ATTACHMENT 1

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-41
December 12-14, 2006

Hilton- Old Town/Alexandria
1767 King Street
Alexandria, VA 22314

Metro: King Street (Blue/Yellow Line)

AGENDA

Tuesday, December 12, 2006

10:00 a..m.	Introductory remarks and approval of NAC/AEGL-40 Highlights (George Rusch, Ernie Falke, and Paul Tobin)
10:15	Federal Register 09- Discussion of Comments- Ethyl acrylate/Butyl acrylate (Carol Wood) Formaldehyde (Sylvia Talmage) Titanium tetrachloride (Claudia Troxel) Benzene (Marc Ruijten)- Tentatively scheduled Methacrylic acid/ Methyl methacrylate (Bob Benson)
11:45	Response to COT Comments- Allyl alcohol (Claudia Troxel) Carbon disulfide (Ernest Falke) Phosphorus trichloride (Bob Young) Sulfur dioxide (Cheryl Bast) n,n-Dimethylformamide (Claudia Troxel)
12:30 p.m.	Lunch
1:30	Response to COT Comments (continued)
2:30	Review of Ethyl benzene (John Hinz/Carol Wood)
3:30	Break
3:45	Review of Ethyl benzene (continued)
4:15	Discussion of data set for Carbonyl Fluoride (Iris Camacho/Sylvia Talmage)
5:30	Adjourn for the day

Wednesday, December 13, 2006

8:30 a.m.	Review of Methacrylaldehyde (Susan Ripple/ Tom Marshall)
10:00	Break
10:15	Review of Methyl Vinyl Ketone (Jim Holler/ Tom Marshall)
12:00 p.m.	Lunch
1:00	Review of Mercury Vapor (Marquea King/ Sylvia Talmage)
2:30	Break
2:45	Review of Propargyl Alcohol (George Cushmac/ Bob Young)
4:00	Break
4:15	Review of Selenium Hexafluoride (George Rusch/ Cheryl Bast)
5:30	Adjourn for the day

Thursday, December 14, 2006

8:30 a.m.	Review of Oxygen Difluoride (Iris Camacho/ Bob Young)
10:00	Review of Thionyl Chloride (Steve Barbee/ Jennifer Rayner)
11:45	Administrative matters
12:00 noon	Adjourn meeting

Chemical: ATTENDANCE 12/12/06 **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____ ATTACHMENT 2

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson					Warren Lederberg				
Steven Barbee					Glenn Leach				
Marc Baril					Richard Niemeier				
Lynn Beasley					Marinelle Payton				
Alan Becker	ABSENT				Susan Ripple				
Robert Benson					George Rodgers				
George Cushmac					Marc Ruijten				
Ernest Falke					George Rusch, Chair				
Alfred Feldt	ABSENT				Daniel Sudakin	ABSENT			
Roberta Grant					Richard Thomas				
Dieter Heinz					Calvin Willhite				
John Hinz					George Woodall				
Jim Holler					TALMAGE				
Paul Tobin					YOUNG				
BAST					BERCNAS TALLY				
WOOD					TROXEL PASS/ FAIL				

MARCY BANTZ Lyondell

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 **Motion by:**_____ **Second by:**_____
AEGL 2 **Motion by:**_____ **Second by:**_____
AEGL 3 **Motion by:**_____ **Second by:**_____
LOA **Motion by:**_____ **Second by:**_____

Approved by Chair:_____ **DFO:**_____ **Date:**_____

Chemical: ATTENDANCE 12/13/06 **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Henry Anderson	✓			
Steven Barbee	✓			
Marc Baril	✓			
Lynn Beasley	✓			
Alan Becker	A			
Robert Benson	✓			
George Cushmac	✓			
Ernest Falke	✓			
Alfred Feldt	A			
Roberta Grant	✓			
Dieter Heinz	✓			
John Hinz	✓			
Jim Holler	✓			
TOBIN	✓			
BAST	✓			
WOOD	✓			

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Warren Jederberg	A			
Glenn Leach	✓			
Richard Niemeier	✓			
Marinelle Payton	A			
Susan Ripple				
George Rodgers	✓			
Marc Ruijten	✓			
George Rusch, Chair	✓			
Daniel Sudakin	A			
Richard Thomas	A			
Calvin Willhite	✓			
George Woodall	✓			
YOUNG	✓			
MARSHALL TALMAGE	✓			
CAMACHO KING TALLY				
PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

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** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 **Motion by:**_____ **Second by:**_____
AEGL 2 **Motion by:**_____ **Second by:**_____
AEGL 3 **Motion by:**_____ **Second by:**_____
LOA **Motion by:**_____ **Second by:**_____

Approved by Chair:_____ **DFO:**_____ **Date:**_____

Response to Federal Register Comments:

Formaldehyde

National Advisory Committee for AEGLs Meeting 41
December 12-14, 2006

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Mark McClanahan

Chemical Reviewers:
George Rusch
George Rodgers

FORMALDEHYDE

Comments from the Formaldehyde Council:

The AEGL values represent the lower end of reasonable values.

National Academy of Sciences (2004):

Selected a 1-hour Emergency and Continuous Exposure Guidance Level (EEGL) of 2 ppm. This is the midpoint of the range (1-3 ppm) at which individuals first notice eye or nose irritation. The 24-hour EEGL is 1 ppm.

Reviews: Paustenbach et al. (1997); Bender et al. (2000); Arts et al. (2006)

Sensory irritation is noticed at levels of 1 ppm or higher. Below 1 ppm, control subjects reported the same number of complaints as formaldehyde-exposed subjects. Mild to moderate irritation does not occur till >2.0 to 3.0 ppm. Up to 4.0 ppm, the mean symptom score is less than moderate nasal irritation. Long-term studies show that 1.0 ppm is a NOAEL for nasal injury.

Formaldehyde Data Base:

22 well-conducted clinical studies with over 350 healthy and asthmatic subjects.
Concentrations ranged from 0.2 to 20 ppm
Exposure durations ranged from 5 minutes to 5 hours
At low concentrations, asthmatics are not a sensitive population.
No response in asthmatics inhaling 3 ppm for 3 hours.
Formaldehyde is well-scrubbed in the upper respiratory tract.

AEGL-1 based on Bender et al. study (1983)
Subjects were sensitive individuals, i.e., subjects that reported irritation at low concentrations were excluded from the study.

The NOAEL of 0.90 ppm for eye irritation in the Bender study shows a level of precision that is not supported by the data.

Suggestions: Use 1, 2, or 3 ppm across all AEGL-1 exposure durations.

AEGL-2: No suggestions; 14 ppm was the highest concentration used in a reliable study.

AEGL-3: Change time scaling? In a recent well-conducted study (Maronpot et al. 1986), mice survived three weeks of exposure to 40 ppm (6 hours/day, 5 days/week).

Formaldehyde AEGLs - Summary

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm
AEGL-2	14 ppm	14 ppm	14 ppm	14 ppm	14 ppm
AEGL-3 n = 1.76	100 ppm 210 ppm	70 ppm 114 ppm	56 ppm 77 ppm	35 ppm 35 ppm	35 ppm 35 ppm

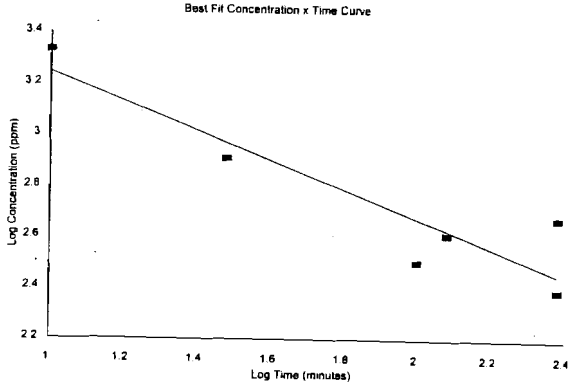
*Most individuals will notice the distinct, pungent odor of formaldehyde at the AEGL-1. The Level of Distinct Odor Awareness is 3.6 ppm.

AEGL-1: NOAEL for eye irritation- sensitive human subjects, 6 minutes (Bender et al. 1983)

AEGL-2: Mild lacrimation with adaptation - humans, 30 minutes, 14 ppm (Sim and Pattle 1957)

AEGL-3: Highest non-lethal value - rat, 4-hours, 350 ppm (Nagorny et al. 1979)

Regression curve of formaldehyde LC_{50} values



Reference	Species	Time	Concentration	Log Time	Log Conc.
Alarie (1981)	mouse	10	2160	1.0000	3.3345
Skog (1950)	rat	30	820	1.4771	2.9138
B&A (1978)	mouse	100	320	2.0000	2.5051
Nagorny	mouse	120	410	2.0792	2.6128
Carpenter	rat	240	250	2.3802	2.3979
Nagorny	rat	240	478	2.3802	2.6794

n = 1.76
k = 5060814
r^2 = 0.8381

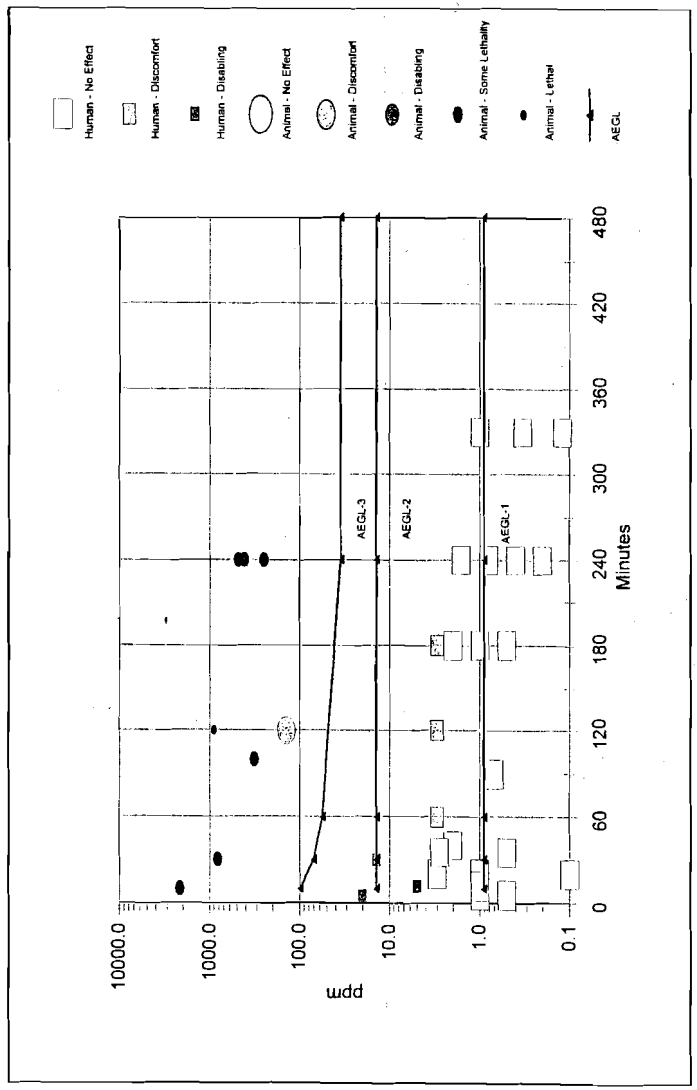


Figure 1. Category Graph of Human and Animal Toxicity Data in Relation to AEGL values.

Response to Federal Register Comments for Titanium Tetrachloride

Comment from Lyondell:

AEGL-1 and AEGL-2 Values:

> ***The available information suppports similar AEGL-1 and AEGL-2 values for titanium tetrachloride. The AEGL-2 values should be adequately protective for the AEGL-1 endpoint of concern; hence, it is recommended that no AEGL-1 values be assigned for titanium tetrachloride.***
>
> *Only limited experimental data was available for setting AEGL-1 and AEGL-2 values. No human exposure data was available nor was data available concerning susceptible subpopulations. Ideally, AEGL values should be derived from human experience or from acute exposures in animals. In the current analysis, it was necessary to use repeated-exposure inhalation studies in rats as the basis for these values. Such an approach is inherently conservative and for this reason, minimal uncertainty factors of 10 (3 for intraspecies and 3 for interspecies) were selected for both the AEGL-1 and AEGL-2 values. Low and mid-dose exposure concentrations from the same study as well as the same endpoint (irritation) were employed for setting the AEGL-1 and AEGL-2 values (Kelly, 1979). The exposure levels chosen from this study that were used to set the AEGL-1 and AEGL-2 values differed only by a factor of 2. Arbitrarily, no time scaling was applied to the AEGL-1 values (based on irritation) but such scaling was employed for the determination of AEGL-2 values. This leads to a situation in which the calculated AEGL-1 (8-Hour) and AEGL-2 (8-Hour values) are, for all practical purposes, identical. It is recommended that no AEGL-1 values be assigned. AEGL-2 values should be adequately protective for the AEGL-1 endpoint of concern.*

AEGL-3 Values:

> *The information provided supports the calculated AEGL-3 values.*

Response:

It is a reasonable request to not recommend AEGL-1 values for titanium tetrachloride. The AEGL-1 values are currently based on the endpoint of no observable clinical signs or changes in clinical chemistry parameters in a repeat-exposure study. The AEGL-2 values are based on data from the same repeat-exposure study, with the endpoint (no clinical signs, reversible clinical chemistry changes) being below that defined by the AEGL-2 tier. One could argue that data consistent with the definition of an AEGL-1 endpoint were not available to derive the AEGL-1 values.

The Executive Summary from the Titanium Tetrachloride Proposed 1: Nov/2004 Technical Support Document:

EXECUTIVE SUMMARY

Titanium tetrachloride is a colorless liquid that fumes when in contact with moist air. The odor of titanium tetrachloride has been described as penetrating, acrid, and irritating. The world-wide production of titanium tetrachloride was estimated at 6 million tons in 1996. The main producers of titanium tetrachloride are the producers of titanium dioxide pigment by the chloride route. Titanium tetrachloride is used in the manufacturing of titanium dioxide pigments, titanium metal, artificial pearls, and iridescent glass; in the production of Ziegler-Natto catalysts; and as a military smoke screen. Titanium tetrachloride has a high affinity for water and is readily hydrolyzed by water, producing titanium oxychlorides and hydrochloric acid.

Skin (particularly moist skin) and eye contact with liquid titanium tetrachloride can result in severe, deep burns. Available data indicate that exposure to titanium tetrachloride fumes will also result in burns. Only a limited amount of data addressing the toxicity of inhaled titanium tetrachloride was available. Human acute toxicity data are confined to case studies in which the inhalation exposure concentrations were unknown.

The only acute exposure animal studies with quantified exposure concentrations of titanium tetrachloride used rats. An extensive mortality study determined the LC_{50} values in male ChR-CD rats for exposure durations ranging from 2 minutes up to 4 hours (Kelly, 1980). Clinical signs reported during exposure included eye closing and gasping, while signs noted after exposure consisted of corneal opacity, weight loss, and lung congestion. Unfortunately, the severity of the signs was not provided for the various exposure concentrations and durations, but rather was given as a general statement. Histopathological examination revealed similar respiratory lesions in rats dying during exposure or post exposure, with death attributed to pulmonary edema. In the same study, Kelly (1980) also assessed the reversibility of the respiratory tract lesions that developed in rats following a 30-minute exposure to the approximate LC_{10} (172 ppm). The severe respiratory tract irritation that was noted in rats at one day post exposure had resolved by 49 days post exposure. This study demonstrated that rats surviving an acute exposure to inhaled titanium tetrachloride should not have any irreversible pulmonary effects. However, one does not have a correlation to the irritant effects one might observe at these concentrations. One study investigating the effect of varying humidity on the approximate lethal concentration reported death in 1/6 rats following exposure to 14 ppm for 4 hours at a relative humidity of 60% (Burgess, 1977).

In a repeated-exposure study, groups of 25 male ChR-CD rats were exposed to 0, 0.7, 1.3, or 6.5 ppm titanium tetrachloride for 6 hours/day, 5 days/week for 4 weeks (Kelly, 1979). Two rats died in the 6.5 pm group: one rat died on test day 15 and the other on test day 23. Pathological findings in these animals included partial dust obstruction of the trachea, denuded tracheal epithelium, acute obliterative bronchiolitis, interstitial pneumonitis and pulmonary edema and hemorrhage. No clinical signs were observed in rats exposed to 0.7 or 1.3 ppm, but rats

exposed to 6.5 ppm exhibited labored breathing and a slightly decreased body weight gain during the exposure interval that returned to normal following a recovery period. Clinical chemistry changes observed in the 1.3 and 6.5 ppm group were reversible (increased urine pH, decreased urine osmolality). Lung:body weight ratios were increased at terminal kill (126, 136, and 178% of controls for the 0.7, 1.3, and 6.5 ppm groups, respectively). The histopathological changes observed in the lungs of exposed rats at the 6- to 12-month recovery period (collagenized fibrosis) are likely the result of the repeated exposure scenario, as the Kelly (1979) study found that all pulmonary lesions following an acute inhalation exposure to the LC_{10} were resolved by 49 days post exposure.

The experimentally derived exposure values are scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, and k is a constant. To calculate n for titanium tetrachloride, a regression plot of LC_{50} values was derived using the 2, 5, 15, 30, 60, 120, and 240-minute LC_{50} values determined by Kelly (1980). From the regression analysis, the derived value of $n = 0.88$ was used in the temporal scaling of the AEGL values ($C^{0.88} \times t = k$).

No acute toxicity data relevant to the definition of an AEGL-1 endpoint are available. The 0.7 ppm exposure for 6 hours/day could be used to provide a baseline concentration at which no one should experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. Based upon a lack of data identifying interspecies and intraspecies variability, a total uncertainty factor of 100 would normally be applied. However, the endpoint selected is below the endpoint defined for the AEGL-1 tier in addition to the fact that the study was a multiple exposure study. Both of these factors make the starting value inherently conservative. Therefore, a total uncertainty factor of 10 was applied (3 for interspecies and 3 for intraspecies). Because this value represents a no-effect level for a threshold effect (irritation) that should not vary over time, the AEGL-1 value is set equal across time.

The AEGL-2 should be based on irritation because of the irritating properties of this chemical. Again, no acute toxicity data were relevant for derivation of an AEGL-2, so repeated-exposure studies were evaluated. One option for the AEGL-2 derivation would be to base the value on labored breathing reported in rats exposed to 6.5 ppm for 6 hours/day, 5 days/week for 4 weeks (Kelly, 1979). There are several problems with this value, however. While it initially appeared that the deaths were due to repeated exposures to titanium tetrachloride, the deaths cannot be discounted. The Burgess (1977) study reported mortality in rats following a 4-hour exposure to 14 ppm. If one extrapolates this value over time to a 6-hour exposure, an exposure concentration of 8.8 ppm would be predicted to result in mortality. The strongest support that this level is too high is seen when one generates an AEGL-2 derivation based upon the 6-hour exposure to 6.5 ppm and extrapolates across time using the n value of 0.88: one obtains nearly identical values to those generated for the AEGL-3 derivation using a threshold for mortality as the endpoint.

Therefore, the AEGL-2 derivation is based upon the next lower exposure concentration of 1.3 ppm titanium tetrachloride for 6 hours/day, 5 days/week for 4 weeks (Kelly, 1979). No

clinical signs were observed at this concentration. Based upon a lack of data identifying interspecies and intraspecies variability, a total uncertainty factor of 100 would normally be applied. However, the endpoint selected is below the endpoint defined for the AEGL-2 tier and the study was a multiple exposure study. Both of these factors make the starting value inherently conservative. Therefore, a total uncertainty factor of 10 was applied (3 for interspecies and 3 for intraspecies). The value was then scaled across time using the derived value of n=0.88. The 10-minute value was set equal to the 30-minute value because the NAC considers it inappropriate to extrapolate from an exposure duration of 6 hours to 10 minutes.

The mortality data by Kelly (1980) were used for the AEGL-3 derivation. This study was specifically designed to evaluate the mortality response for a wide range of exposure durations. One-third of the LC_{50} values are used for the AEGL-3 derivations. The adjusted, empirical values for the 30, 60, and 240-minute exposure durations were used for the respective AEGL timepoints. Using an n=0.88, the adjusted, 15-minute LC_{50} value was used to extrapolate to 10 minutes, while the adjusted 240-minute LC_{50} value was used to extrapolate to 480 minutes. Normal protocol would require that an interspecies uncertainty factor of 10 and an intraspecies uncertainty factor of 10 be applied because insufficient data are available to properly evaluate the response among different species and among individuals to inhaled titanium tetrachloride. However, if one applies a total uncertainty factor of 100 or 30, one obtains 4-hour AEGL-3 values of 0.20 or 0.67 ppm, respectively. The AEGL-3 value is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death. However, a chronic toxicity/carcinogenicity study reported that rats exposed to 1.3 ppm titanium tetrachloride for 6 hours/day, 5 days/week for 24 months exhibited no clinical signs and no differences in morbidity or mortality compared to controls (Lee et al., 1986). The 4-hour AEGL-3 values using a total uncertainty factor of 100 or 30 are not consistent with the available data. Therefore, a total uncertainty factor of 10 was applied.

The calculated values are listed in the tables below.

Summary of Proposed AEGL Values for Name of Titanium Tetrachloride [ppm (mg/m^3)]						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1 (Nondisabling)	0.07 (0.54)	0.07 (0.54)	0.07 (0.54)	0.07 (0.54)	0.07 (0.54)	No clinical signs observed in rats exposed to 0.7 ppm for 6 h/d, 5 d/wk for 4 wks (Kelly, 1979)
AEGL–2 (Disabling)	7.6 (59)	2.2 (17)	1.0 (7.8)	0.21 (1.6)	0.094 (0.73)	Exposure of rats to 1.3 ppm for 6 h/d, 5 d/wk for 4 wks resulted in no clinical signs, but next exposure level approaches lethality threshold (Kelly, 1979)
AEGL–3 (Lethal)	38 (290)	13 (100)	5.7 (44)	2.0 (16)	0.91 (7.1)	One-third the rat LC_{50} values (Kelly, 1980)

References

Burgess, B.A. 1977. Initial submission: Inhalation approximate lethal concentration titanium tetrachloride (99.5%) with cover letter dated 091192. Haskell Laboratory Report No. 630-77; Medical Research Project No. 2795. Dupont Chemical Company. Doc. # 88-920010969.

Kelly, D.P. 1980. Acute inhalation studies with titanium tetrachloride. E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine; Haskell Laboratory Report No. 658-80, October 31, 1980.

Kelly, D.P. 1979. Four-week inhalation study with titanium tetrachloride (TiCl4). Haskell Laboratory Report No. 459-79, October 1, 1979.

Lee K.P., Kelly D.P., Schneider, P.W., and Trochimowicz, H.J. 1986. Inhalation toxicity study on rats exposed to titanium tetrachloride atmospheric hydyrolysis products for two years. Toxicol. Appl. Pharmacol. 83: 30-45.

Memo

Response to the comments of J. Morawetz on the AEGL TSD on benzene Comments dated 13 November 2006.

Response date: 9 December 2006
Response by: Dr. Marcel T.M. van Raaij (author of benzene TSD)

Dear AEGL committee members,

In this memorandum I would like to provide a response to the comments made by J. Morawetz on the benzene TSD as published in the FR . Following some of these comments will indeed improve the quality of the document. Other comments however, have been discussed already in great detail, finally resulting in the current version of the benzene document. Below we will address each comment.

1. Notation for AEGL values above (10 or 50%) LEL values.

These comments are valid. The document and the tables will be updated according to the comments made.

2. Notation based on cancer risk

Indeed notations have to be added on the issue of carcinogenicity. The document will be updated to include these comments.

3. Comments on the description of the Midzenski (1992) study.

In the AEGL meeting of June 2003, this study description has been extensively discussed in the presence of J. Morawetz. The committee agreed to the study description as it is now. However, Morawetz raises a valid point that important qualifiers are lost in the derivation section. We will adjust the document accordingly in our update, including some more qualifiers on this measurement in the derivation sections.

4. Comments on the use of worker studies

Morawetz raises substantial comments on the use of the data of the various occupational studies. An important point of criticism is that the majority of these studies cannot be used as personal exposure levels. Although this comment is correct by itself, it should be noted that nowhere in the document a claim is made that these are personal exposure levels. Neither of the mentioned single studies has been taken as a point of departure. However, all of these studies and the reported workplace measurements as a whole are used to indicate the range of concentrations that have been observed in a broad range of occupational workplaces involving a large number of workers. As such these studies provide a total weight of evidence for deriving the AEGL-3 values. These worker studies have been extensively discussed at the AEGL meeting of June 2003. At that meeting, J. Morawetz (then a committee member), made exactly the same comments as in his document of 13th November 2006. After the discussion at the meeting of June 2003, the benzene AEGL values were set with a highly convincing vote (15 in favor, 1 against, 1 abstain). Therefore, it is proposed not to repeat the same discussion and to leave the use of the worker studies as currently in the document and to keep the AEGL-3 values as they are.

5. Some minor errors and grammatical changes

Morawetz points to some minor mistakes and grammatical errors in the documents. These comments are gratefully acknowledged and will be changed accordingly.

Marcel T.M. van Raaij, PhD
RIVM, Center of Substances and Integrated Risk Assessment
The Netherlands

ATTACHMENT 6

Methacrylic Acid
Methyl Methacrylate

Reply to Comments from Methacrylate Producers Association (MPA)

FoBiG Scientist: Fritz Kalberlah

Chemical Manager: Bob Benson

NAC/AEGL-41

December 12-14, 2006

Methacrylic Acid

MPA is in "general agreement with the current proposed values"

Therefore,

Advance to Interim Status

NAC Action

Advanced methacrylic acid AEGL values to interim status

Methyl Methacrylate

Proposed Values in ppm:

	10 min	30 min	1 hr	4 hr	8 hr
AEGL-1	18	18	18	18	18
AEGL-2	150	150	120	76	50
AEGL-3	630	630	500	310	160

	10 min	30 min	1 hr	4 hr	8 hr
AEGL-1	18	18	18	18	18

Basis: Pinto (1987)

Effect: Degeneration and necrosis of olfactory epithelium in rats at 110 ppm (more severe than allowed by definition of AEGL-1)

Modifying factor: 2

Uncertainty factor: 3 (interspecies 1; intraspecies 3)

Time scaling: none

Derivation = 110/(2 x 3) = 18 ppm

MPA Comments

In "basic agreement with the proposed values"

Focuses on olfactory epithelium lesions and not irritation or notable discomfort as defined by AEGL-1

Complex rationale needed to justify use of the modifying factor

Acknowledge sparse data for humans

Proposed: base on TLV of 50 ppm divided by intraspecies UF of 3, giving 17 ppm for all time points

Chemical Manager Recommendation

Add some wording to Section 5.3 (derivation of AEGL-1) acknowledging the TLV of 50 ppm

Applying an intraspecies UF of 3 on the TLV gets us to the same place (17 ppm) as using the laboratory animal data (18 ppm)

Keep AEGL-1 values at 18 ppm as in the TSD

Advance AEGL-1 values to Interim Status

NAC Action

Keep AEGL-1 values at 18 ppm as in the TSD with no change in wording

Advanced AEGL-1 values to interim status

	10 min	30 min	1 hr	4 hr	8 hr
AEGL-2	150	150	120	76	50

Basis: Mainwaring et al. (2001), Jones (2002)

Effect: Atrophy and demucosation of rat olfactory epithelium after 6-hour exposure to 200 ppm

Support: Human exposures (Coleman letter) of 8 hours with expected marked irritation of URT above 150 ppm but not below 100 ppm

Modifying factor: none

Uncertainty factor: 3 (interspecies 1; intraspecies 3)

Time scaling: n = 3 for 30 minutes, 1 and 4 hour, 10 min = 30 min
n = 1 for 8 hr

MPA Comments

AEGL-2 too low because no serious adverse effects above 300 ppm in humans

Acknowledge that no qualified human data available

Rat too sensitive and different nasal architecture from humans

Proposed: AEGL-3 divided by 3

Chemical Manager Recommendation

Keep AEGL-2 values as proposed with no change in the TSD

There is no valid reason to reject high quality laboratory animal studies and adopt a default procedure used when no data are available

Advance AEGL-2 values to Interim Status

NAC Action

Keep AEGL-2 values as proposed with no change in the TSD

Advanced AEGL-2 values to interim status

	10 min	30 min	1 hr	4 hr	8 hr
AEGL-3	630	630	500	310	160

Basis: Tansy et al. (1980a, abstract)

Effect: $BMCL_{05}$ of 3125 ppm for mortality in rats after 4 hour exposure

Uncertainty factor: 10 (interspecies 3; intraspecies 3)

Time scaling: n = 3 for 30 minutes and 1 hour, 10 min = 30 min
n = 1 for 8 hr

MPA Comments

BMD results from Tansy too low in relation to other studies

Other studies in rats and other species show no lethality below 4000 ppm

Worker experience shows no serious effects at exposures comparable to 4 and 8 hour values

Proposed: Reduce uncertainty factor

Chemical Manager disagrees

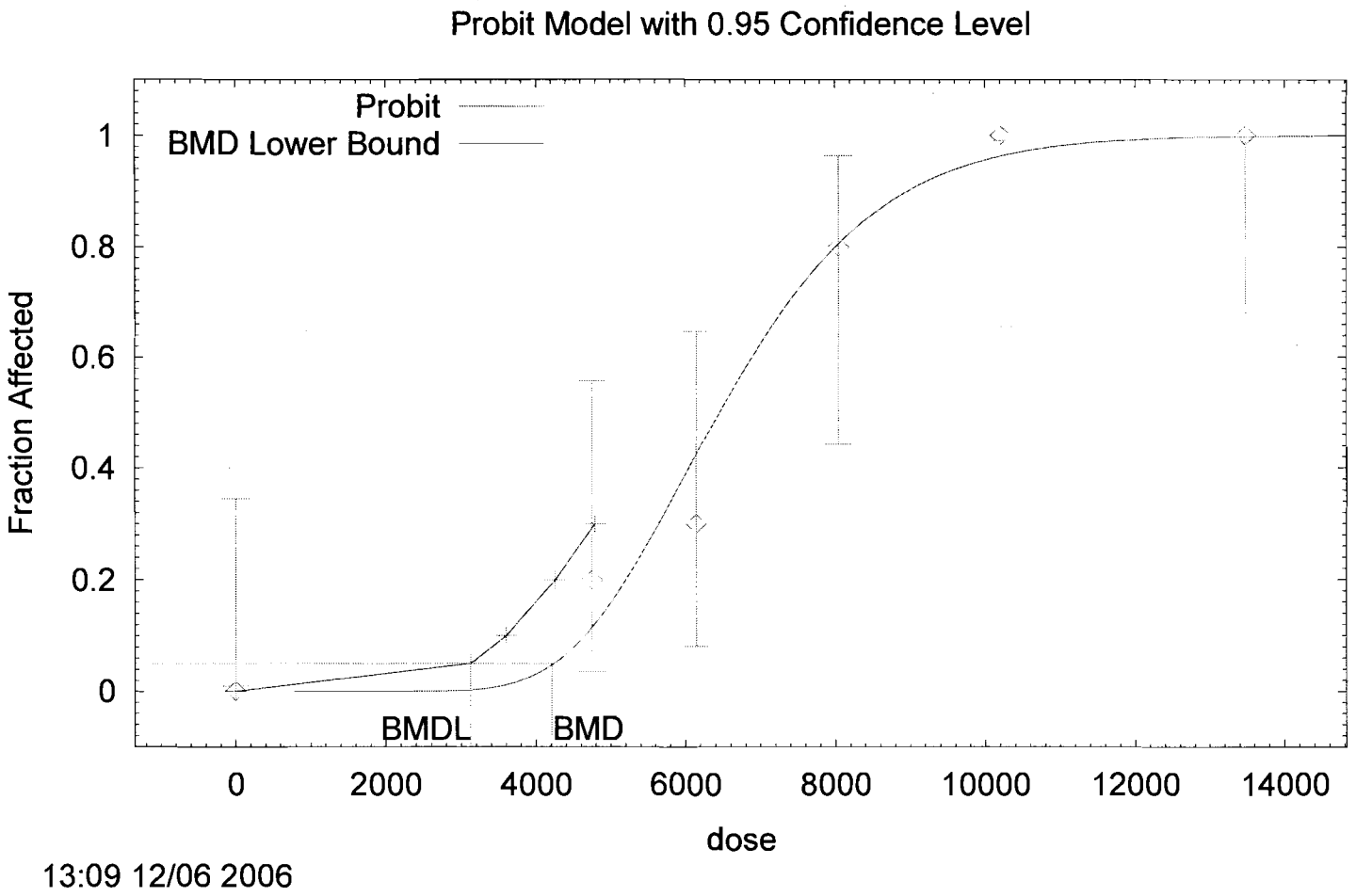
Lethality Data (Tansy)

Exposure (ppm)	Response
4750	2/10
6146	3/10
8044	8/10
10209	10/10
13479	10/10

Lethality Data (NTP, 1986)

Single Exposure Study (4 hours)		Repeat Exposure Study (after 1st 6 hr exposure)	
Exposure	Lethality	Exposure	Lethality
1191 ppm	0/10	0 ppm	0/10
2159 ppm	0/10	500 ppm	0/10
2220 ppm	0/10	1000 ppm	0/10
4055 ppm	0/10	2000 ppm	0/10
4446 ppm	0/10	3000 ppm	0/10
4632 ppm	0/10	5000 ppm	3/10
16000 ppm	9/10		

BMD_{05} Plot (Tansy)
(with added control of 0/10)



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Comparison of Rat Studies

Result	Tansy 4 hr Exposure with control	Tansy 4 hr without control	NTP 4 hr Single Exposure	NTP 6 hr Multiple Exposure
LC_{00}	none	None (LOEL 4750)	4632	3000 (LOEL 5000)
$BMCL_{05}$	3125	3674 (reject)	4519	2355 (reject)
BMC_{01}	3538	5392 (reject)	8523 (reject)	4185

Option 1

Base AEGL-3 values on $BMCL_{01}$ of 3538 ppm for 4 hour exposure from Tansy (1980a); UF = 10; n = 3/1, 10 min = 30 min

	10 min	30 min	1 hr	4 hr	8 hr
new	710	710	560	350	180
old	630	630	500	310	160

Option 2

Base AEGL-3 values on LC_{00} of 4632 ppm for a single 4 hour exposure from NTP (1986); UF = 10; n = 3/1, 10 min = 30 min

	10 min	30 min	1 hr	4 hr	8 hr
new	930	930	740	460	230
old	630	630	500	310	160

Option 3

Base AEGL-3 values on $BMCL_{05}$ of 4519 ppm for a single 4 hour exposure from NTP (1986); UF = 10; n = 3/1, 10 min = 30 min

	10 min	30 min	1 hr	4 hr	8 hr
new	900	900	720	450	230
old	630	630	500	310	160

Option 4

Base AEGL-3 values on LC_{00} of 3000 ppm for a single 6 hour exposure from NTP (1986); UF = 10; n = 3/1, 10 min = 30 min

	10 min	30 min	1 hr	4 hr	8 hr
new	690	690	550	340	230
old	630	630	500	310	160

Option 5

Base AEGL-3 values on BMC_{01} of 4185 ppm for a single 6 hour exposure from NTP (1986); UF = 10; n = 3/1, 10 min = 30 min

	10 min	30 min	1 hr	4 hr	8 hr
new	960	960	760	480	310
old	630	630	500	310	160

Summary of Options for AEGL-3

10 min	30 min	1 hr	4 hr	8 hr	Source
630	630	500	310	160	Tansy 4 hr $BMCL_{05}$
710	710	560	350	180	Tansy 4 hr BMC_{01}
930	930	740	460	230	NTP 4 hr LC_{00}
900	900	720	450	230	NTP 4 hr $BMCL_{05}$
690	690	550	340	230	NTP 6 hr LC_{00}
960	960	760	480	310	NTP 6 hr BMC_{01}

Chemical Manager Recommendation

Adopt Option 3

Base AEGL-3 values on $BMCL_{05}$ of 4519 ppm for a single 4 hour exposure from NTP (1986); UF = 10; n = 3/1, 10 min = 30 min

	10 min	30 min	1 hr	4 hr	8 hr
new	900	900	720	450	230
old	630	630	500	310	160

Advance AEGL-3 values to Interim Status

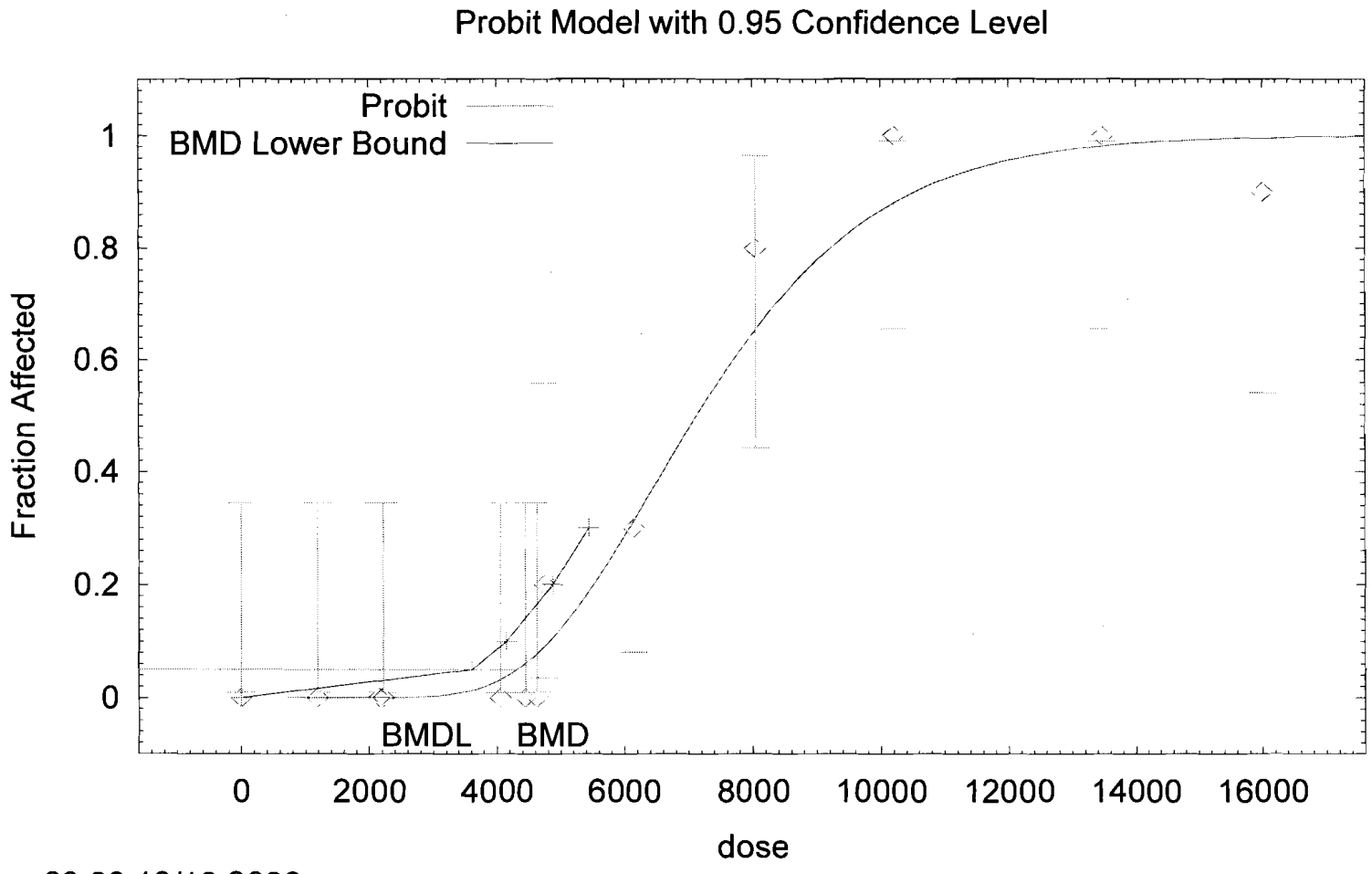
NAC Action

Base AEGL-3 values on $BMCL_{05}$ of 3613 ppm for a single 4 hour exposure from the combined data of Tansy et al (1980) and NTP (1986); UF = 10; n = 3/1, 10 min = 30 min

10 min	30 min	1 hr	4 hr	8 hr
720	720	570	360	180

Advanced AEGL-3 values to interim status

BMD_{05} Plot
Tansy and NTP combined



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December 8, 2006[1]

Docket ID No. EPA-HQ-OPPT-2004-0128
OPPT Document Control Office (DCO)
U.S. Environmental Protection Agency
EPA East, Rm. 6428
1200 Pennsylvania Ave., NW
Washington, DC 20460-0001

RE: Comments on Acute Exposure Guideline Levels for Styrene; 71 Fed. Reg. 60,141 (October 12, 2006), Docket ID No. EPA-HQ-OPPT-2004-0128

The mission of the Styrene Information and Research Center, Inc. (SIRC) is to evaluate existing data on potential health effects of styrene, and develop additional data where it is needed.[2] In doing so, SIRC has gained recognition as a source for information on styrene and helping ensure that regulatory legislation is based on sound science. Accordingly, SIRC appreciates the opportunity to submit comments on the U.S. Environmental Protection Agency's (EPA's) proposed acute exposure guideline levels (AEGLs) for styrene.[3]

These values are intended to describe the threshold exposure concentrations of airborne substances that could cause varying levels of health effects to the public. The proposed AEGLs for styrene are as follows:

AEGL Values for Styrene					
Classification	10-Minute	30-Minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	20 ppm (85 mg/m^3)	20 ppm (85 mg/m^3)	20 ppm (85 mg/m^3)	20 ppm (85 mg/m^3)	20 ppm (85 mg/m^3)
AEGL-2 (Disabling)	230 ppm (980 mg/m^3)	160 ppm (680 mg/m^3)	130 ppm (550 mg/m^3)	130 ppm (550 mg/m^3)	130 ppm (550 mg/m^3)
AEGL-3 (Lethality)	1900 ppm (8090 mg/m^3)	1900 ppm (8090 mg/m^3)	1100 ppm (4690 mg/m^3)	3400 ppm (1450 mg/m^3)	3400 ppm (1450 mg/m^3)

[1] SIRC requested and received from EPA a 30-day extension of the November 13, 2006 comment deadline.

[2] For more information, visit www.styrene.org.

[3] Proposed Acute Exposure Guideline Levels (AEGLs), Styrene (CAS Reg. No. 100-42-5), Document No. EPA-HA-OPPT-2004-0128-002.

AEGLs are not enforceable regulatory limits, although they may be adopted by federal, state or local government agencies for emergency planning, prevention, or response purposes. In this regard, SIRC has no objections to the proposed AEGL values, although they are at the restrictive range of reasonably conservative values. We do submit the following additional comments, however, to address specific discrepancies we identified in our review of the styrene AEGL document.

1. **Page vi, paragraph 2. EPA states:** *Genotoxicity was observed in human cells in vitro; in vivo, no data were available with respect to genotoxicity following acute exposure of humans.*

SIRC submits that the term "genotoxicity" is broad and ambiguous in this context and should not be used in a summary statement without providing the reasons for such a conclusion. Critical information to be provided as part of such a statement, at a minimum, should identify the tests which provided positive results *in vitro* in human cells, and whether those tests generally are regarded as convincing evidence of "genotoxicity."

2. **Page vi, paragraph 2. EPA states:** *In epidemiological studies, evidence for an association of occupational exposure to styrene and genotoxic effects were observed.*

The preceding statement is inaccurate. The underlying discussion on genotoxicity at page 32, Section 3.4 cites a study by Scott and Preston, 1994, which concluded that there was no definitive relationship between styrene exposure and chromosomal aberrations or micronuclei. While SIRC recognizes that a minority of the relevant studies report a relationship between styrene exposure and chromosomal effects, the majority do not support such a conclusion, and the statement should be revised accordingly.

3. **Page vi, paragraph 2. EPA states:** *US-EPA's Office of Research and Development has updated previous assessments on the carcinogenic potential of styrene and concluded that styrene is appropriately classified as a Group C (possible human carcinogen) (US EPA 2003).*

In fact, EPA has not updated its previous assessment on the carcinogenic potential of styrene. The 2003 citation refers to a specific EPA Internet page, http://www.epa.gov/ttn/atw/htlhef/styrene.htm, which is no longer valid. When available, however, the webpage clearly stated that reference to styrene's potential carcinogenicity was from a 1995 memorandum from Robert Huggett to Mary Nichols and does not represent an official classification.

4. **Page vii, paragraph 1. EPA states:** *Data from laboratory animals indicate that styrene exposure may lead to the formation of DNA-adducts, sister chromatid exchange, and chromosomal aberrations.*

This statement is inaccurate. First, the data do not support the conclusion that styrene induces chromosomal aberrations (CAs) in animals, as six of seven studies of styrene demonstrated no increase in CAs. Second, as there is no demonstrated relationship between sister chromatid exchanges and cancer, increased SCEs are not an indication of genotoxicity. Lastly, DNA adducts are not of themselves an indication of genotoxicity. Genotoxicity occurs only if the adducts lead to mutations, which is not demonstrated here.

5. **Page 3. Section 2.2.1 Case Reports, paragraph 4. EPA states:** *Moscato et al. (1987) described two cases of workers employed in plastics factories that had bronchial asthma or runny nose, dry irritating cough and chest tightness. They were exposed to styrene and ethyl benzene and one of them to polyester resin. However, specific inhalation challenges revealed an immediate bronchospastic response only after provoked inhalation exposure to styrene (15 ppm for 15 minutes). In both subjects, symptoms completely disappeared after changing their job. A further case of asthma in a subject occupationally exposed to styrene and showing a positive reaction to styrene in a provoked exposure test was reported by Hayes et al. (1991). A case of skin dermatitis following dermal exposure to styrene was reported by Sjöborg et al. (1982), skin patch tests revealed a strong reaction to styrene and a cross-reaction to vinyl toluene, but a weak one to benzoyl peroxide (used in hardeners for styrene-based plastics) and no reaction to styrene polymerization inhibitors and typical styrene impurities.*

In total, EPA cites to only four cases dating back between 15 and 24 years for the proposition that exposure to styrene may lead to the development of asthma or skin allergies. Given the hundreds of thousands of workers who have worked with styrene since the 1940s, asthma and skin allergies simply do not represent a significant health risk from styrene. Accordingly, SIRC requests that EPA add the following sentence to the end of the preceding paragraph:

> Given that hundreds of thousands of workers have been exposed to styrene vapors and had skin contact with the liquid from the 1940s to the present, the development of asthma or skin allergies does not represent a significant health risk from styrene based on industrial experience.

6. **Page 3. Section 2.2.1 Case Reports, <u>Non-inhalation exposure</u>, paragraph 1. EPA states:** *Repare (sic) of a water tank led to contamination of tap water with styrene and subsequent oral and inhalation exposure (Arnedo-Pena et al. 2003).*

The study by Arnedo-Pena, et al., 2003, reports maximum styrene levels in the drinking water of 0.9 ppm. Given the occupational exposure studies and controlled exposure studies with volunteers, it would appear that the reported symptoms are not an adequate basis for drawing this conclusion. In general, odor detection is not regarded as a toxicologically relevant endpoint -- annoyance does not represent a sensory or

psychological effect, but rather a psychological discomfort from the presence and increasing concentration of an odor. (Arts et al. 2006b).

Foul odors are detected by both olfactory and trigeminal stimulation. The olfactory stimulation relays messages to the brain using the first cranial nerve for odor perception while trigeminal stimulation is responsible for sensing the ocular and nasal irritation of a chemical using the fifth cranial nerve. (Paustenbach and Gaffney 2005). In other words, olfactory receptors detect odor threshold while trigeminal nerve endings in the cornea and nasal mucosa signal sensory irritation thresholds in the eyes and upper respiratory tract, respectively. Olfactory receptors respond to chemical stimuli usually at lower concentrations and with greater selectivity than do the trigeminal endings and are responsible for the discrimination of different odorous substances. (Arts et al. 2006b). Although anatomically distinct, both pathways help people to distinguish and characterize inhaled air.

Studies have shown that even a pure odorous substance, lacking any trigeminal stimulation, elicited reports of sensory irritation. (van Thriel 2006). For the majority of chemicals, odor has a zero correlation with actual exposure risk, but odor may have a substantial correlation with perceived exposure risk. However, as Paustenbach and Gaffney (2005) note, "detection of odors by workers may tap into the person's aversions to unpleasant odors, in general." Because the vast majority of volatile chemicals stimulate the olfactory system at concentrations well below that at which they will elicit trigeminal activation, the evaluation of irritation from volatiles is often confounded by the perception of odor. (Arts et al. 2006b). Styrene is not an irritant at its odor threshold. But, as with many other chemicals, much of the public immediately perceives the substance and its odor as harmful, which strongly influences individuals to indicate irritation where only odor exists. Thus, the results of measurements of sensory irritation can strongly be biased by subjective feelings and interpretations, in many instances caused by the odor of the compound. Therefore, the perception of odor intensity is an important factor that must be considered when evaluating a substance for an occupational exposure limit, especially substances like styrene that have odors which can be perceived as unpleasant. Against this backdrop and given that occupational exposure studies and controlled exposure studies with volunteers revealed no symptoms at higher styrene concentrations, the Arnedo-Pena results appear to be anomalous or failed to properly account for the difference between sensory perception and sensory irritation.

7. **Page 13. Section 2.4 Genotoxicity, paragraph 1. EPA states:** *Genotoxicity studies have been extensively evaluated and summarized in a number of reviews (ATSDR 1992; Bonassi et al. 1996; Cohen et al. 2002; IARC 1994; IARC 2002; Vodicka et al. 2002; WHO 1983; WHO 2000).*

The review by Scott and Preston, 1994 is listed in the reference section and also should be included in the preceding citation.

8. **Page 13. Section 2.4 Genotoxicity, paragraph 2. EPA states:** *In in vitro systems with human cells, styrene induced chromosomal aberrations (CA), sister chromatid exchanges (SCE), micronuclei, and hypoploidy in whole-blood cultures in the absence of exogenous metabolic activation system were observed. CA and SCE were also observed in lymphocyte cultures in the absence of exogenous metabolic activation system.*

This summary conflicts with the conclusions reached by all the cited studies. For example, in the most recent review of styrene, IARC concluded that "Styrene was predominantly inactive in assays for gene mutations in bacteria, although some studies reported mutations in the presence of a metabolic activation system." (IARC, 2002, p. 521). This passage needs to be revised accordingly.

9. **Page 13. Section 2.4 Genotoxicity, <u>Studies with Repeated Inhalation Exposures</u>, paragraph 1. EPA states:** *The number of workers included in individual studies mostly was less than 50. With respect to chromosomal aberrations, the majority of studies revealed a significant increase in CA (including gaps), and dose-responses were observed in several studies. A cross-studies evaluation found a positive association among studies between the level of styrene exposure and the frequency of CA. Fewer studies have looked at sister chromatid exchange (SCE), and the percentage of positive studies was smaller than the percentage of positive studies of CA. However, two regression analyses revealed significant associations between styrene in air or urinary mandelic acid excretion and SCE frequency. There is less evidence of an association between styrene exposure and the frequency of micronuclei, and in a cross-studies evaluation, no such association could be found. Other studies in workers have provided evidence that occupational exposure to exposure may lead to a several-fold increase in the formation of DNA-adducts (O6-deoxyguanosine and N7-deoxyguanosine adducts), DNA single-strand breaks, and gene mutations at the HPRT and the glycophorin A locus.*

The preceding paragraph is inaccurate. According to IARC, 2002:

> Inconsistent results have been reported for chromosomal aberrations, micronuclei and sister chromatid exchange in approximately 30 studies of workers exposed to styrene in various industries. Induction of chromosomal aberrations was reported in 12 of 25 studies, sister chromatid exchange in 6 of 16 and micronuclei in 3 of 14 studies.

The reported variation in the glycophorin A locus was not a mutation that would be suggested by a styrene-induced deletion. There were 2 investigations of HPRT mutations in styrene exposed workers; one reported no increase and one reported a slight increase; thus this outcome is questionable. Further, HPRT mutations in animals with controlled exposures were negative; thus the positive human result is more questionable.

10. **Pages 13-14. Section 2.4 Genotoxicity, <u>Studies with repeated inhalation exposure</u>, paragraph 2. EPA states:** *Recently, physiological modeling of the relative contributions of styrene-7,8-oxide (SO) derived from direct inhalation and from styrene metabolism to the systemic dose in humans has been performed. From these calculations, it has been suggested that SO which is present in the air at workplaces in the reinforced plastics industry could present a greater hazard of cytogenetic damage than inhalation of styrene (Tornero-Velez and Rappaport 2001).*

Filser et al. (1999) suggest that this conclusion may be incorrect, as other studies report much higher levels of blood styrene oxide when measured directly than the level calculated by these authors from styrene-hemoglobin adducts.

11. **Page 14. Section 2.5 Carcinogenicity, <u>studies with repeated exposure,</u> paragraph 3. EPA states:** *Because workers in the reinforced plastics industry have higher styrene exposure and less potential for exposure to other substances than the other cohorts studied, the most informative data with regard to an association between styrene exposure and cancer come from studies of these cohorts. In three studies in such cohorts, an excess of lung or respiratory cancer was found.*

The last sentence in the preceding paragraph is incorrect. There are only three independent cohort mortality studies of styrene in reinforced plastics workers (Okun et al., 1985, Kogevinas et al., 1994, and Wong et al. 1990 and 1994). As observed by Cohen et al. (2002)

> The pattern of results strongly suggests that the elevated rates are not attributable to styrene. In all three studies, the excess of lung or respiratory cancer was confined to workers with lower exposures to styrene; that is, there is no evidence of an increase in risk with increasing exposure.

In the one study that found an increase in lung or respiratory cancer, a nested case-control study demonstrated that the increased lung cancer was attributed to smoking, not to styrene (Wong et al. 1994).

12. **Page 14. Section 2.5 Carcinogenicity, <u>studies with repeated exposure,</u> paragraph 3. EPA states:** *An excess of lymphatic and hematopoietic (LH) cancers was observed in some epidemiological studies in the reinforced plastics industry, but not in others. Such an association also was found in two studies of workers in styrene production, but exposure was poorly documented and may have been also to other chemicals beside styrene. Studies in workers of the styrene-butadiene rubber production also found a small excess of leukemia mortality. However, these findings are difficult to evaluate because of the high correlation between exposure to styrene and butadiene (Cohen et al. 2002).*

Only one of the three studies of reinforced plastics workers identified by Cohen et al. 2002, reported increased LH cancers (Kogevinas et al, 1994). This increase in LH cancer was associated with increases in the Kolstad (1994) subcohort for which; (1) no attempt was made to estimate individual exposures; (2) less than 45% of the workers were actually employed in reinforced plastics activities and even fewer were probably exposed to elevated styrene levels; and (3) increases in LH cancers were only among those employed for less than 1 year. The other two studies, Wong and Okun et al. studies found no significant increase in LH cancers. Further the Okun study has since been updated (Ruder et al., 2004) to an average 26 years of follow-up with no increase in LH cancers.

13. **Page 13. Section 2.5 Carcinogenicity, <u>studies with repeated exposure,</u> paragraph 3. EPA states:** *Reports of increased risks of other cancers (rectal, pancreatic, nervous system) are also reported in some studies. Mostly, the numbers of cases are small, and these findings are not supported from data of larger cohort studies.*

More recent studies by Delzell and coworkers (Macaluso et al., 2004) indicate that the increased risks of other cancers are likely not due to styrene.

14. **Page 16. Section 2.6 Summary, paragraph 1. EPA states:** *In older studies on workers in the manufacture of reinforced plastics, 8-hours TWA concentrations in the breathing zone of up to 292 ppm were reported, with peaks of about 1500 ppm during shorter periods of work for about 5 – 10 minutes (Götell et al. 1972).*

EPA should delete the preceding statement. References to the findings from a 1972 study really are not relevant to current exposures. The statement is particularly misleading because current regulations do not permit such exposures today, and EPA has failed to provide adequate historical context. If EPA concludes that some statement is needed, a more accurate picture can be derived from Cohen et al. (2002) and Miller et al. (1994).

The Occupational Safety and Health Administration (OSHA) regulates styrene on the basis of avoidance of narcosis in the work place. In its final Air Contaminants rulemaking of 1989, OSHA mandated a permissible exposure limit (PEL) for styrene of 50 parts per million (ppm) over an eight-hour time-weighted average (TWA), with a short-term exposure limit (STEL) of 100 ppm for any 15-minute period. In July 1992, a U.S. Court of Appeals Court voided that 1989 OSHA rule. The Labor Department did not appeal the decision, and therefore its styrene occupational standards reverted back to the pre-1989 standards of 100 ppm TWA and 200 ppm STEL. However, some state agencies, notably California, have independently adopted a 50 ppm TWA, which regulates facilities in those states. The U.S. styrene industry associations encouraged facilities to continue to comply with the 50 ppm 1989 standard as an appropriate exposure level for styrene, regardless of its status. In February 1996, four styrene industry trade associations

entered into a precedent-setting arrangement with OSHA to voluntarily adhere to the 50 ppm level set by the 1989 PEL. Their proposal to OSHA required the associations to educate their members and customers on the need for compliance with the 50 ppm level by July 1997.

15. **Page 16. Section 2.6 Summary, paragraph 5. EPA states:** *US-EPA's Office of Research and Development has also updated previous assessments on the carcinogenic potential of styrene and concluded that styrene is appropriately classified as a Group C, possible human carcinogen (US EPA 2003).*

As comment 3 above indicates, the 2003 citation refers to a specific EPA Internet page, http://www.epa.gov/ttn/atw/htlhef/styrene.htm, which is no longer valid. When the page was available, however, it clearly indicated that reference to styrene's potential carcinogenicity was from a 1995 memorandum from Robert Huggett to Mary Nichols and does not represent an official classification. Accordingly, the preceding statement is incorrect, and EPA has not updated previous assessments on the carcinogenic potential of styrene.

16. **Page 28. Section 3.2.3 Mice, Behavioral Studies. EPA states:** *Groups of 10 male animals were exposed to analytically (gas chromatography) confirmed concentrations of 413, 610, 807, or 851 ppm styrene or air in 200-L chambers for 4 hours. Immediately afterwards, total duration of immobility during a 3-minute period in a "despair swimming test" was determined. Immobility was defined as cessation of struggling to get out of the water. Exposure to solvents including styrene caused a dose-dependent decrease in duration of immobility as compared to the corresponding controls. In case of styrene, the mean duration of immobility decreased significantly by 28, 60, 77, or 83 % of control at the concentrations noted above..*

The terminology used in this paragraph needs to be clarified. If immobility is defined as "cessation of struggling to get out of the water," what is meant by "duration of immobility?" It appears that EPA is referring to the amount of time from when the animals stop struggling until it is deceased. Arguably, the term also could be interpreted to refer to the amount of time from styrene exposure until immobility sets in.

17. **Pages 28-29. Section 3.2.3 Mice, Studies with repeated exposures. EPA states:** *Pulmonary toxicity was studied in CD-1 mice (Green et al. 2001b). Groups of 5 female and 5 male mice were exposed "whole body" in 3.4 m^3 chambers to analytically (gas chromatography) controlled concentrations of 0, 40 or 160 ppm styrene for 6 hours. At 40 ppm, in mice killed immediately after exposure, there was evidence of necrosis and loss of cells, believed to be Clara cells, from large bronchioles, while Clara cells in the terminal bronchioles were not overtly affected. At 160 ppm, no significant effect was seen at this time point. In animals killed 18 hours after exposure, minimal necrosis but treatment-related focal loss of cytoplasm from non-ciliated cells was observed, predominantly at*

> *the terminal bronchiolar area. Females seemed slightly more affected than males. The lesions observed at this time point were similar at both styrene concentrations. In mice that had received 5-bromo-2-deoxyuridine 3 days prior to sacrifice, no evidence of an increase in cell replication in the alveoli, terminal or large bronchioles was observed after one day of exposure to styrene.*

Although the description provided is accurate for the first day of exposure, the section is titled "repeated exposures." No characterization of the results from the remaining two-weeks of exposure was included, which demonstrated effects primarily in Clara cells and that inhibition of CYP2F2 eliminated the cytotoxicity from styrene.

18. **Page 30. Section 3.3.1 Rats, <u>Studies with repeated inhalation exposure</u>. EPA states:** *A greater incidence of skeletal variations but no other embryo or fetal developmental effects were observed in offsprings of styrene-treated dams compared to controls... These results suggest that the offspring were susceptible to the effects of styrene on a few developmental landmarks and the results support previous findings of alterations in postnatal development in offsprings of styrene treated dams (Kishi et al. 1992; 1995)*

It is important to note that the studies cited in the above-referenced discussion used small numbers of litters and did not comply with regulatory guidelines for good laboratory practices. A two-generation reproduction study was conducted in S-D rats at concentrations of 50, 150 and 500 ppm. There was no effect on fertility or reproduction, but a slight decrease (~1/2 day) in growth and development of the offspring. In a companion developmental neurotoxicity study, no effects on the developing neurological system occurred in offspring of the F1 generation rats exposed to styrene. The relevant studies are:

> G. Cruzan, W. D. Faber, K. A. Johnson, L. S. Roberts, J. Hellwig, E. Carney, J. T. Yarrington, D. G. Stump. (2005). Two Generation Reproduction Study of Styrene by Inhalation in Crl-CD Rats. Birth Defects Research Part B: Developmental and Reproductive Toxicity 74:211-220.
>
> G. Cruzan, W. D. Faber, K. A. Johnson, L. S. Roberts, J. Hellwig, J. Maurissen, M. J.Beck, Ann Radovsky, D. G. Stump. (2005). Developmental Neurotoxicity Study of Styrene by Inhalation in Crl-CD Rats. Birth Defects Research Part B: Developmental and Reproductive Toxicity 74:221-234.

19. **Page 32. Section 3.4 Genotoxicity, paragraph 1. EPA states:** *A large number of studies have been published in which genotoxic effects (including DNA-adducts) of styrene were investigated in vitro and in vivo.*

The preceding sentence is inaccurate. DNA-adducts are not generally classified as a genotoxic effect. They are markers of exposure and may lead to genotoxicity if not repaired.

20. **Page 32. Section 3.4 Genotoxicity, paragraph 3. EPA states:** *In several studies with bacteria test systems (different strains of Salmonella typhimurium), styrene was not mutagenic in the absence of exogenous metabolic activation system. In the presence of such activation system, in some but not all studies, mutagenic effects were observed.*

According to the first paragraph of Section 3.4, EPA is proposing to summarize the results described in prior reviews. However, the second sentence, reproduced above, contradicts the findings of the IARC, Cohen, and Scott and Preston studies. The implication of that sentence is that styrene was positive in, if not most, then at least a significant number of *in vitro* tests with activation. This is simply inaccurate. Only 1 of 13 studies with TA100 was positive with activation, only 4 of 14 with TA1535, and 0 of 13 with TA98, 0 of 13 with TA1537 and 0 of 13 with TA 1538. Moreover, although it is true that styrene oxide may react with DNA to form adducts, it is not true that the formation of adducts leads to genotoxicity.

21. **Page 33. Section 3.4 Genotoxicity, paragraph 3. EPA states:** *Differences in adduct levels between rats and mice with respect to differences in carcinogenicity between these two species were studied by Otteneder et al.(2002).*

The quoted passage should be expanded to report on the findings of Boogaard et al. (2000), where higher levels of adducts were detected in mouse liver than in mouse lung, and no greater levels of DNA adducts in Clara cells than in other lung cells of mice exposed to 160 ppm. Further, adduct levels were greater in lung and liver of rats exposed to 500 ppm (no increase in tumors) than in mice exposed to 160 ppm (increased lung tumors). The absence of carcinogenic findings in chronic rat studies, as contrasted with mouse studies, further supports the view that DNA adducts in liver and lung were not associated with cancer risk.

22. **Page 33. Section 3.4 Genotoxicity, paragraph 3. EPA states:** *In samples of liver tissue from CD rats treated with styrene via inhalation for 2 years, levels of O^6-SO-guanine adducts were above the limit of detection only in the highest dose group (1000 ppm). It was concluded that rat liver is able to tolerate a comparatively high level of styrene-derived DNA-adducts without a detectable increase of the tumor rate. Further, CD-1 mice were exposed 6 hours/day, 5 days/week, 2 weeks, to 0, 40, or 160 ppm styrene, CD rats were exposed to 0 or 500 ppm. No increase in O^6-SO-guanine adducts could be detected in any of the lung samples despite the observation from carcinogenicity studies that styrene increases the rate of lung tumors in mice but not in rats. The authors concluded that species- and site-specific tumor formation by styrene is not reflected by DNA-adducts in tissues. However, this conclusion has been questioned because the expected levels of O^6-SO-guanine adducts may be far below the detection limit (Vodicka et al. 2002).*

Vodicka et al. (2002) reported DNA adducts in NMRI mice exposed to 175 or 350 ppm styrene for up to 2 weeks. The relationship of these data to any cancer studies in CD-1 mice is questionable because neither CD-1 nor B6C3F1 mice are able to survive concentrations of 175 ppm without some deaths. Further, in CD-1 or B6C3F1 mice considerable cytotoxicity in terminal bronchioles was observed at these doses. Thus, the discussion of Vodicka should be deleted.

23. **Page 35. TABLE 5: Summary of Results on Studies of Cancer in Rats Treated With Styrene. The fifth column is entitled:** *Tumor incidence statistically elevated, type of tumor.*

SIRC submits that the tumor incidence/statistical elevation column of the table is either inaccurately labeled, or incorrect. With regard to the Jersey study, it is incorrect to state in a summary table that mammary adenocarcinoma is increased when it occurred only at the low dose and was within the historical control range. Such a statement implies a treatment-related effect, when in fact no such claim has been made by EPA.

It is also incorrect to state that Cruzan et al. found that testicular tumors were statistically elevated. Cruzan et al. found no statistical increase in testicular tumors—there were no pairwise differences from control and there were no other testicular effects that usually accompany chemically-induced testicular tumors. Although the study did identify a significant "trend" for this tumor type; such a finding is a far cry from a finding that testicular tumors were "statistically elevated."

SIRC also disagrees with Table 5's treatment of the Conti et al. study. In particular, the table fails to reproduce the various caveats EPA expressed on page 34 about the increased mammary tumors in the Conti et al. study.

24. **Page 40. Section 3.6 Summary, last paragraph. EPA states:** *US-EPA's Office of Research and Development has updated previous assessments on the carcinogenic potential of styrene and concluded that styrene is appropriately classified as a Group C, possible human carcinogen (US EPA 2003).*

As comment 3 above indicates, the 2003 citation refers to a specific EPA Internet page, http://www.epa.gov/ttn/atw/htlhef/styrene.htm, which is no longer valid. When the page was available, however, it clearly indicated that reference to styrene's potential carcinogenicity was from a 1995 memorandum from Robert Huggett to Mary Nichols and does not represent an official classification. Accordingly, the preceding statement is incorrect, and EPA has not updated previous assessments on the carcinogenic potential of styrene.

25. **Page 46. Section 4.1 Toxicokinetics, paragraph 3. EPA states:** *Different CYP isozymes are involved in the oxidation of styrene to SO. Based on in vitro studies, CYP2B6 and CYP2E1 seem most important in liver and CYP2F2 in lung, but other isozyms also seem to play a role. In mice devoid of CYP2E1 activity*

(Cyp2e1-null mice), the amount of metabolites derived from SO was higher and that derived from phenylacetaldehyde was lower as compared to control mice. The excretion of total urinary metabolites was higher in "null mice" than in wild-type controls. These data indicate that CYP2E1 may not be a major isozyme involved in the metabolism of styrene to SO in mice (Sumner et al. 2001). In humans with individual differences in xenobiotic metabolism capacity determined with enzyme-specific substrates for CYP2E1, CYP1A2, and CYP2D6, no correlation was found between the blood clearance of styrene and the metabolic capacity as measured by urinary excretion of mandelic and phenylglyoxylic acid. Under the experimental conditions (24 and 84 ppm styrene, 1 hour exposure, light exercise), the apparent blood clearance of styrene (1.4 l/min) was similar to the hepatic blood flow (IARC 2002). These data further support the assumption that styrene metabolism at low concentrations is limited by perfusion and not by the capacity of the metabolism.

This paragraph may reflect the state of knowledge in 2001, but considerable evidence has been developed since then demonstrating that CYP2F2 is critically involved in the metabolic process of styrene to cause cytotoxicity in mouse lung and nasal epithelium. These findings are summarized in Cruzan et al. 2002, and much of these findings are also found in IARC, 2002. Further research has indicated that CYP2E1 plays little role in mouse lung toxicity from styrene, while 2F2 is most important. More recent research has indicated that CYP2F2 results in different metabolites and that styrene-7,8-oxide may not be the toxic metabolite from styrene. (Cruzan et al., 2005. Carlson, Bartels, 2006)

26. **Page 48. Section 4.2 Mechanism of Toxicity, paragraph 2. EPA states:** *Other toxic effects of styrene have been attributed to the formation of reactive metabolites. The main primary metabolite of styrene in mammals is styrene oxide (SO), an electrophilic epoxide that is able to form covalent adducts with nucleophiles such as DNA, but also with proteins and glutathione. In accordance with this, SO binds to DNA and shows genotoxic activity in vitro and in vivo. The respiratory tract toxicity of styrene that is observed in mice also was shown to depend on the metabolism of styrene.*

Attributing styrene's cytotoxicity to SO does not agree with the data. Rats have much more SO in lung and liver at their MTD than do mice at their MTD, yet no cytotoxicity is seen in rat lung or liver. Cytotoxicity is seen only in rat nasal epithelium, where CYP2F4 appears to be very active, possibly creating in rat nose the same metabolites as produced by CYP2F2 in mouse lung and nose. Although SO binds to DNA, it is primarily at sites that are readily repairable; there is no indication that these DNA adducts are responsible for genotoxicity and especially not for carcinogenicity in mouse lung.

27. **Page 49. Section 4.3.2 Species variability, paragraph 3. EPA states:** *In case of styrene, the general view is that the observed toxicity in respiratory tract and liver and the genotoxic and tumorigenic effects are related to the activation of*

styrene to styrene-7,8-epoxide (SO). This view is supported by studies in rats and mice which showed that inhibition of styrene metabolism prevents the development of histological lesions.

This statement is clearly inaccurate. The inhibition of CYP2F2 metabolism prevents the development of histologic lesions, but inhibition of CYP1A, 2B, or 2E do not have any effect. It is also not clear that SO is the toxic agent. Ring-oxidized metabolites of styrene are 5 fold more toxic in mouse lung than SO.

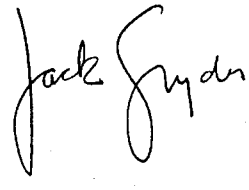
28. **Page 53. Section 6.2 Summary of Animal Data Relevant to AEGL-2, paragraph 6. EPA states:** *Following repeated 6-hour exposure to 300 ppm, but not to 50 ppm, during gestation day 6 – 20, an increased neonatal death rate was observed and delayed postnatal development was observed (Katakura et al. 2001).*

Cruzan et al., 2005 did not find increased neonatal death at 500 ppm. In contrast to Katakura et al., neonatal developmental delay was minimal. The draft report should be revised to reflect the divergent findings in these studies.

* * * * *

Again, thank you for the opportunity to provide comment on the proposed AEGL for Styrene. We trust that our comments will be useful to EPA in finalizing the exposure guidelines. Please let me know if you have any questions regarding the enclosed information.

Very truly yours,



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RESPONSE TO COT'S COMMENTS FOR ALLYL ALCOHOL

Claudia Troxel

Bob Benson

1

Properties:

- Colorless liquid
- Pungent, mustard-like odor

Nonlethal Human Data:

➢ Odor threshold: range of 1.4 - 2.1 ppm; mean of 1.8 ppm (AIHA, 1989)

➢ Exposures: 10 volunteers exposed to 2 ppm for 1-3 minutes reported distinct odor but not irritation (Torkelson et al., 1959)

2

Human sensory response during 5 min. exposure					
Conc. (ppm)	n	Eye irritation		Nose irritation	
		Slight	Severe	Slight	Moderate/ >
0.78	6	0	0	2	0
6.25	6	1	0	3	1
12.5	7	1	0	3	4
25.0	5	0	5	0	5

Dunlap et al., 1958; not stated if nominal/ measured concentrations

3

Summary of Animal Data

Lethal:

- LC_{50} values (rat; Dunlap et al., 1958):
  1 h -1060 ppm; 4 h -165 ppm; 8 h -76 ppm
  (stated that actual conc. was 15-25% less than nominal)

- NOEL for lethality (Union Carbide, 1951):
  200 ppm for 1 hr in rats, mice, rabbits
  (no info about controls, methods of exposure, strain or sex of animals, nominal or measured conc, period of observation)

4

Repeated Exposures

Rat, guinea pig, rabbit (Torkelson et al., 1959)

- 7 (6.6-7.1) ppm : 7 h/d, 5 d/wk, for 28 exp: Reversible liver and kidney damage
- 2 (0.6-3.2) ppm: 7 h/d, 5 d/wk, for ~130 exp:
  No effects (clinical signs, mortality, body and organ weight, gross and microscopic examination)

Rat:

Dunlap et al., 1958; Shell Chemical Corporation, 1957

Same study?

Same LC_{50} values; same exposure concentrations, exposed for 5 d/wk for 60 exp.; similar effects reported; Dunlap work supported by in part by Shell Chemical Corp.

Differences: Dunlap is 7 h/d and Shell is 8 h/day
A few differences in reported effects

5

10 rats/group exposed 7 h/d, 5 d/wk for 60 exposures; Dunlap et al., 1958	
Conc (ppm)	Effect
1, 2, 5	No observable adverse effects
20	↓ bw gain (-18%)
40	Eye irritation, gasping, nasal discharge for first few exposures; ↓ bw gain (-30%)
60	1/10 died after 4 exp.; persistent eye discharge; gasping during first few exp.; ↓ bw gain (-41%); ↑ relative wt of lung (+30%) and kidney (+10%)
100	6/10 died (1st 46 days); irritation; bw gain (-44%)
150	10/10 died: 4 during and 2 following 1st exp; all by 10th exp; hemorrhagic livers, pale/spotted lugs, bloated G.I. tracts, congestion of liver/lungs

6

10 rats/group exposed 8 h/d, 5 d/wk for 60 exposures; Shell Chemical Corporation, 1957 NO FURTHER DETAILS REPORTED	
Conc (ppm)	Effect
1, 2, 5, 20	No observable adverse effects
40	↓ growth; ↑ lung wt; mild to moderate lung congestion
60	1/10 died; mild to moderate lung congestion; ↑ lung and kidney wt
100	10/10 died; did not survive more than thirty-two 8-h exposures
150	10/10 died; did not survive more than 2 exposures

7

Metabolism/Mechanism

Acute and repeated inhalation exposures:

Lacrimation, pulmonary edema and congestion; after high conc. inflammation and hemorrhage of the liver and kidney.

Histopathology of animals exposed to high conc: pulmonary congestion leading to edema and compensatory emphysema, with degeneration of the cells in convoluted tubules of the kidney, liver, myocardium, ganglion cells of the spinal cord, and retina

8

Oral or perenteral exposure produces periportal necrosis of liver

Liver necrosis dependent on conversion to acrolein; mediated by cytosolic ADH with NAD^+ ; acrolein detoxified by metabolism to acrylic acid by aldehyde DH or conjugation with GSH

Lung metabolism → glycidol → glycerol; no acrolein because lungs do not contain appreciable amount of ADH

9

Summary of Interim 4 AEGL values for AllOH					
Level	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	2.1	2.1	2.1	2.1	2.1
AEGL-2	4.2	4.2	4.2	4.2	4.2
AEGL-3	36	25	20	10	10

AEGL-1: Slight to moderate irritation in humans at 6.25 ppm for 5 minutes (Dunlap et al., 1958) [UF = 3]

AEGL-2: No-effect-level for severe eye irritation (represents impaired ability to escape;) in humans exposed at 12.5 ppm for 5 minutes (Dunlap et al., 1958) [UF = 3]

AEGL-3: Highest conc. w/ no mortality in mice, rats, and rabbits of 200 ppm for 1 h (Union Carbide, 1951) [UF = 10] 10

Interim 4 AEGL-3 Derivation:

- **POD:** 200 ppm for 1 hr - no mortality in 3 species
- **n value**: default value of n=1,3.
- **UF:** 30
- **Interspecies UF – 3** because the highest concentration causing no mortality was identical in all three species
- **Intraspecies UF – default of 10**
- **Adjustment factor** of 1/3 applied: values too low with UF of 30
- **MF:** The 4- and 8-hr AEGL-3 values were too conservative; so a **MF of 2 applied to the 1-hr value** to obtain 10 ppm value

11

COT Recommendations for AEGL-3

Total UF of 10;

No adjustment factor

- **Interspecies UF – 3;** no mortality occurred in three species. These data suggest little difference among species in response to allyl alcohol exposure
- **Intraspecies UF – 3;** based on the available data set consisting of toxicology studies in 6 animal species (monkey, dog, rabbit, guinea pig, rat, mouse) that provide consistent toxicological findings (SOP 2.5.3.4.6). In addition, the mechanism of action has been reasonably well studied as the reactive metabolite has been shown to be acrolein (SOP 2.5.3.4.5).

12

COT Recommendations for AEGL-3

- **No Modifying Factor**

Modifying factor of 2 applied to 1-hour AEGL-3 to obtain 4- and 8-hour values: rationale provided not adequate, also not consistent with LC_{50} values (1, 4, and 8 hour). Data demonstrate that a time dependency for acute toxicity; committee recommends default extrapolation

13

Alternative AEGL-3 Derivation:

- **POD:** same; 200 ppm for 1 hour
- **UF:** total 10 (3 inter- and 3 intraspecies)
- **Time scaling:** Value of n = 0.78; derived using Dunlap et al. (1958) LC_{50} data:

  1 h -1060 ppm; 4 h -165 ppm; 8 h -76 ppm

  Not used before due to "unreliability of the data" (measured conc. 15-25% less than nominal, but LC_{50} values not corrected for difference). However, if constant variation, the slope will not vary significantly

14

Alternative AEGL-3 Derivation:

- **Time scaling, con't:**

  Use of default values for n produce values inconsistent with actual data (values w/ no UFs):

  Scaled value for: 4 hours: 34 ppm

  8 hours: 14 ppm

  In repeat-exposure studies (7 or 8 hr/day):

  No animals died at 40 ppm and only 1 animal in each study died at 60 ppm; shows that 8 hr value of 14 ppm not correct.

Can conclude that 60 ppm for a single 7- or 8-hr exposure is no effect level for mortality; can be used as POD

15

- POD of 200 ppm for 1 hr; n=0.78; UF = 10

10 m	30 m	1 hr	4 hr	8 hr
200	49	20	3.4	1.4

- POD of 60 ppm for 7 or 8 hr; n=0.78; UF=10

10 m	30 m	1 hr	4 hr	8 hr	
860	210	86	15	6.0	8-hr
720	180	73	12	5.0	7-hr

- $LC_{50} \div 3$ to approximate $LC_{00;}$ UF=10.

10 m	30 m	1 hr	4 hr	8 hr
NA	NA	35	5.5	2.5

16

- Using the lower value for each time point:

Proposed Alternative AEGL-3 Derivation N=0.78; UF=10				
10-min	30-min	1-hr	4-hr	8-hr
200	49	20	15 (8 hr) 12 (7 hr)	6.0 (8 hr) 5.0 (7 hr)
POD of 200 ppm for 1 hr			POD of 60 ppm for 7/ 8 hr	

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Interim 4 AEGL-2 Derivation:

- POD: No-effect-level for severe eye irritation in humans exposed at 12.5 ppm for 5 min
- UF = 3
- Time scaling – none; irritant effect

COT Recommendations for AEGL-2

Basis is lacking to use 5-min eye irritation data to derive 4- and 8-hr AEGL-2 values. Suggest using two different endpoints: irritation and systemic toxicity. For systemic toxicity, can use interspecies UF of 3 and intraspecies UF of 3 (same justification as described for AEGL-3)

18

- Can derive values that are protective for severe eye irritation that could impair ability to escape and for irreversible systemic toxicity. Time scaling using n=0.78 for systemic toxicity; no time scaling for irritation in humans

- POD: human irritation at 12.5 ppm for 5 min; UF=3

10 m	30 m	1 hr	4 hr	8 hr
4.2	4.2	4.2	4.2	4.2

- POD: animal systemic toxicity: 40 ppm for 7/ 8 hr; n=0.78; UF=10 (effects at 60 ppm exceed AEGL-2)

10 m	30 m	1 hr	4 hr	8 hr	
570	140	58	9.7	4.0	8-hr
480	120	48	8.2	3.4	7-hr

19

➢ Using the lower value for each time point:

Proposed Alternative AEGL-2 Derivation				
10-min	30-min	1-hr	4-hr	8-hr
4.2	4.2	4.2	4.2	4.0 (8 h) 3.4 (7 h)
POD: 12.5 ppm for 5 min; no time scaling; UF=3				POD: 40 ppm for 7/ 8 hr; n=0.78; UF=10

20

Interim 4 AEGL-1 Derivation:

- POD: slight to moderate nose irritation in humans exposed at 6.25 ppm for 5 min
- UF = 3
- Time scaling – none; irritant effect

COT Recommendations for AEGL-1

Basis is lacking to use 5-min irritation data to derive 4- and 8-hr AEGL-2 values.

21

- Can derive values that are protective for notable discomfort (irritation) and for systemic toxicity. Time scaling using n=0.78 for systemic toxicity; no time scaling for irritation in humans

- POD: human irritation at 6.25 ppm for 5 min; UF=3

10 m	30 m	1 hr	4 hr	8 hr
2.1	2.1	2.1	2.1	2.1

- POD: no-effect level for animal systemic toxicity: 20 ppm for 7/ 8 hr; n=0.78; UF=10

10 m	30 m	1 hr	4 hr	8 hr	
290	70	29	4.9	2.0	8-hr
240	59	24	4.1	1.7	7-hr

22

➢ Using the lower value for each time point:

Proposed Alternative AEGL-1 Derivation				
10-min	30-min	1-hr	4-hr	8-hr
2.1	2.1	2.1	2.1	2.0 (8 h) 1.7 (7 h)
POD: 6.25 ppm for 5 min; no time scaling; UF=3				POD: 20 ppm for 7/ 8 hr; n=0.78; UF=10

23

Summary of Interim 4 AEGL Values for AllOH					
Level	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	2.1	2.1	2.1	2.1	2.1
AEGL-2	4.2	4.2	4.2	4.2	4.2
AEGL-3	36	25	20	10	10

AEGL-1: Slight to moderate irritation in humans at 6.25 ppm for 5 min (Dunlap et al., 1958) [UF = 3]

AEGL-2: No-effect-level for severe eye irritation in humans exposed at 12.5 ppm for 5 min (Dunlap et al., 1958) [UF = 3]

AEGL-3: Highest concentration w/ no mortality in mice, rats, and rabbits of 200 ppm for 1 h (Union Carbide, 1951) [UF = 10]

24

Summary of Alternative AEGL Values for AllOH					
Level	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	2.1	2.1	2.1	2.1	2.0 (8 h) 1.7 (7 h)
AEGL-2	4.2	4.2	4.2	4.2	4.0 (h) 3.4 (h)
AEGL-3	200	49	20	15 12	6.0 (h) 5.0 (h)

25

- ***AEGL-1:***
  - Slight/moderate nose irritation (no-effect-level for notable discomfort) in humans at 6.25 ppm for 5 min.; UF=3; no time-scaling (Dunlap)
  - No-effect-level for reversible systemic toxicity at 20 ppm for 8 or 7 h/d; UF=10; n=0.78 (Dunlap; Shell)
- **AEGL-2:**
  - No-effect-level for impaired ability to escape (NOEL for severe eye irritation in humans) 12.5 ppm for 5 min.; UF=3; no time scaling (Dunlap)
  - No-effect level for irreversible toxicity at 40 ppm for 8 or 7 h; UF=10; n=0.78 (Dunlap; Shell)
- **AEGL-3:**

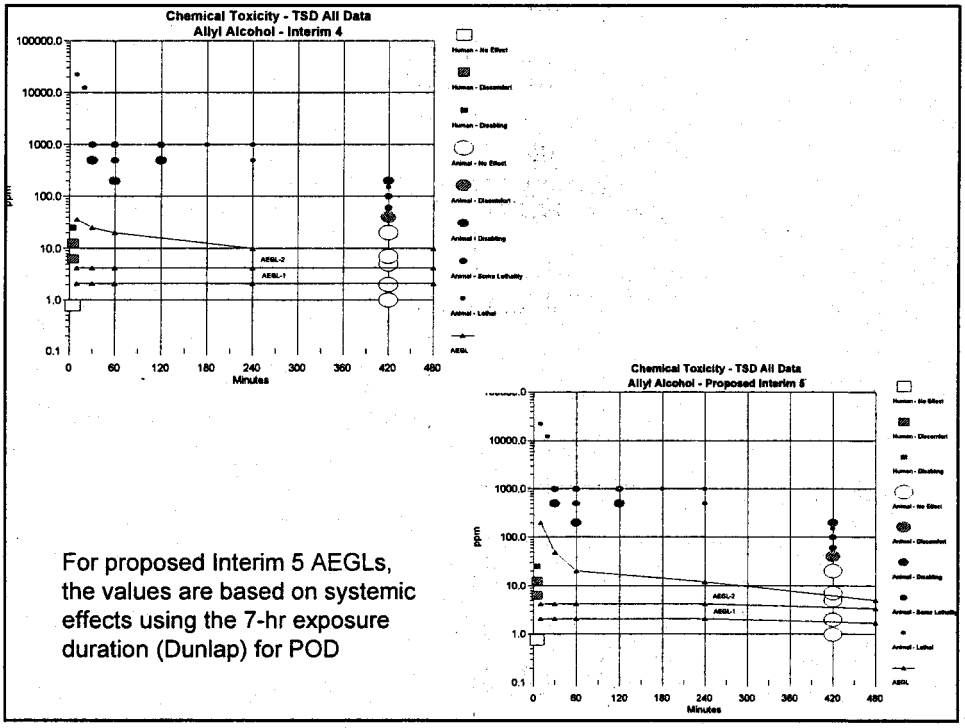
  UF=10; n=0.78
  - Highest concentration w/ no mortality in mice, rats, and rabbits of 200 ppm for 1 h (Union Carbide)
  - No-effect-level for mortality following single exposure to 60 ppm for 8 or 7 h (Dunlap; Shell)

26

Summary of Alternative AEGL Values for AllOH					
Level	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	**2.1**	**2.1**	**2.1**	**2.1**	**2.1**
AEGL-1	2.1	2.1	2.1	2.1	2.0 (8 h) 1.7 (7 h)
AEGL-2	**4.2**	**4.2**	**4.2**	**4.2**	**4.2**
AEGL-2	4.2	4.2	4.2	4.2	4.0 (h) 3.4 (h)
AEGL-3	**36**	**25**	**20**	**10**	**10**
AEGL-3	200	49	20	15 12	6.0 (h) 5.0 (h)

Bold (first row of AEGL value) = interim 4 values;
Second row = alternative AEGL values

27



For proposed Interim 5 AEGLs, the values are based on systemic effects using the 7-hr exposure duration (Dunlap) for POD

NAC/AEGL-41 December 12-14, 2006, Alexandria, VA

Acute Exposure Guideline Levels (AEGLs) for Carbon Disulfide (CAS Reg. No. 75-15-0) S=C=S

Response to COT Comments

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NAS COT 14th Interim Report, 2006, Comments on carbon disulfide

- **AEGL-2 and AEGL-3: values, time scaling, use of UF appropriate, no changes**
- **Specific comments on AEGL-1: endpoint and consideration of sensitive subgroups:**
  - more arguments wanted
  - UF should be 3 instead of 10,
- **„revised document can be finalized if the committee's recommended revisions are made appropriately."**

AEGL-1

- **Critical studies and endpoint: Exposure of humans who ingested alcohol (0.7 g/L in blood) showed an increase in acetaldehyde concentration in blood when exposed to 20 ppm (no effects on well-being etc.)**
- **alcohol intolerance is reported for workers exposed to (unknown concentrations) of CS2.**

- **Similarity between CS2 and certain drugs, e.g. disulfiram ("antabus") which are**
  - inhibitors of aldehyde dehydrogenase (AIDH),
  - increase acetaldehyde level after ethanol intake,
  - lead to characteristic symptoms ("disulfiram effect").

NAS COT 14th Interim Report, 2006, Comments on carbon disulfide, AEGL-1

- …"no consensus in the committee about the use of the key studies … based on data obtained in a population under the influence of alcohol. Although the majority of the committee agrees with the use of this 'sensitive subpopulation', more arguments should be given to defend this decision."

Answer

- "National Institute on Alcohol Abuse and Alcoholism" of the National Institute of Health:
- apparent per capita ethanol consumption (entire population, > 14 a) for the US in 2003: 2.22 gallons/year (=> 8.4 L ethanol/year; 23 mL/d)
- percentage of abstainers in 51 US States in 1999 between ~ 30 and 70 %.
- => percentage of alcohol drinking "non-abstainers" also between ~ 30 and 70 %.
- => considerable alcohol intake in 1/3 to 2/3 of the adult population in each state
- =>This not a 'sensitive subpopulation', this is the normal population.

NAS COT 14th Interim Report, 2006, Comments on carbon disulfide, AEGL-1

- …"UF of 10 … based on … population subgroup with atypical dehydrogenase … more sensitive to the disulfiram effect of CS2 than 'ordinary' ethanol consumers. … sensitivity now counted twice: once for alcohol consumption per se… once for atypical metabolisers."

Answer

- **Sensitivity is not counted twice: alcohol consumption does not characterize a "sensitive subpopulation" but is widespread in the "normal adult population".**
- **Sensitive subgroup is characterized by lower activity of an enzyme in ethanol metabolism**
- **Metabolism of ethanol:**
  - mainly oxidized to acetaldehyde by alcohol dehydrogenase
  - further oxidation of acetaldehyde by aldehyde dehydrogenase (AlDH)

Answer

- **Genetic differences in aldehyde dehydrogenase (AlDH):**
  - "normal" allele, found in Caucasians: AlDH(1)
  - mutant allele, absent in caucasians, but widespread in Asians: AlDH(2)
  - Individuals homozygous in AlDH(2):
    - very low or absent aldehyde dehydrogenase activity,
    - very susceptible to ethanol showing pronounced effects due to high acetaldehyde blood levels, many do not drink at all,
    - "hypersusceptible group"
  - Individuals heterozygous, AlDH(2)/AlDH(1):
    - less susceptible than homozygous
    - more susceptible than "normal" metabolisers
    - frequently show mild effects when drinking alcoholic beverages
    - => "sensitive subgroup" within normal population.

NAS COT 14th Interim Report, 2006, Comments on carbon disulfide, AEGL-1

…"it is unlikely that these atypical metabolisers will drink as much ethanol as ordinary metabolisers, because they feel unwell after drinking small amounts of alcohol."

Answer

It is agreed that very susceptible individuals (homozygous AlDH(2)) will drink less or not at all.

However, since the oxidation of ethanol by alcohol dehydrogenase to acetaldehyde is independent of the ethanol concentration (except for very low concentrations), a lower intake of ethanol will not lower the rate of acetaldehyde formation but shorten the time span during which acetaldehyde is produced.

Therefore, even if the amount of ethanol intake is reduced, sensitive individuals will still be more susceptible than "normal" metabolisers.

NAS COT 14th Interim Report, 2006, Comments on carbon disulfide, AEGL-1

…"Additional exposure to CS2 may contribute to them [i.e., atypical metabolisers] feeling unwell, but is does not justify a UF of 10; a UF of 3 would suffice."

Answer

- The increase in the acetaldehyde blood level in "normal" ethanol drinking individuals exposed to CS2 was not sufficient to cause a disulfiram effect,
- the "sensitive subgroup" can be characterized as showing a mild disulfiram effect after ethanol ingestion, which may be enhanced by CS2 exposure,
- very sensitive individuals already suffer from a pronounced disulfiram effect solely by drinking ethanol. Limitation of CS2 exposure will not offer them protection from this effect.
- => It is agreed that a UF of 3 is sufficient to protect the sensitive subgroup from the additional effects of CS2.

Revised AEGL-1

The revised AEGL-1 are as follows:

SUMMARY TABLE OF AEGL VALUES FOR CARBON DISULFIDE [ppm (mg/m^3)] [a]						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	~~5.0~~ ~~(16)~~ 17 (52)	~~5.0~~ ~~(16)~~ 17 (52)	~~4.0~~ ~~(12)~~ 13 (42)	~~2.5~~ ~~(7.8)~~ 8.4 (26)	~~2.0~~ ~~(6.2)~~ 6.7 (21)	Increase in blood acetaldehyde in humans with moderate intake of alcohol (Freundt et al. 1976b)
AEGL-2 (Disabling)	200 (620)	200 (620)	160 (490)	100 (310)	50 (160)	NOEL for behavioral changes in rats (inhibition of escape response) (Goldberg 1964)
AEGL-3 (Lethality)	600 (1480)	600 (1480)	480 (990)	300 (930)	150 (470)	No lethality in rats (Du Pont 1966)

[a]: Cutaneous absorption may occur. Liquid CS_2 is a severe skin irritant and direct skin contact with the liquid must be avoided.

EXECUTIVE SUMMARY

Phosphorus trichloride (CAS no. 007719-12-2) is a colorless, clear fuming liquid with a pungent, irritating odor. In the presence of water, the chemical decomposes rapidly in a highly exothermic reaction to phosphonic acid, or hydrogen chloride, and pyrophosphonic acids. The primary use of phosphorus trichloride is for the production of phosphonic acid which, in turn, is used in the production of glyphosphate herbicides. Annual domestic production of 294,000 tons has been reported.

No acute lethality data on humans are available. Qualitative data regarding human exposures indicate signs and symptoms of exposure consistent with a highly irritating chemical; ocular and dermal irritation, respiratory tract irritation, shortness of breath, and nausea.

Lethality data are available for rats, cats, and guinea pigs. Cursory studies conducted nearly one hundred years ago in Germany provided preliminary data on lethal and nonlethal effects in cats and guinea pigs following various treatment regimens with inhaled phosphorus trichloride. Although results of the studies indicated the respiratory tract to a be a critical target, the methods and results of these studies were not verifiable. Weeks et al. (1964) reported 4-hr LC_{50} values of 104.5 ppm and 50.1 ppm for rats and guinea pigs, respectively. An unpublished study by Hazleton Laboratories (1983) identified a NOAEL of 3.4 ppm and a LOAEL (histopathologic changes in the respiratory tract) of 11 ppm following repeated exposure (6 hrs/day, 5 days/week for four weeks) of rats. There are no data regarding reproductive/developmental toxicity, genotoxicity, or carcinogenicity of phosphorus trichloride. Definitive data regarding the mechanism of action of phosphorus trichloride are unavailable. Decomposition products (hydrogen chloride, phosphonic acid, and pyrophosphonic acids) are responsible, at least in part, for the contact irritation reported by humans, and the irritation and tissue damage observed in animal species.

The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n x\ t = k$, where the exponent n ranges from 0.8 to 3.5. Due to the limited toxicity data for this chemical, an empirical derivation of n was not possible. In the absence of an empirically derived exponent (n), and to obtain conservative and protective AEGL values, temporal scaling was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n x\ t = k$ equation. **Because phosphorus trichloride is a contact irritant, minor irritation effects are not expected to vary with exposure duration (NRC, 2001). Therefore, all AEGL-1 values were set at 0.34 ppm (the 3.4 ppm point-of departure adjusted by a total uncertainty factor of 10).** The 10-minute AEGL-3 values were set equivalent to the 30-minute values due to uncertainties in extrapolating from the experimental exposure durations of 4 hours and greater.

Quantitative data consistent with AEGL-1 effects were unavailable. Occupational exposures of humans to 1.8-3.6 ppm for 2-6 hours (Sassi et al., 1952) and exposure of rats to 3.4 ppm for 6 hours/day, 5 days/week for 4 weeks (Hazleton Laboratories, 1983) were without notable effect. The occupational exposure data lacked details regarding pairing of the exposure durations (weeks to months) to exposure concentrations. The 3.4 ppm exposure of rats was considered a NOAEL for AEGL-1 effects. These data as well as the AEGL-1 values are supported by the human experience data. The interspecies uncertainty factor was limited to 3 because of the concordance of the animal data with the human experience and because the most sensitive species tested (guinea pig) was only about 2-fold more sensitive. The intraspecies uncertainty factor was limited to 3 because primary effects of phosphorus trichloride (irritation and subsequent tissue damage) appear to be due, in part, to hydrogen chloride and phosphonic acid resulting from chemical dissociation. Additional reduction of the AEGL-1 values would be inconsistent with available human and animal data .

Information consistent with AEGL-2 effects was limited to an occupational exposure report and a multiple exposure study with rats. For occupational exposures, there was notable irritation following 2-6 hours of exposure to approximately 14-27 ppm phosphorus trichloride and more severe but reversible irritation following exposures of 1-8 weeks. Reports providing qualitative information but no exposure terms affirmed the potential for respiratory tract irritation following acute exposures to phosphorus trichloride. Data for rats showed upper respiratory tract involvement following multiple exposures (over 4 weeks) to 11 ppm but not to 3.4 ppm (Hazleton Laboratories, 1983). For development of AEGL-2 values, the 11 ppm exposure in rats was considered a NOAEL for AEGL-2 effects. Uncertainty factor application was the same as for the AEGL-1 tier.

AEGL-3 values were developed based upon a 3-fold reduction of the 4-hr LC_{50} (Weeks et al., 1964) as an estimate of the lethality threshold (104.3 ppm/3 = 34.8 ppm). A total uncertainty factor adjustment of 10 was used to develop the AEGL-3 values. Animal data indicated some variability in the toxic response to phosphorus trichloride with guinea pigs being the more sensitive among the species tested but only about 2-fold compared to the rat. Additionally, further reduction of the AEGL-3 values did not appear warranted based upon the human occupational exposure data. Therefore, uncertainty adjustment regarding interspecies variability was limited to 3. To account for intraspecies variability, a factor of 3 was applied. The uncertainty of intraspecies variability was limited to 3 because primary effects of phosphorus trichloride (irritation and subsequent tissue damage) appear to be due, in part, to hydrogen chloride and phosphonic acid resulting from chemical dissociation. The total uncertainty factor of 10 may be justified by human exposure data showing that repeated 2 to 6-hour exposures of up to 27 ppm were without life-threatening consequences. Furthermore, the results of the Hazleton Laboratories (1983) study showed no fatalities in rats following multiple 6-hour exposures to 11 ppm. The AEGL values for phosphorus trichloride are presented in the table below.

PROPOSED AEGL VALUES FOR PHOSPHORUS TRICHLORIDE						
Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	~~0.78~~ 0.34 ppm	~~0.78~~ 0.34 ppm	~~0.62~~ 0.34 ppm	~~0.39~~ 0.34 ppm	~~0.26~~ 0.34 ppm	NOAEL of 3.4 ppm in rats exposed 6 hrs/day, 5 days/week for 4 weeks; **no time scaling for irritant** (Hazleton Laboratories, 1983)
AEGL-2 (Disabling)	2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	0.83 ppm	NOAEL for AEGL-2 tier effects; based upon respiratory tract histopathology in rats exposed 6 hrs/day, 5 days/week for 4 weeks (Hazleton Laboratories, 1983)
AEGL-3 (Lethal)	7.0 ppm	7.0 ppm	5.6 ppm	3.5 ppm	1.8 ppm	Estimated lethality threshold based upon 3-fold reduction of rat 4-hr LC_{50} 104.3 ppm/3 = 34.8 ppm) (Weeks et al., 1964)[a]

[a] Based upon animal data, lethality may be delayed.

References

Hazleton Laboratories. 1983. Subacute inhalation toxicity study in rats - phosphorus trichloride. *Final Report. Project No. 241-141. Hazleton Laboratories America, Inc.* Unpublished.

NRC (National Research Council). 2001. Standing operating procedures for developing acute exposure guideline levels for hazardous chemicals. Committee on Toxicology, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC

Sassi, C. 1952. Occupational poisoning due to phosphorus trichloride. AMA Arch. Ind. Hyg. Occ. Med. 7, 178. (English translation of abstract.)

Weeks, M.H., Mussleman, N.P., Yevich, P.P., Jacobson, K.H., Oberst, F.W. 1964. Acute vapor toxicity of phosphorus oxychloride, phosphorus trichloride and methyl phosphonic dichloride. *Amer. Ind. Hyg. J.* 25: 470-475.

#7

ATTACHMENT 11

SULFUR DIOXIDE: RESPONSE TO COT COMMENT

REVISION OF AEGL-3

NAC/AEGL-41
December 12-14, 2006
Alexandria, VA

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: George Woodall

CURRENT AEGL-3 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
42 ppm	32 ppm	27 ppm	19 ppm	16 ppm

Reference: Cohen, H.J., Drew, R.t., Johnson, J.L., and Rajagopalan, K.V. 1973. Molecular basis of the biological function of molybdenum. The relationship between sulfite oxidase and the acute toxicity of bisulfite and SO_2. PNAS. 70: 3655-3659.

Test Species/Strain/Sex/Number: CD outbred rats/ 8 males/ concentration

Exposure Route/Concentrations/Durations: Rats/Inhalation: 224, 593, 965, 1168, or 1319 ppm/4 hours
(The $BMCL_{05}$ of 573 ppm, was determinant for AEGL-3)

Endpoint/Concentration/Rationale: $BMCL_{05}$/ 573 ppm/ threshold for death for 4 hour exposure in rats

Effects:

Concentration	Mortality
224 ppm	0/8
593 ppm	0/8
965 ppm	3/8
1168 ppm	5/8
1319 ppm	8/8

Uncertainty Factors/Rationale:
Total uncertainty factor: 30
Intraspecies = 10:due to the wide variability in response to SO_2 exposure between healthy and asthmatic humans.
Interspecies = 3: considered sufficient because no deaths were reported in guinea pigs exposed to 750 ppm SO_2 for 1 hour (Amdur, 1959) or in dogs exposed to 400 ppm SO_2 for 2 hours (Jackson and Eady, 1988).

Time Scaling: $C^n \times t = k$ where n = 4, value derived from mouse lethality data for time-to-death. Data point used for AEGL-3 derivation was 4 hours. Other time points were based on extrapolation.

PROPOSED REVISION: AEGL-3 Values for Sulfur Dioxide					
Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	~~42 ppm~~ 20 ppm	~~32 ppm~~ 20 ppm	~~27 ppm~~ 20 ppm	~~19 ppm~~ 20 ppm	~~16 ppm~~ 20 ppm

Species: Guinea Pig (10-30/group)
Concentration: 200 ppm
Time: 1-hour
Endpoint: No mortality; moderate increase (140%) in SRaw
Reference: Amdur, 1959

Time Scaling: The role of exposure duration to the magnitude of SO_2-induced bronchoconstriction in asthmatics appears to decrease with extended exposure. Data suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10-minutes and increases minimally or resolves beyond 10-minutes of exposure. Therefore, AEGL-3 values for SO_2 were held constant across all time points.

Uncertainty Factors:

Interspecies = 10

Data suggest that the guinea pig is approximately 10-times less sensitive than an asthmatic human. Guinea pigs exposed to 2.6 ppm SO_2 for 1 hour exhibited an increase in Sraw of 20% (Amdur, 1959);whereas, exercising asthmatic humans exposed to 0.25 ppm SO_2 showed no increase in Sraw (Shacter et al., 1984; Roger et al., 1984).

Intraspecies = 1

The interspecies UF of 10 already accounts for extrapolation to a sensitive human subpopulation (asthmatics).

SUPPORT:

Cohen et al., 1973

POD: 4-hour rat $BMCL_{05}$ of 573 ppm

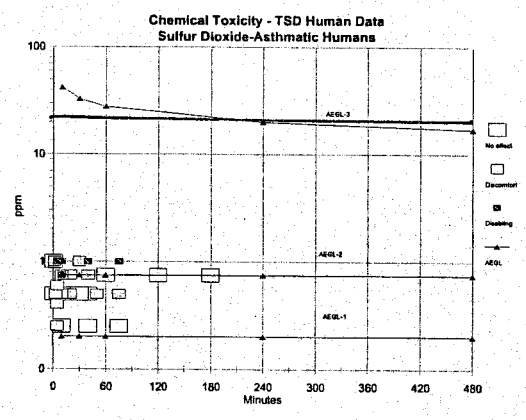
Intraspecies = 10

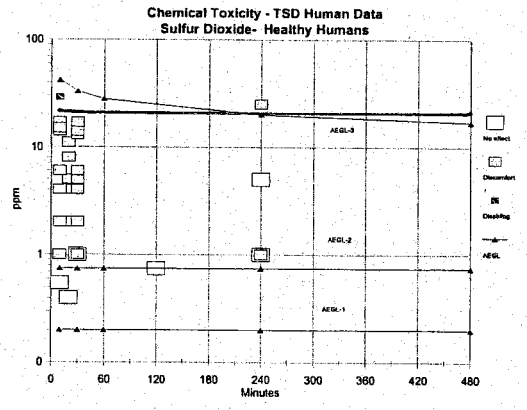
Due to the wide variability in response to SO_2 exposure between healthy and asthmatic humans.

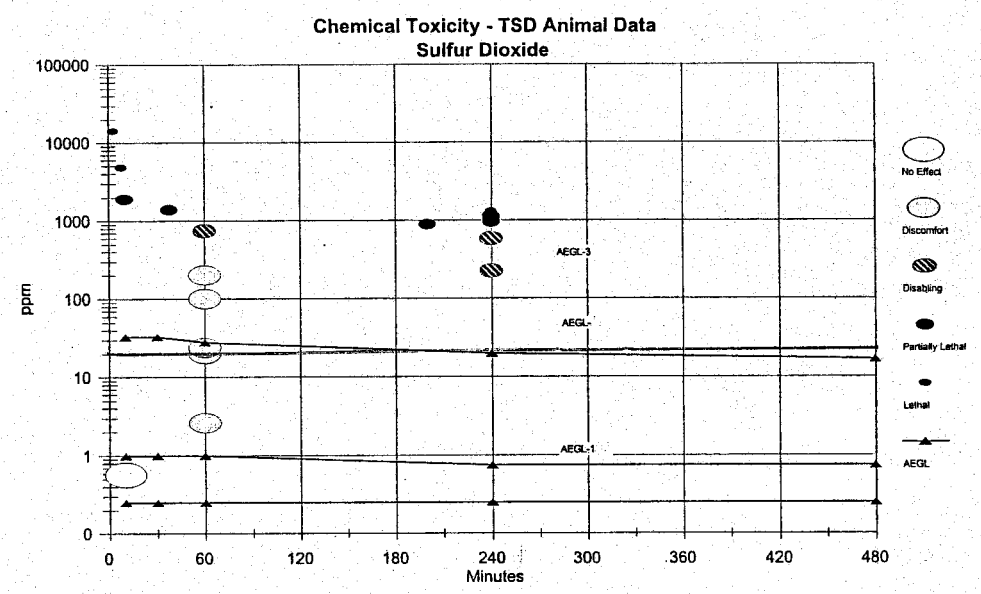
Interspecies = 3

Considered sufficient because, although the rat is not the most sensitive species, this factor accounts for the approximate 3-fold difference in sensitivity with regard to lethality between the rat and the most sensitive animal species, the guinea pig (exposure to approximately 2000 ppm: Rat time to death = 198 minutes; Guinea pig time to death = 68 minutes (Leong et al., 1961)).

Resulting value = 19 ppm: Supports revised value of 20 ppm


Chemical Toxicity - TSD Human Data
Sulfur Dioxide-Asthmatic Humans
100
10
0
ppm
AEGL-3
AEGL-2
AEGL-1
0
60
120
180
240
300
360
420
480
Minutes
No effect
Discomfort
Disabling
AEGL


Chemical Toxicity - TSD Human Data
Sulfur Dioxide- Healthy Humans
100
10
1
0
ppm
AEGL-3
AEGL-2
AEGL-1
0
60
120
180
240
300
360
420
480
Minutes
No effect
Discomfort
Disabling
AEGL


Chemical Toxicity - TSD Animal Data
Sulfur Dioxide
100000
10000
1000
100
10
1
0
ppm
AEGL-3
AEGL-2
AEGL-1
0
60
120
180
240
300
360
420
480
Minutes
No Effect
Discomfort
Disabling
Partially Lethal
Lethal
AEGL

Extant Standards and Guidelines for Sulfur Dioxide					
Guideline	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	0.20 ppm	0.20 ppm	0.20 ppm	0.20 ppm	0.20 ppm
AEGL-2	0.75 ppm	0.75 ppm	0.75 ppm	0.75 ppm	0.75 ppm
AEGL-3	20 ppm	20 ppm	20 ppm	20 ppm	20 ppm
ERPG-1	0.3 ppm				
ERPG-2	3 ppm				
ERPG-3	15 ppm				
NIOSH IDLH	100 ppm				
NIOSH REL					2 ppm
OSHA PEL-TWA					2 ppm
ACGIH TLV-TWA					2 ppm
NIOSH-STEL	5 ppm				
ACGIH TLV-STEL	5 ppm				
NAS EEGL	30 ppm (10 min)	20 ppm (30 min)	10 ppm (60 min)		5 ppm (24 hr)
German MAK					0.5 ppm
Dutch MAC					2 ppm
Swedish OEL-LLV					2 ppm
Swedish OEL-CLV	5 ppm				

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

ETHYLBENZENE
(CAS Reg. No. 100-41-4)

Draft 2: December/2006

ETHYLBENZENE

Almost exclusively used for production of styrene

Mostly produced and used on site

~20% of mixed xylenes

Human data relevant to AGEL derivation

- Six male volunteers (Yant et al. 1930)
  - 1000 ppm: eye irritation with lacrimation which decreased to hardly noticeable after 1-2 min
  - 2000 ppm: severe eye and throat irritation which decreased with continued exposure; vertigo at 5 min
  - 5000 ppm: intolerable

- No adverse effects in pharmacokinetic studies
  - 46 ppm for 8 hrs (Gromiec and Piotrowski 1984)
  - 85 ppm for 8 hours (Bardodej and Bardodejova 1970)
  - 150 ppm for 4 hours (Engström et al. 1984)

- From SMAC document (NRC 1997) (Bardodej and Bardodejova 1961)
  - 100 ppm for 8 hours: no complaints of any problems in nine subjects
  - 180 ppm for 8 hours: irritation of respiratory tract and conjunctiva, headaches, sleepiness in eleven subjects
  - no further information available

Summary of Animal Lethality Data Following Ethylbenzene Exposure				
Species/ sex	Conc. (ppm)	Duration	Effects	Reference
Guinea pig/f	2500	8 hrs 6 hrs	1/8 died no effects	Cappaert et al. 2002
Guinea pig/not stated	10,000	2 hrs	2/6	Yant et al. 1930
Rat/m	2400 1200	6 hrs/d; 4 days	5/5; one on day 1 lacrimation	Bio/ dynamics 1986
Rat/not stated	4000	4 hrs	LC_{50}	Smyth et al. 1962; Mellon Inst. 1949
Mouse/m	2400 1200	6 hrs/d; 4 days	5/5; all on day 2 4/5; on day 3	Bio/ dynamics 1986

Summary of Nonlethal Animal Data Following Ethylbenzene Exposure - Guinea Pig, Rabbit, Mouse				
Species/ sex	Conc. (ppm)	Dura-tion	Effects	Refer-ence
Guinea pig/not stated	1000-10,000	up to 480 min	1000: irritation after 3-8 min disappeared after 30 min 2000: immediate irritation, unsteadiness after 390 min, ataxia after 480 min 5000: immediate irritation, unsteadiness and ataxia after 26-30 min, tremors, abnormal respiration	Yant et al. 1930
Rabbit/ m	400-2400	6 hrs/d; 4 days	2400: lacrimation on 2/4 on day 1 400: lacrimation after 3 days	Bio/ dynamics 1986
Rabbit/ m,f	382-1610	6 hrs/d; 5 d/wk; 4 wk	no clinical signs, decr wt gain at 1610 ppm	Cragg et al. 1989
Mice/ m,f	99-782	6 hrs/d; 5 d/ wk; 4 wk	no clinical signs, incr liver wt at 782 ppm	Cragg et al. 1989
Mice/m	400	6 hrs/d; 4 days	lacrimation after 3 days	Bio/ dynamics 1986

Summary of Nonlethal Animal Data Following Ethylbenzene Exposure - Rat				
Species/ sex	Conc. (ppm)	Duration	Effects	Reference
Rat/f	550	8 hrs/d; 5 days	lesions in inner ear	Cappaert et al. 2002
Rat/m	400, 1200	6 hrs/d; 4 days	400: lacrimation after 3 days 1200: lacrimation on 2/5 after 1 day	Bio/ dynamics 1986
Rat/m	400-2180	4 hrs	400-1500: increased activity >1500: decreased activity 2180: minimum narcotic	Molnár et al. 1986
Rat/m	2000	6 hrs/d; 3 days	no death or clinical signs	Andersson et al. 1981
Rat/m,f	99-782	6 hrs/d; 5 d/wk, 4 weeks	no clinical signs, incr liver wt at 782 ppm	Cragg et al. 1989

Summary of Developmental Toxicity Data Following Ethylbenzene Exposure				
Species /sex	Conc. (ppm)	Duration	Effects	Refer-ence
Rat/f	100 or 1000	7 hr/d, 5 d/wk, 3 wks plus 7 hr/d on GDs 1-19	Maternal: 1000: increased liver, kidney, and spleen weights Developmental: 1000: slight increase in extra ribs	Andrew et al. 1981, Hardin et al. 1981
Rabbit/ f	100 or 1000	7 hr/d on GDs 1-24	Maternal: 1000: increased liver weight relative to body weight Developmental: no effects	Andrew et al. 1981, Hardin et al. 1981
Rat/f	100-2000	6 hr/d on GDs 6-20	Maternal: ≥ 1000: decreased weight gain and food consumption Developmental: ≥ 1000: decreased body weight	Saillen-fait et al. 2003

Summary of Reproductive Toxicity Data Following Ethylbenzene Exposure				
Species /sex	Conc. (ppm)	Duration	Effects	Refer-ence
Rat/m,f	25-500	6 hr/d; 70 d prior to mating; 2- gen	500: parental: incr liver wt (F_0, F_1:m,f) ; incr kidney wt (F_0, F_1:m); decr body wt gain (F_0, F_1:m); offspring: no effects (F_1, F_2)	Faber et al. 2006
Rat/m,f	100-1000	6 hr/d; 2 or 4 wks prior to mating; 1- gen; F_1 exposed PNDs 22 or 29 through 33	500: parental: incr liver wt (m,f); incr kidney wt (m); decr body wt gain (m,f); offspring: clinical signs, decr wt gain, death after two exposures 1000: parental: as for 500; offspring: decr wt at birth; decr survival; decr wt gain, clinical signs and death after day 22	Stump 2003

Proposed AEGL-1 Values for Ethylbenzene				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
27 ppm (117 mg/m^3)	27 ppm (117 mg/m^3)	21 ppm (91 mg/m^3)	13 ppm (57 mg/m^3)	6.7 ppm (29 mg/m^3)

Key Study: Molnár et al. 1986

Exposure: rats; 400 ppm for 4 hours

Effect: Increase in motor activity is a no effect level for asymptomatic non-clinical effects.

Scaling: $C^n \times t = k$
n = 3 for extrapolating to the 30-min and 1-hour time points;
n = 1 for extrapolating to the 8-hr time point

UF: 30: 10 for intraspecies variability because the mechanism of systemic toxicity is unknown
3 for interspecies variability because clinical signs and systemic effects were consistent between experimental animal systems

Support for AEGL-1 values - Human data

Supporting Study: Bardodej and Bardodejova 1961 (cited in NRC 1997)

Exposure: humans; 100 ppm for 8 hours

Effect: No complaints in nine individuals.

Scaling: $C^n \times t = k$
n = 3 for extrapolating to the 30-min, 1-hr, and 4 hr time points

UF: 10: 10 for intraspecies variability because the mechanism of systemic toxicity is unknown

Resulting AEGL-1 values:

32 ppm	32 ppm	25 ppm	16 ppm	10 ppm

Proposed AEGL-1 values:

27 ppm	27 ppm	21 ppm	13 ppm	6.7 ppm

Support for AEGL-1 values - Animal data

Supporting Study: Bio/dynamics 1986

Exposure: rats, mice, rabbits; 400 ppm for 6 hrs/d, 4 days

Effect: Lacrimation after 3 days

Scaling: $C^n \times t = k$
n = 3 for extrapolating to the 30-min, 1-hour, and 4-hour time points;
n = 1 for extrapolating to the 8-hr time point

UF: 30: 10 for intraspecies variability because the mechanism of systemic toxicity is unknown
3 for interspecies variability because clinical signs and systemic effects were consistent between experimental animal systems

Resulting AEGL-1 values:

31 ppm	31 ppm	24 ppm	15 ppm	10 ppm

Proposed AEGL-1 values:

27 ppm	27 ppm	21 ppm	13 ppm	6.7 ppm

Proposed AEGL-2 Values for Ethylbenzene				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
38 ppm (170 mg/m^3)	38 ppm (170 mg/m^3)	30 ppm (130 mg/m^3)	19 ppm (83 mg/m^3)	13 ppm (57 mg/m^3)

Key Study: Stump 2003

Exposure: weanling rats; 500 ppm for 6 hours

Effect: Animals had reduced weight gain in the absence of clinical signs after one exposure.

Scaling: $C^n \times t = k$
n = 3 for extrapolating to the 30-min, 1-hour, and 4-hour time points;
n = 1 for extrapolating to the 8-hr time point

UF: 30: 10 for intraspecies variability because the mechanism of systemic toxicity is unknown
3 for interspecies variability because clinical signs and systemic effects were consistent between experimental animal systems

Support for AEGL-2 values - Human data

Supporting Study: Bardodej and Bardodejova 1961 (cited in NRC 1997)

Exposure: humans; 180 ppm for 8 hours

Effect: Irritation of respiratory tract and conjunctiva, headaches, sleepiness in eleven individuals.

Scaling: $C^n \times t = k$
n = 3 for extrapolating to the 30-min, 1-hr, and 4 hr time points

UF: 10: 10 for intraspecies variability because the mechanism of systemic toxicity is unknown

Resulting AEGL-2 values:

45 ppm 45 ppm 36 ppm 23 ppm 18 ppm

Proposed AEGL-2 values:

38 ppm 38 ppm 30 ppm 19 ppm 13 ppm

Support for AEGL-2 values - Animal data

Supporting Study: Cappaert et al. 2002

Exposure: rats; 550 ppm for 8 hours/d, 5 days

Effect: Damage to inner ear.

Scaling: $C^n \times t = k$
n = 3 for extrapolating to the 30-min, 1-hr, and 4 hr time points

UF: 10: 10 for intraspecies variability because the mechanism of systemic toxicity is unknown
3 for interspecies variability because clinical signs and systemic effects were consistent between experimental animal systems

Resulting AEGL-2 values:

46 ppm 46 ppm 37 ppm 23 ppm 18 ppm

Proposed AEGL-2 values:

38 ppm 38 ppm 30 ppm 19 ppm 13 ppm

Proposed AEGL-3 Values for Ethylbenzene				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
76 ppm (330 mg/m^3)	76 ppm (330 mg/m^3)	61 ppm (270 mg/m^3)	38 ppm (170 mg/m^3)	25 ppm (109 mg/m^3)

Key Study: Stump 2003

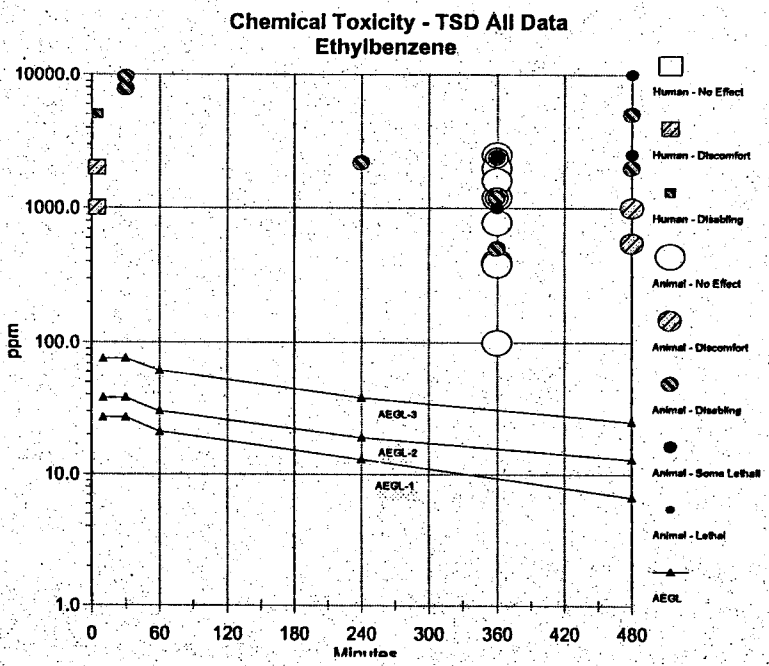
Exposure: weanling rats; 1000 ppm, 6 hours

Effect: Threshold for AEGL 3 effects; approximate threshold for lethality. After one exposure animals had marked decrease in weight gain, clinical signs, gait abnormalities.

Scaling: $C^n \times t = k$
n = 3 for extrapolating to the 30-min, 1-hour, and 4-hour time points;
n = 1 for extrapolating to the 8-hr time point

UF: 30: 10 for intraspecies variability because the mechanism of systemic toxicity is unknown
3 for interspecies variability because clinical signs and systemic effects were consistent between experimental animal systems

Summary of Proposed AEGL Values for Ethylbenzene					
Classification	Exposure Duration				
	10-min	30-min	1-hour	4-hour	8-hour
AEGL-1	27 ppm	27 ppm	21 ppm	13 ppm	6.7 ppm
AEGL-2	38 ppm	38 ppm	30 ppm	19 ppm	13 ppm
AEGL-3	76 ppm	76 ppm	61 ppm	38 ppm	25 ppm



APPLICATION OF UFs

UF_H = 10 because the mechanism of systemic toxicity is unknown

Reduce to 3 for all AEGL levels:

- mechanism is probably CNS depression
- limited data suggest steady-state reached quickly in both rat and human
- rapid metabolism with little tissue retention
- toluene, xylenes, 1,2-dichloroethene use 3 [Among humans the minimum alveolar concentration (MAC) for volatile anesthetics typically varies by about 2-3 fold.]

UF_A = 3 because clinical signs and systemic effects were consistent between experimental animal systems

Reduce to 1 for AEGL-2 and -3:

- weanlings are highly sensitive group at time of high stress
- effects occurred in weanlings first exposed on PND 22 but not when first exposed on PND 29
- weanlings were not affected in main study when group house for first week
- toluene and xylenes use 1

Summary of Alternate AEGL Values for Ethylbenzene					
	Exposure Duration				
	10-min	30-min	1-hour	4-hour	8-hour
AEGL-1	80 ppm	80 ppm	63 ppm	40 ppm	20 ppm
AEGL-2	380 ppm	380 ppm	303 ppm	190 ppm	125 ppm
AEGL-3	760 ppm	760 ppm	606 ppm	380 ppm	250 ppm

UF = 10 (3×3) for AEGL-1
UF = 3 (3×1) for AEGL-2 and -3
Same key and supporting studies

ETHYLBENZENE

Point-of-departure for PBPK model

Questions with model

- Is model validated for concentration range of interest to AEGL endpoints?
- Is model validated for all endpoints of concern, not only CNS? (is ototoxicity CNS toxicity?)
- Is species consistent? Need rat data for rat model.
- COT White Paper to be discussed in January.

AEGL-3: Highest non-lethal				
Species/ sex	**Conc. (ppm)**	**Duration**	**Effects**	**Reference**
Rat/m	2180	4 hrs	"minimum narcotic"	Molnar et al. 1986
Rat/m	2000	6 hr/d; 3 d	No death or clinical signs	Andersson et al. 1981
Rat/m	2400 1200	6 hrs/day; 4 days	5/5; one on day 1 lacrimation	Bio/dynamics 1986
Mouse/m	2400 1200	6 hrs/day; 4 days	5/5; all on day 2 4/5; on day 3	Bio/dynamics 1986
Rabbit/m,f	1610	6 hrs/d, 5 d/wk, 4 wks	No clinical signs, decr wt gain at 1610 ppm	Cragg et al. 1989
Rabbit/m	2400	6 hrs/day; 4 days	2400: lacrimation on 2/4 on day 1	Bio/dynamics 1986
Guinea pig/f	2500	8 hours 6 hours	1/8 died No effects	Cappaert et al. 2002

AEGL-2: Effect levels				
Species/ sex	**Conc. (ppm)**	**Duration**	**Effects**	**Reference**
Rat/f	550	8 hr/d, 5 d	Lesions in inner ear	Cappaert et al. 2002

AEGL-1: Effect levels				
Species/ sex	**Conc. (ppm)**	**Duration**	**Effects**	**Reference**
Rat/m	>400	4 hrs	Increased activity threshold	Molnar et al. 1986
Rat, mouse, rabbit/m	400	6 hrs/day; 4 days	lacrimation after 3 d	Bio/dynamics 1986
Rat, mouse/m,f	782	6 hrs/d, 5 d/wk, 4 wks	No clinical signs, incr liver wt	Cragg et al. 1989

Irritation is not part of model; will not be considered in modeling process.

Human data relevant to AGEL-1 and -2

- From SMAC document (NRC 1997) (Bardodej and Bardodejova 1961)
  - 100 ppm for 8 hours: no complaints of any problems in nine subjects
  - 180 ppm for 8 hours: irritation of respiratory tract and conjunctiva, headaches, sleepiness in eleven subjects
  - Should be getting paper from NASA

Options for Deriving AEGL values

- Data
  - AEGL-3: POD approx. 2000 ppm for 6 hrs
  - AEGL-1 and -2: use human data
- Model
  - AEGL-3: choose POD (approx. 2000 ppm for 6 hrs) to enter into model
  - AEGL-2:
    - choose POD (550 ppm for 8 hrs), or
    - 1/3 AEGL-3
  - AEGL-1:
    - use human data, or
    - Choose POD (approx. 400 ppm for 4 hrs)

Summary of AEGL values based on data					
	10-min	30-min	1-hr	4-hr	8-hr
AEGL 1	84 ppm	84 ppm	67 ppm	42 ppm	33 ppm
AEGL 2	151 ppm	151 ppm	120 ppm	76 ppm	60 ppm
AEGL 3	460 ppm	460 ppm	360 ppm	230 ppm	150 ppm

UF = 3 for AEGL-1 and -2, human data

UF = 10 (3x3) for AEGL-3, highest non-lethal in rats

Data Base for

Carbonyl Fluoride

National Advisory Committee for AEGLs Meeting 41
December 12-14, 2006

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Iris Camacho

Chemical Reviewers:
Paul Tobin
Richard Niemeier

Properties:

Carbonyl fluoride is a colorless, pungent, hygroscopic gas;
instantly hydrolyzed by water (The Merck Index).

Carbonyl fluoride is a chemical analogue of phosgene (carbonyl chloride).

A major source of exposure to carbonyl fluoride is pyrolysis of plastic materials such as polytetrafluoroethylene and polyfluoroethylenepropylene. These polymers yield carbonyl fluoride as the major reaction product.

QUESTION

Does inhaled carbonyl fluoride instantly hydrolyze to carbon dioxide and two moles of hydrogen fluoride in the moist respiratory tract or does (at least some) carbonyl fluoride penetrate to the lungs? If hydrolysis is essentially complete, then the toxicity values for carbonyl fluoride should be one-half those of hydrogen fluoride.

Data Base gives conflicting toxicity data.

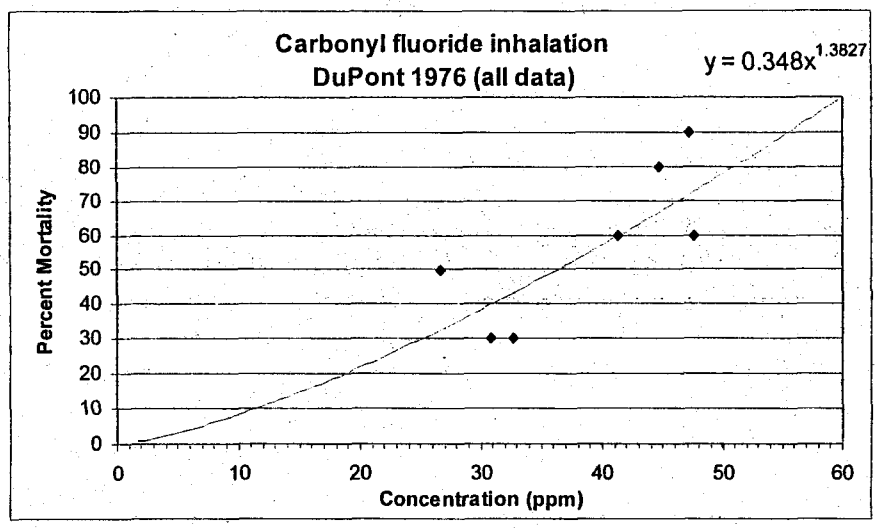
Hydrolysis:
1-hour LC_{50} of 460 ppm (Scheel et al. 1968) (measured concentrations)
4-hour LC_{50} of 90 ppm (Scheel et al. 1968) " "
Results confirmed with LC_{50} values for pyrolysis products of polymer
4-hour LC_{50} of 100 ppm (DuPont & Co. 1959) (nominal concentrations)
Values are roughly one-half of hydrogen fluoride LC_{50} values

Minimal Hydrolysis (measured concentrations):
4-hour LC_{50} of 34.3 ppm (DuPont & Co. 1976)
Values roughly correspond to phosgene values
Dose-response curve ....

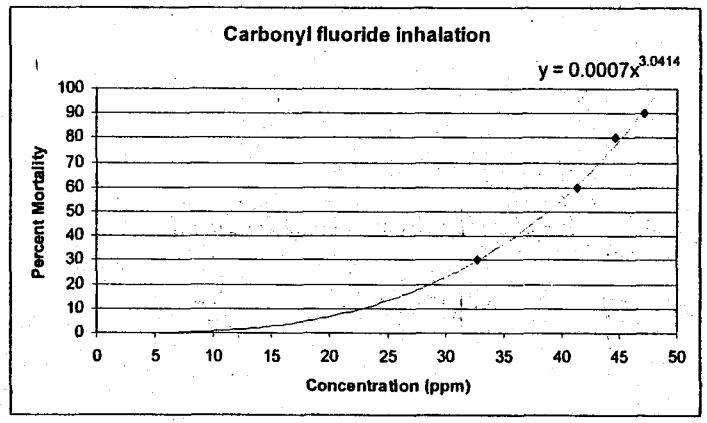
Summary of Acute Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Rat	2.5[a]	2, 2.5 hours	none	DuPont & Co. 1956
	5.0[a]	2, 2.5 hours	slight dyspnea	
Rat	5[a]	4 hours	rapid, shallow respiration	DuPont & Co. 1959
	10[a]	4 hours	rapid, shallow respiration	
	100[a]	4 hours	LC_{50}	
Rat	34.3	4 hours	LC_{50}, rapid, shallow and convulsive respiration	DuPont & Co. 1976
Rat				Scheel et al. 1968
8-weeks old	259	1 hour	mortality threshold	
"	360	1 hour	LC_{50}	
24-weeks old	350	1 hour	mortality threshold	
"	460	1 hour	LC_{50}	
8-weeks old	90	4 hours	LC_{50}	

[a] Nominal concentrations.



ppm	mortality
26.7	50
30.8	30
32.7	30
41.3	60
44.7	80
47.2	90
47.6	60



Niemeier rationale for carbonyl fluoride

Agent	CAS#	unit	AEGL-1					AEGL-2					AEGL-3				
			10 min	30 min	1 hr	4 hr	8 hr	10 min	30 min	1 hr	4 hr	8 hr	10 min	30 min	1 hr	4 hr	8 hr
Phosgene (carbonyl chloride)	75-44-5	ppm	NR	NR	NR	NR	NR	0.6	0.6	0.3	0.08	0.04	3.6	1.5	0.75	0.2	0.09
Hydrogen chloride	7647-01-0	ppm	1.8	1.8	1.8	1.8	1.8	100	43	22	11	11	620	210	100	26	26
Hydrogen fluoride	7664-39-3	ppm	1	1	1	1	1	95	34	24	12	12	170	62	44	22	22
Carbonyl fluoride (fluoro phosgene)	353-50-4	ppm	NR	NR	NR	NR	NR	1.1	0.5	0.3	0.07	0.03	3.2	1.6	0.8	0.2	0.1

Phosgene AEGL-3 values were based on the highest concentration causing no mortality in the rat after a 30-min exposure (15 ppm) (Zwart et al. 1990). A UF of 3 was applied for interspecies extrapolation because little species variability is observed for lethal and nonlethal end points after exposure to phosgene. A UF of 3 was applied to account for sensitive human subpopulations due to the steep concentration-response curve and because the mechanism of phosgene toxicity (binding to macromolecules and causing irritation) is not expected to vary greatly between individuals. Therefore, the total UF is 10. The value was then scaled to the 1-, 4-, and 8-h AEGL periods using $C^n \times t = k$, where n = 1 (Haber's Law), because Haber's Law has been shown to be valid for phosgene within certain limits. The 10-min AEGL-3 value was based on the highest concentration causing no mortality in the rat or mouse (36 ppm) after a 10-min exposure (Zwart et al. 1990). A UF of 3 was applied for interspecies extrapolation because little species variability is observed for lethal and nonlethal end points after exposure to phosgene. A UF of 3 was applied to account for sensitive human subpopulations due to the steep concentration-response curve and because the mechanism of phosgene toxicity (binding to macromolecules and causing irritation) is not expected to vary greatly between individuals (total UF, 10).

Using the DuPont 1976 data for carbonyl fluoride, the all data plot at the bottom corresponds to a ~36 ppm LC_{50}. Approximately 2 ppm x 4 hours is the projected highest concentration causing no mortality. Using a total UF of 10 (rationale as for phosgene) for the 4 hour AEGL-3 = 0.2 ppm, or about the same as phosgene and much lower than ½ the value of HF – approximately 100 times lower.

Acute Exposure Guideline Levels (AEGLs) for Methylacrylaldehyde

Tom Marshall
Susan Ripple
Dieter Heinz

Properties

- Colorless liquid
- Soluble in water at 5.9%
- Atmospheric half-life is ~11.5 hours
- Mechanism of toxicity
  - Contact irritant

Inhalation Toxicity

- Relevant toxicity data in both people and animals
- Summary Tables 3 and 4

Human Data

Exposure	Conc. (ppm)	Effect	Reference
Ten healthy men for 20 min.	0.089 0.189 0.286	Perceived eye irritation: NOAEL = 0.3ppm Increased blink frequency: NOAEL = 0.2 ppm	Nojgaard et al. 2005

Animal Data

Exposure	Conc. (ppm)	Effect	Reference
Mouse: 30 min.	2.0 4.4 6.6 10.2 13.1 26.3	= NOAEL, (10% ↓ respiratory rate) = LOAEL, 30% ↓ respiratory rate = 40% ↓ respiratory rate = 50% ↓ respiratory rate = 55% ↓ respiratory rate = 70% ↓ respiratory rate RD_0 = 1.3 ppm (0.8 - 2.1 = 95% CL)	Larsen and Nielsen 2000
Rat: 4 hr	125	Lethal to 2, 3, or 4/6 rats.	Carpenter et al. 1949
Rat: 4 hr	Not reported	LC_{50} = 195 (560 mg/m^3). Severe irritation of respiratory tract.	BG Chemie 1995

Animal Data (cont.)

Exposure	Conc. (ppm)	Effect	Reference
Rat: 6 hr 6 hr/day; 5 days/wk; 2 wk	77 5 19	Lethal to 9/10 in 48 hr; acute irritation and lung lesions = NOAEL (eyes half-closed during exposure) = LOAEL, multiple clinical signs related to respiratory irritation; respiratory tract lesions	Coombs et al. 1992
Rat: 6 hr/day; 5 days/wk; 13 wk	1.0 4.9 15.3	= NOEL = NOAEL (eyes half-closed during exposure) = LOAEL, multiple clinical signs related to respiratory irritation; respiratory tract lesions; some reversal in 4 wk	Coombs et al. 1994

Animal Data (cont.)

Exposure	Conc. (ppm)	Effect	Reference
Rat: (duration not reported)	10 ≥20	= Maternal toxicity = Maternal and fetal toxicity (reduced birth weight)	BG Chemie 1995

AEGL-1 for Methylacrylaldehyde		
Classification	**ppm**	**mg/m³**
10 min.	0.1	0.3
30 min.	0.1	0.3
1 hr	0.1	0.3
4 hr	0.07	0.2
8hr	0.07	0.2

10 Min., 30 Min., and 1 Hour AEGL- 1

Toxicity End point: Eye irritation in healthy human subjects (Nojgaard et al. 2005)

POD: NOAEL for perceived irritation (0.3 ppm)

Time Scaling: None (20 min. exposure; subtle irritant effect)

UF Application: 3 for protection of sensitive individuals; additional reduction not warranted because the effect is the result of direct contact

AEGL-1: 10 Min. = 0.1 ppm
30 Min. = 0.1 ppm
1 Hr = 0.1 ppm

10 Min., 30 Min., and 1 Hour AEGL- 1

Toxicity End point: Eye irritation in healthy human subjects (Nojgaard et al. 2005)

POD: NOAEL for perceived irritation (0.286 ppm)

Time Scaling: None (20 min. exposure; subtle irritant effect)

UF Application: 3 for protection of sensitive individuals; additional reduction not warranted because the effect is the result of direct contact

AEGL-1: 10 Min. = 0.1 ppm
30 Min. = 0.1 ppm
1 Hr = 0.1 ppm

4- and 8- Hour AEGL- 1

Toxicity End point: Eye irritation in healthy human subjects (Nojgaard et al. 2005)

POD: NOAEL for blink frequency (0.189 ppm)

Time Scaling: None (20 min. exposure; subtle irritant effect)

UF Application: 3 for protection of sensitive individuals; additional reduction not warranted because the effect is the result of direct contact

AEGL-1: 4 Hr = 0.07 ppm
8 Hr = 0.07 ppm

AEGL-2 for Methylacrylaldehyde		
Classification	**ppm**	**mg/m³**
10 min.	2.8	7.8
30 min.	2.8	7.8
1 hr	2.2	6.2
4 hr	1.4	3.9
8hr	0.7	2.0

AEGL-2 Values

- Steep concentration-response curve
- AEGL-2 values are derived by taking one-third of the respective AEGL-3 value

AEGL-3 ÷ 3 = AEGL-2

AEGL-3 for Methylacrylaldehyde		
Classification	**ppm**	**mg/m³**
10 min.	8.3	23
30 min.	8.3	23
1 hr	6.6	19
4 hr	4.2	12
8hr	2.1	5.9

10 Min. and 30 Min. AEGL-3

Toxicity End point: Lethality (Carpenter et al. 1949)

POD: 4 Hr LC_{50} (125 ppm) + 3 = 41.7 ppm

Time Scaling: $C^n \times t = k$ (ten Berge et al.1986), where n = 3 for time periods less than 4 hours and n = 1 for time periods greater than 4 hours

UF Application: 3 for interspecies variability, 3 for intraspecies variability; additional reduction not warranted because the effect is the result of direct contact

AEGL-3: 10 Min. = 8.3 ppm
30 Min. = 8.3 ppm

1 Hr, 4 Hr, and 8 Hr AEGL-3

Toxicity End point: Lethality (Carpenter et al. 1949)

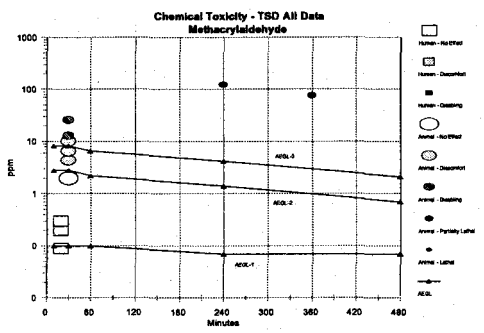
POD: 4 Hr LC_{50} (125 ppm) ÷ 3 = 41.7 ppm

Time Scaling: $C^n \times t = k$ (ten Berge et al.1986), where n = 3 for time periods less than 4 hours and n = 1 for time periods greater than 4 hours

UF Application: 3 for interspecies variability, 3 for protection of sensitive individuals; additional reduction not warranted because the effect is the result of direct contact

AEGL-3: 1 Hr = 6.6 ppm
4 Hr = 4.2 ppm
8 Hr = 2.1 ppm

Summary Inhalation AEGL-s for Methylacrylaldehyde (ppm)			
	AEGL-1	AEGL-2	AEGL-3
10 Min.	0.1	2.8	8.3
30 Min.	0.1	2.8	8.3
1 Hr	0.1	2.2	6.6
4 Hr	0.07	1.4	4.2
8 Hr	0.07	0.7	2.1



Acute Exposure Guideline Levels (AEGLs) for Methyl Vinyl Ketone

Tom Marshall
Jim Holler
Marc Baril
Roberta Grant

Properties

- Colorless to light yellow liquid
- Soluble in water at >10%
- Atmospheric half-life is ~21 hours
- Mechanism of toxicity
  - Contact irritant

Inhalation Toxicity

- Relevant toxicity data in animals only
- Summarized in Table 3

Animal Data

Exposure	Conc. (ppm)	Effect	Reference
Rat: 6 hr/day; 9 days	2.1, 3.9, 7.8	NOAEL = 2.1 ppm 3.9 ppm = 20% mortality (2/10) after 8 days 7.8 ppm = 90% mortality within 9 days	Eastman Kodak 1992
Guinea pig: 6 hr/day; 9 days	2.1, 3.9, 7.8	NOAEL = 2.1 ppm 3.9 ppm = airway lesions (6/6) 7.8 ppm = airway lesions (6/6); 5/6 acute pneumonitis	Eastman Kodak 1992
Rabbit: 6 hr/day; 9 days	2.1, 3.9, 7.8	NOAEL = 2.1 ppm 3.9 ppm = 1/3 mortality in 9 days 7.8 ppm = 3/3 acute pneumonitis	Eastman Kodak 1992

Animal Data (cont.)

Exposure	Conc. (ppm)	Effect	Reference
Rat: 6 hr/day; 12 days	0.25, 0.5, 1, 2, 4, 8	8 ppm = 100% mortality (10/10) after 1 day exposure 4 ppm = nasal cavity and lung necrosis 2 ppm = nasal cavity necrosis; no lung lesions 1 ppm = LOAEL for mild nasal lesions 0.5 ppm = NOAEL	Morgan et al. 2000
Mouse: 6 hr/day; 12 days	0.25, 0.5, 1, 2, 4, 8	8 ppm = 20% mortality (2/10) after 10 days exposure; nasal cavity and lung necrosis 4 ppm = nasal cavity necrosis 2 ppm = nasal cavity necrosis 1 ppm = LOAEL for mild nasal lesions 0.5 ppm = NOAEL	Morgan et al. 2000

Animal Data (cont.)

Exposure	Conc. (ppm)	Effect	Reference
Rat: 6 hr/day; 5 days/wk, 13 wks	0.5, 1, 2	0.5 ppm = NOAEL for nasal lesions	Morgan et al. 2000
Mouse: 6 hr/day; 5 days/wk, 13 wks	0.5, 1, 2	1 ppm = LOAEL for nasal lesions Decreased leukocytes in males at all exposure concentrations 0.5 ppm = NOAEL for nasal lesions	Morgan et al. 2000
Rat	Not specified	LC_{50} = 2.4 ppm	RTECS 2006

Animal Data (cont.)

Exposure	Conc. (ppm)	Effect	Reference
Mouse	Not specified	LC_{50} = 2.8 ppm	*RTECS 2006*

AEGL-1 for Methyl Vinyl Ketone		
Classification	**ppm**	**mg/m³**
10 min.	0.05	0.15
30 min.	0.05	0.15
1 hr	0.05	0.15
4 hr	0.05	0.15
8hr	0.05	0.15

All AEGL- 1 Values

Toxicity End point: Nasal cavity lesions NOAEL (Morgan et al. 2000)

POD: NOAEL = 0.5 ppm

Time Scaling: None

UF Application: 3 for interspecies variability, 3 for intraspecies variability; additional reduction not warranted because the effect is the result of direct contact

All AEGL-1 Values: 0.05 = ppm

AEGL-2 for Methyl Vinyl Ketone		
Classification	**ppm**	**mg/m³**
10 min.	0.66	1.9
30 min.	0.46	1.3
1 hr	0.36	1.1
4 hr	0.23	0.67
8hr	0.15	0.44

10 Min., 30 Min., 1 Hour, 4-Hour AEGL- 2

Toxicity End point: Lung lesions (Morgan et al. 2000)

POD: NOAEL = 2 ppm

Time Scaling: $C^n \times t = k$ (ten Berge et al.1986), where n = 3 for time periods less than 6 hours and n = 1 for time periods greater than 6 hours

UF Application: 3 for interspecies variability, 3 for intraspecies variability; additional reduction not warranted because the effect is the result of direct contact

AEGL-2: 10 Min. = 0.66 ppm
30 Min. = 0.46 ppm
1 Hr = 0.36 ppm
4 Hr = 0.23 ppm

8-Hour AEGL- 2

Toxicity End point: Lung lesions (Morgan et al. 2000)

POD: NOAEL = 2 ppm

Time Scaling: $C^n \times t = k$ (ten Berge et al.1986), where n = 3 for time periods less than 6 hours and n = 1 for time periods greater than 6 hours

UF Application: 3 for interspecies variability, 3 for intraspecies variability; additional reduction not warranted because the effect is the result of direct contact

8 Hr AEGL-2: 0.15 ppm

AEGL-3 for Methyl Vinyl Ketone		
Classification	**ppm**	**mg/m³**
10 min.	1.3	3.8
30 min.	0.92	2.7
1 hr	0.73	2.1
4 hr	0.46	1.3
8hr	0.3	0.87

10 Min., 30 Min., 1 Hour, 4-Hour AEGL- 3

Toxicity End point: Lethality (Eastman Kodak 1992; Morgan et al. 2000)

POD: LC_{10} = 4 *ppm*

Time Scaling: $C^n \times t = k$ (ten Berge et al.1986), where n = 3 for time periods less than 6 hours and n = 1 for time periods greater than 6 hours

UF Application: 3 for interspecies variability, 3 for intraspecies variability; additional reduction not warranted because the effect is the result of direct contact

AEGL-3: 10 Min. = 1.3 *ppm*
30 Min. = 0.92 ppm
1 Hr = 0.73 *ppm*
4 Hr = 0.46 ppm

8-Hour AEGL- 3

Toxicity End point: Lethality (Eastman Kodak 1992; Morgan et al. 2000)

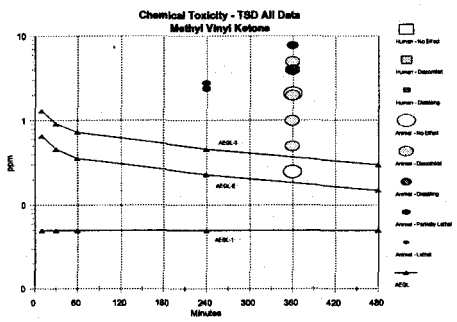
POD: LC_{10} = 4 ppm

Time Scaling: $C^n \times t = k$ (ten Berge et al.1986), where n = 3 for time periods less than 6 hours and n = 1 for time periods greater than 6 hours

UF Application: 3 for interspecies variability, 3 for intraspecies variability; additional reduction not warranted because the effect is the result of direct contact

8 Hr AEGL-3: 0.3 ppm

Summary AEGL-s for Methyl Vinyl Ketone (ppm)			
	AEGL-1	AEGL-2	AEGL-3
10 Min.	0.05	0.66	1.3
30 Min.	0.05	0.46	0.92
1 Hr	0.05	0.36	0.73
4 Hr	0.05	0.23	0.46
8 Hr	0.05	0.15	0.3



Summary AEGL-s for Methyl Vinyl Ketone (ppm)			
	AEGL-1	AEGL-2	AEGL-3
10 Min.			
30 Min.			
1 Hr			
4 Hr			
8 Hr			

Temporal Extrapolation of Data

- Concentration-exposure time relationship for many irritant and systemically-acting gasses: $c^n \times t = k$
  - 'n' ranges from 0.8 to 3.5 (ten Berge et al.,1986)

ACUTE EXPOSURE GUIDELINE LEVELS
for
MERCURY VAPOR (Hg^0)

National Advisory Committee for AEGLs Meeting 41
December 12-14, 2006

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Marquea King

Chemical Reviewers:
Alan Becker
Calvin Willhite
Jim Holler

MERCURY VAPOR (Hg^0)

Physical State:
- Liquid at ambient temperatures
- Colorless, odorless, non-irritating gas; vapor pressure 0.002 mm

Metabolism:
- 70-80% retained/absorbed into blood via pulmonary circulation
- Rapidly oxidized by red blood cells and tissues to Hg^{+2} (mercuric form)
- Hg^0 form distributed to/taken up by all tissues
- Taken up by the metal-binding proteins, the metallothioneins (protective function)
- Excreted in urine and feces

Mechanism of action:
- "High concentrations" - respiratory failure, cardiac arrest, cerebral edema
- "Lower concentrations" - cough, shortness of breath, etc.
- Binds to enzymes and proteins (-SH) resulting in non-specific cell injury or death
- Central nervous system is particularly vulnerable (neurotoxic)
  - Both acute and chronic exposures

No information on time scaling.

Human Studies

Metabolism studies
- Exposures ranged from 0.40 mg/m^3 for 15 minutes to 0.01 mg/m^3 for 7 hours
- Protocol included exercise

Monitoring studies
- Exposures of 0.40 to 2 mg/m^3; symptoms after chronic exposure

Accidental exposures
- Reconstructions based on room size calculations, supported by excretion data
- 0.75-hour exposure to 15 mg/m^3 - no reported effects in high school students
- several hours exposure to 15-16 mg/m^3 - cough, chest tightness, etc. (adults)
  - Death of an infant (susceptible population)

Animal Studies - Acute Inhalation Data

Shimojo et al. (1996)
- 9.8 mg/m^3 for 1 hour - biomarkers of exposure in lung fluid of mice

Morgan et al. (2001)
- 8.0 mg/m^3 for 2 hours - no tissue lesions in pregnant rats

Livardjani et al. (1991)
- 26.7 mg/m^3 for 1 hour - mild lung lesions; no deaths of rats
- 27.0 mg/m^3 for ½ hour - severe lung lesions; death of 20/32 rats

Repeat-dose studies show effects are cumulative.
- There is a linear relationship between tissue concentrations and days of exposure.
- Metallothionein induced in most tissues

Numerous developmental and neurotoxicity studies.
- Developmental studies confounded by repeat-dose accumulation
- Neurotoxicity studies present conflicting results

Uncertainty factors

Interspecies uncertainty factor of 1
Greater uptake by rodents based on higher respiratory rate and cardiac output.

Intraspecies uncertainty factor of 3
The developing fetus and infants may be more susceptible than adults.
Developmental studies confounded by repeat exposures.
Much of the mercury taken up by dams is "trapped" by placental metallothionein.
Placenta and liver high in metallothionein; metallothionein induced by exposure.
Fetal and neonate liver have high levels of metallothionein.
Differences between infants and adults not expected to be greater than 3-fold.
Example: No alteration in neural functions in offspring exposed in utero to 4 mg/m^3 for 10 days; dams unaffected (Herr et al. 2004).

Greater uncertainty factors reduce values below metabolism and/or monitoring data.

AEGL-1:
Not recommended
An AEGL-1 is not recommended because Hg^0 has no odor or warning properties.

AEGL-2:
Limits set by human metabolism, monitoring, and accidental exposure data
Metabolism: 0.40 mg/m^3 for 15 minutes to 0.01 mg/m^3 for 7 hours
Monitoring data: up to 2 mg/m^3
Accidental exposures: ~15 mg/m^3 for <1 hour; no reported effects
Point of departure: (Morgan et al. 2001)
2 hour exposure of pregnant rats to 8.0 mg/m^3 - no lesions
Uncertainty factors:
Interspecies: 1, greater deposition in lungs (and uptake) based on (1) higher respiratory rate and cardiac output of rodents, and (2) incompatibility with monitoring data if greater uncertainty factor is used.
Intraspecies: 3, infants are more susceptible than adults, but there is no evidence from human accidental exposure data that the difference is greater than 3-fold.
Time-scaling: n = 3 and 1 for shorter and longer durations, respectively

AEGL-3:
Point of departure: (Livardjani et al. 1991)
1- hour exposure of rats to 26.7 mg/m^3 - no clinical signs, no deaths (15 days)
Extending the exposure for another hour resulted in 20/32 deaths.
Uncertainty factors:
Interspecies: 1, greater deposition in lungs (and uptake) based on (1) higher respiratory rate and cardiac output of rodents, and (2) incompatibility with repeat-dose data if greater uncertainty factor is used.
Intraspecies: 3, infants are more susceptible than adults, but there is no evidence from human accidental exposure data that the difference is greater than 3-fold.
Time-scaling: n = 3 and 1 for shorter and longer durations, respectively
The 8-hour value was set equal to the 4-hour value because the time-scaled 8-hour value of 1.1 mg/m^3 is below some occupational exposures.

Data Summary

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	Not Recommended	Not Recommended	Not Recommended	Not Recommended	Not Recommended
AEGL-2	6.1 mg/m^3	4.2 mg/m^3	3.4 mg/m^3	1.3 mg/m^3	0.7 mg/m^3
AEGL-3	16 mg/m^3	11 mg/m^3	8.9 mg/m^3	2.2 mg/m^3	2.2 mg/m^3

Mercury Vapor Questions

1. Mercury and Brain Development
   -Serious issues with brain development and chronic exposure

2. Defense of POD for AEGL-2
   Protection of fetus (neurotoxicity)
   -Dams moribund after 10 exposures to 8 mg/m^3

   Response: mercury uptake is cumulative
   Hg concentrations in tissues of dams and fetuses increased with increasing exposure days
   (Morgan et al. 2002; several other studies)
   Hg not elevated in brains of fetal guinea pigs after some exposures (Yoshida et al.1986, etc.)
   Mercury vapor converted to inorganic mercury in the brain is "trapped"
   Fetal Hg tissue levels confounded by metallothionein concentrations
   Metallothionein is induced; considered a protective mechanism

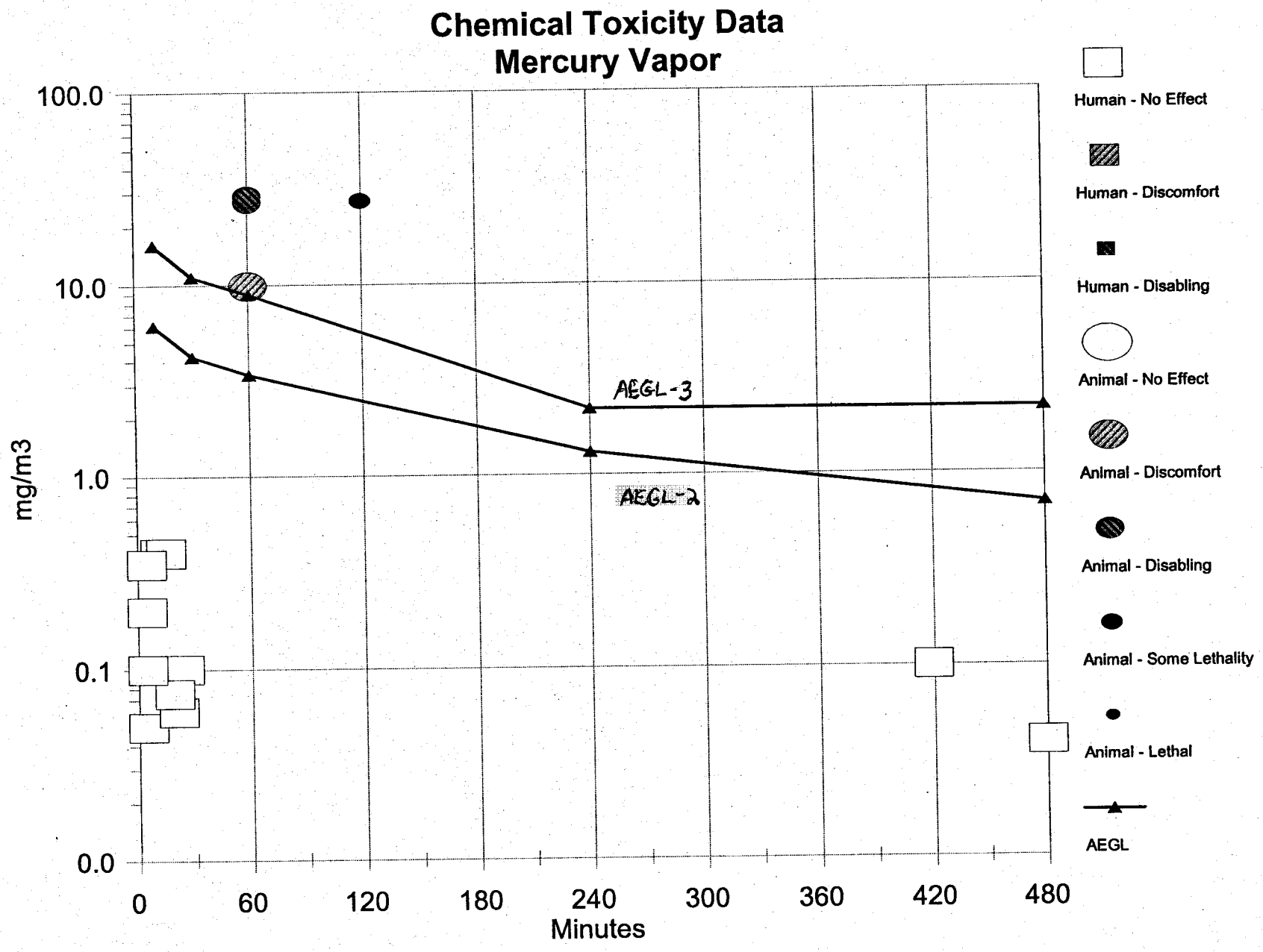
   Conflicting results on neurotoxicity of gestationally-exposed rats
   1.5 mg/m^3 1 or 3 hours for 6 days
   Effect on nerve growth factor in some areas of the brain (Söderström et al 1995)
   1.8 mg/m^3, 1 or 3 hours/day, 3-4 days: hypo-/hyperactivity at some time points;
   no effect on some tests; no effect at 11 months post-exposure (Danielsson et al. 1993)
   4 mg/m^3 concentration for 10 days during gestation
   No alteration of sensory neuronal function in adult rats exposed gestationally
   (Herr et al. 2004)

3. Editorial Additions/Corrections
   -Sources of mercury (amalgam, food), etc.
   - "Mad-Hatter" disease

Summary of Developmental Neurotoxicity Studies
Tissue concentrations/Effects/Neurotoxicity Tests

Species	Concentration	Effect	Reference
Rat	1.5 mg/m^3, 1 or 3 hours/day, GD 6-11 or 13-18	No clinical signs; no developmental effects; nerve growth factor increased or decreased in different areas of the brain	Söderstrom et al. 1995
Rat	1.8 mg/m^3,1 or 3 hr/day, GD 11-14 or 17-20	No clinical signs and no effect on maturation endpoints of offspring. Neurotoxicity tests indicated reduced ability to adapt; hypoactivity at 3 months and hyperactivity at 14 months, but no effect 11 months later; no effect on swim maze test	Danielsson et al. 1993
Rat	1.8 mg/m^3, 1.5 hours/day, GD 14-19	No effect on clinical signs or developmental markers of offspring; hyperactivity in spontaneous motor activity and latencies in some maze tests	Fredriksson et al. 1996
Rat	1, 2, 4, or 8 mg/m3, 2 hours/day, GD 6-15	Concentration-related increases in fetal tissue concentrations after 5 and 10 days	Morgan et al. 2002
Rat	4 mg/m^3, 2 hours/day, GD 6-15	No effect on responses of peripheral nerves, somatosensory (cortical and cerebellar), auditory or visual modalities when tested on PNDs 140-168	Herr et al. 2004
Guinea pig	0.2-0.3 mg/m^3 2 hours/day 4-11 days	After 4 days of exposure, mercury in brain of offspring not increased over control levels (increased in lung, liver, and kidneys)[a]; Hg bound to metallothionein in fetal liver	Yoshida et al. 1986; Yoshida et al. 1987
Guinea pig	8-10 mg/m^3 2 hours	Hg in brain of fetuses of exposed dams not elevated 2 hours after exposure; brain concentrations elevated on days 5 and 10 after exposure due to redistribution	Yoshida et al. 1990

GD = gestation day.
PND = post natal day.
[a] Blood from the placenta passes through the umbilical veins and enters fetal circulation by way of the ductus venosus. Most blood (at least half) then passes through the fetal liver.


Chemical Toxicity Data
Mercury Vapor
100.0
10.0
1.0
0.1
0.0
mg/m3
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

ACUTE EXPOSURE GUIDELINE LEVELS
PROPARGYL ALCOHOL

NAC/AEGL-41

December, 2006
Alexandria, VA

ORNL Staff Scientist:
Robert Young

Chemical Manager:
George Cushmac

Chemical Reviewers:
Lynn Beasley
James Holler

PROPARGYL ALCOHOL - HUMAN EXPOSURE DATA

- **No human exposure data**

PROPARGYL ALCOHOL - ANIMAL DATA
Lethality

Lethality of Inhaled Propargyl Alcohol in Laboratory Species.				
Species	Exposure Duration (minutes)	Exposure Concentration (ppm)	Lethality	Reference
Rat (m) Rat (f)	60 60	1200 1040	LC_{50}[a] LC_{50}[a]	Vernot et al., 1977
Rat	60	1490	10/10	Hazelton Laboratories America, Inc., 1989
Rat	120	850	LC_{50}[b]	Kennedy and Graepel, 1991
Mouse	60	3000	3/10	BASF, 1965
Mouse	120	220 655 875 1500	1/20 1/20 10/20 20/20	Stasenkova and Kochetkova, 1996.
Cat	60	1300	1/2	BASF, 1965

[a] 5 rats/gender/exposure group
[b] no experimental details

PROPARGYL ALCOHOL - ANIMAL DATA
Non Lethal

- Dow Chemical Co. (1964)
  - 90-day repeat exposure study in ♂ and ♀ rats; 100 ppm, 7 hrs/day, 5 days/wk
  - eye irritation and lethargy following 1st exposure; accommodation with additional exposures
  - no deaths; evidence of pulmonary and renal involvement, mild to severe hepatotoxicity

- BASF (1992a)
  - 2-week preliminary study (OECD No. 412) in ♂ and ♀ rats; 0, 9.8, 50.4, 199 ppm, 6 hrs/day, 5 days/wk
  - no clinical signs in controls, 9.8 or 50.4 ppm groups
  - decreased b.w. gain and metaplasia of nasal mucosa at 50 ppm; increased rel. liver wt (♂ and ♀)
  - 200 ppm: 1 death, histopathological changes in nasal mucosa and liver; significantly increased rel. liver wt (♂ and ♀), increased rel. kidney wt. (♀)

PROPARGYL ALCOHOL - ANIMAL DATA
Non Lethal

- BASF (1992b)
  - GLP 90-day repeat exposure study in ♂ and ♀ rats; 0, 1.1, 5.1 or 24.6 ppm, 6 hrs/day, 5days/wk
  - no histopathological findings or clinical signs of toxicity at any exposures
  - increase in absolute and rel. kidney wt.; decrease in serum cholinesterase activity
  - NOAEL = 5.1 ppm; LOAEL = 24.6 ppm

- BASF (1965)
  - Guinea pigs: epithelial irritation following exposure to 1300 ppm for 1 hr
  - Rabbits: mild irritation following exposure to 1300 ppm for 1 hr (14-day observation period)

PROPARGYL ALCOHOL - ANIMAL DATA

NTP (unpubl.): 13-week study with ♂ and ♀ rats; 0, 4, 8, 16, 32 or 64 ppm

Effects in male and female Fischer rats following 13-week whole-body inhalation exposure to propargyl alcohol vapor.						
Effect	**0 ppm**	**4 ppm**	**8 ppm**	**16 ppm**	**32 ppm**	**64 ppm**
	Males					
olfactory epith. necrosis	0/10	0/10	0/10	0/10	2/10	5/10
resp. epithelium hyperplasia sq. metaplasia	2/10 0/10	6/10 0/10	2/10 0/10	4/10 0/10	8/10 0/10	10/10 3/10
incr. kidney/b.w.	-	-	-	-	-	p<0.01
incr. liver wt.	-	-	-	-	-	p<0.01
incr. liver/b.w.	-	-	-	-	p<0.01	p<0.01
	Females					
olfactory epith. necrosis	0/10	0/10	0/10	0/10	3/10	5/10
resp. epithelium hyperplasia sq. metaplasia necrosis	0/10 0/10 0/10	2/10 0/10 0/10	2/10 0/10 0/10	2/10 0/10 0/10	10/10 0/10 0/10	10/10 8/10 2/10
incr. kidney/b.w	-	-	-	-	-	p<0.01
incr. liver/b.w.	-	-	-	-	-	p<0.01

PROPARGYL ALCOHOL - ANIMAL DATA

NTP (unpubl.): 13-week study with ♂ and ♀ mice; 0, 4, 8, 16, 32 or 64 ppm

Effects in male and female B6C3F1 mice following 13-week whole-body inhalation exposure to propargyl alcohol vapor.						
Effect	0 ppm	4 ppm	8 ppm	16 ppm	32 ppm	64 ppm
	Males					
nasal inflammation	0/10	0/10	0/10	0/10	0/10	6/10
olfactory epith.						
necrosis	0/10	0/10	1/10	0/10	1/10	0/10
atrophy	0/10	0/10	0/10	0/10	8/10	10/10
hyaline degen.	0/10	0/10	0/10	0/10	3/10	9/10
hyperplasia	0/10	0/10	0/10	3/10	9/10	9/10
resp. epithelium[a] sq. metaplasia	0/10	0/10	0/10	0/10	5/10	10/10
incr. kidney/b.w.	-	-	p<0.05	p<0.01	p<0.01	p<0.01
incr. liver/b.w.	-	-	-	-	p<0.01	p<010
	Females					
olfactory epith.						
necrosis	0/10	0/10	0/10	9/10	4/10	0/10
atrophy	0/10	0/10	0/10	0/10	7/10	10/10
hyaline degen.	0/10	0/10	0/10	0/10	7/10	8/10
hyperplasia	0/10	0/10	0/10	0/10	8/10	10/10
resp. epithelium[a] sq. metaplasia	0/10	0/10	0/10	1/10	7/10	10/10
incr. kidney/b.w	-	-	-	-	p<0.01	p<0.01

PROPARGYL ALCOHOL - ANIMAL DATA
Non Lethal

- Zissu (1995)
  - Groups of 10 mice exposed to 25.3 or 88 ppm, 6 hrs/day for 4, 9, or 11 days.
  - 25.3 ppm NOAEL for clinical signs and olfactory/respiratory epithelial lesions
  - 88 ppm produced notable histological changes following 4-day exposure; no increase in severity after 11 days of exposure.

PROPARGYL ALCOHOL AEGL-1

Critical effect/POD: No effects on olfactory or respiratory epithelium following exposure of male mice to 25.3 ppm for 6 hrs/day for up to 9 days (Zissu, 1995).

Support: BASF (1992) prelim. study showed ten 6-hr exposures of rats to 9.8 ppm to be without effect; 50.4 ppm produced metaplasia of olfactory mucosa

Uncertainty factors: Total uncertainty adjustment of 10.

Interspecies: UF = 3; similar exposure-response among several species

Intraspecies: UF = 3; effects appear to be the result of direct-contact irritation; POD is based upon multiple exposure regimen

Time scaling: none applied; same values for all AEGL-1 exposure durations (equivalent to the value based upon the 6-hr POD)

AEGL-1 Values for Propargyl Alcohol				
10-min	30-min	1-hr	4-hr	8-hr
2.5 ppm	2.5 ppm	2.5 ppm	2.5 ppm	2.5 ppm

PROPARGYL ALCOHOL AEGL-2

Critical effect/POD: Histological changes in respiratory tract epithelium of male mice exposed to 88 ppm, 6 hrs/day for 4 days (Zissu, 1995)

Support: BASF (1992) prelim. study showed ten 6-hr exposures of rats to 50 ppm produced metaplasia of olfactory mucosa but no clinical signs

Uncertainty factors: Total uncertainty adjustment of 10.

Interspecies: UF = 3; similar exposure-response among several species

Intraspecies: UF = 3; effects appear to be the result of direct-contact irritation; POD is based upon multiple exposure regimen

Time scaling: Default of $n = 3$ for extrapolating to durations less than that of the POD and $n = 1$ for extrapolating to durations greater than that of the POD; 10-min value equivalent to 30-min. value due to uncertainties in extrapolating from the 6-hr experimental duration.

AEGL-2 Values for Propargyl Alcohol				
10-min	30-min	1-hr	4-hr	8-hr
20 ppm	20 ppm	16 ppm	10 ppm	6.6 ppm

PROPARGYL ALCOHOL AEGL-3

Critical effect/POD: 2-hr $BMCL_{05}$ of 584 ppm for mice exposed to 220, 655, 875, or 1500 ppm (lethal response: 1/20, 1/20, 10/20, and 20/20, respectively)

Uncertainty factors: Total uncertainty adjustment of 10.

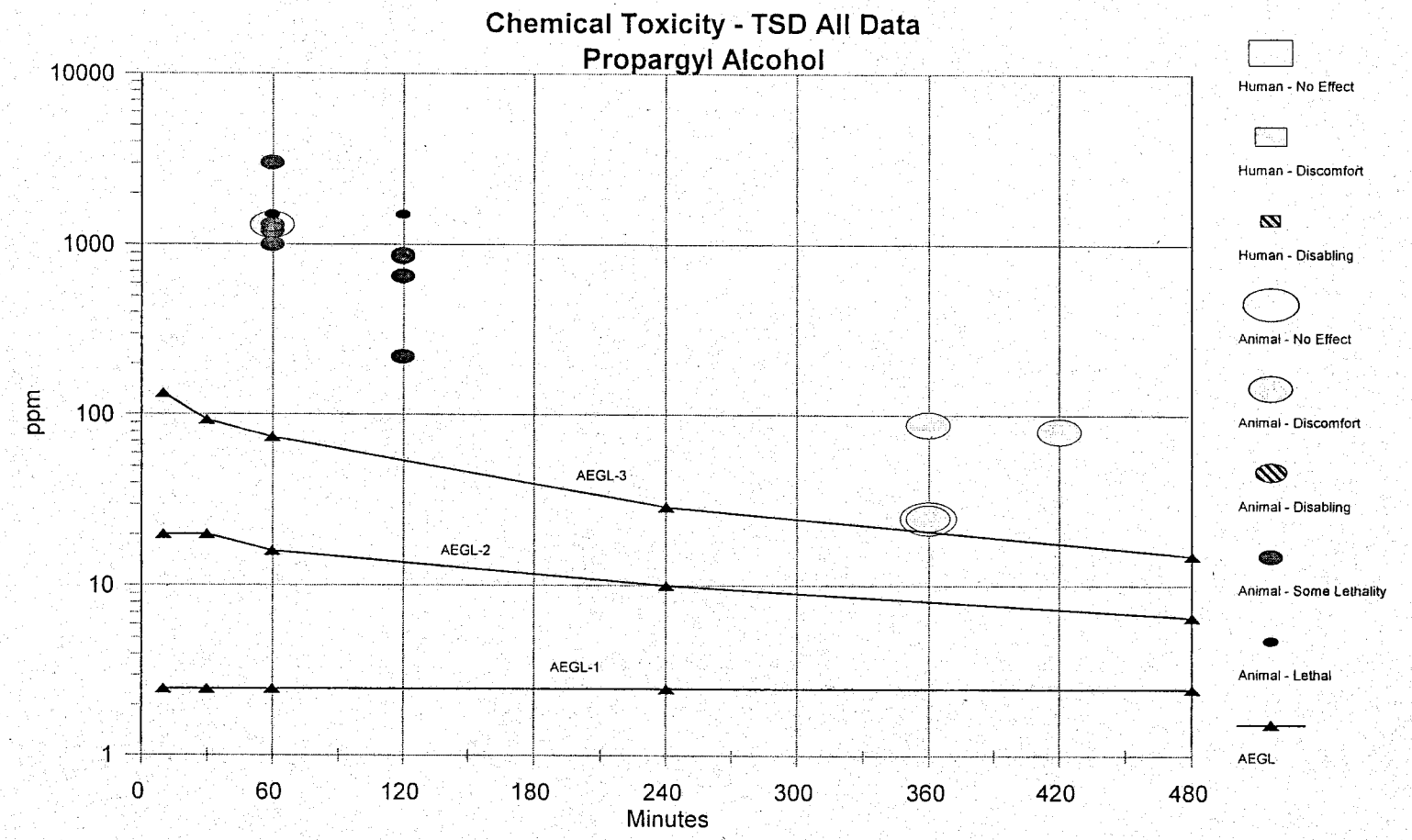
Interspecies: UF = 3; similar exposure-response among several species

Intraspecies: UF = 3; toxic response appears to involve direct-contact damage to epithelial surfaces

Time scaling: Default of $n = 3$ for extrapolating to durations less than that of the POD and $n = 1$ for extrapolating to durations greater than that of the POD

AEGL-3 Values for Propargyl Alcohol				
10-min	30-min	1-hr	4-hr	8-hr
130 ppm	93 ppm	74 ppm	29 ppm	15 ppm

Summary of AEGL Values for Propargyl Alcohol						
Classification	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1	2.5 ppm	2.5 ppm	2.5 ppm	2.5 ppm	2.5 ppm	25.3 ppm, 6-hr multiple exposure as NOAEL for histopathologic changes respiratory tract of mice (Zissu, 1995)
AEGL-2	20 ppm	20 ppm	16 ppm	10 ppm	6.6 ppm	88 ppm, 6-hr multiple exposure produced lesions in olfactory and respiratory epithelium. (Zissu, 1995)
AEGL-3	130 ppm	93 ppm	74 ppm	29 ppm	15 ppm	Estimated lethality threshold (2-hr $BMCL_{05}$ of 584 ppm) in mice. (Stasenkova and Kochetkova, 1966)


Chemical Toxicity - TSD All Data
Propargyl Alcohol
10000
1000
100
10
1
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

ATTACHMENT 19

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR SELENIUM HEXAFLUORIDE

NAC/AEGL-41
December 12-14, 2006
Alexandria, VA

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: George Rusch

Chemical Reviewers: Marc Baril and Paul Tobin

Hydrolyzes into hydrogen fluoride and selenium oxide

Effects of are consistent with severe irritation/corrosivity

One mole of selenium hexafluoride may decompose in moist atmospheres to form up to 6 moles of hydrogen fluoride

However, the limited data set suggests that selenium hexafluoride is much more than 6-times as toxic as hydrogen fluoride.

HF: 1-hour rat LC_{50} values: 966-1395 ppm (NAS, 2004)

HF: 1-hour mouse LC_{50} values: 342-501 ppm (NAS, 2004)

If the acute inhalation toxicity of selenium hexafluoride was due only to the hydrogen fluoride hydrolysis product, then approximate 1-hour LC_{50} values for selenium hexafluoride would range from 57-84 ppm for mice and 161-233 ppm for rats.

However, 2/4 mice and 2/2 rats died when exposed to only 10 ppm selenium hexafluoride for 1 hour (Kimmerle, 1960).

The increased relative toxicity of selenium hexafluoride may be due to the selenium moiety and the slow hydrolysis rate of selenium hexafluoride.

BOTTOM LINE: **AEGL values for selenium hexafluoride cannot be derived by analogy to Hydrogen fluoride**

Kimmerle, 1960

4-hour exposures followed by 3-week observation period

Rabbit (1/group)
Guinea pig (1/group)
Rats (2/group)
Mice (4/group)

1 ppm: No effects

5 ppm: Difficulty breathing and pulmonary edema:
both resolved during observation period

10, 25, 50, 100 ppm: 100% Mortality

Time to Death (min.) for Animals Exposed to Selenium Hexafluoride for 4-hours

	1 ppm	5 ppm	10 ppm	25 ppm	50 ppm	100 ppm
Rabbit	-	-	240	190	65	31
Guinea Pig	-	-	240	170	80	42
Rat-1	-	-	240	165	80	15
Rat-2	-	-	240	240	80	28
Mouse-1	-	-	240	210	85	40
Mouse-2	-	-	180	165	80	32
Mouse-3	-	-	200	145	90	30
Mouse-4	-	-	605	205	100	25

Little species variability

Time-to-death generally concentration-dependent

Kimmerle, 1960

10 ppm
1-hour exposures followed by 3-week observation period

Rabbit (1)- survived 3-week follow-up period

Guinea pig (1)- died in exposure chamber

Rats (2)- both died in exposure chamber

Mice (4)- 2 died in exposure chamber; 2 survived 3-week follow-up

The presence or absence of clinical signs was not reported.

Kimmerle, 1960

1 or 5 ppm
1-hour/day for 5 days, followed by 3-week observation period

Rabbit (1/group)
Guinea pig (1/group)
Rats (2/group)
Mice (4/group)

All survived the 3-week follow-up period

1 ppm: No treatment-related clinical signs or gross effects

5 ppm: difficulty breathing and were "in bad shape overall."

AEGL-1 VALUES: SELENIUM HEXAFLUORIDE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.067 ppm	0.067 ppm	0.053 ppm	0.033 ppm	0.017 ppm

Species: Rabbit (1/group); Guinea pig (1/group); Rat (2/group); Mouse (4/group)
Concentration: 1 ppm
Time: 4-hours
Endpoint: NOEL for Irritation
Reference: Kimmerle, 1960

Time Scaling:
$C^n \times t = k$, where $n = 3$ for the 30-minute and 1-hour time periods, and $n = 1$ for the 8-hour time period. 30-min value was adopted as the 10-min value. (Not held constant due to potential selenium moiety enzymatic effects)

Uncertainty Factors:

Interspecies = 3
Highly irritating and corrosive. Much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly between species. Limited data suggest that the guinea pig, rabbit, rat, and mouse are similarly sensitive to the acute effects of selenium hexafluoride

Intraspecies = 3
Highly irritating and corrosive, and much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among individuals.

MF = 3
Account for potential enzymatic effects of the selenium moiety and the sparse data base

AEGL-2 VALUES: SELENIUM HEXAFLUORIDE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.11 ppm	0.11 ppm	0.087 ppm	0.057 pm	0.028 ppm

Endpoint: 3-Fold reduction in AEGL-3 values
Reference: Kimmerle, 1960

Justified based on a steep concentration response curve:

Rabbit, guinea pig, rat, or mouse: 4-hour exposure

1 ppm: No effects

5 ppm: Difficulty breathing and pulmonary edema; no mortality

10 ppm: 100% mortality

AEGL-3 VALUES: SELENIUM HEXAFLUORIDE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.33 ppm	0.33 ppm	0.26 ppm	0.17 ppm	0.083 ppm

Species: Rabbit (1/group); Guinea pig (1/group); Rat (2/group); Mouse (4/group)
Concentration: 5 ppm
Time: 4-hours
Endpoint: Highest concentration causing no mortality
Reference: Kimmerle, 1960

Time Scaling:
$C^n \times t = k$, where $n = 3$ for the 30-minute and 1-hour time periods, and $n = 1$ for the 8-hour time period. 30-min value was adopted as the 10-min value.

Uncertainty Factors:

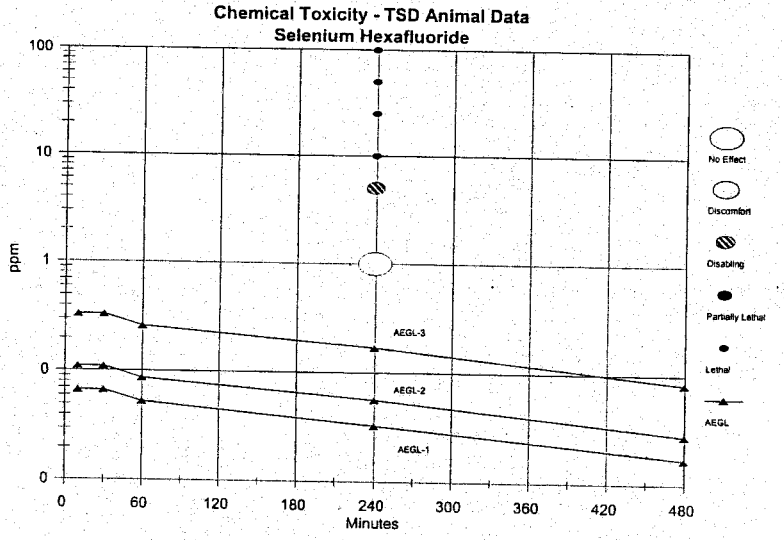
Interspecies = 3
Highly irritating and corrosive. Much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly between species. Limited data suggest that the guinea pig, rabbit, rat, and mouse are similarly sensitive to the acute effects of selenium hexafluoride

Intraspecies = 3
Highly irritating and corrosive, and much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among individuals.

MF = 3
Account for potential enzymatic effects of the selenium moiety and the sparse data base

Selenium Hexafluoride

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	0.067 ppm	0.067 ppm	0.053 ppm	0.033 ppm	0.017 ppm
AEGL-2	0.11 ppm	0.11 ppm	0.087 ppm	0.057 pm	0.028 ppm
AEGL-3	0.33 ppm	0.33 ppm	0.26 ppm	0.17 ppm	0.083 ppm
IDLH (NIOSH)	2 ppm				
REL-TWA (NIOSH)					0.05 ppm
PEL-TWA (OSHA)					0.05 ppm
TLV-TWA (ACGIH)					0.05 ppm
MAC Peak Limit (The Netherlands)					0.025 ppm



ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR THIONYL CHLORIDE, $SOCl_2$ (CAS NO. 7719-09-7)

NAC/AEGL-41
December 12-14, 2006

ORNL Staff Scientist: Jennifer Rayner

Chemical Manager: Steve Barbee

Chemical Reviewers: Bob Benson and Marc Ruijten

Thionyl Chloride-$SOCl_2$

Common Synonyms: Sulfurous oxychloride, sulfinyl chloride, sulfur chloride oxide, thionyl dichloride

Physical Characteristics:

- Liquid- colorless, pale yellow, or red with suffocating odor
- Reacts with water or water vapor to form SO_2 and HCl

Uses:

- Synthesis of drugs, vitamins, dyes
- Electrolyte in lithium batteries
- Preparation of organic chlorine compounds and acyl chlorides

HUMAN DATA

Effects at lethal concentrations

Respiratory distress
Fatal pulmonary edema

Effects at non-lethal concentrations

Burning sensation in eyes, upper airways, and chest
Feelings of suffocation
Coughing
Dyspnea
Hyperinflated lungs

ANIMAL DATA

Single Inhalation Exposure for 60 min in Rat

Kinkead and Einhaus (1984)- mixture of SO_2 and HCl

Conc. ppm	Effects
906	Eye irritation, shallow breathing and gasping
1080	Eye irritation, shallow breathing and gasping
1239	Pulmonary edema, 40% mortality
1509	Severe lung irritation, pulmonary edema, 60% mortality
1983	Severe lung irritation, pulmonary edema, 80% mortality

Pauluhn (1987)- $SOCl_2$

Conc. ppm	Effects
71	Reddened, swollen noses, dyspnea, piloerection, (all signs slight)
407	Reddened, swollen noses, dyspnea, piloerection, (all signs moderate)
769	Reddened, swollen noses, dyspnea, piloerection (all signs moderate), necrotic changes in nasal speculum, lung distention, wheezing sounds
2121	Severe dyspnea, reduced motility, cornea opacity, pulmonary edema, 80% mortality
3441	Pulmonary edema, cornea opacity, 90% mortality

Nachreiner (1993)-$SOCl_2$

Conc. ppm	Effects
196	Color change in lungs
371	Color change in lungs
593	Color change in lungs, audible respiration, 58% mortality
954	Hyperinflation of the lungs, perinasal and periocular encrustation, 58% mortality
1241	Hyperinflation of the lungs, perinasal and periocular encrustation, 83% mortality

Thionyl Chloride Mechanism of Toxicity

$SOCl_2 + H_2O = SO_2 + 2\ HCl$

SO_2- Dissolves in surface fluid, stimulates bronchoconstriction and mucus secretion in upper airways, injures cells lining airway passages causing airway narrowing and increased airflow resistance

HCl- Dissolves in nasal passages, irritates respiratory tract, breaks down epithelial barrier in alveolar zone, causes pulmonary edema

Susceptible Populations

Asthmatics- enhanced response to sulfur dioxide

AEGL-1 Values for Thionyl Chloride

10-minute	30-minute	1-hour	4-hour	8-hour
NR	NR	NR	NR	NR

Not recommended due to insufficient data.

AEGL-2 Values for Thionyl Chloride

10-minute	30-minute	1-hour	4-hour	8-hour
4.3 ppm	3.0 ppm	2.4 ppm	0.59 ppm	0.3 ppm

Key Study: Pauluhn (1987), based upon slight dyspnea and reddened and swollen noses at 71 ppm for one hour.

Toxicity endpoint: Slight dyspnea.

Time scaling: $C^n \times t = k$, temporal scaling, using n = 3 when extrapolation to shorter time points and n = 1 when extrapolating to longer time points due to lack of data to derive the value of n (NRC 2001).

Uncertainty Factors/Rationale: Total uncertainty factor: 30
Interspecies: 3- Mechanism of action (bronchoconstriction, irritation of the epithelial lining, and increased mucus production via goblet cell proliferation) would not differ across species.
Intraspecies: 10- Although data on a sensitive subpopulation are lacking for thionyl chloride, it is known that asthmatics are sensitive to sulfur dioxide.

AEGL-3 Values for Thionyl Chloride

10-minute	30-minute	1-hour	4-hour	8-hour
25 ppm	17 ppm	14 ppm	3.4 ppm	1.7 ppm

Key Studies: Pauluhn (1987) and Nachreiner (1993), based upon an estimate of a lethality threshold experimental concentration of 407 ppm. Experimental concentrations greater than 407 ppm produced mortality.

Toxicity endpoint: Threshold for lethality (407 ppm)

Time scaling: $C^n \times t = k$, temporal scaling, using $n = 3$ when extrapolation to shorter time points and $n = 1$ when extrapolating to longer time points due to lack of data to derive the value of n (NRC 2001).

Uncertainty Factors/Rationale: Total uncertainty factor: 30
Interspecies: 3- Mechanism of action (bronchoconstriction, irritation of the epithelial lining, and increased mucus production via goblet cell proliferation) would not differ across species.
Intraspecies: 10- Although data on a sensitive subpopulation are lacking for thionyl chloride, it is known that asthmatics are sensitive to sulfur dioxide.

Summary of AEGL Values for Thionyl Chloride

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Notable discomfort)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	4.3 ppm	3.0 ppm	2.4 ppm	0.59 ppm	0.30 ppm
AEGL-3 (Lethal)	25 ppm	17 ppm	14 ppm	3.4 ppm	1.7 ppm