National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-44
December 5-7, 2007

Orlando World Center Marriott
8701 World Center Drive
Orlando, FL

AGENDA

Wednesday, December 5, 2007

10:00 a.m.	*Development team meetings: Carbonyl fluoride, Chloropicrin, Methanesulfonyl chloride, Methyl iodide, N,N-dimethyl formamide
11:00	Introductory remarks and approval of NAC/AEGL-43 Highlights (George Rusch, Ernie Falke, and Paul Tobin)
11:15	Status Update: Chloropivaloyl chloride, Ethylene fluorohydrin, Thiophosgene (Cheryl Bast)
11:30	Review of Federal Register Comments: MTBE
12:30 p.m.	Lunch
1:30	Review of Diethyldichlorosilane, Dimethylchlorosilane, Ethyltrichlorosilane, and Methylvinyldichlorosilane (Ernie Falke/Cheryl Bast)
2:00	Status Update: Nerve Agent VX (Glenn Leach/Bob Young)
2:15	Revisit of N,N-Dimethylformamide (George Woodall/Claudia Troxel)
3:15	Break
3:30	Review of Carbonyl Fluoride (Iris Camacho/Jennifer Rayner)
4:30	Revisit of Tetrachloroethylene: PBPK Issues (Bob Benson/Claudia Troxel)
	Revisit of 1,1,1-Trichloroethane: PBPK Issues (Bob Benson/Sylvia Talmage)
5:30	Adjourn for the day

Thursday, December 6, 2007

8:30 a.m.	*Development team meetings: Allyl chloride, Boron tribromide, 2-Chloroethanol, Carbonyl sulfide
9:30	Review of Stibine (Marcel van Raaij/Jennifer Rayner)
10:30	Review of Boron Tribromide (Bob/Benson/Sylvia Talmage)
11:00	Break
11:15	Review of Chloropicrin (Gail Chapman/Bob Young)
12:30 p.m.	Lunch
1:30	Toxicological Data Systems (Gary Perlman)
2:00	Review of Methyl iodide (Alan Becker/Sylvia Talmage)
3:30	Break
3:45	Review of Allyl chloride (Richard Niemeier/Jennifer Rayner)
4:45	Review of Methanesulfonyl chloride (Roberta Grant/Cheryl Bast)
5:30	Adjourn for the day

Friday, December 7, 2007

8:00 a.m.	Review of Sulfuryl fluoride (Susan Ripple/Jennifer Rayner)
9:30	Break
9:45	Review of Carbonyl Sulfide (Ralph Gingell/Cheryl Bast)
10:45	Review of 2-Chloroethanol (George Rusch/Bob Young)
11:45	Administrative matters
12:00 noon	Adjourn meeting

*See page 2.

ANY INFORMATION DISCUSSED AT THE NAC/AEGL MEETINGS IS CONSIDERED PUBLIC INFORMATION.

NAC/AEGL Meeting 44: December 5-7, 2007 ATTACHMENT 2

Chemical: ATTENDANCE 12/5/07 **CAS Reg. No.:**

Jennifer Rayner
Sylvia Talmage
ORNL Cheryl Bast
Robert Young

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

Chemical Manager:					Staff Scientist:				
NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	✓				John Hinz	✓			
Marc Baril	Absent				Jim Holler	✓			
Lynn Beasley	✓				Glenn Leach	✓			
Alan Becker	✓				Richard Niemeier	✓			
Robert Benson	✓				Susan Ripple	✓			
Edward Bernas	✓				George Rusch, Chair	✓			
Gail Chapman	✓				Martha Steele	✓			
George Cushmac	Absent				Daniel Sudakin	✓			
Ernest Falke	✓				Marcel vanRaaij	✓			
David Freshwater	✓				Calvin Willhite	✓			
Ralph Gingell	✓				George Woodall	✓			
Roberta Grant	✓				Alan Woolf	✓			
Dieter Heinz	✓				Luis Camado	✓			
Paul Tolin	✓				TISSOT Sylvie TALLY	✓ France			
Drew Lyke					PASS/ FAIL				

Mary Ann Latko AIHA (observer)

MARCY BANTON LYONDELL Michael Acuff - FLORIDA FRUIT & VEGETABLE ASSN

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:** 12/5/2007

ATTACHMENT 3

MTBE

NAC/AEGL-44
December 5, 2007
Orlando, FL

Proposed AEGLs for MTBE

	10 min ppm	30 min ppm	1 hr ppm	4 hr ppm	8 hr ppm	Endpoint (Reference)
AEGL-1	50	50	50	50	50	NOAEL in humans; 50 ppm for 2 hr; UF = 1 (Nihlén et al., 1998)
AEGL-2	1400	800	570	400	400	Ataxia, piloerection, and decreased hindlimb strength; 4,000 ppm for 6 hr; UF = 10, n = 2 (Daughtrey et al., 1997) ADD: no loss of consciousness; NOEL for inability to escape
AEGL-3	13,000* *>10% LEL **>50% LEL (# to footnote)	7,500 7,500* *>10% LEL	5,300 5,300*	2,700 2,700*	1,900 1,900*	$BMCL_{05}$ = 26,690 for 4 hr; UF = 10; n = 2 (Arco, 1978) FIX: LEL = 16,000 ppm

Public Comments on MTBE

- One comment received

- "The AEGL values proposed for MTBE are appropriate and protective for the specified time exposure and endpoints"

Public Comments on MTBE

- Comment requested that the TSD include updated information on human exposure and epidemiological studies
- Comment requested clarification of some aspects of the genotoxicity and carcinogenicity data
- Comment requested clarification of some aspects of the metabolism section and inclusion of the metabolic scheme for MTBE
- Comment requested clarification of Appendix D on pharmacokinetic modeling

Disposition of Comments

- Changes will be made to the TSD to the extent feasible, keeping in mind that the COT often asks us to remove extraneous detail
- As none of the requested changes will change the AEGL values, recommend that MTBE be raised to interim status

RESPONSE TO COT'S COMMENTS FOR DIMETHYLFORMAMIDE

Claudia Troxel
George Woodall
Calvin Willhite
Glenn Leach
Bob Benson

1

COT Comments on Interim 1: 7/2005:

- (DMF) is returning for consideration of developmental endpoints. Although COT did not specifically recommend the use of developmental endpoints, a review of the TSD before the DMF discussion revealed that we never discussed the potential developmental effects resulting from DMF exposure. COT therefore verbally recommended that the TSD return to NAC to address this issue.

- The written COT Comments did express concern over the development of the AEGL-2 in the Interim 1 TSD, which are the AEGL-3 values divided by 2. Although AEGL-3 levels are generally divided by 3 in cases such as these, a 2 was used for this derivation because the AEGL-3 values are highly protective based on data in monkeys. No effects (clinical signs, b.w., hematology, clinical chemistry, urinalysis, semen, or gross necropsy) were observed in monkeys exposed to 500 ppm for 6 hours/day, 5 days/week for 2 or 13 weeks (Hurtt et al., 1991; 1992).

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Summary of Interim 1: 7/2005 AEGL values for DMF					
Level	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	160	110	90	55	38
AEGL-3	320	220	180	110	76

AEGL-1: Not recommended; no data consistent with AEGL-1

AEGL-2: AEGL-3 ÷ 2 (because NAC felt the AEGL-3 values were protective base on monkey data)

AEGL-3: No mortality in rats exposed to 3700 ppm for 3 hours (Macdonald, 1982). Possible that proposed values are conservative. No effects observed in monkeys exposed to 500 ppm for 6 h/d, 5 d/wk for 2 or 13 wk.

3

➢Total UF of 30

3 for interspecies: appears there are limited species differences regarding toxic response to DMF. Similar hepatic effects in humans as in animals. The mechanism of hepatotoxicity related to metabolism by CYP2E1 to reactive metabolite. Study demonstrates similar K_m and V_{max} between rat and human liver

10 for intraspecies:

- CYP2E1 can be induced by alcohol, diabetes, and obesity
- Prior consumption of alcohol can exacerbate DMF toxicity
- Detoxification is partly dependent of glutathione conjugation; if GSH depleted, increased exposure to reactive metabolite
- DMF exposure can result in hepatotoxicity, so those with compromised liver function at increased risk

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Time scaling:

Default value of n should be used in the temporal scaling of AEGL values across time. However, if one applies the default value of n = 1 for extrapolating from shorter to longer exposure periods, one obtains a 4-h value of 93 ppm and an 8-h value of 46 ppm. Using a default value results in AEGL values that are inconsistent with the available human data. Humans were exposed by inhalation to 87 ppm DMF for 4 h in a study designed to assess the metabolism of DMF (Kimmerle and Eben, 1975b). Although the study was not designed to assess the toxic effects resulting from DMF exposure, whatever effects may have been encountered were clearly not severe enough to be classified as AEGL-3 endpoints. Therefore, in the absence of any further data, an n of 2 was selected as a reasonable compromise between the possible values for n as reported by ten Berge et al. (1986).

AEGL-3 values are therefore derived using an n=3 for extrapolation to 10- and 30-min and 1- h duration, and an n=2 for extrapolation to 4- and 8-h duration.

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Possible Alternative AEGL Derivations:

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AEGL-2

- Stay with AEGL-3 ÷ 2

  OR

- Use a rabbit developmental study

  Groups of 15 pregnant rabbits exposed to 0, 50, 150, or 450 ppm DMF for 6 h/d on GD 7-19 (Hellwig et al., 1991).

  Maternal toxicity evident at 150 and 450 ppm as:
  - ↓ bw gain or weight loss over GD 7-19 and GD 0-29

  Developmental toxicity evident at 450 ppm as:
  - ↑ in external malformations and total malformations (external, soft tissue, and skeletal combined);
  - ↓ in fetal weight (86% of controls);
  - ↑ in litter incidence of skeletal variations (splitting of skull bones; fused, irregular shaped, and bipartite sternebrae).

  No developmental effects were observed at 150 ppm.

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- AEGL-2 POD: 150 ppm for 6 h to protect against irreversible developmental effects (malformations) (Hellwig et al., 1991).
- Total UF of 3:

  Interspecies UF of 1: primates are not as sensitive as rodents (rodents have ↑ DMF metabolism)
  - Monkeys inhaled 500 ppm DMF for 6 h/d, 5 d/wk, for up to 13 wks with no measurable adverse effects.
  - In rodents, subchronic exposure produced hepatic effects (from ↑ serum enzymes to hepatic degeneration and necrosis) in rats at 200, 300, and 400 ppm, and in mice at 100, 150, and 200 ppm.
  - From these exposure data, it would be expected that humans are less sensitive than rodents.
  - Mechanism of hepatotoxicity is related to metabolism of DMF to reactive intermediate; and it is expected that fetal toxicity will result from exposure to parent DMF or metabolites. Based on an oral study in pregnant rats, it is concluded that the fetus and/or placenta will not provide any additional protection or enhancement of DMF toxicity, since their exposure to DMF and metabolites depends on metabolism by the dam.

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- Total UF of 3; con't

  Intraspecies UF of 3:

10 would normally be applied because: 1) CYP2E1 can be induced by alcohol, diabetes, and obesity 2) Prior consumption of alcohol can exacerbate DMF toxicity; occupational exposure data suggest synergistic effect 3) detoxification partly dependent on glutathione conjugation, so GSH depletion can result in ↑ exposure to reactive metabolite; 4) DMF exposure can result in hepatotoxicity, so those with compromised liver function at ↑ risk

However, a total UF of 10 produces AEGL-2 values internally inconsistent: Values for 10-m, 30-m, 1-, 4-, and 8-h AEGL-2 using default time-scaling would be 49, 34, 27, 17, and 11 ppm, resp.

Monkeys exposed to 500 ppm for 6 h/d, 5 d/wk for up to 13 wks had no effects; using the 500 ppm for 6 h as POD; UF of 10; default time scaling, values are 110, 110, 91, 57, and 38 ppm, resp.

Therefore, the intraspecies UF is reduced to 3, resulting in a total UF of 3. Default time scaling is applied, and the 30-m AEGL-2 value was set equal to the 10-m value because of the uncertainty in extrapolating from a 6-h exposure duration to a 10-m duration.

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SUMMARY AEGL-2:

- AEGL-2 POD: 150 ppm for 6 h in rabbits to protect against irreversible effects (malformations) (Hellwig et al., 1991).
- Total UF of 3:
  - ⇨ Interspecies UF of 1: expected that humans are less sensitive than rodents
  - ⇨ Intraspecies UF of 3: use of default value of 10 produces values internally inconsistent
- Time scaling: Default using n=3,1
  - ❖ Note: These values are identical to those produced using the monkey data (exposure to 500 ppm for 6 hours)

Alternative AEGL-2 Values					
10-min	30-min	1-hr	4-hr	8-hr	UF
110	**110**	**91**	**57**	**38**	**3**

10

AEGL-3

- Leave as is, with n values = 3,2 and UF of 30

  OR

- Reduce UF to 10 and use the default time scaling values of n=3, 1

  Key study: groups of 3 male and 3 female rats were exposed to 3700 ppm DMF for 1 or 3 hours with no mortality, while exposure for 7 hours resulted in 83% mortality (Macdonald, 1982). Clinical signs limited to excess grooming in all exposure groups, with lethargy also noted in rats exposed for 7 hours.

  POD: no mortality in rats exposed to 3700 ppm for 3 h

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- Total UF of 10:

  Interspecies UF=1: primates not as sensitive as rodents (rodents have ↑ DMF metabolism)

  Monkeys inhaled 500 ppm DMF for 6 h/d, 5 d/wk, for up to 13 wks with no measurable adverse effects.

  In rodents, subchronic exposure produced hepatic effects (from ↑ serum enzymes to hepatic degeneration and necrosis) in rats at 200, 300, and 400 ppm, and in mice at 100, 150, and 200 ppm.

  From these exposure data, it would be expected that humans are less sensitive than rodents.

  Intraspecies UF= 10:

  1) CYP2E1 can be induced by alcohol, diabetes, and obesity
  2) Prior consumption of alcohol can exacerbate DMF toxicity; occupational exposure data suggest synergistic effect
  3) Detoxification partly dependent on glutathione conjugation, so GSH depletion can result in ↑ exposure to reactive metabolite;
  4) DMF exposure can result in hepatotoxicity, so those with compromised liver function at ↑ risk

- Time scaling: default n=3,1

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SUMMARY AEGL-3:

- AEGL-3 POD: 3700 ppm for 3 h is no effect level for mortality in rats (Macdonald, 1982)
- Total UF of 10:
  - ⇨Interspecies UF of 1: expected that humans are less sensitive than laboratory animals
  - ⇨Intraspecies UF of 10
- Time scaling: Default using n=3,1

Alternative AEGL-3 Values					
10-min	30-min	1-hr	4-hr	8-hr	UF
970	**670**	**530**	**280**	**140**	**10**

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Summary						
Level	**10 m**	**30 m**	**1 h**	**4 h**	**8 h**	**UF**
New Alternative AEGL Values						
1	NR	NR	NR	NR	NR	
2	110	110	91	57	38	3
3	970	670	530	280	140	10
Interim 1 Values (7/2005)						
1	NR	NR	NR	NR	NR	
2	160	110	90	55	38	AEGL3÷2
3	320	220	180	110	76	30

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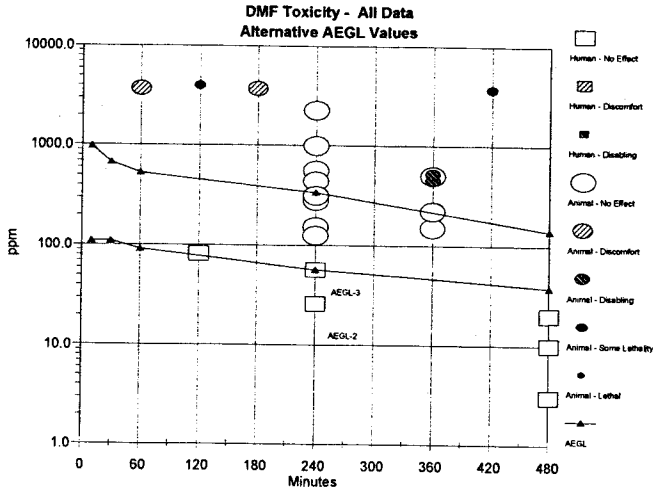
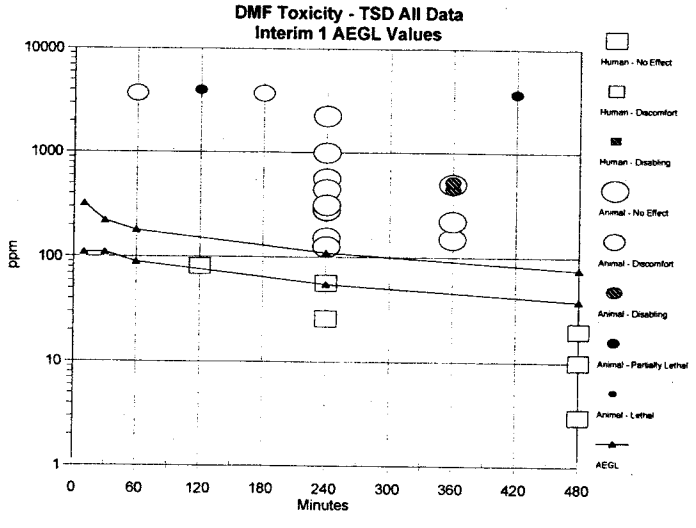
Category Plot: Alternative AEGL Values

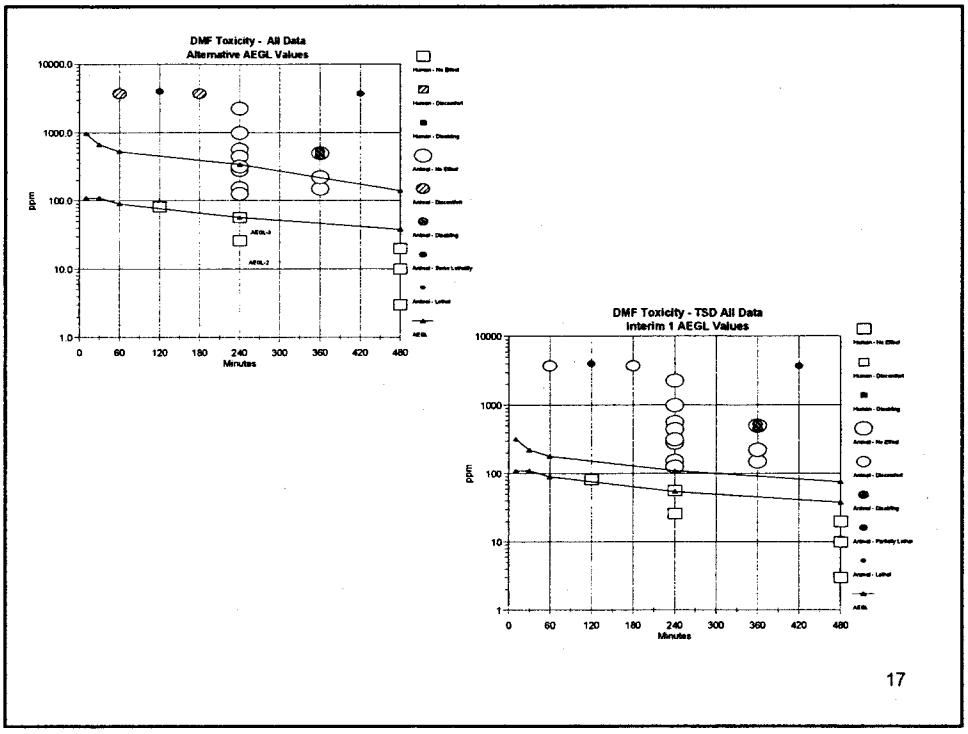


15

Category Plot: Interim 1 AEGL Values



16


DMF Toxicity - All Data
Alternative AEGL Values
10000.0
1000.0
100.0
10.0
1.0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-1
AEGL-2
DMF Toxicity - TSD All Data
Interim 1 AEGL Values
10000
1000
100
10
1
ppm
0
60
120
180
240
300
360
420
480
Minutes
17

ATTACHMENT 5

AEGL VX: New Data Revisit

Recent studies on the nerve agent VX have become available. These data were evaluated and analyzed with respect to the previously published (NRC, 2003) AEGL values for VX. The results of this analysis are summarized below and in the accompanying tables.

VX AEGL-1:
AEGL-1 values developed using recent data of Benton et al. (2006a) would eliminate MF and use a VX-specific "*n*" of 1.65 (for miosis) resulting in slightly greater (8-hr value is slightly lower) but operationally equivalent values. Published values (NRC, 2003) are protective and validated by new data.

VX AEGL-2:
New data (Benton et al., 2006a; Genovese et al., 2007) would result in slightly increased AEGL-2 values (operationally equivalent) due to interspecies UF of 3 vs 1 and time-scaling "*n*" value of 1.65 vs 2. Both the published (NRC, 2003) and new values address peripheral neuromuscular effects as well as miosis. Published values are more protective and validated by new data.

VX AEGL-3:
New data from Benton et al. (2006b) would justify elimination of the MF for a sparse database. Time scaling "*n*" of 0.92 vs 2 results in slightly lower values for the 4-hr and 8-hr durations but slightly higher values for the durations of 1 hour and less. However, the "*n*" of 0.92 may be a function of percutaneous absorption. The published values are sufficiently protective.

Overall, the new data support the approach/rationale used to develop the AEGL values for VX as published by the National Research Council.

AEGL-1 Values for VX (mg/m^3)

	10-min	30-min	1-hr	4-hr	8-hr	POD	Inter UF	Intra UF	MF	n	Reference
Published	0.00057	0.00033	0.00017	0.00010	0.000071	Relative potency to GB (GB POD was EC_{50} for miosis in adult female rats)	1: miosis response to nerve agent vapor is similar across species	10: Some individuals possess abnormally low levels of blood cholinesterase and carboxyesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents	3: sparse VX database	2: GB lethality & miosis data)	NRC, 2003
New data	0.00070	0.00036	0.00020	0.00010	0.000066	$EC_{50}$for miosis in adult female rats: 10-min: $0.007 mg/m^3$ 1-hr: $0.002 mg/m^3$ 4-hr: $0.001 mg/m^3$	1: as above	10: as above	1: well-conducted study with VX	1.65: VX miosis data	Benton et al., 2006a

AEGL-2 Values for VX (mg/m^3)											
	10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**	**POD**	**Inter UF**	**Intra UF**	**MF**	**n**	**Key Reference**
Published	0.0072	0.0042	0.0029	0.0015	0.0010	Relative potency to GB (GB POD was miosis, dyspnea, RBC-ChE inhibition, SFEMG changes in human volunteers) 0.5 mg/m^3 for 30-min	1: human data	10: Some individuals possess abnormally low levels of blood cholinesterase and carboxyesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents	3: sparse VX database	2: GB lethality & miosis data)	NRC, 2003
New data	0.015	0.0076	0.0050	0.0022	0.0014	Pinpoint pupils, NOEL for ataxia in rats: 0.15 mg/m^3 for 1-hr	3: even though miosis is similar across species and argues for a UF of 1, a 3 is applied to protect against ataxia. Also, allows for better separation from AEGL-3 values and more protective AEGL-2 values.	10: as above	1: well-conducted study with VX	1.65: VX miosis data (Benton et al., 2006a)	Genovese et al., 2007

AEGL-3 Values for VX (mg/m^3)											
	10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**	**POD**	**Inter UF**	**Intra UF**	**MF**	**n**	**Key Reference**
Published	0.029	0.015	0.010	0.0052	0.0038	Relative potency to GB (GB POD was female rat LC_{01} values between 10-min and 6-hr.	3: mechanism of toxicity is same in rodents and humans	10: Some individuals possess abnormally low levels of blood cholinesterase and carboxyesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents	3: sparse VX database	2: GB lethality data)	NRC, 2003
New data	0.108	0.032	0.018	0.0041	0.0019	LC_{01} in female rats: 10-min: 3.24 mg/m^3 1-hr: 0.525 mg/m^3 4-hr: 0.123 mg/m^3	3: as above	10: as above	1: well-conducted study with VX	0.92: VX rat lethality data	Benton et al., 2006b

References:

Benton, B.J., J. M. McGuire, D.R. Sommerville, et al. (2006a). "Low-level effects of VX vapor exposure on pupil size and cholinesterase levels in rats," Chapter 5, pp. 91-108 In HA Salem and SA Katz (eds) *Inhalation toxicology, 2nd Edition*, CRC Press, Taylor and Francis, Boca Raton, FL.

Benton, B.J., J. M. McGuire, D.R. Sommerville, et al. (2006b). "Effects of whole-body VX vapor exposure on lethality in rats," *Inhalation Toxicology* 18: 1091-1099.

Genovese, R.F., B.J. Benton, E. H. Lee, et al (2007). "Behavior and biochemical evaluation of sub-lethal inhalation exposure to VX in rats." Toxicology 232 (104): 109-118.

NRC (National Research Council) (2003). Acute Exposure Guideline Levels for Selected Airborne Chemicals, vol 3. "Nerve agents GA, GB, GD, GF and VX Acute Exposure Guideline Levels. Chapter 1, pp. 15-300. The National Academies Press, Washington, DC.

ATTACHMENT 6

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
SELECTED CHLOROSILANES

NAC/AEGL-44
December 5-7, 2007
Orlando, FL

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Ernest Falke

Chemical Reviewers: George Cushmac and Paul Tobin

HCl AEGL document: Published in Volume 4.

NAC has previously derived AEGL values for five chlorosilanes:

Methyltrichlorosilane:	COT-Approved
Dimethyldichlorosilane:	COT-Approved
Trimethylchlorosilane:	COT-Approved
(FL District 3, #7 on EHS list)	
Methyldichlorosilane:	Interim: FR-10
Methylchlorosilane:	Interim: FR-10

For chlorosilanes where chemical-specific data existed, chemical-specific experiment used for AEGL value derivation.

For future chlorosilanes (the ones being discussed at this meeting and those discussed at NAC-43), the COT subcommittee suggested that values simply be derived by analogy to HCl

However, we should not go back and re-do the five previous chlorosilanes. (Values almost identical using either method)

Previously considered chlorosilanes may be included in "Selected Chlorosilanes" TSD.

All will be published in the same volume.

At NAC-43 AEGL values were derived for 17 Chlorosilanes:

Allyl trichlorosilane (CAS Reg. No. 107-37-9)

Amyl trichlorosilane (CAS Reg. No. 107-72-2)

Butyl trichlorosilane (CAS Reg. No. 7521-80-4)

Chloromethyl trichlorosilane (CAS Reg. No. 1558-25-4)

Dichlorosilane (CAS Reg. No. 4109-96-5)

Diphenyl dichlorosilane (CAS Reg. No. 80-10-4)

Dodecyl trichlorosilane (CAS Reg. No. 4484-72-4)

Hexyl trichlorosilane (CAS Reg. No. 928-65-4)

Nonyl trichlorosilane (CAS Reg. No. 5283-67-0)

Octadecyl trichlorosilane (CAS Reg. No. 112-04-9)

Octyl trichlorosilane (CAS Reg. No. 5283-66-9)

Propyl trichlorosilane (CAS Reg. No. 141-57-1)

Tetrachlorosilane (Silicon Tetrachloride) (CAS Reg. No. 10026-04-7)

Trichloro(dichlorophenyl)silane (CAS Reg. No. 27137-85-5)

Trichlorophenylsilane (CAS Reg. No. 98-13-5)

Trichlorosilane (CAS Reg. No. 10025-78-2)

Vinyl trichlorosilane (CAS Reg. No. 75-94-5)

Revisions to the NAC-43 TSD Include:

Statement added to Executive Summary and introduction saying that only HCl is released into the air.

Paragraph added to the introduction on reported chlorosilane releases (amount, reason, etc).

Footnotes have been added to tables showing the formula to convert ppm to mg/m^3.

Done so that separate tables would not be required for each of the 21 chlorosilanes at several places in the document.

A footnote has also been added to suggest that for mono-, di-, and tri- chlorosilanes not discussed in the TSD, use of an HCl equivalents approach may be considered for AEGL- value derivation.

AEGL Values for Four "New" Chlorosilanes.

Ethyl trichlorosilane (FL District 3, #6 on EHS list)

Diethyl dichlorosilane

Dimethylchlorosilane

Methylvinyl dichlorosilane*

Alkylchlorosilanes react rapidly with water to produce hydrogen chloride gas and a silanol, which condenses spontaneously to form a highly cross-linked polymeric gel.

One-hour LC_{50} studies of ten chlorosilanes and hydrogen chloride (Jean et al., 2006)

GLP Protocol:

Five F344 rats/sex/concentration; 14-day follow-up

Clinical signs in chlorosilane studies were consistent with hydrogen chloride exposure:

Lacrimation, salivation, dried material around or on the eyes and/or nose, green staining around the nose and mouth, and perineal urine staining.

Labored breathing, rales, hypoactivity, closed or partially closed eyes, prostration, corneal opacity or opaqueness, and swollen and/or necrotic paws

Hemorrhage, congestion and/or consolidation of the lungs, ectasia of the lungs, alopecia around the eyes and discoloration of hair were observed at necropsy.

Measured and predicted (based on molar HCl equivalents) 1-hr LC_{50} values for chlorosilanes

Compound	Measured LC_{50} (ppm)	Predicted LC_{50} (ppm)	Predicted Ratio of LC_{50} values	Measured Ratio of LC_{50} values
Hydrogen chloride	3627 ppm			
Tetrachlorosilane*	1312 ppm	3627 ÷ 4 = 907	4 : 1	2.8 : 1
Propyl trichlorosilane*	1352 ppm	3627 ÷ 3 = 1209	3 : 1	2.7 : 1
Vinyl trichlorosilane*	1611 ppm	3627 ÷ 3 = 1209	3 : 1	2.3 : 1
Methyl trichlorosilane**	1365 ppm	3627 ÷ 3 = 1209	3 : 1	2.7 : 1
Ethyl trichlorosilane*	1257 ppm	3627 ÷ 3 = 1209	3 : 1	2.9 : 1
Methylvinyl Dichlorosilane*	2021 ppm	3627 ÷ 2 = 1814	2 : 1	1.8 : 1
Dimethyldichlorosilane**	2092 ppm	3627 ÷ 2 = 1814	2 : 1	1.7 : 1
Methyl dichlorosilane**	1785 ppm	3627 ÷ 2 = 1814	2 : 1	2: 1
Trimethyl chlorosilane**	4257 ppm	3627 ÷ 1 = 3627	1 : 1	0.9 : 1
Dimethyl chlorosilane*	4478 ppm	3627 ÷ 1 = 3627	1 : 1	0.8 : 1

*Chlorosilane in TSD for Value Derivation
**AEGL Values Proposed or Interim

CONCLUSIONS (Jean et al., 2006)

Predicted 1-hr LC_{50} values for the mono-, di-, and tri-chlorosilanes are comparable to the experimentally-derived 1-hr LC_{50} values

log* log regression analysis of chlorosilane LC_{50} values vs. number of chlorine groups yielded an r^2 value of 0.97

The within-class LC_{50} values were not significantly influenced by the number or type of hydrocarbon R-group(s) present (methyl, ethyl, propyl, vinyl).

Data suggest that the acute toxicity of the chlorosilanes is similar to or slightly less than what would be expected based on hydrogen chloride molar equivalents

Cases where the predicted value is less may be attributed to incomplete hydrolysis in the test atmosphere

However, continued hydrolysis and generation of hydrogen chloride would be expected for any remaining chlorosilane when in contact with moist tissues (mucous membranes, lung)

Dichlorosilane (Nakashima et al., 1996):

4-Hr Mouse LC_{50} = 144 ppm

Hydrogen Chloride (NRC, 2004):

1-Hr Mouse LC_{50} = 1108 ppm

Scale 1-hr LC_{50} to 4-hr using $c^n \times t = k$ relationship, where n=1 based on regression analysis of combined rat and mouse LC_{50} data (1 min. to 100 min.)

Approximate 4-hr LC_{50} = 277 ppm for HCl

Predicted 4-hr LC_{50} for dichlorosilane:

277 ppm ÷ 2 = 139 ppm

Agrees with experimentally-derived value of 144 ppm

Predicted LC_{50} values for the mono-, di-, and trichlorosilanes are comparable to the experimentally-derived LC_{50} values

This information taken in conjunction with the observed clinical signs suggests:

The acute toxicity of the chlorosilanes is both quantitatively and qualitatively similar to hydrogen chloride and therefore, the hydrogen chloride hydrolysis product is responsible for the acute inhalation toxicity of chlorosilanes.

Therefore, AEGL values for chlorosilanes will be derived by analogy to hydrogen chloride AEGL values

Summary of AEGL Values for Monochlorosilanes

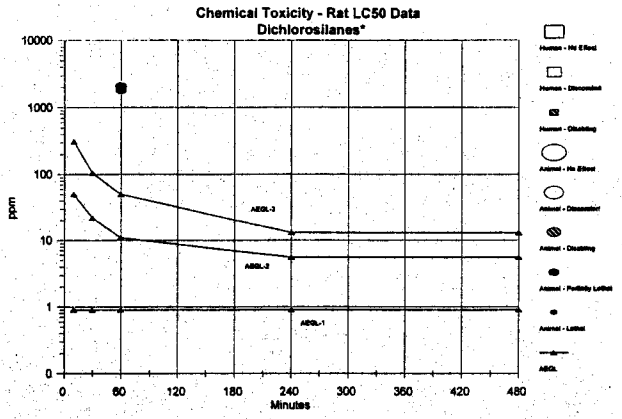
Compound	Classification	10-min	30-min	1-h	4-h	8-h	Endpoint
MONOCHLOROSILANE	AEGL-1	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	Hydrogen chloride (HCl) AEGL-1 values adopted as AEGL-1 values for Monochlorosilanes (NRC, 2004)
Dimethylchlorosilane	AEGL-2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm	Hydrogen chloride (HCl) AEGL-2 values adopted as AEGL-2 values for Monochlorosilanes (NRC, 2004)
	AEGL-3	620 ppm	210 ppm	100 ppm	26 ppm	26 ppm	Hydrogen chloride (HCl) AEGL-3 values adopted as AEGL-3 values for Monochlorosilanes (NRC, 2004)

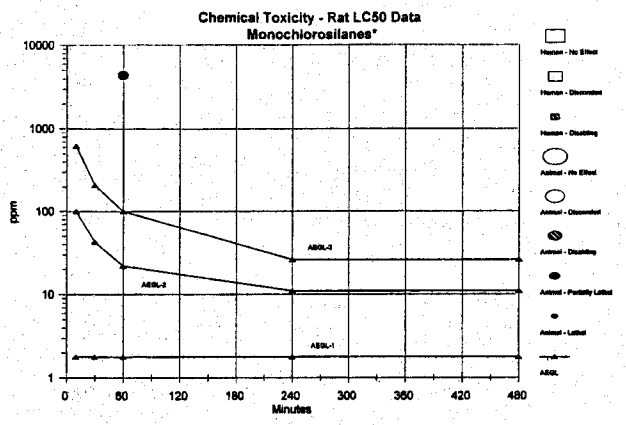
Summary of AEGL Values for Trichlorosilanes

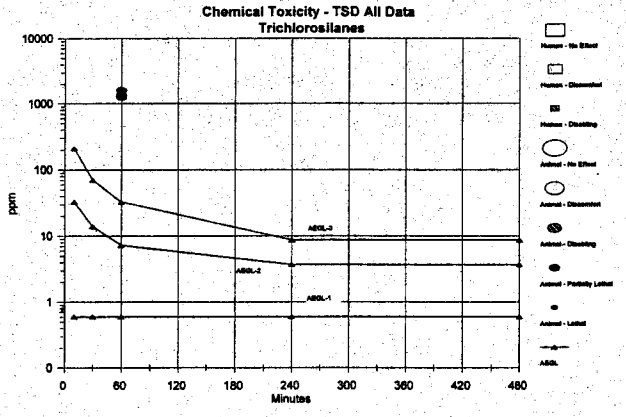
Compound	Classification	10-min	30-min	1-h	4-h	8-h	Endpoint
TRICHLOROSILANES	AEGL-1	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm	Hydrogen chloride AEGL-1 values divided by a molar adjustment factor of 3
Allyl trichlorosilane Amyl trichlorosilane Butyl trichlorosilane Chloromethyl trichlorosilane Dodecyl trichlorosilane	AEGL-2	33 ppm	14 ppm	7.3 ppm	3.7 pm	3.7 ppm	Hydrogen chloride AEGL-2 values divided by a molar adjustment factor of 3
Ethyl trichlorosilane Hexyltrichlorosilane Nonyl trichlorosilane Octadecyl trichlorosilane Octyl trichlorosilane Propyl trichlorosilane Trichloro(dichlorophenyl) silane Trichlorophenylsilane Trichlorosilane Vinyl trichlorosilane	AEGL-3	210 ppm	70 ppm	33 ppm	8.7 ppm	8.7 ppm	Hydrogen chloride AEGL-3 values divided by a molar adjustment factor of 3

Summary of AEGL Values for Dichlorosilanes

Compound	Classification	10-min	30-min	1-h	4-h	8-h	Endpoint
DICHLOROSILANES	AEGL-1	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	Hydrogen chloride AEGL-1 values divided by a molar adjustment factor of 2
Dichlorosilane *Diethyl dichlorosilane* Diphenyl dichlorosilane	AEGL-2	50 ppm	22 ppm	11 ppm	5.5 pm	5.5 ppm	Hydrogen chloride AEGL-2 values divided by a molar adjustment factor of 2
Methylvinyl dichlorosilane	AEGL-3	310 ppm	105 ppm	50 ppm	13 ppm	13 ppm	Hydrogen chloride AEGL-3 values divided by a molar adjustment factor of 2


Chemical Toxicity - Rat LC50 Data
Dichlorosilanes*
ppm
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Partially Lethal
Animal - Lethal
AEGL


Chemical Toxicity - Rat LC50 Data
Monochlorosilanes*
ppm
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Partially Lethal
Animal - Lethal
AEGL


Chemical Toxicity - TSD All Data
Trichlorosilanes
ppm
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Partially Lethal
Animal - Lethal
AEGL

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR CARBONYL FLUORIDE, COF_2 (CAS NO. 353-50-4)

NAC/AEGL-44
December 5-7, 2007

ORNL Staff Scientist: Jennifer Rayner

Chemical Manager: Iris Comacho

Chemical Reviewers: Richard Niemeier, Paul Tobin

Carbonyl Fluoride

Common Synonyms: Carbonyl difluoride, fluorophosgene, carbon fluoride oxide

Conversion
1 ppm = 2.7 mg/m^3
1 mg/m^3 = 0.38 ppm

Physical Characteristics:
- Gas- colorless, pungent

Uses:
- Chemical intermediate in synthesis of fluoroalkanes, fluorinated alkyl isocyanates

Mechanism of Toxicity

$COF_2 + H_2O = CO_2 + 2\ HF$

COF_2- Tracheal, pulmonary, liver congestion; pulmonary edema

CO_2- Dangerous at high concentrations, NIOSH TWA-TLV is 5000 ppm

HF- Irritates respiratory tract and eyes, causes pulmonary edema and hemorrhage

Susceptible Populations
Asthmatics- possible enhanced response to HF

HUMAN DATA

None available

ANIMAL DATA

Carbonyl Fluoride Exposures

DuPont (1956)- Single exposure for 2 or 2.5 hours
Nominal concentration

Conc. ppm	Effects
2.5	No effect
5	Slight dyspnea and cyanosis

DuPont (1959)- Single exposure for 4 hours

Conc. ppm	Effects
5	Rapid, shallow respiration
10	Rapid. shallow respiration
100	LC_{50}, pulmonary congestion

DuPont (1976)- Single exposure for 4 hours

Conc. ppm	Effects
26.7	50% mortality
30.8	30% mortality
32.7	30% mortality
41.3	60% mortality
44.7	80% mortality
47.2(48.8)	90% mortality
47.6	60% mortality
34.3	LC_{50} (calculated)

Effect: rapid shallow to convulsive respiration; pulmonary edema

Polytetrafluoroethylene Pyrolysis Exposures

Scheel et al. (1968)- Single exposure for 1 hour
Polytetrafluoroethylene pyrolyzed at 550°C

Conc. ppm	Effects
250	Mortality threshold for 8 week old rat
360	LC_{50}, focal hemorrhage of lung, pulmonary edema
350	Mortality threshold for 24 week old rat
460	LC_{50}, focal hemorrhage of lung, pulmonary edema
90	LC_{50} for 4 hour exposure

AEGL-1 Values for Carbonyl Fluoride

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 Carbonyl Fluoride

10-minute	30-minute	1-hour	4-hour	8-hour
1.0 ppm	0.70 ppm	0.56 ppm	0.33 ppm	0.17 ppm

Key Study: DuPont (1976) Acute Inhalation Toxicity Studies of Hydrogen Fluoride and Carbonyl Fluoride. Haskell Laboratory Report No. 485-76. DuPont Co., Haskell Laboratory, Newark. DE.

Rationale: In the absence of empirical data, and in accord with AEGL derivation guidelines for chemicals with steep dose-response curves (NAS 2001), the AEGL-2 values for carbonyl fluoride were set at one-third of the AEGL-3 values.

AEGL-3 Values for ~~Sulfuryl~~ Carbonyl Fluoride

10-minute	30-minute	1-hour	4-hour	8-hour
3.0 ppm	2.1 ppm	1.7 ppm	1.0 ppm	0.52 ppm

Key Studies: DuPont (1976) Acute Inhalation Toxicity Studies of Hydrogen Fluoride and Carbonyl Fluoride. Haskell Laboratory Report No. 485-76. DuPont Co., Haskell Laboratory, Newark. DE.

Toxicity endpoint: Threshold for lethality, BMC_{01} (10.4 ppm) [$LC_{50}/3$ = 34.3 ppm/3 = 11.4 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: 10
Interspecies: 3- The concentration at which tissue damage occurs should not differ across species. As a respiratory irritant, the mechanism of toxicity is not expected to differ between animals and humans.
Intraspecies: 3- Although data on a sensitive subpopulation are lacking for carbonyl fluoride, it has a steep concentration curve which may be an indication of small variations of toxic effects within a population.

Summary of AEGL Values for Carbonyl Fluoride

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)	1.0 ppm	0.70 ppm	0.56 ppm	0.33 ppm	0.17 ppm
AEGL-3 (Lethal)	3.0 ppm	2.1 ppm	1.7 ppm	1.0 ppm	0.52 ppm

AEGL Values for Phosgene

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)	0.60 ppm	0.60 ppm	0.30 ppm	0.080 ppm	0.040 ppm
AEGL-3 (Lethal)	3.6 ppm	1.5 ppm	0.75 ppm	0.20 ppm	0.090 ppm

AEGL Values for Hydrogen Fluoride

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Notable discomfort)	1 ppm	1 ppm	1 ppm	1 ppm	1 ppm
AEGL-2 (Disabling)	95 ppm	34 ppm	24 ppm	12 ppm	12 ppm
AEGL-3 (Lethal)	170 ppm	62 ppm	44 ppm	22 ppm	22 ppm

Extant Standards and Guidelines for Carbonyl Fluoride

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	1.0 ppm	0.70 ppm	0.56 ppm	0.33 ppm	0.17 ppm
AEGL-3	3.0 ppm	2.1 ppm	1.7 ppm	1.0 ppm	0.52 ppm
AEGL-1 HF	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm
AEGL-2 HF	95 ppm	34 ppm	24 ppm	12 ppm	12 ppm
AEGL-3 HF	170 ppm	62 ppm	44 ppm	22 ppm	22 ppm
REL-TWA (NIOSH)					2 ppm
REL-STEL (NIOSH)					5 ppm
TLV-TWA (ACGIH)					2 ppm
TLV-STEL (ACGIH)					5 ppm
MAC Peak Limit (The Netherlands)					0.5 ppm

NR - not recommended due to insufficient data. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR STIBINE, SbH_3 (CAS NO. 7803-52-3)

NAC/AEGL-44
December 5-7, 2007

ORNL Staff Scientist: Jennifer Rayner

Chemical Manager: Marcel van Raaij

Chemical Reviewers: Lynn Beasley, Paul Tobin

Stibine

Common Synonyms: Antimony hydride, hydrogen antimonide

Conversion
1 ppm = 5.11 mg/m^3
1 mg/m^3 = 0.196 ppm

Physical Characteristics:

- Gas- hydrogen sulfide-like odor
- Reacts with water or water vapor to form SO_2 and HCl

Uses:

- Used in infrared devices and solid-state lasers
- Dopant in computer industry (intentionally introducing impurities into an extremely pure semiconductor)

HUMAN DATA

Effects at lethal concentrations
None known

Effects at non-lethal concentrations
Possible ocular and respiratory irritation

Concurrent Exposures:
Arsine
Sulfuric Acid

Epidemiologic Studies:
Data consists mostly of air sample data in battery production and assembly plants with no health related effects reported.
One study reported health effects (sore throats, eye and respiratory irritation) with concurrent exposures to arsine and sulfuric acid (Lucas and Cone 1982).

Mechanism of Toxicity

Unknown mechanism causing pulmonary inflammation, edema, and congestion. Changes in guinea pig erythrocyte morphology

Susceptible Populations
Workers, asthmatics- The respiratory irritation of stibine may cause increased bronchial response.

ANIMAL DATA

Webster (1946). Volatile hydrides of toxicological importance.

Species	Conc (ppm)	Exposure Time (min)	Effect
Cat	40-45	60	Pulmonary congestion and edema, death within few hours up to one day
Dog	40-45	60	Pulmonary congestion and edema, death within few hours up to one day
Guinea pig	65	30	Irreversible erythrocyte morphology changes, hemoglobinuria, anemia

Price et al. (1979). Toxicity evaluation for establishing IDLH values (Final Report) TR 1518-005.

Species	Conc (ppm)	Duration (min)	Effect
Rat	29.1	30	No untoward effects
Guinea Pig	29.1	30	No untoward effects
Rat	191	30	Eye irritation and closure, generalized depressed activity 15 min into exposure, renal tubular dilation
Guinea Pig	191	30	Generalized depressed activity 25 min into exposure, renal tubular dilation, pulmonary inflammation
Rat	333	30	Generalized depressed activity, dyspnea, pulmonary congestion and edema, 70% mortality
Guinea Pig	333	30	Generalized depressed activity, tremors, pulmonary congestion and edema, 80% mortality

AEGL-1 Values for Stibine

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 Stibine

10-minute	30-minute	1-hour	4-hour	8-hour
4.2 ppm	2.9 ppm	1.5 ppm	0.36 ppm	0.18 ppm

Key Study: Price et al. (1979). Toxicity evaluation for establishing IDLH values (Final Report) TR 1518-005. Salt Lake City, UT.

Toxicity endpoints: Highest experimental exposure (29.1 ppm for 30 minutes) without AEGL-2 effects- eye closure, generalized depressed activity with ability to escape.

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

Uncertainty factors: A factor of 3 was applied for interspecies variability. In addition to dog and cat differences, Webster (1946) noted that three- or four-fold higher concentrations were needed to produce death in guinea pigs, however, the studies were not well documented. An uncertainty factor of 3 was used to account for intraspecies variability to protect sensitive individuals and reflect individual variability. Although the mechanism of action is unknown, it is unlikely that the response of normal and sensitive or susceptible individuals would differ significantly because the respiratory irritant action is not expected to vary much among individuals.

AEGL-3 Values for Stibine

10-minute	30-minute	1-hour	4-hour	8-hour
23 ppm	16 ppm	8.1 ppm	2.0 ppm	1.0 ppm

Key Studies: Price et al. (1979). Toxicity evaluation for establishing IDLH values (Final Report) TR 1518-005. Salt Lake City, UT.

Toxicity endpoint: Threshold for mortality, $BMCL_{05}$ 161 ppm for 30 minute exposure.

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

Uncertainty factors: A factor of 3 was applied for interspecies variability. In addition to dog and cat differences, Webster (1946) noted that three- or four-fold higher concentrations were needed to produce death in guinea pigs, however, the studies were not well documented. An uncertainty factor of 3 was used to account for intraspecies variability to protect sensitive individuals and reflect individual variability. Although the mechanism of action is unknown, it is unlikely that the response of normal and sensitive or susceptible individuals would differ significantly because the respiratory irritant action is not expected to vary much among individuals.

Summary of AEGL Values for Stibine

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)	4.2 ppm	2.9 ppm	1.5 ppm	0.36 ppm	0.18 ppm
AEGL-3 (Lethal)	23 ppm	16 ppm	8.1 ppm	2.0 ppm	1.0 ppm

Extant Standards and Guidelines for Stibine

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	4.1 ppm	2.9 ppm	1.5 ppm	0.36 ppm	0.18 ppm
AEGL-3	23 ppm	16 ppm	8.1 ppm	2.0 ppm	1.0 ppm
ERPG-1 (AIHA)[a]			ID		
ERPG-2 (AIHA)[a]			0.5 ppm		
ERPG-3 (AIHA)[a]			1.5 ppm		
PEL-TWA(OSHA)[b]					0.1 ppm
IDLH (NIOSH)[c]		5 ppm			
REL-TWA (NIOSH)[d]					0.1 ppm
TLV-TWA (ACGIH)[e]					0.1 ppm
MAC (The Netherlands)[f]					0.1 ppm

ATTACHMENT 9

ACUTE EXPOSURE GUIDELINE LEVELS FOR BORON TRIBROMIDE (BBr_3)

National Advisory Committee for AEGLs Meeting
December 5-7, 2007

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Bob Benson

Chemical Reviewers:
Marc Baril
Calvin Willhite

BORON TRIBROMIDE

Colorless, fuming liquid

Important industrial chemical, but no data on production were located

Hydrolysis in the presence of moisture is rapid and violent (Albemarle Corp. 2007)
Hydrolysis complete in aqueous environment;
yields three moles of hydrogen bromide and one mole of boric acid

Mechanism of action: irritation, likely due to hydrogen bromide breakdown product
Inhalation toxicity of boric acid in the mouse (Krystofiak and Schaper 1996):
300 mg/m^3 for 3 hours (~120 ppm): <20% decrease in respiratory rate
sensory irritation, no pulmonary effects

Human Studies:
No data.

Animal Studies:
No data.

Comparison of LC_{50} Data - Hydrogen Halides and Boron Trihalides

Hydrogen chloride and boron trichloride:
1-hour LC_{50} values in the rat (Vernot et al. 1977)
Hydrogen chloride: 3124 ppm (males)
Boron trichloride: 2541 ppm (males)
4418 ppm (females)
Similar pathological findings

Hydrogen fluoride and boron trifluoride:
1-hour LC_{50} in rats:
Hydrogen fluoride: 966-1300 ppm (NAS 2004)
4-hour LC_{50} for boron trifluoride in male and female rats (Rusch et al. 1986)
1.21 mg/L (~435 ppm); tested as dihydrate
Time scaled to 1 hour = 690-1740 ppm (n = 3 to 1)
2 ppm for 13 weeks: no toxic response
Boron trifluoride also rapidly reacts with moisture

Relative toxicity of hydrogen halides: HF > HCl ≥ HBr (Stavert et al. 1991)
Relative toxicity of boron trihalides: $BF_3 > BCl_3$ ..... > BBr_3 ?
Boron trihalides more toxic than/similar in toxicity to hydrogen halides....

BORON TRIBROMIDE

In absence of empirical data, the AEGLs were based on the breakdown product, hydrogen bromide.

Hydrogen Bromide AEGL Values					
Classification	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1	1 ppm	1 ppm	1 ppm	1 ppm	1 ppm
AEGL-2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm
AEGL-3	740 ppm	250 ppm	120 ppm	31 ppm	31 ppm

AEGL-1: based on a NOAEL for notable discomfort (3 ppm) in a study with six human volunteers exposed to 2, 3, 4, 5, or 6 ppm HBr for several minutes (Connecticut State Department of Health 1955). An intraspecies uncertainty factor of 3 was applied.
AEGL-2: Analogy with HCl (1300 ppm for 30 minutes; Stavert et al. 1991); however, mortality in rats exposed to HBr at this concentration/duration was 8%.
AEGL-3: Based on 1-hour $BMCL_{05}$ of HBr in rats of 1239 ppm (MacEwen and Vernot 1972). Based on the mechanism of direct-acting irritation, UFs of 3 and 3 for a total of 10 were applied. Because HBr is well scrubbed in the upper respiratory tract, the 8-hour AEGL-2 and AEGL-3 values were set equal to the respective 4-hour values.

BORON TRIBROMIDE

Boron tribromide hydrolyzes into three moles of hydrogen bromide
Hydrogen bromide considered the toxic breakdown product

AEGL-1: In the absence of empirical data, the AEGL-1 for boron tribromide was derived by dividing the AEGL-1 for hydrogen bromide by 3. For both hydrogen bromide and boron tribromide, the same value was used across all exposure durations because there is adaptation to the slight irritation defined by the AEGL-1.

AEGL-1 Values for Boron Tribromide				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm

BORON TRIBROMIDE

AEGL-2:
In the absence of empirical data and because the value for hydrogen bromide is two chemicals removed from boron tribromide, the AEGL-2 for boron tribromide was based on one-third of the hydrogen bromide AEGL-3 (according to SOP guidelines for chemicals with steep dose-response curves).

AEGL-2 Values for Boron Tribromide				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
83 ppm	28 ppm	13 ppm	3.3 ppm	3.3 ppm

BORON TRIBROMIDE

AEGL-3: In the absence of empirical data and based on the breakdown of boron tribromide into three moles of hydrogen bromide, the AEGL-3 values for boron tribromide were set at one-third of the hydrogen bromide AEGL-3 values.

AEGL-3 Values for Boron Tribromide				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
250 ppm	83 ppm	40 ppm	10 ppm	10 ppm

PROPOSED BORON TRIBROMIDE AEGLs

Classification	Exposure Duration				
	10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm
AEGL-2	83 ppm	28 ppm	13 ppm	3.3 ppm	3.3 ppm
AEGL-3	250 ppm	83 ppm	40 ppm	10 ppm	10 ppm

ALTERNATIVE BORON TRIBROMIDE AEGLs*

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm
AEGL-2	33 ppm	14 ppm	7.3 ppm	3.7 ppm	3.7 ppm
AEGL-3	250 ppm	83 ppm	40 ppm	10 ppm	10 ppm

*Based on 1/3 of all HBr values.

Statements Concerning Boric Acid Added to Boron Tribromide TSD
2. Human Toxicity Data

No information on the inhalation toxicity of boric acid was located. Boric acid is used as an astringent and antiseptic. Orally, boric acid is of low acute toxicity to adults, but there are reports of fatalities (Jordan and Crissey 1957). Death has occurred from intake of <5 g in infants and from 5 to 20 g in adults (O'Neil et al. 2001). Very high doses (4.6-14 g) ingested by infants killed 5 of 14 within 2-3 days and those who survived consumed 2-4.5 g (Wong et al. 1964). Mortality was 70% among infants who were accidentally poisoned with oral boric acid (Goldbloom and Goldbloom 1953).

Boric acid has been held responsible for systemic intoxication after ingestion, injection, application to damaged skin or enema (Brooke and Boggs 1951; Ducey and Williams 1953; Johnstone et al. 1955; Jordan and Crissey 1957; Mcintyre and Burke 1937; Rosen and Haggerty 1956). There is no evidence boric acid or borates are absorbed through intact skin (Sciarra 1958). Whether the apparent increased susceptibility of infants and children is due to immaturity of the kidney (which accounts for the primary route of elimination) (Locksley and Sweet 1949) or is related to the relatively high administered dose on a body weight basis (Young et al. 1949) is not clear. Autopsy is generally unremarkable with deaths delayed several days after exposure, but pancreatic lesions and those in kidney and brain have been described (McNally and Rust 1928; Valdes-Dapena and Arey 1962). Although seizures can precede death, the hyperchloremic metabolic acidosis is a characteristic feature (Wong et al. 1964).

3. Animal Toxicity

No data on the lethality, developmental/reproductive effects, genotoxicity, or chronic toxicity/carcinogenicity of boron tribromide were available. Data on the breakdown products, boric acid and hydrogen bromide were available. Inhalation exposure of male Swiss-Webster mice to 300 mg/m^3 boric acid aerosol (approximately 120 ppm), the highest achievable concentration, resulted in a decrease in respiratory rate of <20%. The effect was attributed to sensory irritation; there were no pulmonary effects (Krystofiak and Schaper 1996). The oral LD_{50} in rats for boric acid is 5 g/kg (O'Neil et al. 2001).

7.3. Derivation of AEGL-3

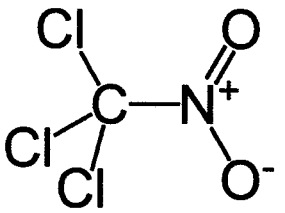
The toxicity of boric acid is of consideration. The intake of boric acid at the AEGL-3 for infants, the most susceptible population, can be calculated. The AEGL-3 is 100 mg/m^3 for 8 hours. The breathing rate of a child is 12 m^3/day. Boron tribromide is 4.32% boron. Assuming complete uptake of boron from the respiratory tract the resulting uptake for a child is:

100 mg/m^3 x 12 m^3/24 hours x 8 hours x 0.0432 = 17 mg of boron potentially absorbed.

This value is low compared to the 2-5 g needed for lethality in a child.

ATTACHMENT 10

Chloropicrin
(CAS Reg. No. 6581-06-2)



NAC/AEGL-44
Orlando, FL
December 5-7, 2007

ORNL Staff Scientist: **Robert A. Young**
Chemical Manager: **Gail Chapman**
Chemical Reviewer: **Henry Anderson**
Chemical Reviewer: **Jim Holler**

Chloropicrin

- **Fumigant, soil insecticide**
- **Riot-control agent (Agent PS)**

Chloropicrin
Human Exposure

- **Lethality following acute exposure**
  - **120 ppm, 30 min (Vedder, 1925)**
  - **300 ppm, 10 min (Prentiss, 1937)**
  - **120 ppm, 30 min (Prentiss, 1937)**
  - **No details on above**

- **Nonlethal effect of acute exposure**
  - **Odor threshold - 0.78 ppm (Speck et al., 1982)**
  - **Ocular and respiratory tract irritation**

Effects of acute chloropicrin exposure on human volunteer subjects				
Exposure Duration	**Exposure Concentration**	**LOAEL (ppm)**	**Comments**	**Reference**
Immediate to 30 seconds	1, 2.5, 5.0, 7.5, 10.0, 15.0, 20.0, 25 ppm	1	Eyes remain open (as a measure of irritation); at 2.5 to 20 ppm eyes close within 3 to 30 seconds depending on concentration and individual susceptibility; eyes close immediately at 25 ppm	Fries and West 1921
Immediate	1 ppm	1	Immediate eye irritation	Fairhall 1957
Few seconds	26 mg/m^3 (3.9 ppm)	26	Unfit for combat	Flury and Zernick, 1931
Few seconds	100 mg/m^3 (15 ppm)	15	Non-specified injury to respiratory tract	
Unspecified (presumably immediate or within 10 min)	0.002 mg/L (0.30 ppm)	0.3	Lacrimation	Prentiss 1937
10 min	0.05 mg/L (7.4 ppm)	7.4	Intolerable ocular and respiratory tract irritation	
	2.00 mg/L (300 ppm)	300	Lethality; no further details	
30 min	0.80 mg/L (120 ppm)	120		
30 min	0.8 mg/L (120 ppm)	120	Lethality; no further details	Vedder 1925
1 h/d for 4 d	0, 0.1, 0.15 ppm	0.1	Ocular irritation at 0.1 ppm	Cain 2004 (summarized in Reaves 2004, 2006a,b)[a]

Note: age, gender, and number of subjects not reported except as footnoted.
[a] 15 males; 17 females

Chloropicrin
Human Effects Data

➢ Sensory irritation (Reaves, 2004)

Summary of Human Sensory Irritation Testing with Chloropicrin			
Test Phase	**Concentration (ppb)**	**Exposure Duration**	**Results**
Phase I	0, 356, 533, 800, or 1200	"sniff"	Median odor detection: 700 ppb (males 590 ppb; females 810 ppb Median eye detection: 900 ppb (males790 ppb; females 1010 ppb)
Phase II	0, 50, 75, 100, or 150	20-30 minutes	1 Female subject left at 75 ppb 4 Subjects (2 of each gender) left at 150 ppb 16 of 42 Subjects detected chloropicrin at 50 ppb Ocular and nasal detection by sensitive individuals
Phase III	100, or 150	60 min/day; 4 consecutive days	NOAEL: not established <100 ppb LOAL: 100 ppb; ocular irritation, differential ventilatory flow; time for recognition at either concentration was 5 minutes

Reaves, 2004

Chloropicrin
Human Effects Data

- **Phase 3 was most comprehensive assessment of sensory, physiological, and clinical effects**

- **Sensory perception by volunteer subjects (Phase 3)**
  - **0: no symptoms**
  - **1: mild (easily tolerated)**
  - **2: moderate (notable, bothersome but tolerated)**
  - **3: severe (difficult to tolerate; possibly interfere with daily activity or sleep)**

Chloropicrin
Human Effects Data

Human Subject Response to Chloropicrin During a 1-h Exposure[a]							
	Eyes			Nose		Throat	
Exposure	Rating	Response Frequency	Time for Recognition	Average Symptom Rating	Time for Recognition	Average Symptom Rating	Time for Recognition
0 ppb (0 mg/m^3)	0.1	Not available in summary report	NA	0.1	5 min	0.1	5 min
100 ppb (0.67 mg/m^3)	0.5	Sporadic "severe" irritation in 8/32 subjects (25%) over the 60-min exposure duration	30 min	0.1	5 min	0.1	5 min
150 ppb (1.0 mg/m^3)	1	Sporadic "severe" eye irritation scores in 7/32 subjects (22%) over the 60-min exposure duration	20 min	0.2	5 min	0.1	5 min

[a] Assessments made while subjects were in exposure chamber, with ratings given 30 seconds from initial exposure and every minute thereafter for the 60-minutes exposure duration.

Chloropicrin
Animal Lethality Data
Rats

- **Yoshida et al. (1987a)**
  - **4-hour: groups of 6-8 male F-344 rats exposed to 8.8, 11.0, 11.4, 12.1, 13.6 or 16.0 ppm (analytical); 14-day observation**
    - **4-hr LC_{50}: 11.9 ppm**
    - **Biphasic lethality pattern**
    - **Primary target: respiratory tract**
  - **30-min: 21.7 or 45.5 ppm**
    - **No deaths at 21.7 ppm**
    - **100% lethality at 45.5 ppm**

Toxicity of Chloropicrin Vapor in Male Fischer Rats (4-hr Exposure)[a]					
Effect	Dose in ppm[b]				
	8.8	11.0	11.4	12.1	13.6
Mortality	0/8	2/8	3/8	5/8	7/8
Pathology					
Hydrothorax	0/8	0/8	0/8	3/8	5/8
Lung					
Edema	3/8	6/8	6/8	7/8	7/8
Emphysema	3/8	7/8	2/8	3/8	4/8
Dark red patches	0/8	1/8	3/8	2/8	1/8

Yoshida et al. 1987a.

[a]All rats in the 16.0 ppm group died within 24 hours and all exhibited hydrothorax, pulmonary edema, emphysema, and gaseous distention of the stomach. [b] Mean analytical concentration of chloropicrin vapor.

Chloropicrin
Animal Lethality Data
Rats

- **Yoshida et al. (1991)**
  - **4-hour nose-only or whole-body exposure of 8 male F-344 rats**
    - **Nose-only: 5.3, 5.9, 6.6 , or 81. ppm**
      - **4-hr LC_{50}: 6.6 ppm**
    - **Whole-body: 12.3, 13.9, or 15.4 ppm**
      - **4-hr LC_{50}: 14.4 ppm**
    - **14-day observation**

Lethality in rats exposed for 4 hours to chloropicrin.								
	Days post exposure							
Test Group	0[a]	1	2-7	8	9	10	11-14	Total
Whole-body								
12.3 ppm	1	0	0	0	0	0	0	1/8
13.9 ppm	2	0	0	0	0	0	0	2/8
15.4 ppm	5	0	0	0	2	0	0	7/8
Nose-only								
5.3 ppm	0	0	0	0	0	0	0	0/8
5.9 ppm	1	0	0	0	0	0	0	1/8
6.6 ppm	6	0	0	0	0	0	0	6/8
8.1 ppm	6	0	0	0	0	0	0	6/8

[a] Represents 0-24 hrs.

Yoshida et al., 1991

Chloropicrin
Animal Lethality Data
Rats

- **Hoffman (1999)**
  - **4-hr whole-body, 5 rats/gender; 0, 10.6, 18.0 or 28.5 ppm**
  - **4-hr LC_{50}: ~17 ppm (males), ~20 ppm (females)**
  - **10.5 ppm NOAEL for lethality**
  - **Only 2-day observation period**
  - **Respiratory tract involvement**

- **U.S. Testing Co., Inc. (1976)**
  - **1-hr LC_{50}: 25.2 ppm**
  - **14-day observation**

Chloropicrin
Animal Lethality Data
Mice

- **Kawai (1973) aerosol vs vapor**
  - **Vapor: 30-min exposure**
    - **NOAEL for lethality: 18 ppm**
    - **LC_{50}: 56 ppm**
    - **LC_{100}: 134 ppm**

  - **Aerosol: 240-min exposure**
    - **NOAEL for lethality: 4.7 ppm (31 mg/m^3)**
    - **LC_{50}: 99 ppm (370 mg/m^3)**
    - **LC_{100}: 26 ppm (171 mg/m^3)**

Chloropicrin
Animal Nonlethal Toxicity

- **Yoshida et al. (1987a)**
  - **21.7 ppm, 30 min: no lethality in rats**
    - **gastric distention, red patches in lungs**

- **Yoshida et al. (1991)**
  - **5.3 ppm (nose-only), 4 hrs: no lethality in rats**
    - **Salivation and rhinorrhea reversible at 24 hrs**
    - **Red stains around muzzle reversible by 48 hrs**
    - **Body wt. loss by Day 7, recovered by Day 14**

Chloropicrin
Animal Developmental Toxicity

- **Schardein (1993) – Rats; 30/group**
  - **0, 0.4, 1.2, 3.5 ppm (whole-body), 6 hrs/day, g.d. 6-15**
  - **Maternal NOAEL 0.4 ppm**
  - **Maternal LOAEL 1.2 ppm**
  - **Developmental NOAEL 1.2 ppm**

- **York et al. (1994) – Rabbits; 20/group**
  - **0, 0.4, 1.2, 2 ppm (whole-body), 6 hrs/day, g.d. 6-18**
  - **Maternal NOAEL 0.4 ppm**
  - **Maternal LOAEL 1.2 ppm (2/20 dead)**
  - **Developmental NOAEL 0.4 ppm**
  - **Developmental LOAEL 1.2 ppm**

Chloropicrin
Mode of Action

- **Direct-contact**
  - **Lacrimation**
  - **respiratory tract irritation**

- **Systemic**
  - **Reacts with sulfhydryl groups**
    - **Reduced O_2 transport by Hb**
    - **Inhibition of pyruvate dehydrogenase activity**

Chloropicrin
AEGL-1

AEGL-1 Values for Chloropicrin (ppm)					
Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	0.15	0.097	0.073	0.041	0.031

Key Study: Reaves, E. 2006a. Memorandum from Elissa Reaves, Ph.D., US EPA Health Effects Division to Nathan Mottl, Chemical Review Manager, Special Review and Reregistration Division. Review of the TERA Document: "Use of Benchmark Concentration Modeling and Categorical Regression to Evaluate the Effects of Acute Exposure to Chloropicrin Vapor. MRID 46614801."

Critical effect: $BMCL_{10}$ (0.073 ppm) for ocular irritation in human volunteers exposed to chloropicrin vapor for up to 30 minutes

Time scaling: $C^n \times t = k$ where $n = 2.4$

Uncertainty factors: Total uncertainty factor adjustment was 1
Interspecies: 1; human volunteers (42 subjects, 18-35 years old)
Intraspecies: 1; tests with human volunteers included sensitive individuals

Chloropicrin
AEGL-2

AEGL-2 Values for Chloropicrin (ppm)					
Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	0.32	0.20	0.15	0.084	0.063

Key Study: Reaves, E. 2006b. Memorandum from Elissa Reaves, Ph.D., Toxicologist, US EPA Health Effects Division, to Tina Levine, Ph.D., Director, US EPA Health Effects Division, "Human Studies Review Board: Weight of Evidence Discussion for Trichloronitromethane (Chloropicrin.)." June 7.

Critical effect: POD 150 ppb (0.15 ppm) 60 min.; intolerable ocular irritation, threshold for ventilatory effects in human volunteers

Time scaling: $C^n \times t = k$ where $n = 2.4$

Uncertainty factors: Total uncertainty factor adjustment was 1
Interspecies: 1; human volunteers (42 subjects, 18-35 years old)
Intraspecies: 1; tests with human volunteers included sensitive individuals

Chloropicrin
AEGL-3

AEGL-3 Values for Chloropicrin(ppm)					
Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	3.0	1.9	1.4	0.79	0.59

Key Study: Yoshida M., Ikeda, T., Iwasaki, M., Tsuda, S., Shirasu, Y. 1987a. Acute inhalation toxicity of chloropicrin vapor in rats. J. Pesticide Sci. 12:237-244.

Yoshida, M., Murao, N., Tsuda, S., Shirasu, Y. 1991. Effects of mode of exposure on acute inhalation toxicity of chloropicrin vapor in rats. Nippon Noyaku Gakkaishi (Journal of the Pesticide Science Society of Japan) 16:63-69.

Critical effect: Estimated lethality threshold in rats; POD $BMCL_{05}$ of 7.5 ppm, 240-min. exposure

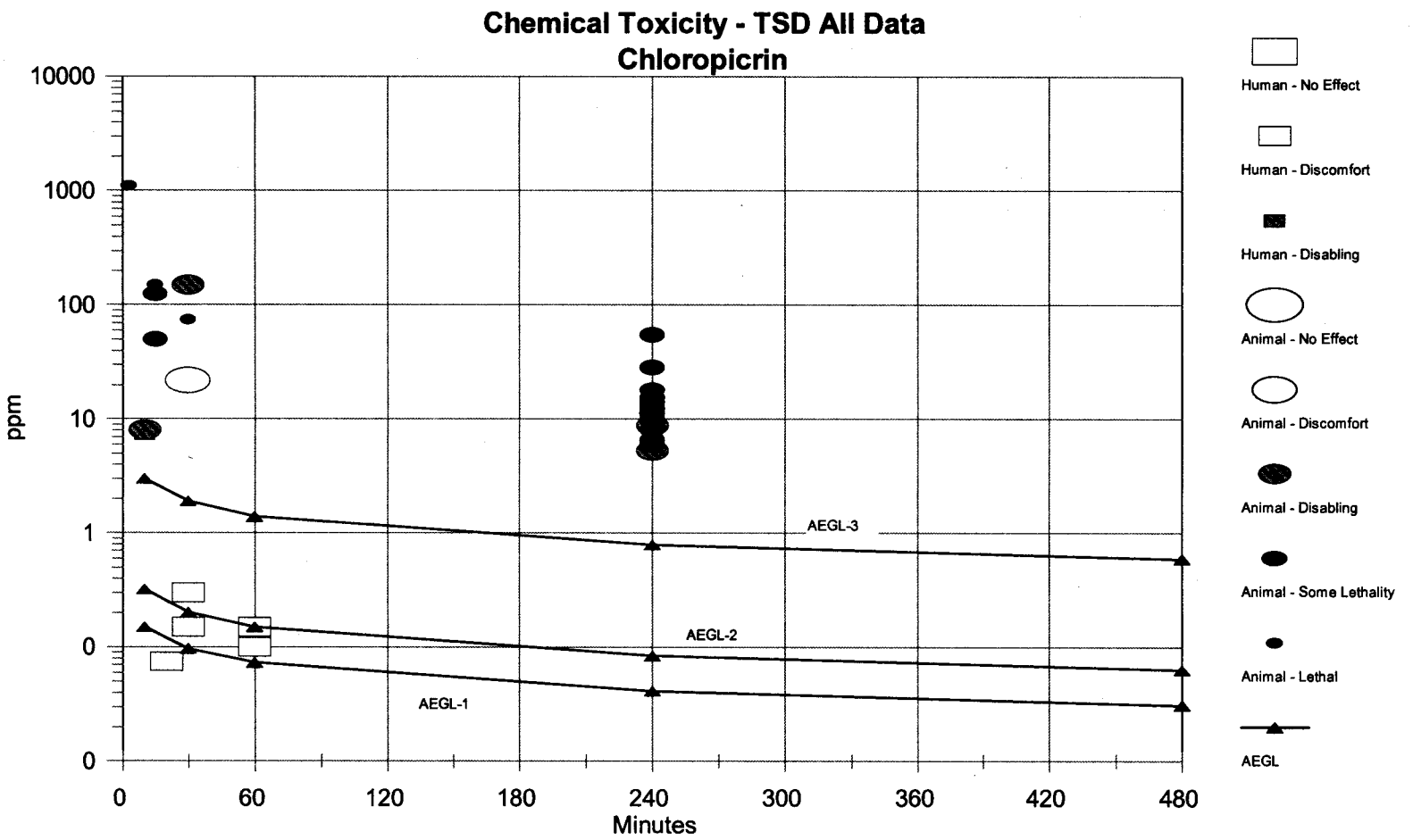
Time scaling: $C^n \times t = k$ where $n = 2.4$.

Uncertainty factors: Total uncertainty factor adjustment was 10

Interspecies: 3; variability in lethal response was not great; 3-fold adjustment sufficient for dosimetric variability across species.

Intraspecies: 3; lethality likely due to respiratory tract damage resulting from contact damage to epithelial surfaces.

Summary of AEGL Values for Chloropicrin					
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1 (Nondisabling)	**0.15 ppm 1.0 mg/m^3**	**0.097 ppm 0.65 mg/m^3**	**0.073 ppm 0.49 mg/m^3**	**0.041 ppm 0.27 mg/m^3**	**0.031 ppm 0.21 mg/m^3**
AEGL-2 (Disabling)	**0.32 ppm 2.1 mg/m^3**	**0.20 ppm 1.3 mg/m^3**	**0.15 ppm 1.0 mg/m^3**	**0.084 ppm 0.56 mg/m^3**	**0.063 ppm 0.42 mg/m^3**
AEGL-3 (Lethality)	**3.0 ppm 20 mg/m^3**	**1.9 ppm 13 mg/m^3**	**1.4 ppm 9.4 mg/m^3**	**0.79 ppm 5.3 mg/m^3**	**0.59 ppm 4.0 mg/m^3**


Chemical Toxicity - TSD All Data
Chloropicrin
10000
1000
100
10
1
0
0
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 11

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHYL IODIDE (CH_3I)

National Advisory Committee for AEGLs Meeting
December 5-7, 2007

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Alan Becker

Chemical Reviewers:
David Freshwater
John Hinz

METHYL IODIDE

Liquid at ambient temperatures, but readily volatilizes

Sweet ethereal odor, poor warning property

New use – soil pesticide; no recent production data

Human Studies:
Clinical and case studies provide insufficient data to derive AEGL values

Animal Studies:
Acute toxicity, including neurotoxicity; repeat-dose, developmental/reproductive toxicity; genotoxicity; and chronic toxicity/carcinogenicity
Recent well-conducted toxicity studies available only from secondary source – (U.S. EPA 2006)

METHYL IODIDE

Effects and Metabolism

Effects:
Lesions of the nasal passages, specifically the olfactory epithelium
Neurotoxicity

Metabolism:
Monohalomethanes are conjugated with glutathione.
Glutathione is a tripeptide present in significant concentrations in all tissues. The function of glutathione is to protect cells from oxidizing agent which might otherwise damage them. Oxidizing agents react with the –SH group of cysteine of the glutathione instead of doing damage elsewhere.... acts as a detoxifying agent.
Conjugation may be either enzymatic, via glutathione transferase, or non-enzymatic. For other monohalomethanes, enzymatic conjugation with glutathione is thought to vary no more than 3-fold in humans (Nolan et al. 1984).

METHYL IODIDE

Uncertainty factors and time-scaling

Uncertainty factors:
Interspecies: 1: greater chemical uptake in rodents based on higher respiratory rate and cardiac output

Intraspecies; 3: metabolism via glutathione conjugation is not expected to vary greatly among humans (Nolan et al. 1985). Furthermore, conjugation with glutathione may be non-enzymatic, which could further minimize individual differences.

Time-scaling:
The glutathione depletion which may be responsible for olfactory epithelial lesions and neurotoxicity is considered on a continuum with lethality. Therefore, all AEGL levels were time-scaled. The time-scaling value of n of 1.8 was calculated by entering two sets of lethality data for rats into the ten Berge (2006) probit analysis program. The $BMCL_{05}$ was calculated for each exposure duration.

METHYL IODIDE

AEGL-1: Animal Data (Rat) – Weight-of-evidence approach

27 ppm for 6 hours: NOAEL for neurotoxicity (U.S. EPA 2006)
100 ppm for 1 hour: no observable change, nasal passages (Reed et al. 1995)
100 ppm for 6 hours: no effect on respiratory parameters (DeLorme et al. 2005)
25 ppm for 6 hours/day, 5 days/week, 4 weeks: NOAEL for nasal lesions, neurotoxicity (Monsanto et al. 1983)
21 ppm for 6 hours/day, 5 days/week for 13 weeks: NOAEL for nasal lesions and other effects (U.S. EPA 2006)

Point of departure: 27 ppm for 6 hours
To time-scale or not to time-scale?
Values were time-scaled ($C^{1.8} \times t = k$)

Proposed AEGL-1 Values for Methyl Iodide				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
66 ppm	35 ppm	24 ppm	11 ppm	11 ppm

METHYL IODIDE

AEGL-2

Animal data – Rat (Reed et al. 1995)

100 ppm for 0.5 hours: no observable change, nasal passages
100 ppm for 1 hour: no observable change, nasal passages
100 ppm for 2 hours: minimal lesions, olfactory epithelium
100 ppm for 3 hours: slight lesions, olfactory epithelium
100 ppm for 4 hours: moderate lesions, olfactory epithelium
100 ppm for 6 hours: reversible lesions of the olfactory epithelium

Point of departure was 100 ppm for 6 hours
Values were time-scaled ($C^{1.8} \times t = k$)

Proposed AEGL-2 Values for Methyl Iodide				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
240 ppm	130 ppm	90 ppm	42 ppm	28 ppm

METHYL IODIDE

AEGL-3

Animal data – Rat
1-Hour study (Eastman Kodak Co. 1987)
Mortalities of 20%, 60%, 90% at 1190 ppm, 1554 ppm, 1973 ppm, respectively

4-Hour study (U.S. EPA 2006)
Mortalities of 0%, 80%, 80%, 100% at 581 ppm, 710 ppm, 797 ppm, and 1198 ppm

Both data sets entered into ten Berge probit analysis program:
Values set at $BMCL_{05}$
Values automatically time-scaled; time scaling value (n) = 1.8

Proposed AEGL-3 Values for Methyl Iodide				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
670 ppm	390 ppm	280 ppm	130 ppm	86 ppm

METHYL IODIDE

Proposed Methyl Iodide AEGL Values					
	Exposure Duration				
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1	66 ppm	35 ppm	24 ppm	11 ppm	11 ppm
AEGL-2	240 ppm	130 ppm	90 ppm	42 ppm	28 ppm
AEGL-3	670 ppm	390 ppm	280 ppm	130 ppm	86 ppm

AEGL-1: based on weight of evidence approach. The point of departure was a NOAEL for clinical signs in the rat, 27 ppm for 6 hours. Interspecies and intraspecies uncertainty factors of 1 and 3, respectively, were applied.
AEGL-2: based on reversible lesions of the olfactory epithelium, 100 ppm for 6 hours. Inter- and intraspecies uncertainty factors of 1 and 3, respectively, were applied.
AEGL-3: based on 1- and 4-hour $BMCL_{05}$ values calculated with the ten Berge probit analysis program. Inter- and intraspecies uncertainty factors of 1 and 3, respectively, were applied

METHYL IODIDE

Comparison of AEGL values for monohalomethanes:

AEGL Values for Halomethanes					
Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
Methyl Iodide					
AEGL-1	66 ppm	35 ppm	24 ppm	11 ppm	11 ppm
AEGL-2	240 ppm	130 ppm	90 ppm	42 ppm	28 ppm
AEGL-3	670 ppm	390 ppm	280 ppm	130 ppm	86 ppm
Methyl Bromide					
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	940 ppm	380 ppm	210 ppm	67 ppm	67 ppm
AEGL-3	3300 ppm	1300 ppm	740 ppm	230 ppm	130 ppm
Methyl Chloride					
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	1100 ppm	1100 ppm	910 ppm	570 ppm	380 ppm
AEGL-3	3800 ppm	3800 ppm	3000 ppm	1900 ppm	1300 ppm

NR = Not Recommended; values are not recommended because there are no odor or warning properties and toxic effects may occur below the odor threshold.

AEGL values reflect the known toxicity: MeI>MeBr>MeCl.

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR ALLYL CHLORIDE, C_3H_5Cl (CAS NO. 107-05-1)

NAC/AEGL-44
December 5-7, 2007

ORNL Staff Scientist: Jennifer Rayner

Chemical Manager: Richard Niemeier

Chemical Reviewers: Marc Baril, Roberta Grant

Allyl Chloride

Common Synonyms: 3-Chloropropene, Chlorallylene, 1-Chloro-2-propene

Conversion
1 ppm= 3.13 mg/m^3
1 mg/m^3= 0.32 ppm

Physical Characteristics:
- Liquid- colorless, pale yellow, purple, brown, read
- Odor- irritating, unpleasant, and pungent odor, similar to garlic

Uses:
- Synthesis of allyl compounds

Mechanism of Toxicity
Unknown- It is possible that toxic metabolites are formed and cause kidney lesions.

Susceptible Populations
Asthmatics- possible increased bronchial response from respiratory irritation

HUMAN DATA

Effects at lethal concentrations
None known

Effects at non-lethal concentrations

Torkelson et al. (1959). Vapor toxicity of allyl chloride as determined in laboratory animals.

Species	Concentration (ppm)	Exposure Time	Effect
Human	3	1-3 min	Odor detection in 10 of 13 volunteers, no irritation

Shell Chemical Company (1959). Industrial Hygiene Bulletin No. SC-57-80.

Species	Concentration (ppm)	Exposure Time	Effect
Human	3-6	5 min	Threshold, $Odor_{50}$
Human	25	5 min	Threshold, $Odor_{100}$
Human	> 25	5 min	Threshold, Nose $Irritation_{50}$; Pulmonary $Discomfort_{50}$
Human	50-100	5 min	Threshold, Eye $Irritation_{50}$

ANIMAL DATA

Adams et al. 1940. The acute vapor toxicity of allyl chloride

Species	Conc. (ppm)	Exposure Time (hr)	Mortality (%)	Effect
Rat	290	2 3 4 6 7 8 9	0 0 20 20 0 100 100	Drowsiness, unsteadiness, eye irritation, unconsciousness, death within 24 hr
Rat	2,900	0.5 1 2 2 3 4 4	0 0 80 66 100 100 100	Slight eye and nose irritation, increased death during exposure
Rat	5,800	0.5 1 2	0 20 100	Eye and nose irritation, drowsiness, death within 24 hr
Rat	14,500	0.5 1 1.25 1.25 2	0 80 100 100 100	Eye and nose irritation, drowsiness, weakness, instability, labored breathing, death within 24 hr
Rat	29,300	0.25 0.5 0.5 1	0 100 100 100	Eye and nose irritation, unconsciousness, death within a short time

Adams et al. (1940) cont.

Species	Conc. (ppm)	Exposure Time (hr)	Mortality (%)	Effect
Guinea Pig	290	1 2 4 6 9	0 20 100 100 100	Drowsiness, unsteadiness up to 4 hr; eye irritation, unconsciousness up to 6 hr; death within 24 hr
Guinea Pig	2,900	0.5 1 2	0 0 100	Slight eye and nose irritation in 2 hr; death after exposure
Guinea Pig	14,500	0.16 0.25 0.5 0.5 0.5 0.75 1	0 0 50 100 66 100 100	Eye and nose irritation, drowsiness, weakness, instability, labored breathing, death within 24 hr

Quast et al. 1982a. Results of Single 6-Hour Inhalation Exposure Studies in Laboratory Rodents

Species	Conc. (ppm)	Exposure Time (hr)	Mortality (%)	Effect
Rat	200	6 hr	0	Slight palpebral closure and conjunctival hyperemia; 500 and 800 ppm diarrhea, lethargy; female ≥ 300 ppm and males ≥ 500 ppm acute renal tubular degeneration, recoverable
	300		0	
	500		0	
	800		0	
	1000		5	
	1000		5	
	2000		55	
Mouse	500	6 hr	0	Slight to moderate palpebral closure; females 800 ppm acute renal tubular degeneration, recoverable
	800		0	
	1000		70	
	1000		50	
	1200		25	
	2000		100	

AEGL-1 Values for Allyl Chloride

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

Key Study: Torkelson et al. 1959. Vapor toxicity of allyl chloride as determined in laboratory animals. Am. Ind. Hyg. Assoc. J. 20:217-223; Shell Chemical Co. 1959. Allyl Chloride. Industrial Hygiene Bulletin No. SC-57-80. New York: Shell Chemical Co., Industrial Hygiene Department, January 1959. pp. 1-6.

Toxicity endpoint: No observed adverse effect level

Time scaling: None

Uncertainty factors: An intraspecies uncertainty factor of 3 was used to protect asthmatics who may have increased bronchial response in the presence of allyl chloride. No interspecies uncertainty factor was used because the number was derived from human data.

The AEGL level was held constant across all exposure time points. That approach was considered appropriate because mild irritant effects generally do not vary greatly over time.

AEGL-2 Values for Allyl Chloride

10-minute	30-minute	1-hour	4-hour	8-hour
69 ppm	69 ppm	54 ppm	34 ppm	22 ppm

Key Study: Quast et al. 1982a. Allyl Chloride- Acute Studies. Results of Single 6-Hour Inhalation Exposure Studies in Laboratory Rodents. Final Report, Toxicology Research Laboratory, Dow Chemical, U.S.A., Midland, MI (June 4, 1982).

Toxicity endpoints: AEGL-2 values were based upon lowest concentration (300 ppm) at which reversible kidney tubular degeneration was observed and the highest concentration for slight eye closure and redness. This estimate of a threshold for irreversible effects was justified because of the absence of exposure-response data related to irreversible or other serious, long-lasting effects.

Time scaling: Temporal scaling was performed, using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001). The 30-minute value was also adopted as the 10-minute value.

Uncertainty factors: A factor of 3 was applied for interspecies variability because it is expected that the mechanism of action (eye and respiratory tract irritation) would not differ across species, but the guinea pig appears to be more sensitive to allyl chloride than the rat (Adams et al. 1940; Lu et al. 1982). Although data on sensitive subpopulations are lacking for allyl chloride, an intraspecies uncertainty factor of 3 is protective of asthmatics and other sensitive individuals.

AEGL-3 Values for Allyl Chloride

10-minute	30-minute	1-hour	4-hour	8-hour
180 ppm	180 ppm	140 ppm	90 ppm	60 ppm

Key Study: Quast et al. 1982a. Allyl Chloride- Acute Studies. Results of Single 6-Hour Inhalation Exposure Studies in Laboratory Rodents. Final Report, Toxicology Research Laboratory, Dow Chemical, U.S.A., Midland, MI (June 4, 1982).

Toxicity endpoint: The AEGL-3 values were based upon the highest experimental concentration with no mortality (800 ppm). Moderate eye closure, diarrhea, and lethargy were observed. Concentrations equal to and greater than 1000 ppm produced mortality.

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). The 30-minute value was adopted for the 10-minute value.

Uncertainty factors: A total uncertainty factor of 10 was applied to account for interspecies extrapolation (3) and intraspecies variability (3). A factor of 3 was applied for interspecies variability because it is expected that the mechanism of action (eye and respiratory tract irritation) would not differ across species. Although human data did not provide quantitative exposure information, they described effects similar to those seen in rats; eye and respiratory tract irritation. Although data on sensitive subpopulations are lacking for allyl chloride, an intraspecies uncertainty factor of 3 is protective of asthmatics and other sensitive individuals.

Summary of AEGL Values for Allyl Chloride

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Notable discomfort)	1 ppm	1 ppm	1 ppm	1 ppm	1 ppm
AEGL-2 (Disabling)	69 ppm	69 ppm	54 ppm	34 ppm	22 ppm
AEGL-3 (Lethal)	180 ppm	180 ppm	140 ppm	90 ppm	60 ppm

Extant Standards and Guidelines

Guideline	Exposure Duration				
	10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
AEGL-1	1 ppm	1 ppm	1 ppm	1 ppm	1 ppm
AEGL-2	69 ppm	69 ppm	54 ppm	34 ppm	22 ppm
AEGL-3	180 ppm	180 ppm	140 ppm	90 ppm	60 ppm
ERPG-1 (AIHA)[a]			3 ppm		
ERPG-2 (AIHA)			40 ppm		
ERPG-3 (AIHA)			300 ppm		
PEL-TWA (OSHA)[b]					1 ppm
IDLH (NIOSH)[c]		250 ppm			
REL-TWA (NIOSH)[d]					1 ppm
REL-STEL (NIOSH)[e]					2 ppm
TLV-TWA (ACGIH)[f]					1 ppm
TLV-STEL (ACGIH)[g]					2 ppm
MAC (The Netherlands)[h]					1 ppm

ATTACHMENT 13

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
METHANESULFONYL CHLORIDE

NAC/AEGL-44
December 5-7, 2007
Orlando, FL

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Roberta Grant

Chemical Reviewers: George Rusch and Richard Niemeier

Document History:

NAC-43 (June, 2007):

Document tabled due to extremely sparse data.

Dr. Sylvie Tissot offers to try to obtain unpublished data- Success!

TABLE 1. Mortality in rats exposed to methanesulfonyl chloride for 4-hours*

Concentration	Mortality		
	Males	Females	Combined
0 ppm	0/5	0/5	0/10
20 pppm	1/5	0/5	1/10
28 ppm	4/5	5/5	9/10
54 ppm	5/5	5/5	10/10
LC_{50}			25 ppm
BMC_{01}			17.4 ppm
$BMCL_{05}$			15.5 ppm

Pennwalt Corporation, 1987

TABLE 2. Mortality in rats exposed to methanesulfonyl chloride for 1-hour

Concentration	Mortality		
	Males	Females	Combined
165 pppm	1/5	0/5	1/10
174 ppm	1/5	1/5	2/10
300 ppm	5/5	5/5	10/10

Pennwalt Corporation, 1986

The data did not allow for the calculation of an LC_{50} value; however, the study authors stated that the one-hour LC_{50} is most likely in the range of 175 to 250 ppm.

AEGL-1 VALUES: METHANESULFONYL CHLORIDE				
10 minute	30 minute	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR

NR: Not Recommended due to insufficient data.

AEGL-2 Values for Methanesulfonyl Chloride				
10-min	30-min	1-h	4-h	8-h
1.0 ppm	1.0 ppm	0.83 ppm	0.53 ppm	0.26 ppm

Endpoint: Three-fold reduction of AEGL-3 values.

Approach justified by steep concentration-response curve

4-hr Rat data (Pennwalt Corporation, 1987)

10% mortality at 20 ppm

90% mortality at 28 ppm

AEGL-3 VALUES: METHANESULFONYL CHLORIDE				
10 minute	30 minute	1 hour	4 hour	8 hour
3.1 ppm	3.1 ppm	2.5 ppm	1.6 ppm	0.78 ppm

Species: Rat
Concentration: 15.5 ppm
Time: 4 hours
Endpoint: $BMCL_{05}$
Reference: Pennwalt Corporation, 1987

Time Scaling: $c^n \times t = k$, where the exponent, n, is the conservative default of 1 (8-hr) or 3 (30-min and 1-hr. 30-Min value is adopted as 10-min value.

Uncertainty Factors:
Interspecies = 3: Irritant
Intraspecies = 3: Irritant

Proposed AEGL-3 values are considered protective.

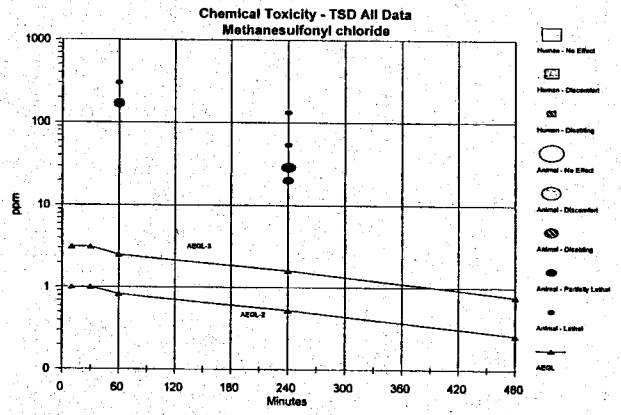
Using the TerHaar (1978) study (POD of 29 ppm for 6-hours; no mortality, but severe irritation present) and applying time scaling and uncertainty factors as described above:

10 minute	30 minute	1 hour	4 hour	8 hour
6.6 ppm	6.6 ppm	5.3 ppm	3.3 ppm	2.2 ppm

Summary of AEGL Values for Methanesulfonyl Chloride				
Classification	Exposure Duration			
	10-min	30-min	1-h	4-h	8-h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	1.0 ppm	1.0 ppm	0.83 ppm	0.53 ppm	0.26 ppm
AEGL-3	3.1 ppm	3.1 ppm	2.5 ppm	1.6 ppm	0.78 ppm

NR: Not Recommended due to insufficient data. Absence of an AEGL-1 value does not imply that concentrations below the AEGL-2 are without effect.

There are no other standards or guidelines for methanesulfonyl chloride!


Chemical Toxicity - TSD All Data
Methanesulfonyl chloride
1000
100
10
1
0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-1
AEGL-2
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Partially Lethal
Animal - Lethal
AEGL

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR SULFURYL FLUORIDE, SO_2F_2 (CAS NO. 2699-79-8)

NAC/AEGL-44
December 5-7, 2007

ORNL Staff Scientist: Jennifer Rayner

Chemical Manager: Susan Ripple

Chemical Reviewers: Daniel Sudakin, Alan Woolf

Sulfuryl Fluoride

Common Synonyms: Sulfonyl fluoride, Vikane, ProFume, sulfuryl difluoride, sulfur fluoride oxide

Conversion
1 ppm = 4.17 mg/m^3
1 mg/m^3 = 0.2392 ppm

Physical Characteristics:
- Gas- colorless, odorless

Uses:
- Restricted use fumigant- Insecticide, rodenticide
- Used in organic drug and dye synthesis

Mechanism of Toxicity

Sulfuryl Fluoride- The toxicity is thought to be due to the fluoride ion. Sulfuryl fluoride is hydrolyzed to fluorosulfate and then to sulfate with the fluoride ion being released.

Susceptible Populations
Workers using the fumigant, people entering fumigated structures prematurely

HUMAN DATA

Effects at lethal concentrations
Cardiopulmonary arrest
Fatal pulmonary congestion edema
Generalized seizures
Dyspnea

Effects at non-lethal concentrations
Nausea
Vomiting
Nasal mucosa inflammation

Concurrent exposures
Small amount of chloropicrin is mixed in to serve as warning agent

ANIMAL DATA

Miller et al. (1980). Sulfuryl fluoride (Vikane fumigant): An LC_{50} determination.

Species	Conc. (ppm)	Exposure Time	Mortality (%)	Effect
Rat	2025	4 hr	100 B	Central nervous system depression; convulsions; ocular irritation; lesions of the respiratory tract, kidneys, and liver
	1425		100 B	
	1250		60 M	
	1200		90 F	
	1020		10 F	
	1000		10 M	
	1000		100 F	
	1122		LC_{50} M	
	991		LC_{50} F	
	790		0	Some reduced body weight gain
	700		0	
	450		0	
	320		0	

Gorzinski and Streeter (1985). Effect of acute Vikane exposure on selected physiological parameters in rats.

Species	Conc. (ppm)	Exposure Time	Mortality (%)	Effect
Rat	20000	20 min	100	↓ Body temperature; ↓ heart rate; ↓ respiration; pale extremities
	4000		100	

Nitschke et al. (1986). Incapacitation and treatment of rats exposed to a lethal dose of sulfuryl fluoride.

Species	Conc. (ppm)	Exposure Time	Mortality (%)	Effect
Rat	40000	~ 6 min	100	Tonic convulsions; incapacitation; ↑ serum fluoride; cyanosis at ≥ 10000 ppm
	20000	~10 min	100	
	10000	~17 min	100	
	4000	~42 min	100	

Nitschke and Lomax (1989). Sulfuryl fluoride: Acute LC_{50} study with B6C3F1 mice.

Species	Conc. (ppm)	Exposure Time	Mortality (%)	Effect
Mouse	1003	4 hr	100	Tremors; lethargy
	603		100	
	404		0	No effects

Nitschke and Quast (1990). Sulfuryl fluoride: Acute LC_{50} study with CD-1 mice.

Species	Conc. (ppm)	Exposure Time	Mortality (%)	Effect
Mouse	806	4 hr	70	Tremors; lethargy; visceral congestion
	692		80	
	596		0	No effects

AEGL-1 Values for Sulfuryl Fluoride

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

AEGL-1 values were not derived due to steep dose response relationship and lack of effects below 603 ppm. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

AEGL-2 Values for Sulfuryl Fluoride

10-minute	30-minute	1-hour	4-hour	8-hour
37 ppm	26 ppm	20 ppm	13 ppm	6.3 ppm

Key Study: Nitschke and Lomax (1989). Sulfuryl fluoride: Acute LC_{50} study with B6C3F1 mice. The Dow Chemical Company. Midland, MI (March 22, 1989).

Toxicity endpoints: AEGL-2 values were based upon a 3-fold reduction in the AEGL-3 values. This estimate of a threshold for irreversible effects was justified because of the steep dose-response curve. In acute studies with the most sensitive species tested (mouse), no signs of toxicity were found at 404 or 596 ppm, but mortality occurred at 603 and 692.

Time scaling: Not directly applicable; AEGL-2 values derived from 3-fold downward adjustment of AEGL-3 values

Uncertainty factors: See discussion in the AEGL-3 section; AEGL-2 is 1/3 of the AEGL-3.

AEGL-3 Values for Sulfuryl Fluoride

10-minute	30-minute	1-hour	4-hour	8-hour
110 ppm	77 ppm	61 ppm	38 ppm	19 ppm

Key Studies: Nitschke and Lomax (1989). Sulfuryl fluoride: Acute LC_{50} study with B6C3F1 mice. The Dow Chemical Company. Midland, MI (March 22, 1989).

Toxicity endpoint: The AEGL-3 was based upon the $BMCL_{05}$ (383 ppm) in mice exposed for 4 hr. Mortality was present at 603 ppm.

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

Uncertainty factors: A total uncertainty factor of 10 was applied to account for interspecies extrapolation and intraspecies variability. A factor of 3 was applied for interspecies variability because a more sensitive species was used. Mortality in rats was observed at concentrations around 1000 ppm while a lower concentration 600 ppm caused mortality in mice. The calculated 4 hr LC_{50}s for rats was 991 and 1122 ppm and 642 and 660 ppm for mice. An uncertainty factor of 3 was used to account for intraspecies variability to protect sensitive individuals.

Summary of AEGL Values for Sulfuryl Fluoride

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)	37 ppm	26 ppm	20 ppm	13 ppm	6.3 ppm
AEGL-3 (Lethal)	110 ppm	77 ppm	61 ppm	38 ppm	19 ppm

AEGL-1 values were not derived due to steep dose response relationship and lack of effects below 603 ppm. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

Extant Standards and Guidelines for Sulfuryl Fluoride

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	37 ppm	26 ppm	20 ppm	13 ppm	6.3 ppm
AEGL-3	110 ppm	77 ppm	61 ppm	38 ppm	19 ppm
PEL-TWA (OSHA)					5 ppm
IDLH (NIOSH)		200 ppm			
REL-TWA (NIOSH)					5 ppm
REL-STEL (NIOSH)					10 ppm
TLV-TWA (ACGIH)					5 ppm
TLV-STEL (ACGIH)	10 ppm				
MAC (The Netherlands)					5 ppm

AEGL-1 values were not derived due to steep dose response relationship and lack of effects below 603 ppm. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR CARBONYL SULFIDE

NAC/AEGL-44
December 5-7, 2007
Orlando, FL

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Ralph Gingell

Chemical Reviewers: Ed Bernas and Ernest Falke

Similar to hydrogen sulfide:

An irritant at low concentrations

Causes respiratory paralysis and neurotoxicity at higher concentrations.

The hydrogen sulfide produced from the metabolism of carbonyl sulfide via carbonic anhydrase is thought to be responsible for carbonyl sulfide toxicity

STEEP CONCENTRATION-RESPONSE CURVE

Mortality in rats exposed to carbonyl sulfide for 4-hours (DuPont, 1981)	
Concentration (ppm)	Mortality
943	0/10
1090	4/10
1210	10/10

Mortality in rats exposed to carbonyl sulfide for 4-hours (Monsanto, 1985a)	
Concentration (ppm)	Mortality
993	0/12
1060	4/12
1147	11/12

Thiess et al. (1968) : Rats

No mortality: 1000 ppm for 75-min

3/6 dead: 1000 ppm for 90-min

AEGL-1 Values for Carbonyl Sulfide				
10-min	30-min	1-h	4-h	8-h
26 ppm	26 ppm	23 ppm	16 ppm	14 ppm

Species: Rat
Concentration: 150 ppm
Time: 6 hours
Endpoint: NOEL for all effects (next highest concentration of 300 ppm is a NOEL for severe clinical signs and brain pathology)
Reference: Morgan et al, 2004

Time Scaling: $c^n \times t = k$, where the exponent, n, is 4.4, derived from hydrogen sulfide rat lethality data ranging from 10-min to 6-hr. 30-Min value is adopted as 10-min value.

Uncertainty Factors:
Intraspecies: 3: Considered sufficient due to the steep concentration-response curve

Interspecies: 3
Although the animal data suggest some species variability and the rat is not the most sensitive species, use of the full default interspecies UF of 10 would yield AEGL-1 values that are less consistent with the overall database.

Proposed AEGL-1 values are considered protective:

No treatment-related effects in rats repeatedly exposed to 51 ppm, 6-hr/day for 11 days (Monsanto, 1985b).

AEGL-2 Values for Carbonyl Sulfide				
10-min	30-min	1-h	4-h	8-h
53 ppm	53 ppm	45 ppm	33 ppm	28 ppm

Species: Rat
Concentration: 300 ppm
Time: 6 hours
Endpoint: NOEL for clinical signs and brain pathology
Reference: Morgan et al, 2004

Time Scaling: $c^n \times t = k$, where the exponent, n, is 4.4, derived from hydrogen sulfide rat lethality data ranging from 10-min to 6-hr. 30-Min value is adopted as 10-min value.

Uncertainty Factors:
Intraspecies: 3: Considered sufficient due to the steep concentration-response curve

Interspecies: 3
Although the animal data suggest some species variability and the rat is not the most sensitive species, use of the full default interspecies UF of 10 would yield AEGL-2 values that are less consistent with the overall database.

Proposed AEGL-2 values are considered protective:

No treatment-related effects in rats repeatedly exposed to 51 ppm, 6-hr/day for 11 days (Monsanto, 1985b) and 75 or 150 ppm 6-hr/day for 4 days (Morgan et al., 2004).

No other standards or guidelines!

Summary of AEGL Values For Carbonyl Sulfide					
Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1	26 ppm	26 ppm	23 ppm	16 ppm	14 ppm
AEGL-2	53 ppm	53 ppm	45 ppm	33 ppm	28 ppm
AEGL-3	150 ppm	150 ppm	130 ppm	95 ppm	81 ppm

AEGL-3 Values for Carbonyl Sulfide				
10-min	30-min	1-h	4-h	8-h
150 ppm	150 ppm	130 ppm	95 ppm	81 ppm

Species: Rat
Concentration: 952 ppm
Time: 4 hours
Endpoint: Lethality threshold ($BMCL_{05}$ and BMC_{01})
Reference: Monsanto, 1985a

Time Scaling: $c^n \times t = k$, where the exponent, n, is 4.4, derived from hydrogen sulfide rat lethality data ranging from 10-min to 6-hr. 30-Min value is adopted as 10-min value.

Uncertainty Factors:
Intraspecies: 3: Considered sufficient due to the steep concentration-response curve

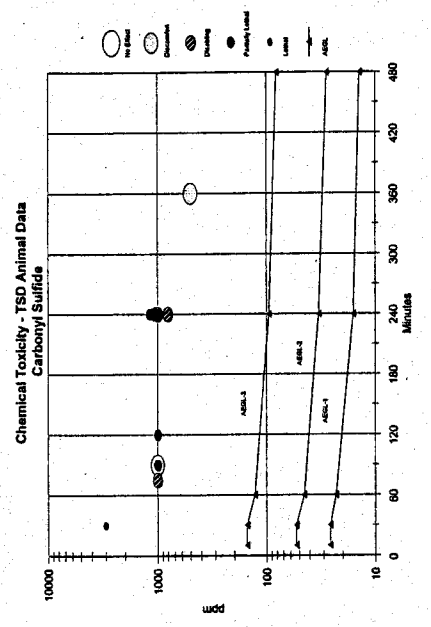
Interspecies: 3
Although the animal data suggest some species variability and the rat is not the most sensitive species, use of the full default interspecies UF of 10 would yield AEGL-2 values that are less consistent with the overall database.

Proposed AEGL-3 values are considered protective:

No treatment-related effects in rats repeatedly exposed to 75, 150, or 300 ppm 6-hr/day for 4 days (Morgan et al., 2004).

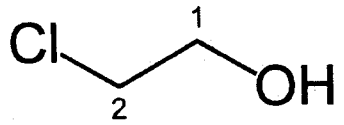
No treatment-related clinical signs of FOB effects in male and female rats exposed to 300 ppm, 6 hr/day, 5 days/week for 12 exposures in a two-week period; brain lesions were noted only in 1/5 females in this study (Morgan et al., 2004).

No mortality or clinical signs in rats exposed to 200, 300, or 400 ppm 6 hr/day, 5 days/week for 12-weeks; however, significant decreases in brain cholinesterase activity were noted at all three concentrations (Morgan et al., 2004).



ATTACHMENT 16

2-Chloroethanol
(Ethylene Chlorohydrin)
(CAS Reg. No. 107-07-3)



NAC/AEGL-44
Orlando, FL
December 5-7, 2007

ORNL Staff Scientist: Robert A. Young
Chemical Manager: George Rusch
Chemical Reviewer: Martha Steele
Chemical Reviewer: Dieter Heinz

2-Chloroethanol

- Intermediate for pesticides, plasticizers, dyes, ethylene oxide
- High production volume; generally >99% purity

2-Chloroethanol
Human Exposure

- **Lethality**
  - **2 hrs, 300ppm (est.) (Dierker and Brown, 1944)**
  - **Exposure terms insufficient or absent**

- **Nonlethal effects (multi-organ involvement)**
  - **Odor threshold - 0.4 ppm (Semenova et al., 1980)**
  - **Qualitative information only**
    - **Nausea, epigastric pain**
    - **Shock, circulatory effects**
    - **Headache, giddiness, incoordination**
    - **Rhonchi, cough**
    - **Dermal erythema**

2-Chloroethanol
Animal Lethality

- **Data for multiple species**
  - **Generally, lethality occurred post exposure**
  - **Exposure-response relationship data are limited**
    - **Most data for nonlethality or 100% (or near 100%) lethality**

- **Additional data may be available (BASF ??)**

2-Chloroethanol
Animal Lethality

Lethality in Laboratory Species Following a single Exposure to 2-Chloroethanol Vapor.			
Species/Exposure Concentration	**Exposure Duration (min.)**	**Cumulative Exposure (ppm · min.)**	**Response**
Rat			
0.003 g/L (840 ppm)	15	12,600	Non lethal
0.004 g/L (1120 ppm)	30	33,600	3/3 dead next day
0.003 g/L (678 ppm)	60	40,680	Lethal next day
0.003 g/L (226 ppm)	120	27,120	Non lethal
32 ppm	240	7,680	LC_{50}
33 ppm	240	7,920	LC_{50}
Mouse			
0.001 g/L (280 ppm)	120	33,600	Non lethal
0.003 g/L (840 ppm)	60	50,400	3/3 dead next day
0.0032 g/L (896 ppm)	60	53,760	3/3 dead next day
0.0039 g/L (1,090 ppm)	15	16,350	2/3 dead after 2 days
0.0039 g/L (1,090 ppm)	120	130,800	3/3 dead in 140-170 min.
0.0045 g/L (1,260 ppm)	30	37,800	3/3 dead next day
0.0052 g/L (1,460 ppm)	60	87,600	3/3 dead in 100 min. to next day
0.007 g/L (1,960 ppm)	120	235,2000	3/3 dead in 110-129 min.
Guinea Pig			
0.003 g/L (840 ppm)	30	25,200	Non lethal
0.003 g/L (840 ppm)	120	100,800	Dead next day
0.0039 g/L (1,090 ppm)	108	117,720	Dead next day
0.005g/L (1,460 ppm)	55	80,300	Non lethal

2-Chloroethanol
AEGL-2

AEGL-2 Values for 2-Chloroethanol (ppm)					
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-2	**11**	**4.7**	**3.2**	**1.3**	**0.63**

- **Data are insufficient for developing AEGL-2 values for 2-chloroethanol.**

- **AEGL-2 values estimated as one third of AEGL-3 values (NRC, 2001)**
  - **Limited data suggest steep exposure-response relationship**
    - **280 ppm, 120 min - not lethal to mice**
    - **1,090 ppm 120 ppm - 100% lethality (3/3) in mice**

2-Chloroethanol
AEGL-1

AEGL-1 Values for 2-Chloroethanol (ppm)					
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1	**NR**	**NR**	**NR**	**NR**	**NR**

Data are unavailable with which to develop AEGL-1 values for 2-chloroethanol

2-Chloroethanol
AEGL-2

AEGL-2 Values for 2-Chloroethanol (ppm)					
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-2	**11**	**4.7**	**3.2**	**1.3**	**0.63**

- **Data are insufficient for developing AEGL-2 values for 2-chloroethanol.**

- **AEGL-2 values estimated as one third of AEGL-3 values (NRC, 2001)**
  - **Limited data suggest steep exposure-response relationship**
    - **280 ppm, 120 min - not lethal to mice**
    - **1,090 ppm 120 ppm - 100% lethality (3/3) in mice**

2-Chloroethanol
AEGL-3

AEGL-3 Values for 2-Chloroethanol (ppm)					
Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	32	14	9.5	3.8	1.9

Key Study: Goldblatt, M.W. 1944. Toxic effects of ethylene chlorohydrin. Part II. Experimental. Br. J. Ind. Med. 1:213-223.

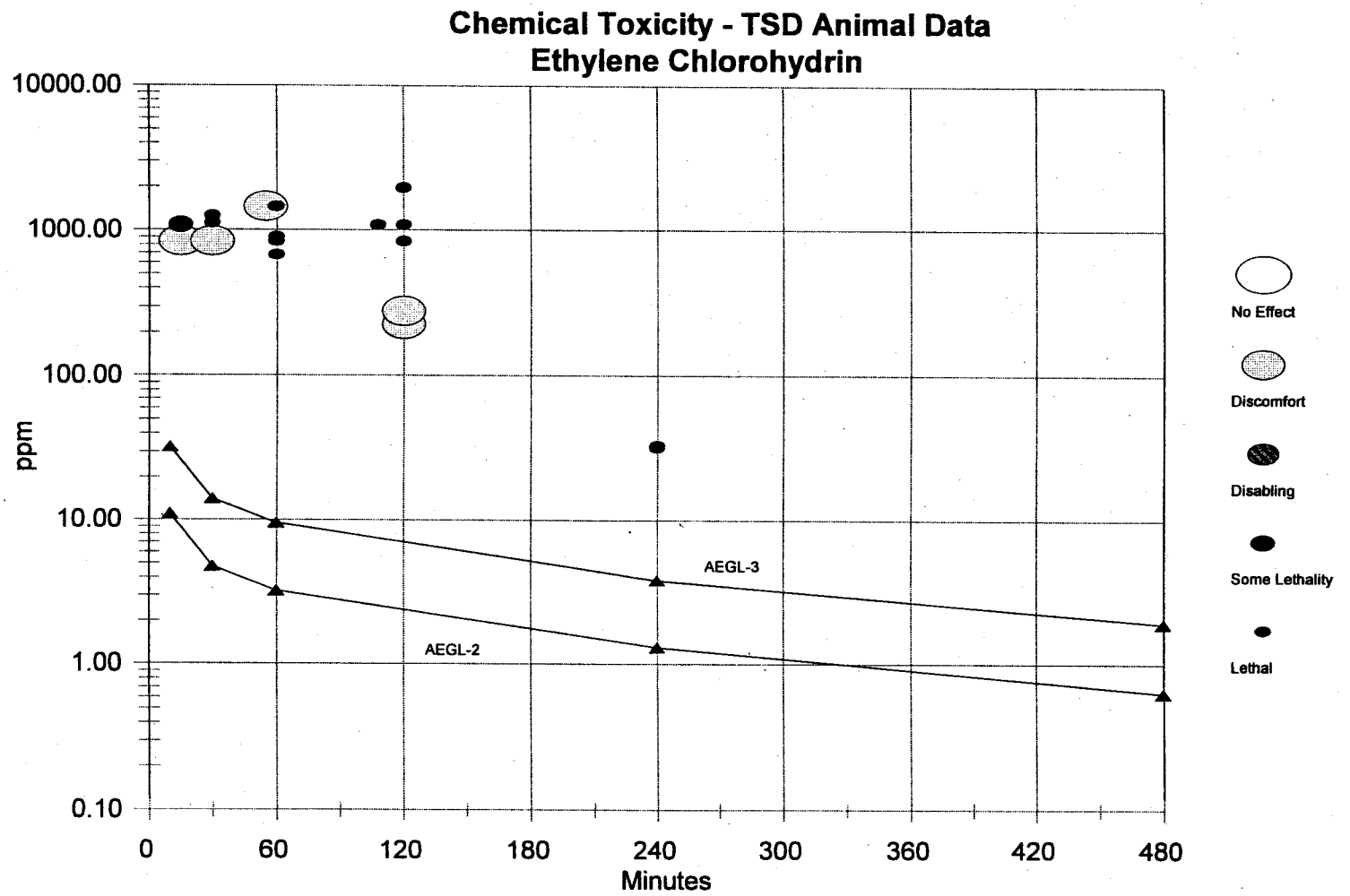
Critical effect/POD: Estimated lethality threshold in rats based upon lowest nonlethal exposure.
840 ppm, 15 min. (for 10-min and 30-min AEGL-3 values)
226 ppm, 120 min. (for 1-hr, 4-hr, and 8-hr AEGL-3 values)

Time scaling: $C^n \times t = k$, where $n = 1$ or 3

Uncertainty factors Total uncertainty factor: 30
Interspecies: 3; Based upon the differences in the lethal response between the rats and mice, an interspecies uncertainty factor of 3 was considered appropriate.

Intraspecies: 10; 2-Chloroethanol does not appear to be a direct-contact irritant and death in animals does not appear to be a function of damaged respiratory tract epithelial tissue. In the absence of data regarding the mode of action of 2-chloroethanol toxicity and because of the small numbers of animals used in the reported studies, an intraspecies uncertainty of 10 is retained.

Summary of AEGL Values for 2-Chloroethanol					
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1 (Nondisabling)	**NR**	**NR**	**NR**	**NR**	**NR**
AEGL-2 (Disabling)	**11 ppm 36 mg/m^3**	**4.7 ppm 15 mg/m^3**	**3.2 ppm 11 mg/m^3**	**1.3 ppm 4.3 mg/m^3**	**0.63 ppm 2.1 mg/m^3**
AEGL-3 (Lethality)	**32 ppm 110 mg/m^3**	**14 ppm 46 mg/m^3**	**9.5 ppm 31 mg/m^3**	**3.8 ppm 13 mg/m^3**	**1.9 ppm 6.3 mg/m^3**


Chemical Toxicity - TSD Animal Data
Ethylene Chlorohydrin
10000.00
1000.00
100.00
10.00
1.00
0.10
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
No Effect
Discomfort
Disabling
Some Lethality
Lethal