spacecraft by several routes including incomplete oxidation of alcohols in the Environmental Control and Life Support System (ECLSS) air revitalization subsystem, as a byproduct of human metabolism, through materials off-gassing, or during food preparation. These aldehydes have been detected in the atmosphere of manned space vehicles in the past. Analysis performed by NASA of crew cabin air samples from the Russian Mir Space Station revealed the presence of C3 to C8 aldehydes at concentrations peaking at approximately 0.1 mg/m^3 (unpublished NASA technical data from 1995 reported by James, 2000).

Table 1. Physical Properties of C3 to C8, Straight-chain, Aliphatic Aldehydes

Name:	Propanal	Butanal	Pentanal	Hexanal	Heptanal	Octanal
$CH_3(CH_2)_nCHO$:	n = 1	n = 2	n = 3	n = 4	n = 5	n = 6
CAS nos:	171426-73-6	171339-76-7	110-62-3	66-25-1	111-71-7	124-13-0
Molecular weights:	58.1	72.1	86.1	100.2	114.2	128.2
Boiling points (°C):	49	76	103	128	154	171
Melting point (°C):	-81	-99	-92	-56	-45	N/A
Vapor pressures (mmHg):	687	92	50	10	3	N/A
(at °C):	45	20	25	20	25	
Conversion factors:[†]						
1 ppm =	2.3 mg/m^3	2.9	3.5	4.1	4.6	5.2
1 mg/m^3 =	0.422 ppm	0.340	0.284	0.245	0.215	0.191

CAS, Chemical Abstracts Service

[†] 1 ppm converted to milligrams per cubic meter, and 1 mg/m^3 converted to parts per million.

N/A, not available.

The majority of the existing reports pertaining to aliphatic aldehyde toxicity have been previously reviewed by NASA in support of establishment of the SMACs published in 2000. This report is intended as a companion document to complement and update the existing C3-C8 saturated aliphatic aldehyde SMAC document. This update will summarize the approach taken in developing the existing SMACs, identify recent data that may impact existing SMAC values, and establish and provide rational for a new 1000-day SMAC.

REVIEW OF EXISTING SMACs AND SUMMARY OF ORIGINAL APPROACH

The initial review in 2000 resulted in establishment of 1 and 24 hour as well as 7, 30, and 180 day SMACs for the group of C3 to C8 straight-chained, aliphatic aldehydes. Table 2 presents SMACs established by NASA for these compounds. Respiratory irritation potential threshold (RD_{50}) data from rats and mice indicate similar properties (sensory irritation) within this group of compounds and the closely related compound – acetaldehydes (Steinhagen and Barrow, 1984; Babiuk et al., 1985; Sim and Pattle, 1957). Due to the similarity in toxicity exhibited on this particular endpoint by the C3 to C8 aldehydes, the Committee on Spacecraft Exposure

Guidelines chose to establish SMACs for these compounds as a group rather than setting separate SMACs. The toxicological endpoints of concern identified previously include mucosal irritation, nasal cavity injury, nausea and vomiting, and liver damage. SMACs for each exposure time were selected based on the most conservative Acceptable Concentration (AC) for each toxicological endpoint.

Table 2. Spacecraft Maximum Allowable Concentrations (SMACs) for C3 to C8 Aliphatic Saturated Aldehydes - 2000

Duration	ppm	mg/m^3	Toxic Endpoint to Avoid
1 h	50	125-250[a]	Mucosal irritation
24 h	50	125-250	Mucosal irritation
7 d	6	15-30	Liver injury, mucosal irritation
30 d	1.5	4-8	Liver injury
180 d	1.5	4-8	Liver injury

[a] The value depends on the molecular weight of the aldehyde.

Protection against mucosal irritation

An early study reported irritancy to mucosal surfaces in humans resulting from exposure to propanal for 30 minutes (mildly irritating at 134 ppm, Sim and Pattle, 1957). The same study found that exposure to 230 ppm butanal and 207 ppm isobutanal for 30 minutes was not irritating to the human subjects. Human data was only available for the three aldehydes mentioned above. However, animal data available at the time indicated the possibility that other aldehydes in the group may be two to three times more irritating than propanal (Salem and Cullumbine 1960; Abdo et al., 1998). Thus, ACs for the 1-hr and 24-hr SMACs were set at 50 ppm (Eq. 1).

Equation 1: 1- and 24-h SMACs based on mucosal irritation.

134 ppm $_{(LOAEL)}$ reduced downward by a factor of approximately two to three)

1- and 24-h $AC_{(Mucosal\ irritation)}$ = 50 ppm

Although short-term ACs were established conservatively to protect against mucosal irritation, some risk of this toxicological endpoint is allowed. However, for exposure durations exceeding 24 h, mucosal irritation should be precluded. Therefore, the NASA 7, 30, and 180 day SMAC was established by dividing the human-derived mildly irritating concentration of 134 ppm (for propanal, Sim and Pattle, 1957) by ten, yielding an AC of 13 ppm (James, 2000) (Eq. 2).

Equation 2: 7-, 30-, and 180-day SMACs based on mucosal irritation.

134 ppm $_{(LOAEL)}$ • 1/10

7-, 30-, and 180-day $AC_{(Mucosal\ irritation)}$ = 13 ppm

Protection against nasal-cavity injury

Long-term isobutanal exposure studies in rats and mice were utilized to estimate ACs protective for injury to the nasal-cavity (squamous metaplasia and olfactory epithelial degeneration in the nose; Abdo, 1998). In the first study of this report, an isobutanal vapor cumulative exposure time of 390 hours (6 h/d, 5 d/wk for up to 13 weeks) resulted in a no observable adverse effect level (NOAEL) of 500 ppm in both rats and mice. Similarly, 500 ppm was reported as the

lowest observed adverse effect level (LOAEL) in female rats. In the second study from this report, the cumulative exposure time to isobutanal vapor was 3120 hours (6 h/d, 5 d/wk for 2 years). NASA ACs protective of nasal-cavity injury based on the NOAEL and LOAEL values from Abdo, 1998 are (Eq. 3, Eq. 4, and Eq. 5):

Equation 3: 7-day SMAC based on nasal-cavity injury.

$$500 \text{ ppm}_{(\text{NOAEL})} \cdot 1/10_{(\text{species factor})}$$
$$\text{7-day AC}_{(\text{Nasal-cavity injury})} = 50 \text{ ppm}$$

Equation 4: 30-day SMAC based on nasal-cavity injury.

$$500 \text{ ppm}_{(\text{NOAEL})} \cdot 1/10_{(\text{species factor})} \cdot 390 \text{ h}/720 \text{ h}_{(\text{time extrapolation})}$$
$$\text{30-day AC}_{(\text{Nasal-cavity injury})} = 27 \text{ ppm}$$

Equation 5: 180-day SMAC based on nasal-cavity injury.

$$500 \text{ ppm}_{(\text{LOAEL})} \cdot 1/3_{(\text{LOAEL to NOAEL})} \cdot 1/10_{(\text{species factor})} \cdot 3120 \text{ h}/4320 \text{ h}_{(\text{time extrapolation})}$$
$$\text{180-day AC}_{(\text{Nasal-cavity injury})} = 12 \text{ ppm}$$

Protection against liver injury

Acceptable Concentrations protective for possible liver injury from accumulation of organic acids from aldehyde metabolism were conservatively set at 6.4 ppm (7-day AC) and 1.5 ppm (30- and 180-day AC) (James, 2000). Choice of liver injury as a presumptive toxicological endpoint was based on the observation of vacuoles within hepatocytes of rats exposed 6 times to 1,300 ppm propanal for 6 h each exposure (Gage, 1970). To derive the ACs, NASA used, as a point of departure, the 90 ppm exposure level reported by Gage (20 exposures of 6 h each) to yield no observable liver changes (cumulative exposure of 120 hours). It was assumed that harmful metabolites would not accumulate in liver cells below a threshold exposure concentration. Extrapolations to adjust for exposure duration based on application of Haber's rule would correct the AC to a level below this threshold concentration. The resulting NASA ACs protective for liver injury are (Eq. 6 and Eq. 7):

Equation 6: 7-day SMAC based on liver injury.

$$90 \text{ ppm} \cdot 1/10_{(\text{species factor})} \cdot 120 \text{ h}/168 \text{ h}_{(\text{time extrapolation})}$$
$$\text{7-day AC}_{(\text{Liver injury})} = 6.4 \text{ ppm}$$

Equation 7: 30- and 180-day SMACs based on liver injury.

$$90 \text{ ppm} \cdot 1/10_{(\text{species factor})} \cdot 120 \text{ h}/720 \text{ h}_{(\text{time extrapolation})}$$
$$\text{30- and 180-day AC}_{(\text{Liver injury})} = 1.5 \text{ ppm}$$

As reviewed previously, the toxicities of the C3-C8 aliphatic saturated aldehydes appear to be similar (James, 2000). Upon review of the AC established for each toxicological endpoint, group SMACs were established for toxic effects by selecting the acceptable concentration for the most active compound for that endpoint. Table 3 presents the individual ACs for each toxicological endpoint of concern.

Table 3. Acceptable Concentrations for Identified Toxicological Endpoints - 2000

End Point	Uncertainty Factors				Acceptable Concentrations (ppm)				
	NOAEL	Time	Species	Spaceflight	1 h	24 h	7 d	30 d	180 d
Mucosal irritation	2-3	1	1	1	50	50	--	--	--
	10	1	1	1	--	--	13	13	13
Nasal-cavity injury	1	HR[†]	10	1	--	--	50	27	--
	3	HR	10	1	--	--	--	--	12
Potential liver injury	1	$HR_{threshold}$	10	1	--	--	6	1.5	1.5
SMACs[‡]					50	50	6	1.5	1.5

[†] HR, Haber's rule

[‡] SMACs for each exposure time are selected based on the most conservative AC for each toxicological endpoint

SUMMARY OF NEW RELEVANT DATA FROM LITERATURE

No toxicity studies at all (including those examining any relevant routes of pulmonary exposure) subsequent to 2000 having bearing on C3 to C8 aliphatic saturated aldehydes SMACs were located during this assessment.

ADDITIONAL CONSIDERATION OF NON-TOXIC ODOR THRESHOLD

The group of C3 to C8 aliphatic saturated aldehydes have varied odors described as agreeably fruity to choking and suffocating (NIOSH, 1994; Furia and Bellanca, 1975; Furia, 1980; U.S. Coast Guard, 1984-5; National Fire Protection Association, 1986). The reported odor threshold for one aldehyde in this group, pentanal, is 0.028 ppm (pentanal was the only member of this group for which an odor threshold value is available; Amoore and Hautala, 1983). A summary of reported odor characteristics for the C3 to C8 aliphatic saturated aldehydes is presented in Table 4.

Odor thresholds – the lowest concentration of a chemical in the air that people can smell – are imprecise measurements. Humans exhibit a naturally wide sensitivity to odors. This sensitivity can be further affected by factors such as illness. Because odor threshold detection can vary to a great extent, the concentrations are often reported as ranges. Odor threshold values are not

TABLE 4. Selected Odor Characteristics of C3 to C8 Aliphatic Saturated Aldehydes.

Compound	Odor	Odor Threshold	Reference
Propanal	Suffocating, fruity, similar to acetaldehyde, pungent, unpleasant, choking	Not available	NFPA,1986; Furia and Bellanca, 1975; USCG,1984-5; Furia,1980
Butanal	Pungent, aldehyde	Not available	Lewis, 1997
Pentanal	Powerful, acrid, pungent, strong	0.028 ppm	Amoore and Hautala, 1983; NIOSH, 1994
Hexanal	Fruity, strong green grass, sharp aldehyde	Not available	Furia and Bellanca, 1975; Furia,1980; Lewis, 1997
Heptanal	Fatty pungent, penetrating fruity	Not available	Furia,1980; Budavari, 1989
Octanal	Sharp fatty, fruity	Not available	Furia and Bellanca, 1975

NFPA, National Fire Protection Association; USCG, U.S. Coast Guard; NIOSH, National Institute for Occupational Safety and Health

absolute points but rather an average of the sampled populations' response. In addition, “fruity,” “chocking,” and “suffocating” are only descriptions of smells reported by individuals. Detection of odor in the case of many chemicals can also be affected by continued exposure to that chemical odor. Olfactory adaptation is a very common phenomena resulting from continued exposure to an odor and is characterized by a reduction or loss in smell sensitivity to a particular chemical (Pryor et al., 1970).

Irritation threshold, demonstrated as the lowest concentration of a chemical causing acute stinging, burning sensations, or tear generation in the nose and eyes, is reported as irritation threshold values. Irritation threshold values, which are distinctly different from odor thresholds, usually require higher ambient chemical concentrations to elicit an irritation response when compared to detection of odor (Amoore and Hautala, 1983). Acetaldehyde, while not included in the group of C-3 to C-8 aldehydes, exhibits similar human irritancy to that of pentanal and propanal. Like propanal, human subjects exposed for 30 minutes to 134 ppm acetaldehyde were reported to experience slight irritation (Sim and Pattle, 1957). Acetaldehyde has a pungent suffocating odor with an odor threshold of 0.05 ppm and a TLV of 25 ppm which are again very similar to values for propanal and pentanal (ACGIH, 1999; U.S. EPA, 1987; Amoore and Hautala, 1983). Amoore and Hautala (1983) reported an irritation threshold of 2,200 ppm for the nose and an ocular level of 11,000 ppm for acetaldehyde – approximately 44,000 times higher (nose) than the odor threshold value for this compound. Both acetaldehyde and pentanal are classified by Amoore and Hautala (1983) as “Class A” substances, which because their odor threshold values are much lower than their respective threshold limit values, can serve as bellwether indicators.

The low odor threshold of pentanal (and by inference, the other members of the C3-C8 aldehydes) could serve as a means to alert the spacecraft crew to the presence of a substance at levels far lower than would be expected to cause toxicological effects. Granted, crewmembers could experience smell aversion as a result of exposure to noxious chemical smells. Although such aversion could impede crew performance, it should not be categorized as a toxic effect. Therefore odor threshold values are not utilized herein as a toxicological endpoint. The odor threshold for pentanal (0.028 ppm) is several times higher than the lowest SMAC values for the C3 to C8 aldehydes (approximately 143 times higher). Therefore, it is understood that the SMAC levels, which are designed to protect against adverse health effects, will not necessarily prevent spacecraft crewmember from experiencing smell aversion due to noxious odors. A footnote will be included with the revised SMAC table describing the concentration where the odor of a representative compound – pentanal - may become a concern.

REVISION OF EXISTING SMACs AND ESTABLISHMENT OF 1000-DAY SMAC

After review of the studies considered in setting the original SMACs in 2000, the Committee on Spacecraft Exposure Guidelines has decided to revise all the ACs for the C3-C8 aldehydes.

The uncertainty factor of “two to three” originally applied to the acute 1-h and 24-h SMAC in 2000 will be revised to a factor of three. A factor of three is considered the most conservative for this group of aldehydes and reflects animal data suggesting that some members of this group

of compounds are two to three times more irritating than the base compound – propanal (Salem and Cullumbine 1960; Abdo et al., 1998). The 1-h and 24-h ACs remain based on the point of departure of 134 ppm (mildly irritating to mucosal surfaces after 30 min exposure in humans; Sim and Pattle, 1957). Therefore, the revised 1-h and 24-h C3-C8 aldehyde SMACs are set at 45 ppm (Eq. 8).

Equation 8: Revised 1- and 24-h SMACs based on mucosal irritation.

$$134 \text{ ppm}_{(\text{LOAEL})} \times 1/3$$

$$\text{1- and 24-h } AC_{(\text{Mucosal irritation})} = 45 \text{ ppm}$$

The 2006 Committee revisited the original rational used in setting the 7- through 180-d SMACs in 2000. In 2000, the long-term SMACs were predicated on protecting against liver pathology, which was based on acute (5-day) exposure data from rats (Gage, 1970). The study reported by Gage utilized discontinuous exposures to propanal. The 2000 SMACs subsequently utilized a factor to correct for continuous vs. discontinuous exposure conditions. No additional factors were applied to account for exposure duration differences (i.e. 5 day to 7, 30, or 180 days) based on the assumption that a threshold dose - below which no liver pathology would occur – had been established. However, upon reevaluation, the acute exposure protocol and the now questioned relationship between cellular vacuoles and liver pathology eliminated the use of the NOAEL reported by Cage as a point of departure for the longer-term SMACs. The Committee chose instead to select the study of Abdo et al., 1998. This stud design more closely corresponds to exposure durations bounded by the longer-term SMACs (7- through 1000-d). In addition, the endpoint (squamous metaplasia of respiratory epithelium) was felt to be more toxicologically appropriate and defensible.

Abdo et al employed exposure of rats and mice to select concentrations of isobutanal vapor for 6 h/d, 5 d/wk for up to 13 weeks or 2 years. The 13-week study revealed a NOAEL of 500 ppm in both rats and mice while the 2-year study revealed a LOAEL of 500 ppm in female rats. The LOAEL of 500 ppm reported for female rats exposed for 2 years was selected as the point of departure for the 7-d through 1000-d SMACs. A factor of ten was applied to extrapolate from a LOAEL to a NOAEL. A correction factor of three was applied to account for interspecies differences in response. Finally, a factor of three was applied as was the case for the new 1- and 24-hr ACs (discussed previously) - to reflect animal data suggesting differences in irritating potential for these aldehydes (Salem and Cullumbine 1960; Abdo et al., 1998). The revised 7-, 30-, 180-d, and the new 1000-d SMACs are set at 4.5 ppm (Eq. 9).

Equation 9: 7-, 30-, 180-, 1000-d SMAC based on nasal-cavity injury.

$$500 \text{ ppm}_{(\text{LOAEL})} \bullet 1/10_{(\text{LOAEL to NOAEL})} \bullet 1/3_{(\text{species factor})} \bullet 1/3$$

$$\text{7- through 1000-d } AC_{(\text{Nasal-cavity injury})} = 4.5 \text{ ppm}$$

The 2006 SMACs for C3 to C8 aliphatic saturated aldehydes are presented in Table 5.

Table 5. Spacecraft Maximum Allowable Concentrations (SMACs) for C3 to C8 Aliphatic Saturated Aldehydes - 2006

Duration	ppm	mg/m^3	Toxic Endpoint to Avoid
1 h	45	113	Mucosal irritation
24 h	45	113	Mucosal irritation
7 d	4.5	11	Nasal-cavity injury
30 d	4.5	11	Nasal-cavity injury
180 d	4.5	11	Nasal-cavity injury
1000 d	4.5	11	Nasal-cavity injury

Note: A representative average odor threshold concentration for the C3 to C8 aliphatic saturated aldehydes is 0.028 ppm (pentanal; Amoore and Hautala, 1983). Some aldehydes in this group exhibit strong noxious odors detectable by humans at levels well below SMAC levels for these compounds.

DIFFERENCES BETWEEN THE ORIGINAL AND CURRENT NATIONAL RESEARCH COUNCIL COMMITTEE ON TOXICOLOGY APPROACH

The National Research Council Committee on Toxicology, as well as other regulatory bodies are primarily interested in using benchmark dose modeling (BMD) to interpret toxicological data. Favor of this relatively new tool over traditional threshold dose (NOAEL, LOAEL) data treatments is predicated on assumed advantages inherent in BMD application. The NRC recommends that BMD methods be utilized when sufficient and appropriate dose-response data are available (NRC, 2000). However, the NOAEL/ LOAEL-based method is recommended by the NRC in the absence of sufficient data or when special considerations are warranted.
The current SMACs for C3 to C8 straight-chained, aliphatic aldehydes were established based on a LOAEL/NOAEL and safety factor method. BMD methodology was applied to data from the long-term SMAC (7- through 1000-day) base study of Abdo et al., 1998. A summary of the BMD analysis is presented below.

Background for BMD analysis of long-term exposure data

Isobutyraldehyde was administered to both sexes of F344/N rats and $B6C3F_1$ mice by inhalation (6 hours per day, 5 days per week) for up to 13 weeks or two years (Abdo *et al.,* 1998). These results were used to the calculate benchmark concentration (BMC) for various toxic effects. Uncertainty factors were applied to the lower 95 % confidence limit of the benchmark concentration (BMCL) in order to arrive at maximum allowable concentrations. These values are compared with the proposed current spacecraft maximum allowable exposure concentrations (SMACs).

13-Week exposures reported by Abdo et al., 1998

Ten animals per group were exposed to 0, 500, 1000, 2000, 4000, and 8000 ppm of isobutyraldehyde. All rats died at 8000 ppm and 3 male and 6 female rats died at 4000 ppm. All mice died at 4000 and 8000 ppm, except for one male mouse at 4000 ppm. Body weight gains were reduced at 4000 ppm in both sexes of rats and reduced in both sexes of mice at 1000 ppm. Several endpoints could not be ascertained at 8000 ppm. Hence, data from the 8000 ppm group were not used for estimating low-dose benchmark concentrations. Incidence rates for the most sensitive endpoint for each sex of rats and mice are listed in Table 6.

Since the multistage (exponential polynomial) model can describe a wide variety of dose response shapes, it was used to estimate the dose response relationships. BMCs and BMCLs associated with an excess risk of 10% are listed in Table 6. Since a 10% incidence above background is the lowest rate that can be directly observed with 10 animals in a group, a 10% risk was selected for the BMC. Further, with 10 animals per group, at least 4 animals are required with an effect in order to achieve a statistically significant increase ($P \leq 0.05$) above a background of 0 out of 10 animals. Hence, using the BMCL10 as a point of departure for establishing a maximum allowable concentration is generally more conservative (stringent) than using the NOAEL.

Table 6. Incidence of effects in the most sensitive endpoint in each sex of rats and mice (10 animals per dose group) and estimates of BMC10 and BMCL10 for 13-week exposures.

Species/Sex Endpoint	Exposure (ppm)					BMC	BMCL
	0	500	1000	2000	4000	(ppm)	
Rat (male) Olfactory epithelium degeneration	0	0	0	10	10	880	680
Rat (female) Suppurative inflammation	2	6	2	0	10	2030	1000
Mice (male) Serous exudate	0	2	0	4	10	1000	340
Mice (female) Serous exudate	0	0	0	3	10	1480	1020

Consistent with the calculation of SMACs, an uncertainty factor of 10 was used for interspecies extrapolation and no uncertainty factor is used for intraspecies variability or a potential risk at the point of departure (NOAEL or BMCL). Further, adjustment for the duration of exposure employed Haber's Rule which assumes equal toxic effects for equal cumulative exposures. Hence, experimental exposures of 6 hours per day for 5 days per week are assumed to be equivalent to continuous exposures of (6 / 24) x (5 / 7) = 0.18 times the exposure administered over the (13 x 7) = 91 days.

The most sensitive endpoint, lowest BMCL10 = 340 ppm, occurred for serous exudate in male mice (Table 6). This results in a 30-day SMAC of

$$\text{SMAC (30 days)} = (340 / 10) \times (6 / 24) \times (5 / 7) \times (91 / 30) = 18.4 \text{ ppm}$$

and a 180-day SMAC of

$$\text{SMAC (180 days)} = (340 / 10) \times (6 / 24) \times (5 / 7) \times (91 / 180) = 3.1 \text{ ppm.}$$

These results are complementary to the proposed SMAC of 4.5 ppm which is based on a LOAEL/NOAEL method.

Further, average severity scores were examined using a polynomial model with the dose response data procedure for continuous data in the EPA Benchmark Dose Software (BMDS) program. The most sensitive endpoint for severity was for olfactory epithelium degeneration in

male rats. The benchmark response corresponding to an average severity grade of one (minimal effect) produced a BMCL = 1110 ppm, which exceeds the minimum BMCL = 340 ppm obtained for the incidences of effects.

2-Year exposures reported by Abdo et al., 1998

Initially, 50 animals per group were exposed to 0, 500, 1000, and 2000 ppm of isobutyraldehyde. Incidence rates for the most sensitive endpoint for each sex of rats and mice are listed in Table 7. Since the multistage (exponential polynomial) model can describe a wide variety of dose response shapes, it was used to estimate the dose response relationships. BMCs and BMCLs associated with an excess risk of 5% are listed in Table 7. With 50 animals per group, at least 5 animals (10%) are required with an effect in order to achieve a statistically significant increase ($P \leq 0.05$) above a background of 0 out of 50 animals with the effect. Hence, using the BMCL5 as a point of departure for establishing a maximum allowable concentration is generally more conservative (stringent) than using the NOAEL.

Table 7. Incidence of effects and estimates of BMC5 and BMCL5 for 2-year exposures.

Species/Sex Endpoint	Exposure (ppm)				BMC	BMCL
	0	500	1000	2000	(ppm)	
Respiratory epithelium squamous metaplasia						
Rat (male)	1/50[†]	1/49	10/49	44/50	590	450
Rat (female)	1/49	11/50	9/49	44/50	270	150
Olfactory epithelium degeneration						
Mice (male)	0/50	0/50	11/50	45/50	580	480
Mice (female)	1/50	1/50	27/50	49/50	440	320

[†] observed / total

Consistent with the calculation of SMACs, an uncertainty factor of 10 was used for interspecies extrapolation and no uncertainty factor is used for intraspecies variability or a potential risk at the point of departure (NOAEL or BMCL). Further, adjustment for the duration of exposure employed Haber's Rule which assumes equal toxic effects for equal cumulative exposures. Hence, experimental exposures of 6 hours per day for 5 days per week are adjusted by the factor (6 /24) x (5 / 7) for equivalency to continuous exposure.

The most sensitive endpoint, lowest BMCL5 = 150 ppm, occurred for respiratory epithelium squamous metaplasia in female rats (Table 7.). Presumably a 2-year lifetime exposure in rodents would be adequate to provide protection for a 1000-day exposure to humans. The resulting 1000-day SMAC is

$$\text{SMAC (1000 days)} = (150 / 10) \times (6 / 24) \times (5 / 7) = 2.7 \text{ ppm}.$$

These results again are complementary to the proposed SMAC of 4.5 ppm which is based on a LOAEL/NOAEL method.

Further, average severity scores were examined using a polynomial model with the dose response data procedure for continuous data in the EPA Benchmark Dose Software (BMDS) program. The most sensitive endpoint for severity was for olfactory epithelium degeneration in female mice. The benchmark response corresponding to an average severity grade of one

(minimal effect) produced a BMCL = 1420 ppm, which exceeds the minimum BMCL = 150 ppm obtained for the incidences of effects.

Summary of conclusions from BMD analyses

Results from the 13-week exposures to isobutyraldehyde were used to calculate 30-day and 180-day SMACs. The most sensitive endpoint was the incidence of serous exudate in male mice giving 30-day and 180-day SMACs of 18.4 and 3.1 ppm, respectively. The most sensitive endpoint from the 2-year exposures was the incidence of respiratory epithelium squamous metaplasia in female rats producing a 1000-day SMAC of 2.7 ppm. The proposed 7 to 1000-day SMAC of 4.5 ppm, derived via application of a LOAEL/NOAEL method should provide protection for the effects observed in the study by Abdo *et al.* (1998).

COMPARISON TO OTHER AIR QUALITY LIMITS

Exposure guidelines for a limited subset of C3 to C8 aliphatic saturated aldehydes exist with various public-health and occupational-health entities as well as with industry and government advisory bodies. Table 8 presents a list of some of these guidelines and regulatory standards for comparison to the current and proposed NASA SMACs.

TABLE 8. Selected Inhalation Exposure Levels for Selected C3 to C8 Aliphatic Saturated Aldehydes.

Compound	Organization	Exposure Guideline	Exposure Level
Propanal	ACGIH (2004)	TLV (8 h TWA)	20 ppm
Pentanal	ACGIH (2005)	TLV (8 h TWA)	50 ppm
Pentanal	NIOSH (2005	REL (10 h TWA)	50 ppm
Pentanal	Australia (1990)		50 ppm
Butanal	AIHA (2001)	WEEL (8 h TWA)	25 ppm
C3-C8 aliphatic aldehydes	NASA[†]	SMAC (1 h and 24 h)	45 ppm

ACGIH, American Conference of Governmental Industrial Hygienist; NIOSH, National Institute for Occupational Safety and Health; AIHA, American Industrial Hygiene Association; NASA, National Aeronautics and Space Administration; REL, Recommended Exposure Limit; TLV, Threshold Limit Value; WEEL, Workplace Environmental Exposure Level; SMAC, Spacecraft Maximum Acceptable Concentration

[†] Only 1 h and 24 h SMACs are listed here for comparison to similar exposure duration guidelines from other organizations.

The current NASA 1-h and 24-h SMACs are very similar to exposure levels from other organizations at comparable exposure durations. Exposure limits and guidelines for pentanal (for which values are available for comparison) have remained stable for several years. There are no guidelines available for long-term exposure durations to compare to the 7-, 30-, 180-, and 1000-day SMACs.

RECOMMENDATIONS FOR ADDITIONAL RESEARCH

Shortcomings in the toxicity database pertaining to C3 to C8 aliphatic saturated aldehydes persists. Lack of data concerning the effects of acute (humans) and chronic (humans and animals) exposures, as well as elucidation of non-lethal exposure effects to animals confounds attempts to establish exposure guidelines. Recommendations for additional research pertaining

to toxicity of this group of aldehydes are unchanged from those proposed by James, 2000. Increasing the number of exposure concentrations employed as well as expansion of the endpoint measurements examined for all aldehydes in this group would be most beneficial. The long-term exposure guidelines established herein are designed to protect against extra-pulmonary organ damage, specifically liver damage. Long-term pulmonary studies would be beneficial in confirming and extending the work of Gage (1970) and validating the protective assumptions made in the establishment of our intermediate and long-term SMACs.

REFFERENCES

Abdo, K.M., Haseman, J.K., and Nyska, A. (1998). Isobutyraldehyde administererd by inhalation for 13 w or 2 y was a respiratory tract toxicant but was not carcinogenic in F344/N rats and B6C3F$_1$ mice. Toxicol Sci 42:136-151.

American Conference of Governmental Industrial Hygienists (ACGIH). 1999 TLVs and BEIs. Threshold Limit Values for Chemical Substances and Physical Agents, Biological Exposure Indices. Cincinnati, OH. 1999.

Amoore, J.E., Hautala, E. (1983). Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air water dilution. J Appl Toxicol 3(6):272-90.

Appelman, L.M., Woutersen, R.A., Feron, V.J. (1982). Inhalation Toxicity of Acetaldehyde in Rats. I. Acute and Subacute Studies. Toxicology 23:293-307.

Appelman, L.M., Woutersen, R.A., Feron, V.J. Hoofman, R.N., Notten, W.R.F. (1986). Effect of Variable Versus Fixed Exposure Levels on the Toxicity of Acetaldehyde in Rats. J. Appl. Toxicol. 6:331-336.

Budavari, S. (1989). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Budavari, S. ed. Merck and Co., Inc., Rahway, NJ.

Canadian Environmental Protection Act. (2000). Priority Substances List Assessment Report. Acetaldehyde. Ministry of Public Works and Government Services: Ottawa, Canada.

Furia and N. Bellanca, (1975). Fenaroli's Handbook of Flavor Ingredients. Volume 2. 2nd ed. The Chemical Rubber Co., Cleveland, OH.

Furia, T.E. (1980). CRC Handbook of Food Additives. 2nd ed. Volume 2. Furia, T.E. ed. CRC Press, Inc., Boca Raton, Florida.

James, T.J. (2000). C3 to C8 Aliphatic Saturated Aldehydes. Vol 4., pp. 42-59. Subcommittee on Spacecraft Maximum Allowable Concentrations, Committee on Toxicology, Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC.

Lewis, R.J., Sr, (1997). Hawley's Condensed Chemical Dictionary. 13th ed. Lewis, R.J., Sr, ed. John Wiley & Sons, Inc. New York, NY.

National Fire Protection Association, (1986). Fire Protection Guide on Hazardous Materials. 9th ed. National Fire Protection Association, Boston, MA.

NIOSH, (1994). NIOSH Pocket Guide to Chemical Hazards. Department of Health and Human Services, (NIOSH) Publication No. 94-116. U.S. Government Printing Office, Washington, D.C.

NIOSH, (2005). NIOSH Pocket Guide to Chemical Hazards. DHHS (NIOSH) No. 2005-151. National Institute for Occupational Safety and Health, Center for Disease Control and Prevention, US Department of Health and Human Services, Cincinnati, OH.

NRC. (2000). Methods for Developing Spacecraft Water Exposure Guidelines. Subcommittee on Spacecraft Water Exposure Guidelines, Committee on Toxicology, Board on Environmental Studies and Toxicology, National Research Council. National Academy Press, Washington, DC.

Pryor, G.T., Steinmetz, G., and Stone, H. (1970). Changes in absolute detection threshold and in subjective intensity of supra-threshold stimuli during olfactory adaptation and recovery. Percept. Psychophys. 8:331-335.

Salem, H. and Cullumbine, H. (1960). Inhalation toxicities of some aldehydes. Toxicol Appl Pharmacol 2:183-187.

Sim, V.M. and Pattle, R.E. (1957). Effect of possible smog irritants on human subjects. J. Am. Med. Assoc. 165(15):1908-1913.

U.S. Coast Guard, (1984-5). Department of Transportation. CHRIS - Hazardous Chemical Data. Volume II. U.S. Government Printing Office, Washington, D.C.

U.S. Environmental Protection Agency. Health Assessment Document for Acetaldehyde. EPA/600/8-86-015A. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, Research Triangle Park, NC. 1987.