National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-46
June 25-27, 2008

Boston Radisson
200 Stuart Street
Boston, MA

AGENDA

Wednesday, June 25, 2008

10:00 a.m.	*Development team meetings: Trimethyl acetyl chloride; Methyl iodide; n-Butyl isocyanate
11:00	Introductory remarks and approval of NAC/AEGL-45 Highlights (George Rusch, Ernie Falke, and Paul Tobin)
11:15	Status Update/ No Data Chemicals: 3,5-Dichloro-2,4,6-trifluoropyridine; Acetyl chloride; Arsenic pentaoxide; Ethylphosphonoous dichloride; Methyl paroxon; Nitrosyl chloride; Sodium dithionite; Trifluoroacetyl chloride (Cheryl Bast)
11:30	Phosgene: Approach to New Data (Cheryl Bast/Ernie Falke)
12:30 p.m.	Lunch
1:30	Review of Methyl Iodide (Alan Becker/Sylvia Talmage)
3:00	Break
3:15	Revisit of n-Butyl isocyanate: New Data for AEGL-1 and AEGL-2 (Susan Ripple/Bob Young) [No data chemicals: Isobutyl isocyanate; Isopropyl isocyanate; Methoxymethyl isocyanate; n-Propyl isocyanate; t-Butyl isocyanate]
4:30	Review of Trimethylacetyl chloride (George Rusch /Cheryl Bast)
5:30	Adjourn for the day

Thursday, June 26, 2008

8:30 a.m.	*Development team meetings: Organophosphates (Methyl Parathion; Parathion; Phorate); tert-Octyl Mercaptan; Ethyl Benzene
9:30	Revisit of 1,1,1-Trichloroethane: PBPK Issues (Bob Benson/Sylvia Talmage)
10:45	Break
11:00	Review of Germane (David Freshwater/Cheryl Bast)
12:00 p.m.	Lunch
1:00	Review of Methyl Parathion (Jim Holler/Bob Young)
2:00	Review of Parathion (Jim Holler/Bob Young)
3:00	Break
3:15	Review of Phorate (Susan Ripple/ Tom Marshall/ Sylvia Talmage)
4:15	Revisit of Ethyl benzene AEGL-2 (John Hinz/Carol Wood)
5:30	Adjourn for the day

Friday, June 27, 2008

8:30 a.m.	Review of tert-Octyl Mercaptan (Glenn Leach/Cheryl Bast)
10:30	Break
10:45	Administrative matters
12:00 noon	Adjourn meeting

*See page 2.

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

Pre-meeting Small Discussion Groups: NAC-45

	Chemical	Staff Scientist	CM	Reviewer	Reviewer	Other Attendees
Wed. 6/25/08 10:00 a.m.						
	Methyl Iodide	Talmage	Becker	Hinz**	Bernas	Camacho, Grant, VanRaaij, Willhite, Woolf
	n-Butyl isocyante	Young	Ripple	Freshwater*	Gingell*	Anderson, Cushmac, Leach, Steele, Sudakin, Woodall
	Trimethyl acetyl chloride	Bast	Rusch	Tobin	Beasley	Baril, Chapman, Heinz, Holler, Niemeier, (Hinz**)
Thurs. 6/26/08 8:30 a.m.	Organophosphates: Methyl Parathion Parathion Phorate	 Young Young Marshall/Talmage	 Holler** Holler** Ripple**	 VanRaaij VanRaaij VanRaaij	 Woolf Woolf Sudakin	Anderson, Becker, Freshwater, Niemeier, Willhite, Woodall
	Tert-Octyl Mercaptan	Bast	Leach	Ripple**	Steele	Beasley, Bernas, Chapman, Grant, Rusch
	Ethyl Benzene	Wood	Hinz	Camacho	Holler**	Baril, Benson, Cushmac, Heinz

At this time, the following chemical does not have a formal pre-meeting discussion scheduled: Germane; 1,1,1-Trichloroethane

*David Freshwater will not be available for this pre-meeting discussion. Ralph Gingell is not attending NAC-46.

**These individuals are "double-booked." This was unavoidable due to CM/Reviewer assignments and attendance/scheduling constraints.

NAC/AEGL Meeting 46: June 25-27, 2008

ATTACHMENT 2

Chemical: NAC/AEGL 46 ATTENDANCE **CAS Reg. No.:**

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

Chemical Manager:

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Henry Anderson ✓				
Marc Baril ✓				
Lynn Beasley				
Alan Becker ✓				
Robert Benson ✓				
Edward Bernas ✓				
Iris Camacho ✓				
Gail Chapman ✓				
George Cushmac ✓				
David Freshwater				
Ralph Gingell				
Roberta Grant ✓				
Dieter Heinz ✓				
Mathias Öberg				
~~Amanda Hartman~~ Beth Mileson				

Staff Scientist:

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
John Hinz				
Jim Holler				
Glenn Leach				
Richard Niemeier				
Susan Ripple ✓				
George Rusch, Chair ✓				
Martha Steele				
Daniel Sudakin ✓				
Marcel vanRaaij ✓				
Calvin Willhite ✓				
George Woodall ✓				
Alan Woolf ✓				
Amanda Hartman ✓				
TALLY				
PASS/ FAIL				

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

*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:** 6/25/08

ATTACHMENT 3

PHOSGENE: APPROACH TO RECENT DATA

NAC/AEGL-46
June 25-27, 2008
Boston, MA

Cheryl Bast

Bill Bress
David Belluck
Larry Gephart

Phosgene AEGL Values: Recent data considerations

Steep concentration-response

Time scaling: n = 1.15

UF: 3 x 3 = 10

Rat lethality study: Pauluhn, J. 2006a. Acute nose-only exposure of rats to phosgene. Part I. Concentration x time dependence of LC_{50}s, non-lethal-threshold concentrations and analysis of breathing patterns. Inhalation Toxicology 18:423-435.

Rat lung parameter study: Pauluhn, J. 2006b. Acute nose-only exposure of rats to phosgene. Part II. Concentration x time dependence of changes in bronchoalveolar lavage during a follow-up period of 3 months. Inhalation Toxicology 18:595-607.

Dog study: Pauluhn, J. 2006c. Acute head-only exposure of dogs to phosgene. Part III. Comparison of indicators of lung injury in dogs and rats. Inhalation Toxicology 18:609-621.

Dogs sacrificed 24-hr post-exposure

Pauluhn Conclusions:

Dog is better model to extrapolate to humans (physiology of respiratory tract and acinar structure of the lung)

Pauluhn studies suggest that phosgene is slightly more toxic than found in Zwart et al., study *(nose-only vs. whole body?)*

Current Phosgene AEGL Values

Published in Volume 2

Little species variability

Steep concentration-response

Time scaling: n = 1

UF: 3 x 3 = 10

AEGL-2:

Key Study: Gross, P., W.E. Rinehart and T. Hatch. 1965. Chronic pneumonitis caused by phosgene: an experimental study. Arch Environmental Health 10:768-775.

POD: Chemical pneumonia in rats (2 ppm; 1.5 hr); Chronic pneumonitis noted at lower concentrations/durations

AEGL-3:

Key Study: Zwart, A., J.H.E. Arts and J.M. Klokman-Houweling. 1990. Determination of concentration-time-mortality relationships to replace LC_{50} values. Inhalation Toxicology 2:105-117.

Whole body study. Exposure atmospheres well-circulated in chamber.

POD: Highest concentration causing no death in rats after a 10-min (36 ppm) or 30-min (15 ppm) exposure.

TABLE 8. ***Pauluhn (2006a)* vs. Zwart et al. (1990) rat lethality data**

Duration	Concentration (ppm)	Mortality	LC (ppm)
10-minutes			
	12	0/10	LC_{50} = 82 ppm
	*36	0/10	*LC_{50} = 62 ppm*
	41.1	*3/10*	
	44.8	*0/10*	$BMCL_{05}$ = 55.6 ppm
	52.3	*2/10*	*$BMCL_{05}$ = 24.3 ppm*
	61.9	*6/10*	
	74	3/10	BMC_{01} = 60.8 ppm
	79	1/10	*BMC_{01} = 32.6 ppm*
	87	4/10	
	91	9/10	
	105	9/10	
30-minutes	12	0/10	LC_{50} = 21 ppm
	12.6	*4/10*	*LC_{50} = 13.5 ppm*
	13.4	*4/10*	
	**15	0/10	$BMCL_{05}$ = 12.6 ppm
	16	1/10	*$BMCL_{05}$ = 5.0 ppm*
	16.7	*10/10*	
	17	5/10	BMC_{01} = 10.7 ppm
	21.4	*9/10*	*BMC_{01} = 7.4 ppm*
	24	9/10	
1-hour	6.4	1/10	LC_{50} = 12 ppm
	7.4	*4/10*	*LC_{50} = 7.7 ppm*
	8.8	2/10	
	9.0	0/10	$BMCL_{05}$ = 7.8 ppm
	9.7	*9/10*	*$BMCL_{05}$ = 3.9 ppm*
	11.8	*10/10*	
	12	9/10	BMC_{01} = 9.8 ppm
			BMC_{01} = 5.3 ppm

* POD for 10-min AEGL-3
**POD for 30-min, 1-hr, 4-hr, and 8-hr AEGL-3

Comparison of Published (Volume 2) Phosgene AEGL values with Values derived from new rat data.

Summary of AEGL Values for Phosgene [ppm]						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hour**	**Endpoint (Reference)**
AEGL-1	NR *NR*	NR *NR*	NR *NR*	NR *NR*	NR *NR*	-
AEGL-2	0.60	0.60	0.30	0.08	0.04	POD: 2 ppm, 1.5 hours. Chemical pneumonia rats Reference: Gross et al., 1965 n=1 UF = 3 x 3
	0.52	*0.20*	*0.11*	*0.020*	*0.011*	*10-min, 30-min, & 1-hr POD: 2 ppm, 30 min.* *4-hr & 8-hr POD: 0.2 ppm, 4 hr.* *LOAEL for increased protein in BAL fluid in rats, resolved by Day 7 post-exposure* *Reference: Pauluhn, 2006b* *n = 1.15* *UF = 3 x 3*
AEGL-3	3.6	1.5	0.75	0.20	0.09	10-min POD: 36 ppm, 10-min 30-min, 1-hr, 4-hr, & 8-hr POD: 15 ppm, 30-min. Highest concentration causing no mortality in the rat after a 10-, or 30-min exposure Reference: Zwart et al., 1990 n=1 UF = 3 x 3
	2.4	*0.50*	*0.39*	*0.12*	*0.064*	*10-min POD: 24.3 ppm, 10-min; 10-min rat $BMCL_{05}$* *30-min POD: 5.0 ppm, 30-min; 30-min rat $BMCL_{05}$* *1-hr, 4-hr, & 8-hr POD: 3.9 ppm, 1-hr; 1-hr rat $BMCL_{05}$* *Reference: Pauluhn, 2006b* *n = 1.15 (4- & 8-hr)* *UF = 3 x 3*

AEGL for ETHYLBENZENE

NAC-AEGL #46
[25-27 June 08]

Chemical manager	John P. Hinz
Chemical Reviewers	Jim Holler
	Iris Camacho
Principal Author	Carol S. Wood

PREVIOUS ACTION ON ETHYLBENZENE

1. September, 2006
   - ✓ New data presented from industry
2. December, 2006
   - ✓ Agreed on PBPK modeling for AEGL 2 and 3
3. March, 2008
   - ✓ AEGL 1 & 3 passed
     - AEGL 1 (human data): Yes: 18; No: 0
     - AEGL 3 (highest non-lethal): Yes: 17; No: 0
   - ✓ Endpoint and POD for AEGL 2 chosen
4. June, 2008
   - ➢ Finish this !

SUMMARY OF AEGL VALUES FOR ETHYLBENZENE
(PBPK model used for derivation of AEGL 3)

	10-min	30-min	1-hr	4-hr	8-hr
AEGL 1 (UF = 3)	33 ppm	33 ppm	33 ppm	33 ppm	33 ppm
AEGL 2 (UF = ?)					
AEGL 3 (UF = 3)	4700 ppm	2600 ppm	1800 ppm	1000 ppm	910 ppm

ISSUES

- Comments from LyondellBasell Industries
  - AEGL 2 values may not be protective of ototoxicity
  - Hair cell loss in rats:
    - 200 ppm, 6 hr/d, 13 weeks
    - 550 ppm, 8 hr/d, 5 days
  - Also seen with toluene, styrene from repeated exposure (no evidence with xylenes)
  - Styrene effects may be concentration-dependent, not duration-dependent
- No single exposure studies with EB for ototoxicity

ISSUES (con't)

- AEGLs for styrene
  - 1 and 2: irritation and CNS in humans
  - 3: no lethality, rat
- AEGLs for toluene (PBPK model for -2 and -3)
  - 1: notable discomfort in humans
  - 2: NOAEL for narcosis, rat
  - 3: NOAEL for lethality, rat
- AEGLs for ethylbenzene (PBPK model for -2 and -3)
  - 1: highest no effect in humans
  - 2: NOAEL for narcosis, rat
  - 3: highest non-lethality, rat

AEGL 2: KEY STUDY AND POD

- Molnar et al. 1986
  - 1500 ppm for 4 hours **[NOT 2180 ppm as in TSD]**
  - Threshold for narcosis
- Same PBPK model used for derivation as for AEGL 3
  - Using a PBPK model, the internal dose (Cv) for narcotic threshold in rats was determined.
  - Then, the human PBPK model was run for each defined AEGL time point to determine the equivalent exposure concentration producing the target Cv.
  - Total UF = 3 was applied to the AEGL-2 and -3 dose metrics.
    - Interspecies UF = 1 because PBPK modeling reduced the uncertainty factor to 1 because it appears similar exposure effects (central nervous system effects) occur in humans and animals.
    - Intraspecies UF = 3 because the MAC (minimum alveolar concentration) for volatile anesthetics should not vary by more than a factor of 2-3-fold among humans.

PBPK MODEL FOR ETHYLBENZENE

- Lisa Sweeney, *The Sapphire Group, Inc.*
- Supported by ACC EB Panel
- Peer review by Jim Dennison
- Used for derivation of AEGL 2 and 3
- AEGL 3 passed at NAC 45
- Vote on AEGL 2

PROPOSED AEGL VALUES FOR ETHYLBENZENE
(PBPK model used for derivation of AEGL 2 and 3)

	10-min	30-min	1-hr	4-hr	8-hr
AEGL 1 (UF = 3)	33 ppm	33 ppm	33 ppm	33 ppm	33 ppm
AEGL 2 (UF = 3)	**2900 ppm**	**1600 ppm**	**1100 ppm**	**660 ppm**	**580 ppm**
AEGL 3 (UF = 3)	4700 ppm	2600 ppm	1800 ppm	1000 ppm	910 ppm

- ***Need vote on AEGL 2***
- ***Add caveat that may not be protective of ototoxicity?***

n-BUTYL ISOCYANATE (BI)

REVISIT

n-BUTYL ISOCYANATE (BI)
Human Data

- **Du Pont, 1986: industrial hygiene survey**
  - **5 to 10 ppb (0.005 to 0.01 ppm) resulted in ocular irritation**
  - **50 ppb (0.05 ppm) normal work operations were not possible but not expected to impair escape**

- **Du Pont, 1994: reassessment of sampling analysis for BI exposure**
  - **XAD7/HPLC vs impinger/GC method**
    - **at BI levels < 20 ppb, ~2-4 fold higher values using XAD7/HPLC**
    - **20-40 ppb (0.02 - 0.04 ppm) rather 5-10 ppb (0.005-0.01 ppm)**

n-BUTYL ISOCYANATE (BI)
Human Data

- Review of newer sampling data (1994)
  - Personal air samples (7 to 8-hr sampling)
    - exposures of 12.9-52.8 ppb (0.013-0.053 ppm) were without eye irritation
  - Log book data
    - exposure to 8-40 ppb (0.008-0.040 ppm) were without eye irritation
  - 5-10 ppb (0.005-0.01 ppm) levels reportedly causing eye irritation in the 1970s were more realistically 20-40 ppb (0.02-0.04 ppm)

Adjustment of AEGL-1

- Use lower range of updated estimate of 0.02 ppm (vs 0.005 ppm) for DuPont & Co. (1986) worker data as POD
  - 0.02 ppm/3 = 0.0067 ppm (vs original value of 0.0017 ppm)

OR

- Simply increase original AEGL-1 values by 4-fold as per new assessment
  - 0.0017 ppm x 4 = 0.0068 ppm

Adjustment of AEGL-2

- New assessment does not provide an AEGL-2 critical effect level
  - all exposures were without ocular irritation

- Proposal: increase AEGL-2 values by 40% as per new assessment
  - 0.017 ppm x 1.4 = 0.024 ppm

Adjustment of AEGL-3

- Assumption: exposure levels in DuPont & Co. (1968) rat study also too low

- Proposal: increase AEGL-3 values by 40% as per new assessment
  - 10-min: 0.22 ppm x 1.4 = 0.31 ppm
  - 30-min: 0.22 ppm x 1.4 = 0.31 ppm
  - 1-hr: 0.18 ppm x 1.4 = 0.25 ppm
  - 4-hr: 0.11 ppm x 1.4 = 0.15 ppm
  - 8-hr: 0.057 ppm x 1.4 = 0.080 ppm

AEGL values for n-butyl isocyanate (ppm)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	0.0017 0.0068	0.0017 0.0068	0.0017 0.0068	0.0017 0.0068	0.0017 0.0068
AEGL-2 (Disabling)	0.017 0.024	0.017 0.024	0.017 0.024	0.017 0.024	0.017 0.024
AEGL-3 (Lethality)	0.22 0.31	0.22 0.31	0.18 0.25	0.11 0.15	0.057 0.080

Comparison of AEGL Values for Selected Isocyanates				
	Methyl Isocyanate*	n-Butyl Isocyanate	Ethyl Isocyanate	Phenyl Isocyanate
AEGL-1				
10-min	NR	0.0017 0.0068	NR	0.020
30-min	NR	0.0017 0.0068	NR	0.020
1 hour	NR	0.0017 0.0068	NR	0.020
4 hours	NR	0.0017 0.0068	NR	0.020
8 hours	NR	0.0017 0.0068	NR	0.020
AEGL-2				
10-min	0.40	0.017 0.024	0.070	0.18
30-min	0.13	0.017 0.024	0.070	0.18
1 hour	0.067	0.017 0.024	0.053	0.15
4 hours	0.017	0.017 0.024	0.033	0.092
8 hours	0.008	0.017 0.024	0.023	0.060
AEGL-3				
10-min	1.2	0.22 0.31	0.21	0.30
30-min	0.40	0.22 0.31	0.21	0.30
1 hour	0.20	0.18 0.25	0.16	0.24
4 hours	0.05	0.11 0.15	0.10	0.15
8 hours	0.025	0.057 0.080	0.068	0.075

* NRC, 2003

Physical-Chemical Properties of Butyl Isocyanates and Propyl Isocyanates

	n-butyl isocyanate	Isobutyl isocyanate	t-butyl isocyanate	n-propyl isocyanate	Isopropyl isocyanate
Chemical formula	C_5H_9NO	C_5H_9NO	C_5H_9NO	C_4H_7NO	C_4H_7NO
Structure	CH_3-CH_2-CH_2-CH_2- N=C=O	CH_3-CH(CH_3)-CH_2-N=C=O	CH_3-C(CH_3)(CH_3)-N=C=O	CH_3-CH_2-CH_2- N=C=O	CH_3-CH(CH_3)- N=C=O
Molecular weight	99.1	99.1	99.1	85.1	85.1
CAS Registry No.	111-36-4	1873-29-6	1609-86-5	110-78-1	1795-48-8
Physical state	Liquid	-	Liquid	Liquid	Liquid
Solubility in water	-	Insoluble/reactive	-	-	Insoluble
Vapor pressure	17 mm Hg @ 24°C	-		-	-
Relative vapor density	3.4	-		-	-
Flash point/boiling point	19°C/115 °C	22.8°C/–		-1°C /83 °C	-10°C /74 °C
Melting point	-	-		-30°C	-

ATTACHMENT 6

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR TRIMETHYLACETYL CHLORIDE

C_5H_9ClO

NAC/AEGL-46
June 25-27, 2008, 2008
Boston, MA

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: George Rusch

Chemical Reviewers: Lynn Beasley and Paul Tobin

No human Data

Limited Animal Data:

Species	Duration	Concentration	Mortality	Clinical signs	Reference
Rat	6-hr	78 ppm	0/3	Rough coat, Labored breathing, Decreased BW	Eastman Kodak, 1992
		249 ppm	3/3 (in 3.5 hr)	Labored breathing, Loss of Coordination, Gasping, Jumping, Prostration in 3-hr	
Rat	*1-hr*	*200 ppm*	*None*	-	*BASF, 1969 (cited in IUCLID)*
Mouse	30-min	115 ppm	1/4	Increased lung weight	Hardy and Kieran, 1992
		180 ppm	3/4	Vascular congestion	
		634 ppm	3/4	Alveolar edema Lung Necrosis	
		290 ppm	RD_{50}		
		101-182 ppm	Estimated LC_{50}		

Mechanism:

Irritation, Corrosion, Other?

Structural Analogs:

-Acetyl chloride- No data

-Chloroacetylchloride and Dichloroacetyl chloride-

Hydrolyze rapidly to form HCl which is responsible for acute inhalation toxicity

AEGL-1 VALUES: TRIMETHYLACETYL 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 Trimethylacetyl Chloride				
10-min	30-min	1-h	4-h	8-h
2.0 ppm (9.8 mg/m^3)	2.0 ppm (9.8 mg/m^3)	1.6 ppm (7.8 mg/m^3)	1.0 ppm (4.9 mg/m^3)	0.67 ppm (3.3 mg/m^3)

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

Approach is justified by the steep concentration-response curve

RATS (Eastman Kodak, 1992)

0% mortality in rats exposed to 78 ppm for 6-hours

100% mortality at 249 ppm for 3.5-hours

MICE (Hardy and Kieran, 1992)

25% mortality in mice exposed to 115 ppm for 30-minutes

75% mortality at 180 ppm for 30-minutes

AEGL-3 Values for Trimethylacetyl Chloride				
10-min	30-min	1-h	4-h	8-h
5.9 ppm (29 mg/m^3)	5.9 ppm (29 mg/m^3)	4.7 ppm (23 mg/m^3)	3.0 ppm (15 mg/m^3)	2.0 ppm (9.8 mg/m^3)

Species: Rat
Concentration: 78 ppm
Time: 6 hours
Endpoint: No mortality (100% mortality occurred at next highest concentration tested (249 ppm)
Reference: Eastman Kodak, 1992

Time Scaling: $c^n \times t = k$, where the exponent, n, is the conservative default of 1 (8-hr) or 3 (30-min, 1-hr, and 4-hr. 30-Min value is adopted as 10-min value)

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

Portal of entry/primary irritant effects are not expected to vary greatly within or between species.

Modifying Factor: 3, Sparse database

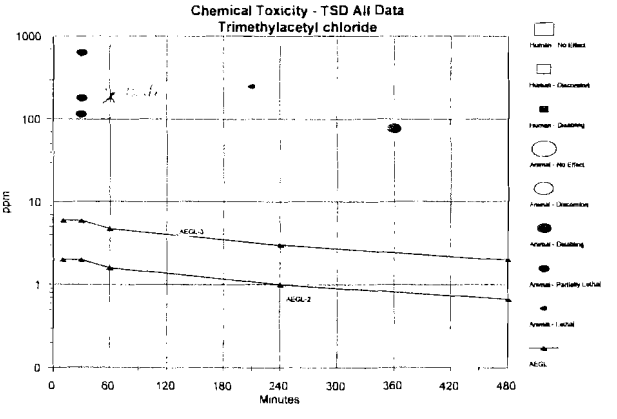
Values are considered protective:

The 30-minute AEGL-3 value is approximately 25-fold lower than the estimated 30-minute LC_{50} value of 101-182 ppm from the mouse RD_{50} study (Hardy and Kieran, 1992).

The 4-hour AEGL-3 value is approximately 100-fold lower than the 249 ppm that caused 100% mortality in rats exposed to trimethylacetyl chloride for 3.5 hours (Eastman Kodak, 1992).

Summary of AEGL Values					
Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	2.0 ppm (9.8 mg/m^3)	2.0 ppm (9.8 mg/m^3)	1.6 ppm (7.8 mg/m^3)	1.0 ppm (4.9 mg/m^3)	0.67 ppm (3.3 mg/m^3)
AEGL-3	5.9 ppm (29 mg/m^3)	5.9 ppm (29 mg/m^3)	4.7 ppm (23 mg/m^3)	3.0 ppm (15 mg/m^3)	2.0 ppm (9.8 mg/m^3)

There are no other standards or guidelines for trimethylacetyl chloride!



ATTACHMENT 7

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

GERMANE

GeH_4

NAC/AEGL-46
June 25-27, 2008
Boston, MA

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: David Freshwater

Chemical Reviewers: John Hinz and Calvin Willhite

Colorless gas with a pungent odor

Used as a doping agent for solid-state electronic components

Shipped as a compressed gas

Inhalation exposure may result in malaise, headache, dizziness, fainting, dyspnea, nausea, vomiting, kidney injury, and hemolytic effects (NIOSH, 2005).

Described as a hemolytic agent, similar in properties to arsine and stibine.

Extremely sparse data set

TABLE 3. Exposure of Mice, Guinea pigs and Rabbits to Germane (Paneth and Joachimoglu, 1924)

Species (No. of animals)	Concentration (ppm)	Duration	Effect
Mouse (1)	2170	1 hour	Mouse sick; died 1 day after exposure
Mouse (1)	195	30 min	Slight dyspnea during exposure; No clinical signs 4 days after exposure; died 8 days after exposure
Mouse (1)	185	1 hour	Dyspnea during exposure; No clinical signs 7 and 11 days after exposure; died 13 days after exposure
Mouse (1)	153	1 hour	Died 1 day after exposure
Guinea pig (1)	185	1 hour	Hemoglobin and protein in urine 1 and 3 days after exposure; died 4 days after exposure; pneumonia at necropsy
Guinea pig (1)	153	1 hour	Animal appeared sick; hemoglobinuria
Rabbit (1)	100	1 hour	Slight dyspnea; No other effects through 1 month after exposure

TABLE 1. Comparative toxicity of Germane and Arsine (Paneth and Joachimoglu, 1924)

Compound	Species	Conc. (ppm)	Duration	Clinical Signs	Death
Germane	Mouse (1)	2170	1 hour	Mouse sick	1 day post-exposure
Arsine	*Mouse (1)*	*1300*	*42 minutes*	*20 min: nervous* *33 min: lying on side* *40 min: Seizures*	*42 min*
Arsine	*Mouse (1)*	*550*	*1 hr*	*15 min:dyspnea* *1 hr: Seizures*	*1 hr, 4 min*
Arsine	*Mouse (1)*	*440*	*47 minutes*	*40 min: Seizures* *45 min: breathing difficulty, twitching*	*47 min*
Arsine	*Mouse (1)*	*207*	*1 hr*	*55 min: breathing difficulty*	*1 hr, 48 min*
Germane	Mouse (1)	195	30 min	Slight dyspnea during exposure; No clinical signs 4 days after exposure	8 days post-exposure
Germane	Mouse (1)	185	1 hour	Dyspnea during exposure; No clinical signs 7 and 11 days after exposure	13 days post-exposure
Germane	Mouse (1)	153	1 hour	NA	1 day post-exposure
Arsine	*Guinea Pig (1)*	*550*	*2 hours*	*1 hr: Increased respiratory rate*	*1 day post-exposure*
Arsine	*Guinea Pig (1)*	*440*	*2 hours*	*49 min: nervous* *1 hr 33 min: Lying on side* *1 hr 38 min: Seizures*	*1 hr, 48 min*
Arsine	*Guinea Pig (1)*	*207*	*2 hours*	*55 min: Increased respiratory rate; hemoglobin in urine*	4 days post-exposure
Germane	Guinea pig (1)	185	1 hour	1 & 3 days post exposure; Hemoglobin and protein in urine	4 days post-exposure
Germane	Guinea pig (1)	153	1 hour	Animal appeared sick; hemoglobinuria	NA

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Paneth and Joachimoglu, 1924

Concluded that both arsine and germane are hemolytic toxins and germane is less toxic than arsine.

A mouse exposed to 207 ppm arsine for 1 hour exhibited difficulty breathing within 55 minutes and died within 1 hr, 48 minutes.

A mouse exposed to 185 ppm germane for 1 hour exhibited dyspnea during exposure, no clinical signs 7 and 11 days post-exposure, and the animal died 13 days post-exposure.

A guinea pig exposed to 207 ppm arsine for 2 hours exhibited increased respiratory rate within 55 minutes; hemoglobin was noted in the urine, and the animal died 4 days post-exposure.

A guinea pig exposed to 185 ppm germane for 1 hour exhibited hemoglobin and protein in the urine, and the animal died 4 days post-exposure.

Although these data are limited and not well described, the studies were conducted in the same laboratory.

Therefore, the relative toxicity data are considered acceptable.

Data suggest that germane is less toxic than arsine in the mouse and no more toxic in the guinea pig.

Therefore, the AEGL values for arsine are proposed as AEGL values for germane.

In the absence of chemical-specific data for germane, these values should be protective.

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TABLE 2. Extant Standards and Guidelines for Germane

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.30 ppm	0.21 ppm	0.17 ppm	0.040 ppm	0.020 ppm
AEGL-3	0.91 ppm	0.63 ppm	0.50 ppm	0.13 ppm	0.060 ppm
REL-TWA (NIOSH)[a]					0.2 ppm
TLV-TWA (ACGIH)[b]					0.2 ppm
TLV-STEL (ACGIH)[c]	Deleted				
MAC (The Netherlands)[d]					0.2 ppm

The ACGIH TLV-TWA was derived by analogy to stibine which was derived by analogy to arsine.

In a Health-based Reassessment of Administrative Occupational Exposure limits (Health Council of the Netherlands, 2000), the committee concluded that the toxicological data base in germane was too poor to justify recommendation of a health-based occupational exposure limit. The committee concluded that there is insufficient information to comment on the level of the present MAC value.

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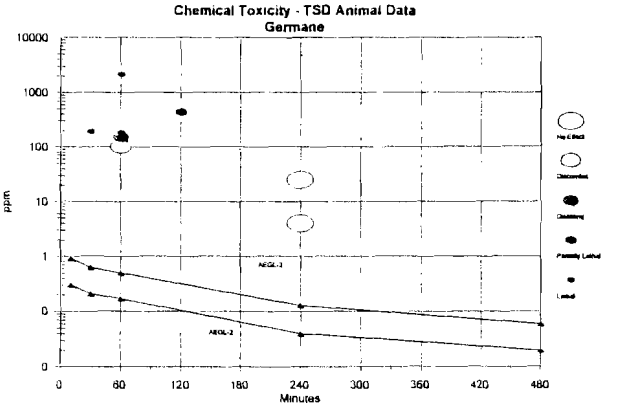


9

METHYL PARATHION

- **Anticholinesterase pesticide**
- **Little data regarding inhalation exposures**
- **As a phosphorothioate, it requires metabolism for its anti-AChE activity**

METHYL PARATHION
Human

- **No lethality data for inhalation exposure**
- **No quantitative exposure-response data for inhalation**
  - **accidental/occupational exposure results in typical cholinergic effects (e.g., headache, dizziness, excessive salivation and sweating, etc)**

METHYL PARATHION
Animal Lethal

Inhalation lethality of methyl parathion in rats		
Duration	Value (mg/m^3)	Reference
4-hr LC_{50}	34 mg/m^3	Molnar et al., 1980
4-hr LC_{50}	185 mg/m^3 (males) 170 mg/m^3 (females)	Thyssen, 1979 (cited in WHO, 1993)
4-hr LC_{50} $BMCL_{05}$ BMC_{01}	135 mg/m^3 (nose-only) 66.6 mg/m^3 83.6 mg/m^3	U.S. EPA, 1998
1-hr LC_{50} 4-hr LC_{50}	200 mg/m^3 120 mg/m^3	Kimmerle and Lorke, 1968
1-hr LC_{50}	257 mg/m^3 (males) 287 mg/m^3 (females)	U.S. EPA, 1968 (cited in ATSDR, 2001)

METHYL PARATHION
Animal Nonlethal

Effects of methyl parathion on rats following acute inhalation exposure.		
Exposure (mg/m^3)	Mortality	Observations
108	2/10	2 males dead at 98 min.; surviving animals normal at 5 days post exposure
134	3/10	3 males dead at 120-129 min.; surviving animals normal at 4 days post exposure
168	9/10	5 males, 4 females dead at 43-96 min.; lone survivor exhibited unkempt appearance until post exposure day 9 but normal thereafter

U.S. EPA, 1998

- Thyssen (1979): rats exposed to 9.7 mg/m^3 for 6 hrs/day, 5 days/wk for 3 wks
  - no deaths
  - brain and plasma ChE significantly decreased in high-dose group
    - high-dose rats also exhibited clinical signs of toxicity consistent with anticholinesterase activity and decreased body weight gain.

PARATHION
AEGL-1

AEGL-1 values for methyl parathion					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	NR	NR	NR	NR	NR

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

- Not recommended - insufficient data

METHYL PARATHION
AEGL-2

AEGL-2 values for methyl parathion (mg/m^3)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	1.5	1.5	1.2	0.73	0.37

- Insufficient data (?? use highest dose in Thyssen [1979] study ???)

- AEGL-2 values estimated as three-fold reduction of AEGL-3 values (NRC, 2001)
  - Exposure-response curve is steep – little margin between AEGL-2 severity effects and AEGL-3

METHYL PARATHION
AEGL-3

AEGL-3 values for methyl parathion (mg/m^3)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	4.4	4.4	3.5	2.2	1.1

Key study: U.S. EPA. 1998. Methyl parathion. MRID Nos. 40364103 and 142803. EPA special docket EPA HQ-OPP-2007-0151.

Critical effect/POD: 4-hour $BMCL_{05}$ of 66.6 mg/m^3 used as estimate of the lethality threshold in rats.

Uncertainty factors: Total uncertainty factor adjustment is 30
Interspecies: 3; variability in the toxic responses is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind anticholinesterases such as methyl parathion than do other species.
Intraspecies: 10; the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justifies retention of the intraspecies uncertainty factor of 10.
Time scaling: $C^n \times t = k$, where n = 1 or 3

AEGL values for methyl parathion (mg/m^3)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	1.5 0.73	1.5 0.73	1.2 0.58	0.73 0.37	0.37 0.24
AEGL-3 (Lethality)	4.4	4.4	3.5	2.2	1.1

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

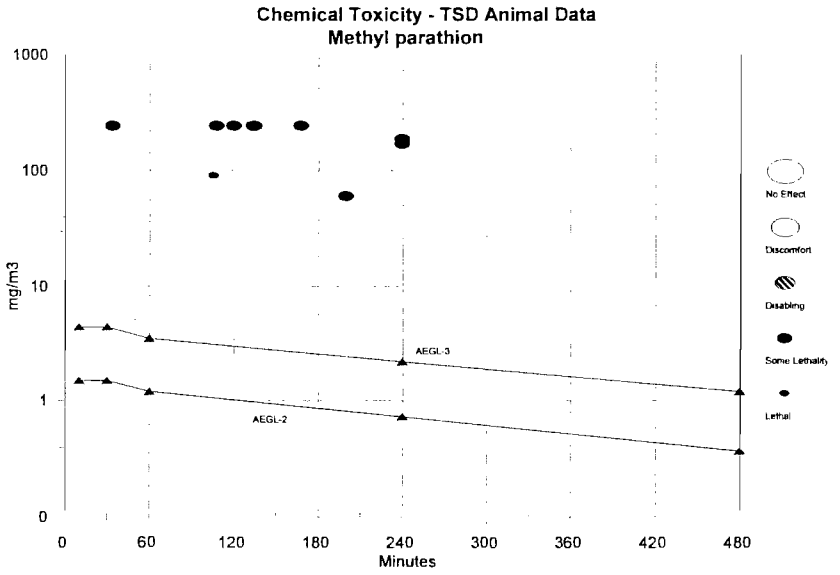
Alternate AEGL-2 values

AEGL-2 values for methyl parathion (mg/m^3)					
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-2	**0.73**	**0.73**	**0.58**	**0.37**	**0.24**

POD: 9.6 mg/m^3, 6 hrs/d, 5 d/wk for 3 wks – no lethality; decreased brain and plasma ChE in rats; observed cholinergic effects consistent with ChE inhibition (Thyssen, 1979)

UF: 30 (3 x10)

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



AEGL-1 value not recommended due to insufficient data.

PARATHION

- **Anticholinesterase pesticide**
- **Little data regarding inhalation exposures**
- **As a phosphorothioate, it requires metabolism for its anti-AChE activity**

PARATHION
Human

- **No lethality data for inhalation exposure**
- **workers at a parathion manufacturing plant exposed to average levels estimated at 0.2-0.3 mg/m^3 (Brown and Bush, 1950)**
  - **plasma ChE activity levels declined about 25% but fully recovered**

PARATHION
Animal

- Kimmerle and Lörke (1968)
  - rat 1-hr LC_{50}: 115 mg/m^3
  - rat 4-hr LC_{50}: 31.5 mg/m^3
  - 20 male rats, 14-day observation period; analytically determined concentrations
- Cheminova Agro A/S (1986) [IUCLID, 2000 summary]
  - rat 4-hr LC_{50} of 30 mg/m^3 (21-44 mg/m^3, c.i.) for rats
    - 2 female rats exhibited tremors following exposure (time not specified) to 12 mg/m^3
    - all surviving female rats exhibited lethargy and hypokinesia at 1 day post exposure.

PARATHION
AEGL-1

AEGL-1 values for parathion					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	NR	NR	NR	NR	NR

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

○ Not recommended - insufficient data

PARATHION
AEGL-2

AEGL-2 values for parathion (mg/m^3)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	2.5	0.83	0.43	0.11	0.057

- Insufficient data

- AEGL-2 values estimated as three-fold reduction of AEGL-3 values (NRC, 2001)
  - Exposure-response curve is steep – little margin between AEGL-2 severity effects and AEGL-3

PARATHION
AEGL-3

AEGL-3 values for parathion (mg/m^3)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	7.6	2.5	1.3	0.33	0.17

Key study: IUCLID (International Uniform Chemical Information Database). 2000. Parathion, CAS No. 56-38-2.European Commission, European Chemicals Bureau. (Summary of Cheminova Agro study).
Kimmerle, G. and D. Lorke. 1968. Toxicology of insecticidal organophosphates. Pflanzenschutz-Nacher 21:111-142.

Critical effect/POD: lethality; in the absence of exposure-response data, 3-fold reduction of the 1-hr and 4-hr LC_{50} for rats (115 $mg/m^3 \div 3 = 38$ mg/m^3; 30 $mg/m^3 \div 3 = 10$ mg/m^3, respectively) used as estimate of the lethality threshold.
POD for 10 min., 30-min. and 1-hr AEGL-3 values was 38 mg/m^3
POD for the 4-hr and 8-hr AEGL-3 was 10 mg/m^3.

Uncertainty factors: Total uncertainty factor adjustment is 30
Interspecies: 3
Intraspecies: 10

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

AEGL values for parathion (mg/m^3)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	2.5	0.83	0.43	0.11	0.057
AEGL-3 (Lethality)	7.6	2.5	1.3	0.33	0.17

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

PARATHION
Animal

- NIOSH/Edgewood Arsenal
  - rat 4-hr LC_{50} of 84 mg/m^3 (78.0-90.4 mg/m^3)
    - 34 rats/group (50-230.5 mg/m^3)
  - 4-hr $BMCL_{05}$ = 41.1 mg/m^3
  - 4-hr BMC_{01} = 37.5 mg/m^3
  - 4-hr ED_{50} (tremors) = 73.7 mg/m^3 (67.2-80.8 mg/m^3)
    - $BMCL_{05}$ = 27.3 mg/m^3
    - BMC_{01} = 23.4 mg/m^3
  - 4-hr ED_{50} (convulsions) = 110.6 mg/m^3 (96.0-127.4 mg/m^3)

Response frequency of male rats exposed to parathion for4 hrs			
Parathion conc. (mg/m^3)	Tremors	Convulsions	Mortality
31.0	0/34	0/34	0/34
35.0	0/34	0/34	0/34
50.0	8/34	3/34	3/34
71.0	19/34	4/34	10/34
97.0	28/34	19/34	25/34
100.6	26/34	21/34	22/34
118.5	29/34	21/34	28/34
230.5	31/34	25/34	34/34

NIOSH/Edgewood Arsenal
parathion (99.3%)

PARATHION
AEGL-1

Still not recommended

PARATHION
AEGL-2

AEGL-2 values for parathion (mg/m^3)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	1.6 0.83	1.6 0.83	1.2 0.67	0.78 0.43	0.39 0.21

- Use BMC_{01} of 23.5 mg/m^3 (tremors in rats exposed for 4 hrs) from NIOSH/Edgewood study

OR

- AEGL-2 values estimated as three-fold reduction of AEGL-3 values (NRC, 2001)
  - Exposure-response curve is steep – little margin between AEGL-2 severity effects and AEGL-3

PARATHION
AEGL-3

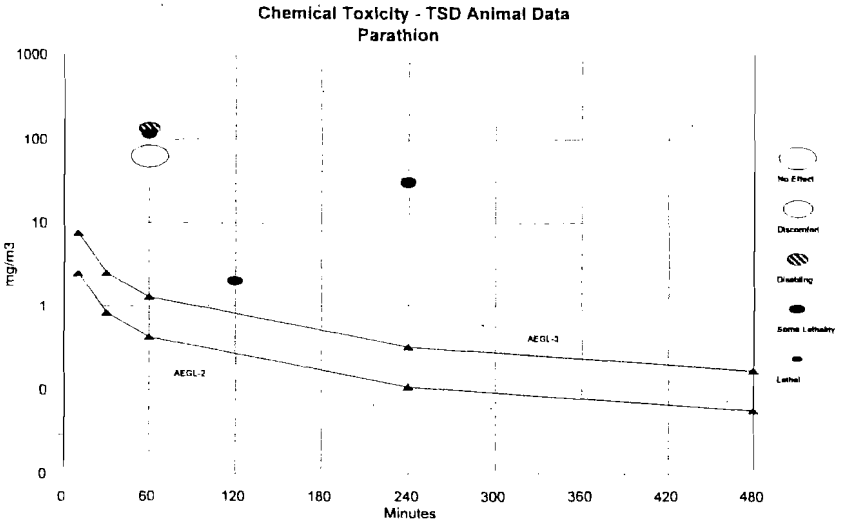
AEGL-3 values for parathion (mg/m^3)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	2.5	2.5	2.0	1.3	0.63

Key study: NIOSH/Edgewood Arsenal; Inhalation and oral studies of ethyl parathion administered acutely and sub-acutely to the rat and dog

Critical effect/POD: 4-hr BMC_{01} for tremors in rats ($BMCL_{05}$ = 27.3 mg/m^3)

Uncertainty factors: Total uncertainty factor adjustment is 30
Interspecies: 3
Intraspecies: 10

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



AEGL Values for Parathion (mg/m^3)						
AEGL-1	NR	NR	NR	NR	NR	All
AEGL-2	2.5 1.6 0.83	0.83 1.6 0.83	0.43 1.2 0.67	0.11 0.78 0.43	0.057 0.39 0.21	TSD BMC_{01} tremors 1/3 of AEGL-3 based on BMC_{01} for lethality
AEGL-3	7.6 2.5	2.5 2.5	1.3 2.0	0.33 1.3	0.17 0.63	TSD BMC_{01} lethality

- Less than a 2-fold difference between AEGL-2 and AEGL-3 values using BMC as POD
  - While this accurately reflects the toxicity data, it allows little margin between the effect tiers

- TSD values are currently based on summary "data"

ATTACHMENT 10

ACUTE EXPOSURE GUIDELINE LEVELS FOR PHORATE ($C_7H_{17}O_2PS_3$)

National Advisory Committee for AEGLs Meeting 46
Boston, MA
June 25-27, 2008

ORNL Staff Scientist:
Tom Marshall

Chemical Manager:
Susan Ripple

Chemical Reviewers:
Daniel Sudakin
Marcel van Raaij

PHORATE

Organophosphate insecticide (liquid)

Mechanism of action: cholinesterase inhibition

No quantitative human data

Single inhalation study with rats, two data sets (Newell and Dilley 1978)
Respirable aerosols generated
Nose-only exposure to range of four measured concentrations of 8 to 266 mg/m^3
    Acute Lethality
        1-hour LC_{50}:
            Males: 60 mg/m^3
            Females: 11 mg/m^3
        Signs of salivation, lacrimation, exophthalmos, defecation, urination, muscle fasciculations
        No additional information

PHORATE

Developmental Toxicity:
    Concentrations of 0, 0.15, 0.40, and 1.94 mg/m^3
    One hour/day for 8 days
    Death of 5 of 10 pregnant rats inhaling 1.94 mg/m^3, beginning with the third day
    No deaths following repeated exposure to lower concentrations
        No maternal or fetal effects

PHORATE

Uncertainty Factors
    Interspecies: 3; humans have greater levels of plasma cholinesterase activity than other species, leading to protective detoxification
    Interspecies: 10; genetic polymorphism among humans; variable sensitivity among age groups and gender

Time-scaling ($C^n \times t = k$): default values of n = 3 and 1 when scaling to shorter and longer exposure durations, respectively

AEGL-1:
Data were insufficient to derive AEGL-1 values.

Proposed AEGL-1 Values for Phorate				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
NR	NR	NR	NR	NR

NR = Not Recommended.

AEGL-2:
Insufficient data; organophosphates generally have steep dose-response curves.
Therefore, AEGL-2 values can be derived by dividing the AEGL-3 values by 3.

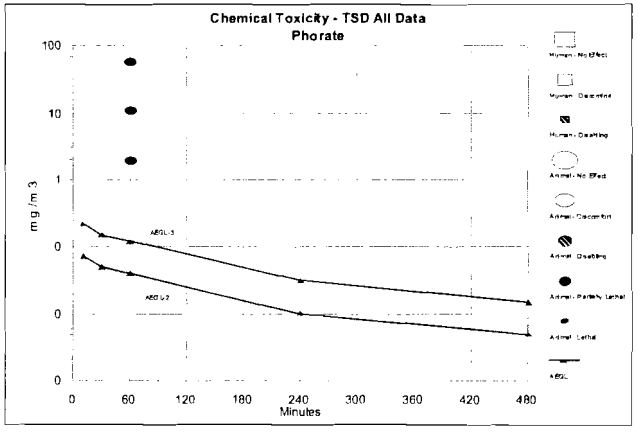
Proposed AEGL-2 Values for Phorate				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
0.073 mg/m^3	0.050 mg/m^3	0.040 mg/m^3	0.010 mg/m^3	0.0050 mg/m^3

AEGL-3
Lethality study of Newell and Dilley 1978
1-hour LC_{50} of 60 mg/m^3 in male rats and 11 mg/m^3 in female rats
POD: 11 mg/m^3 divided by 3 to estimate a non-lethal concentrations (3.67 mg/m^3)

Uncertainty factors of 3 and 10 for a total of 30
Default time scaling

Proposed AEGL-3 Values for Phorate				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
0.22 mg/m^3	0.15 mg/m^3	0.12 mg/m^3	0.031 mg/m^3	0.015 mg/m^3

Proposed AEGL Values for Phorate					
Level	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.073 mg/m^3	0.050 mg/m^3	0.040 mg/m^3	0.010 mg/m^3	0.0050 mg/m^3
AEGL-3	0.22 mg/m^3	0.15 mg/m^3	0.12 mg/m^3	0.031 mg/m^3	0.015 mg/m^3



ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR TERT-OCTYL MERCAPTAN

$C_8H_{18}S$

NAC/AEGL-46
June 25-27, 2008, 2008
Boston, MA

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Glenn Leach

Chemical Reviewers: Susan Ripple and Martha Steele

No human data.

Animal data for rats and mice suggest:

Steep Concentration-response

4-hour exposures

Concentration	Mortality	Reference
Male Rats		
38 ppm	0%	Fairchild and Stokinger, 1958
64 ppm	100%	
59 ppm	0%	Atochem, 1982
71 ppm	80%	
Female Rats		
12 ppm	10%	Atochem, 1982
18 ppm	100%	
Male Mice		
38 ppm	0%	Fairchild and Stokinger, 1958
64 ppm	100%	

Females more sensitive than males

Inhalation of tert-octyl mercaptan in Sprague-Dawley rats for 4-hr			
Concentration (ppm)	Mortality		
	Male	Female	Combined
0	0/5	0/5	0/10
7 ± 0.7	0/5	0/5	0/10
15 ± 3.0	0/5	1/5	1/10
19 ± 3.0	0/5	5/5	5/10
29 ± 2.0	0/5	5/5	5/10
59 ± 3.0	0/5	5/5	5/10
71 ± 1.0	4/5	5/5	9/10
110 ± 3.0	5/5	5/5	10/10
LC_{50}	59 ppm	17 ppm	33 ppm (16-66)
$BMCL_{05}$	52 ppm	11.3 ppm	
BMC_{01}	59.7 ppm	13.8 ppm	

Atochem, 1982

Summary of 4-hr animal lethality data				
Species/Sex/Strain	LC_{50} (ppm)	$BMCL_{05}$(ppm)	BMC_{01}(ppm)	Reference
Rat/Male/Wistar	51	31.8	34.4	Fairchild & Stokinger, 1958
Rat/Male/ Sprague-Dawley	59	52	-	Atochem, 1982
Rat/Male/ Charles River	79	63.9	65.9	Amoco, 1979
Rat/Female/ Sprague-Dawley	17	11.3	13.8	Atochem, 1982
Rat/Female/ Sprague-Dawley	17	10.1	10.7	Atochem, 1982 (2^{nd} test)
Rat/Female/ Charles River	24	21.5	22.3	Amoco, 1979
Mouse/Male/Swiss	47	33.5	34.3	Fairchild & Stokinger, 1958

Mechanism of Toxicity:

Most mercaptans act similarly to hydrogen sulfide and cyanide by interrupting electron transport through inhibition of cytochrome oxidase, and general signs of acute mercaptan poisoning are indicative of central depression and respiratory paralysis, followed by death from respiratory failure.

However, data suggest that tert-octyl mercaptan is acting differently

An initial effect of CNS stimulation is observed.

Fairchild and Stokinger (1958) state that the stimulatory effects of tert-octyl mercaptan were typical of other CNS stimulants such as picrotoxin and metrazol, and that the compound appeared to act at various levels of the cerebrospinal axis.

Convulsive seizures were spontaneous in origin (not triggered by external stimuli), and tert-octyl mercaptan had an analeptic action on the higher CNS centers, as evidenced by the fact that sub-convulsant doses stimulated the respiratory and vasomotor centers.

The analeptic action was demonstrated by the ability of tert-octyl mercaptan to counteract depression produced by barbiturates.

Even though the CNS stimulation is unique to tert-octyl mercaptan, the final result of acute toxicity is similar to other mercaptans: the CNS stimulation was followed by central depression, then by death due to respiratory failure.

Structure Activity:

Rat acute intraperitoneal, oral and inhalation data and mouse inhalation data suggest that tert-octyl mercaptan is more toxic than other mercaptans tested (with the exception of phenyl mercaptan) and more toxic than hydrogen sulfide .

Comparative toxicity of mercaptans					
Compound	Rat IP LD_{50} (mg/kg)	Rat Oral LD_{50} (mg/kg)	4-hr Inhalation LC_{50} (ppm)		Reference
			Rats	Mice	
Hydrogen sulfide			444		Tansy et al., 1981
Methyl Mercaptan			675		Tansy et al., 1981
Ethyl mercaptan	226	682	4420	2770	Fairchild & Stokinger, 1958
Propyl mercaptan	515	1790	7200	4010	
Isobutyl mercaptan	917	7168	>25000	>25000	
tert-Butyl mercaptan	590	4729	22200	16500	
n-Butyl mercaptan	399	1500	4020	2500	
n-Hexyl mercaptan	396	1254	1080	528	
Phenyl mercaptan	9.8	46.2	33	28	
Benzyl mercaptan	373	493	>235	178	
Tert-Octyl mercaptan	12.9	83.5	51 (males)	47 (males)	

AEGL-2 Values for tert-Octyl Mercaptan					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	0.67 ppm	0.67 ppm	0.53 ppm	0.33 ppm	0.17 ppm

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

Approach is justified by the steep concentration-response curve

AEGL-1 VALUES: TERT-OCTYL MERCAPTAN				
10 minute	30 minute	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR

NR: Not Recommended due to insufficient data.

4-hour exposures

Concentration	Mortality	Reference
Male Rats		
38 ppm	0%	Fairchild and Stokinger, 1958
64 ppm	100%	
59 ppm	0%	Atochem, 1982
71 ppm	80%	
Female Rats		
12 ppm	10%	Atochem, 1982
18 ppm	100%	
Male Mice		
38 ppm	0%	Fairchild and Stokinger, 1958
64 ppm	100%	

The AEGL-2 values are considered protective.

No effects (clinical signs or mortality) were noted in male and female rats exposed to 7 ppm for 4-hours (Atochem, 1982).

Using the 7 ppm concentration as a POD and applying time scaling and uncertainty factors as proposed, yields:

	10-min	30-min	1-h	4-h	8-h
AEGL-2	1.4 ppm	1.4 ppm	1.1 ppm	0.70 ppm	0.35 ppm

AEGL-3 Values for tert-Octyl Mercaptan					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	2.0 ppm	2.0 ppm	1.6 ppm	1.0 ppm	0.51 ppm

Species: Female Rat
Concentration: 10.1 ppm
Time: 4 hours
Endpoint: $BMCL_{05}$
Reference: Atochem, 1982

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

Uncertainty Factors:
Intraspecies = 3:

POD from more sensitive female animals;
Steep concentration-response implies limited variability

Interspecies = 3:

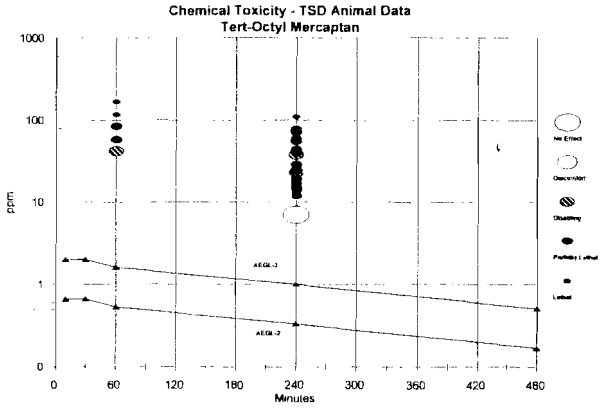
Limited data show no difference in sensitivity between rats and mice

Male rat 4-hr LC_{50} = 51 ppm

Male mouse 4-hr LC_{50} = 47 ppm
(Fairchild and Stokinger, 1958)

AEGL Values for tert-Octyl Mercaptan					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.67 ppm 4.0 mg/m^3	0.67 ppm 4.0 mg/m^3	0.53 ppm 3.2 mg/m^3	0.33 ppm 2.0 mg/m^3	0.17 ppm 1.0 mg/m^3
AEGL-3	2.0 ppm 12 mg/m^3	2.0 ppm 12 mg/m^3	1.6 ppm 9.6 mg/m^3	1.0 ppm 6.0 mg/m^3	0.51 ppm 3.1 mg/m^3

There are no other standards or guidelines for tert-octyl mercaptan!



Ethyl Mercaptan- Interim							
Classification	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)	4-hr LC50
							Rat / Mouse
AEGL-1	1 ppm	1 ppm	1 ppm	1 ppm	1 ppm	NOEL for irritation in rabbits (Shibata, 1966b)	4420 ppm / 2770 ppm
AEGL-2	150 ppm	150 ppm	120 ppm	77 ppm	37 ppm	3-fold reduction of AEGL-3 values	
AEGL-3	450 ppm	450 ppm	360 ppm	230 ppm	110 ppm	LC_{01} in mice (Fairchild and Stokinger, 1958)	

Methyl Mercaptan- Interim							
Classification	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)	4-hr LC50
							Rat / Mouse
AEGL-1	NR	NR	NR	NR	NR	Insufficient data	675 ppm / -
AEGL-2	59 ppm	59 ppm	47 ppm	30 ppm	19 ppm	Shallow breathing and hypoactivity in mice (Elf Atochem, 1996)	
AEGL-3	120 ppm	86 ppm	68 ppm	43 ppm	22 ppm	LC_{01} in rats (Tansy et al., 1981)	

Phenyl Mercaptan- Interim							
Classification	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)	4-hr LC50
							Rat / Mouse
AEGL-1	NR	NR	NR	NR	NR	Insufficient data	33 ppm / 28 ppm
AEGL-2	1.0 ppm	0.70 ppm	0.53 ppm	0.33 ppm	0.17 ppm	3-fold reduction of AEGL-3 values	
AEGL-3	3.0 ppm	2.1 ppm	1.6 ppm	1.0 ppm	0.52 ppm	LC_{01} in rats (Fairchild and Stokinger, 1958)	

Tert-Octyl Mercaptan- Draft							
Classification	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)	4-hr LC50
							Rat / Mouse
AEGL-1	NR	NR	NR	NR	NR	Insufficient data	Male: 51-79 ppm / Male: 47 ppm
AEGL-2	0.67 ppm	0.67 ppm	0.53 ppm	0.33 ppm	0.17 ppm	3-fold reduction of AEGL-3 values	Female: 17-24 ppm
AEGL-3	2.0 ppm	2.0 ppm	1.6 ppm	1.0 ppm	0.51 ppm	$BMCL_{05}$ in female rats (Atochem, 1982)	