National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-50
April 13-15, 2010

California Room
InterContinental Mark Hopkins San Fransicso
Number One Nobb Hill
San Francisco, CA 94108

AGENDA

Tuesday, April 13, 2010

10:00 a.m.	*Development Team Meetings (Vinyl Chloride, Dichlorvos, Carbon Dioxide, Ricin, Hydrogen Bromide/Hydrogen Iodide)
11:00	Introductory Remarks and Approval of NAC/AEGL-49 Highlights (George Rusch, Ernest Falke, Paul Tobin)
11:30	Revisit of Vinyl Chloride (Robert Benson)
12:00 p.m.	Lunch
1:00	Revisit of Dichlorvos – Update (Ernest Falke/John Hinz/Julie Klotzbach)
1:30	Carbon Dioxide: Ethics Review
1:45	Review of Carbon Dioxide (Marcel van Raaij/Gary Diamond)
3:00	Break
3:30	Revisit of Ricin – Update (Jim Holler/Gary Diamond)
4:00	Revisit of Hydrogen Bromide/Hydrogen Iodide (Ernest Falke/Susan Ripple/Heather Carlson-Lynch)
5:00	Adjourn for the Day

Wednesday, April 14, 2010

8:30 a.m.	*Development Team Meetings (Chlorine Pentafluoride, Bromine Pentafluoride, Chloroacetone, Selenium Hexafluoride, Red Phosphorus/Butyl Rubber, Monoethanolamine)
9:30	Revisit of Chlorine Pentafluoride (William Bress/Heather Carlson-Lynch)
10:00	Revisit of Bromine Pentafluoride (William Bress/Heather Carlson-Lynch)
10:30	Revisit of Chloroacetone (Susan Ripple/Julie Klotzbach)
11:00	Break
11:30	Revisit of Selenium Hexafluoride (George Rusch/Gary Diamond)
12:00 p.m.	Lunch
1:00	Review of Red Phosphorus/Butyl Rubber (Glenn Leach/Julie Klotzbach)
2:00	Review of Monoethanolamine (Ernest Falke/Heather Carlson-Lynch)
3:00	Break
3:30	Review of Hydrogen selenide (George Woodall)
5:00	Adjourn for the Day

Thursday, April 15, 2010

8:30 a.m.	*Development Team Meetings (Methyl Isothiocyanate)
9:00	Revisit of Methyl Isothiocyanate (Susan Ripple/Ernest Falke)
10:00	Break
10:30	Next Meeting and Committee Business
11:00	Adjourn Meeting

*See page 2

Pre-Meeting Small Discussion Groups: NAC-50					
Chemical	**Staff Scientist**	**CM**	**Chem Reviewer 1**	**Chem Reviewer 2**	**Other Attendees**
Tuesday, April 13, 2010					
Vinyl Chloride	–	Benson	–	–	Gingell, Erraguntla
Dichlorvos	Klotzbach	Falke	Camacho	Hinz	Beasley, Erickson
Carbon Dioxide	Diamond	van Raaij	Freshwater	–	Baril, Bernas, Cushmac, Oberg
Ricin	Diamond	Holler	Anderson	Leach	Sudakin, Woolf,
HBr/HI	Carlson-Lynch	Falke, Ripple	Niemeier	–	Becker, Woodall
Wednesday, April 14, 2010					
ClF_5	Carlson-Lynch	Bress		McClanahan	Cushmac, Freshwater, Woodall
BrF_5	Carlson-Lynch	Bress		McClanahan	Cushmac, Freshwater, Woodall
Chloroacetone	Klotzbach	Ripple		Barbee	Gingell, Becker
SeF_6	Diamond	Rusch	Tobin	Baril	Benson, Oberg, Sudakin
RP/BR	Klotzbach	Leach	Niemeier	Woolf	Anderson, Erickson, Heinz,
Monoethanolamine	Carlson-Lynch	Beasley	Falke	–	Bernas, Beril, Camacho

NAC/AEGL Meeting 50: April 13-15, 2010

ATTENDANCE

Chemical: Vinyl chloride **CAS Reg. No.: 75-01-4**

Action: Proposed_____ **Interim**_____ **Other: NAS Return**

Chemical Manager: Benson **Staff Scientist: Kalberlah**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson					John Hinz				
Marc Baril					Jim Holler	AB			
Lynn Beasley					Clarion Johnson	AB			
Alan Becker					Glenn Leach	AB			
Robert Benson					Richard Niemeier				
Edward Bernas					Mattias Oberg				
Iris Camacho					Susan Ripple				
George Cushmac					George Rusch, Chair	✓			
Richard Erickson					Daniel Sudakin				
Neeraja Erraguntla					Marcel vanRaaij	AB			
David Freshwater					George Woodall				
Ralph Gingell					Alan Woolf				
					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:** 4/13/10

Vinyl Chloride

Response to COT Comments

Bob Benson
NAC # 50
April 13-15, 2010

1

History

AEGL values approved by NAC in 2003 or 2004

Proposed 9/2006, No public comments

To Interim 12/2006 (NAC # 47)

To COT 5/2008

COT Comments 9/2009

2

Time Scaling

Comment: Pick a value for n without using an average based on different endpoints

Response: Used side position plot, n = 2

3

Time Scaling

Comment: AEGL-1 (headache) and AEGL-2 (dizziness to anesthesia) both CNS effects, use same n

Response: MOA for headache not known and likely not directly related to VC in blood. Used default (n = 3 or 1) from 3.5 hrs.

N = 3/1	450	310	250	140	70
N = 2	570	330	230	160	160

4

Time Scaling

Comment: AEGL-3 (cardiac sensitization) not CNS effect, use different n

Response: Cardiac sensitization and dizziness progressing to anesthesia are both a function of VC in blood. No data for n for any chemical for cardiac sensitization. Keep n = 2 for AEGL-3.

5

Cancer

Comment: Develop a sound rationale for cancer risk as driver for AEGL-3. Compare with other known human carcinogens.

Response: Cancer value lower than AEGL-1 at 8 hours for VC, benzene, BCME, and 1,3-butadiene. See table in response document.

Human data inconsistent with cancer values from lab animal data. Therefore, not appropriate to base AEGL values on lab animal cancer data.

6

Cancer

Response (continued): Deleted calculations B and D from Appendix C.

Removed cancer calculation table from Executive Summary for consistency with other final documents.

7

AEGL-2

Comment: Why not use liver effects from Tatrai and Ungvary (1981)?

Response: Mice appear to be unusually sensitive to VC and not a suitable model for derivation of AEGL values.

No serious liver effects in rats at exposures giving CNS effects in people. Therefore, retained Lester et al. (1693) as basis of AEGL-2.

8

AEGL-2

Comment: Provide supporting information in section 6.3 regarding steady state at 2 hours.

Response: Cross reference to section 4.1 and Appendix B added to section 6.3 and section 7.3.

9

AEGL-2

Comment: Explain "…sufficient margin of safety to avoid mutational events or malignancies…" in section 6.3.

Response: Because of changes in cancer and mutagenicity sections, the sentence will be deleted here and other places.

10

AEGL-3

Comment: Justify the interspecies UF of 1 for cardiac sensitization.

Response: Added sentence from other final documents using cardiac sensitization as an endpoint for AEGL-3.

11

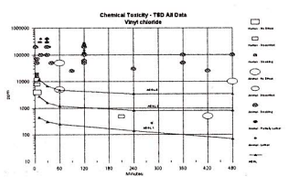
Category Plot

Comment: There is at least a 100-fold concentration difference for similar effects.

Response: The reviewer has misread the plot.

12

Category Plot



13

Editorial Comments

Comment: Revise wording in several places.

Response: Done.

14

REVISIT AEGL FOR DICHLORVOS (CAS Reg. No. 62-73-7)

NAC/AEGL Meeting 50
San Francisco, CA
April 13-15, 2010

Chemical Manager: Ernest Falke
Chemical Reviewers: Iris Camacho, John Hinz
SRC Staff Scientist: Julie Klotzbach
Author and ORNL Staff Scientist:

Dichlorvos

Overview

- Dimethoxy organophosphorus compound
- Cholinesterase inhibitor
- Chemistry
  - Colorless-to-amber liquid at room temperature
  - VP=0.012 mmHg, 20°C
  - soluble in water (10 g/L)
- Uses: contact and systemic insecticide (crops, livestock, buildings, aircraft, outdoor areas)

Dichlorvos

Issues

- **Re-**consider revised proposed AEGLs values derived using as an intraspecies UF of 1 (total UF = 1)
- What data are available to support reduction of the intraspecies UF 10?
  - Age-dependence
  - A-esterase polymorphism
  - Liver disease
  - Liver metabolism
  - Significance of plasma cholinesterase

Dichlorvos

Intraspecies UF: Age-Dependence (1)

- In animals, age-dependence of dose response (neonates more sensitive than adults) noted for other OPs (e.g., chlorpyrifos, Moser et al. 2000); no analogous assessment of DDVP.
- Age-dependence of A-esterase activity (chlorpyrifos, paroxon) in blood and liver (lower activities in neonates; Moser et al. 1998; Ecibichon and Stephens, 1973); no data on DDVP.
  - What is the importance of A-esterase activity in DDVP metabolism?
  - Is A-esterase activity an indicator of susceptibility?

Dichlorvos

Intraspecies UF: A-Esterase Polymorphism

- For plasma A-esterases, population distributions are not the same:
  - For paroxon metabolism, plasma A-esterase exhibit a biomodal distribution
  - For chlorpyrifos, plasma A-esterase exhibit a unimodal distribution (Furlong et al. 1988; Lee et al. 2003)
- No evidence of polymorphism of plasma A-esterase activity in humans. Distribution of plasma A-esterase activity for DDVP was unimodal in a small sample of 60 adults (26 female).
  - Mean ± SD 122 ± 22 nmol/min/ml (~95^{th}:5^{th} %tile: 1.8) (Traverso et al. 1989)

Dichlorvos

Intraspecies UF: Liver Disease

- Cavagna et al (1969) reported inhibition of plasma cholinesterase in 2 adult liver disease patients in association with exposure to 0.008-0.09 mg/m^3 DDVP
- Among 66 adult patients who did not exhibit liver disease, exposures to DDVP concentration below 0.1 mg/m^3 did not result in inhibition of plasma cholinesterase activity (Cavagna et al. 1969)

Dichlorvos

Intraspecies UF: Liver Metabolism

- DDVP is metabolized in various tissues, including blood and liver
- Direct comparison of activity of blood and liver A-esterase that metabolize DDVP has not been reported
- Liver:plasma activity ratio of A-esterase for parathion is ~52 (based on Karanth and Pope, 2000), and for chlorpyrifos is ~3 (based on Moser et al, 1998)

Dichlorvos

Intraspecies UF: Significance of Plasma ChE

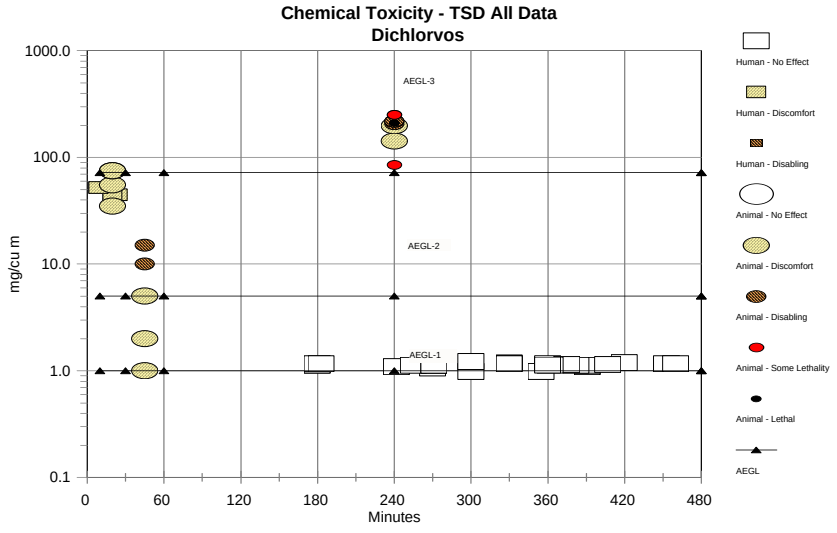
- What level of inhibition of plasma ChE would constitute a significant risk for toxicity?
- In adult rats, weight loss produced by oral dosing with sarin was significantly correlated with inhibition of plasma ChE. A 10% weight loss was associated with a 65% inhibition of cholinesterase (Young et al 2001).

Dichlorvos

Proposed and Alternative AEGL Values

Summary of Proposed[a] and *Alternative*[b] AEGL Values for Dichlorvos [ppm(mg/m^3)]						
	10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**	
AEGL-1	0.11 (1) ***0.037 (0.33)***	0.11 (1) ***0.037 (0.33)***	0.11 (1) ***0.037 (0.33)***	0.11 (1) ***0.037 (0.33)***	0.11 (1) ***0.037 (0.33)***	No effects in human volunteers exposed for 3-7.7 hrs to 1 mg/m^3 (Hunter 1970a)
AEGL-2	0.56 (5) ***0.19 (1.7)***	0.56 (5) ***0.19 (1.7)***	0.56 (5) ***0.19 (1.7)***	0.56 (5) ***0.19 (1.7)***	0.56 (5) ***0.19 (1.7)***	Highest experimental exposure in rats without an AEGL-2 tier effect, 5 mg/m^3 for 45 min (Atis et al. 2002)
AEGL-3	8.0 (72) ***2.7 (24)***	8.0 (72) ***2.7 (24)***	8.0 (72) ***2.7 (24)***	8.0 (72) ***2.7 (24)***	8.0 (72) ***2.7 (24)***	Highest experimental exposure in mice without a lethal effect, 72 mg/m^3 for 16 hr (Dean and Thorpe 1972a)

[a]UF = 1 x 1 (intraspecies x interspecies)
[b]UF= 3 x 1 (intraspecies x interspecies)



Development Team Discussion Points

- Develop summary table for all OPs
  - AEGL values, UFs and justifications, POD, species, endpoints
- Indentify inconsistencies in approach to OPs
- Bring back all OPs to NAC to re-evaluate approach to uncertainty factors or other inconsistencies.

END

REVISIT AEGL FOR RICIN (CAS Reg. No. 9009-86-3)

NAC/AEGL Meeting 50
San Francisco, CA
April 13-15, 2010

Chemical Manager: Jim Holler
Chemical Reviewers: Henry Anderson, Glenn Leach
SRC Staff Scientist: Gary Diamond
Author and ORNL Staff Scientist: Robert Young

Ricin Overview

- Glycoprotein (55-64 kDa) found in Castor beans (seeds of *Ricinus sp*)
- White solid/crystal at room temperature, soluble in dilute salt solutions
- Vapor pressure: negligible
- Binds to and 28s ribosomal RNA and irreversibly inactivates ribosomal protein synthesis

Ricin Data Overview

- Acute exposures in humans – no data
- Animals – inhalation

  Acute (2-40 min) lethality studies in monkeys (Wilhelmsen and Pitt 1996), rats, (Bide et al. 1997; Brown and White, 1997; Gomez et al. 2009; Griffiths et al., 1995a,b; Smallshaw et al. 2006) and mice (DaSilva et al. 2003; Roy et al. 2003;

  – Pathology: lung edema, apoptosis, necrosis

Ricin TSD History

- Draft 1 prepared by Bob Young (ORNL) was reviewed at NAC/AEGL-47 (12/2008).
- NAC/AEGL-48 (04/2009): New data on acute lethality of ricin in mice and rats discussed (Gomez et al. 2009). The data were from an SOT presentation; Lovelace has not released a full report.
- Potential implications of Gomez et al. (2009) data on AEGL-3 were explored (notes distributed to NAC, 03/2010).
- Smallshaw et al. 2007 inhalation lethality study in mice (cited in Gomez et al. 2009).

Summary of Proposed and Alternative AEGL Values for Ricin (mg/m³)					
	10-min	30-min	1-hr	4-hr	8-hr
AEGL 1	NR	NR	NR	NR	NR
AEGL 2	NR	NR	NR	NR	NR
AEGL 3	*0.033*[a]	*0.010*[a,c]	*0.0048*[a,c]	NR	NR
Revised[a]	***0.0040***[b]	***0.0013***[b]	***0.00067***[b]		

[a] Lethality threshold (LC_{01}) in rats estimated from $C^n t$ binary probit analysis of RZ ricin preparation(Griffiths et al. 1995a); values incorporate a 2.7- fold reduction for lower potency of RZ preparation compared to a commercial ricin preparation (i.e., $LC \cdot t_{50}$ ratio); UF=10 (3x3, intraspecies x interspecies).

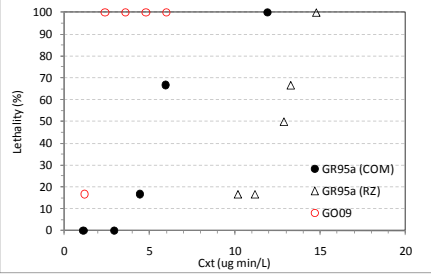
[b] Estimated based on exposure concentration equivalent to the MLD in rats (Gomez et al. 2009); values incorporate a 3-fold reduction for steep DR , UF=10 (3x3); n=1, k=0.40 mg min/m³.

[c] Values for LC_{01} for 30-min and 60-min are extrapolated outside of C and t observation limits; however, estimates are conservative (n=0.95) relative to default assumption of n=1.

NR= Not recommended due to insufficient data.

	Griffiths et al. 1995a	Smallshaw et al. 2007	Gomez et al. 2009
Animal	Porton strain rat (sex NR)	Mice (strain and sex NR)	Sprague-Dawley rats (female) BALB/c mice (female)
Ricin	Commercial (Sigma) Purified from seeds (RZ)	Prepared by authors	Biodefense and Emerging Infections Research Resources Repository
Exposure	Head-only (with head wash after exposure)	Nose-only	Nose-only
Aerosol generation	single-jet nebulizer, no recirculation	Lovelace (*InTox)* nebulizer	*Aero-Tech* nebulizer
Aerosol size	MMAD 0.81-0.91 µm (GSD 1.6)	MD 2 µm (GSD NR)	MMAD 1 µm (GSD 2.5)
Exposure Concentration	0.57 – 2.98 µg/L estimated from fluorescein indicator	NR	0.12 µg/L (rat) 0.01 µg/L (mouse) breathing space sample/ELISA
Exposure Duration	2-40 min	NR	10, 20, 30, 40, 50 min (rat) 10, 20, 40, 60, 80 min (mouse)
Inhaled dose	1-86 µg/kg bw (based on Vm for controls)	1-15 µg/kg bw	0.15-0. 6µg/kg bw[a] (rat) 0.16-1.28 µg/kg bw[a] (mouse)
Observation Time	14 days	14 days	8 days
LD_{50}	Sigma: 3.7 µg/kg RZ: NR	~4 µg/kg	0.15 µg/kg (rat) 0.56 µg/kg (CI: 0.36-0.79) (mouse)
$LCxt_{50}$	Sigma: 4.54-5.96 µg min/kg RZ: 12.7 µg min/kg	NR	NR
Pathology	lung (edema, apoptosis, necrosis)	lung (alveolar cell necrosis)	lung (hemorrhage, edema, apoptosis, necrosis), larynx and trachea (inflammation, apoptosis, necrosis), thymus (thymocyte atrophy and apoptosis), spleen (lymphocytic and/or hematopoietic apoptosis), hematology

Comparison of C·T - Response

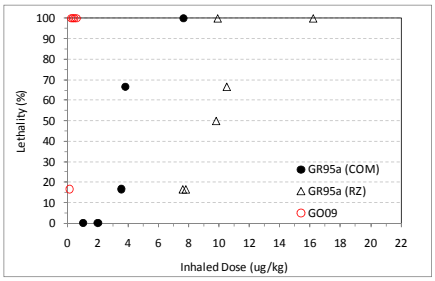


Gomez et al. 2009 (GO09) ricin (weaponized) shows higher potency than Griffiths et al. 1995a (GR95).

Potency difference larger when *inhaled dose* is the dose metric than when Cxt is the dose metric.

Commercial ricin preparation in GR95 shows higher potency than ricin purified from *R. zanzibariensis* seeds

Comparison of Inhaled Dose - Response



Calculated Minute Volumes for Griffiths et al. 1995a

Ricin Preparation	Exposure Time (min)	Exposure Concentration (µg/L)	CxT (µg-min/L)	Inhaled Dose[a] (µg/kg bw)	Minute Volume[b] L/min kg
COM	2	0.57	1.51	1.05	0.70
COM	2	1.48	3.01	2.02	0.67
COM	3	1.48	4.54	3.55	0.78
COM	2	2.98	5.96	3.83	0.64
COM	4	2.98	11.93	7.67	0.64
COM	40	2.98	119.3	85.77	0.72
RZ	6	1.71	10.2	7.8	0.76
RZ	7.5	1.49	11.2	7.6	0.68
RZ	6.5	1.99	12.9	9.8	0.76
RZ	7.3	1.82	13.3	10.5	0.79
RZ	8	1.85	14.8	9.9	0.67
RZ	12	1.74	20.9	16.2	0.78
				AVERAGE	**0.69**
				SD	**0.06**

[a]As reported in Griffiths et al. 1995a
[b] Calculated: Minute Volume = Inhaled Dose/CxT

Calculated Minute Volumes for Gomez et al. 2009

Species	Exposure Time (min)	Exposure Concentration (µg/L)	CxT (µg-min/L)	Inhaled Dose[a] (µg/kg bw)	Minute Volume[b] L/min kg
Rat	10	0.12	1.20	0.15	0.12
Rat	20	0.12	2.40	0.24	0.10
Rat	30	0.12	3.60	0.36	0.10
Rat	40	0.12	4.80	0.48	0.10
Rat	50	0.12	6.00	0.60	0.10
				AVERAGE	**0.10**
				SD	**0.01**
Mouse	10	0.01	0.10	0.16	1.6
Mouse	20	0.01	0.20	0.32	1.6
Mouse	40	0.01	0.40	0.64	1.6
Mouse	60	0.01	0.60	0.96	1.6
Mouse	80	0.01	0.80	1.28	1.6
				AVERAGE	**1.6**
				SD	**--**

[a]As reported in Gomez et al. 2009
[b] Calculated: Minute Volume = Inhaled Dose/CxT

Comparison of Minute Volumes Calculated for Griffiths et al. (1995a) and Gomez et al. (2009)

	Minute Volume (L/min-kg bw)		
	Griffiths et al. 1995a	**Gomez et al. 2009**	**EPA, 1986[a]**
Rat	0.69 ±0.06	0.1 ±0.01	1.26
Mouse	NR	1.6 (no SD)	2.58

[a] U.S. EPA Reference Values for Risk assessment
Minute volume (m^3/day) for 0.25 kg rat =$1.58BW^{0.9}$
Minute volume (m^3/day) for 0.025 kg mouse =$2.57BW^{0.9}$

Griffiths et al. 1995a

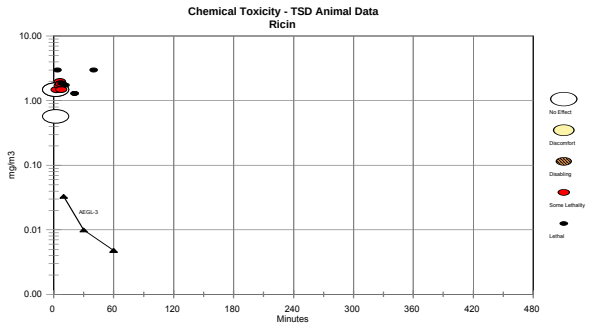
- Ricin aerosol: 0.81-0.91 μm MMAD (GSD 1.6) (head-only)
- Commercial (Sigma) ricin or in-house purification from *R. zanzibarenis* seeds (RX)
- 6 Porton rats (sex NR)/group: 0.57 – 2.98 μg/L (mg/m3); 2 – 40 min
- Median lethal dose:
  - 3.7 μg/kg (CI NR) for commercial preparation
  - MLD for RZ preparation was not reported
- $CCxt_{50}$:
  - 4.54 – 5.96 μg min/kg for commercial preparation
  - 12.7 μg min/kg MLD for RZ preparation

Gomez et al. 2009

- Ricin aerosol: 1μm MMAD; 2.5 GSD (nose-only)
- 6 ♀ BALB/c mice/group: 0.01 μg/L (0.01 mg/m^3); 10, 20, 40, 60, or 80 min
- 6 ♀ S-D rats/group: 0.12 μg/L (0.12 mg/m^3); 10, 20, 30, 40, or 50 min
- Median lethal dose:
  - 0.15 μg/kg rats (no CI)
  - 0.56 μg/kg mice (0.36-0.79, 95% CI)
- Estimated MLD in rats was 23-fold lower than estimate reported by Griffiths et al. 1995a (0.15 μg/kg vs 3.5 μg/kg)

Smallshaw et al. 2007

- Ricin aerosol: 2 µm MD, GSD not reported (nose-only)
- Total of 40 mice (strain and sex not reported) were exposed to ricin aerosol to achieve inhaled doses ranging from 1-16 µg/kg (exposure concentrations, duration and number of animals per exposure group were not reported)
- Median lethal dose reported as "~4 µg/kg" (CI not reported)
- Histopathology of lungs showed alveolar necrosis
- Study is not adequately documented in Smallshaw et al. 2007 to support derivation of a POD:
  - Outcome of lethality study is reported in Figure 2 (no tabular data are reported)
  - Exposure concentrations and durations are not reported



Extant Standards and Guidelines for Ricin

No standards or guidelines available

Issues to Consider

- Use data from Gomez et al. 2009 SOT presentation as a basis for AEGL-3 POD?
- Ricin in Gomez et al. 2009 was weaponized and would result in lower AEGL-3 values than Griffiths et al. 1995a
- Smallshaw et al. 2006 is poorly reported, ricin was not weaponized, and is likely to result in a higher AEGL-3 than Gomez et al. 2009

Development Team Discussion Points

- TBD

END

REVISIT AEGLs FOR HYDROGEN BROMIDE (CAS Reg. No. 10035-10-6) AND HYDROGEN IODIDE (CAS Reg. No. 10034-85-2)

NAC/AEGL Meeting 50

San Francisco, CA

April 13-15, 2010

Chemical Manager: Ernie Falke, Susan Ripple
Chemical Reviewers: Richard Niemeier
SRC Staff Scientist: Heather Carlson-Lynch
Author and ORNL Staff Scientist: Sylvia Talmage

HBr and HI Data Overview

- Little acute exposure data on HBr
  - One human experiment (Conn State Dept of Health, 1955),
  - Two studies in rats and mice (MacEwen and Vernot, 1972; Stavert et al., 1991)
  - Data comparing HBr toxicity with HCl and HF (Stavert et al., 1991)
- No acute exposure data on HI
  - AEGLs for HI set equal to those for HBr

PREVIOUS ACTION ON HBr/HI

- December, 2007
  - Interim TSD
- May, 2008
  - NAS COT subcommittee review
- April, 2010
  - Response to COT comments

HBr and HI: Summary of AEGLs

Summary of REVISED AEGLs (ppm)						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1 (Non-disabling)	1.0	1.0	1.0	1.0	1.0	Nasal irritation with HBr- human (Connecticut State Dept. of Health 1955) POD= 3 ppm; UF=3
AEGL-2 (Disabling) **Revised**:	*100* **150**	*43* **50**	*22* **25**	*11* **13**	*11* **13**	Respiratory tract lesions with HBr- rat (Stavert et al. 1991) POD=1300 ppm; UF=10; MF=3 **Revised POD = 1000 ppm; UF = 10; MF=2**
AEGL-3 (Lethal)	740	250	120	31	31	Benchmark dose ($BMCL_{05}$) for HBr – rat (MacEwen and Vernot 1972) POD=1239 ppm; UF=10

COT COMMENT/RESPONSE

- Comment: AEGL-2 POD of 1300 ppm should be replaced with 1000 ppm since there was mortality at 1300 ppm.
  - AEGL-2 POD changed to 1000 ppm
  - MF reduced from 3 to 2
    - No lethality at new POD
    - Lesions restricted to nasal region with no damage to lungs

Development Team Discussion Points

- TBA

END

REVISIT AEGLs FOR CHLORINE PENTAFLUORIDE (CAS Reg. No. 13637-63-3)

NAC/AEGL Meeting 50
San Francisco, CA
April 13-15, 2010

Chemical Manager: William Bress
Chemical Reviewers: Mark McClanahan
SRC Staff Scientist: Heather Carlson-Lynch
Author and ORNL Staff Scientist: Sylvia Talmage

Overview of ClF_5

- Extremely reactive
  - explodes on contact with organic materials
  - violently hydrolyzed by water
  - reacts vigorously or explosively with metals, fuels, ammonia, CO, hydrogen sulfide, SO_2, and H_2 gas
- No significant industrial use except as fluorinating and oxidizing agent

Overview of ClF_5 Data

- No human data
- Acute (10-min to 60-min) lethality and toxicity data in primates, dogs, rats, mice (Darmer et al., 1972; Weinberg and Goldhamer, 1967; MacEwen and Vernot, 1973)

PREVIOUS ACTION ON ClF_5

- September, 2007
  - Interim TSD
- May, 2008
  - NAS COT subcommittee review
- April, 2010
  - Response to COT comments

ClF_5 : Summary of AEGLs

Summary of REVISED Interim AEGLs (ppm)						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1 (Non-disabling) **Revised:**	*0.30* **NR**	*0.30* **NR**	*0.30* **NR**	*0.30* **NR**	*0.30* **NR**	No observed irritation - rat (MacEwen and Vernot 1973) POD=3 ppm; UF=10 **Inadequate data**
AEGL-2 (Disabling) **Revised:**	3.0 (no change)	2.0 (no change)	*1.0* (no change)	*0.50* **0.48**	*0.36* **0.33**	Sensory irritation, mild lung congestion - monkey and rat (MacEwen and Vernot 1972; 1973) PODs=30, 20, and 10 ppm; UF=10; *n=2* **n=1.9**
AEGL-3 (Lethal) **Revised:**	*20* **21**	*11* **12**	8.0 (no change)	*4.0* **3.9**	*2.8* **2.7**	Highest 1-hour non-lethal concentration in rats; $BMCL_{05}$ (Darmer et al. 1972) POD= 80 ppm; UF=10; *n=2.0* **n=1.9**

COT COMMENT/RESPONSE

- Recommend additional rationale for using same concentration across all time periods for AEGL-1
  - AEGL-1 no longer recommended. Slight irritation that defines AEGL-1 is considered concentration-related; time-scaling not recommended. If 10-minute exposure to 3 ppm is used as AEGL-1 POD and divided by UF of 10 (3 each for inter- and intraspecies) the 8-hour AEGL-1 value would be 0.30 ppm; this is nearly equal to 8-hr AEGL-2 (0.33 ppm), reflecting extremely steep concentration-response curve

COT COMMENT/RESPONSE

- Recommend using n=1.86 (3 significant figures) not n=2 for time scaling ($C^2 \times t = k$)
  - During NAC-36, resolution was passed to use 2 significant figures (giving n=1.9)
  - 4- and 8-hour AEGL-2, and all AEGL-3 values recalculated using n=1.9 ($C^{1.9} \times t = k$)

Development Team Discussion Points

- TBA

END

REVISIT AEGLs FOR BROMINE PENTAFLUORIDE (CAS Reg. No. 7789-30-2)

NAC/AEGL Meeting 50

San Francisco, CA

April 13-15, 2010

Chemical Manager: William Bress

Chemical Reviewers:

SRC Staff Scientist: Heather Carlson-Lynch

Author and ORNL Staff Scientist: Sylvia Talmage

Overview of BrF_5

- Colorless, pungent, corrosive gas
  - Can cause fire after contact with combustibles
  - Violent reaction with water, releasing Br, F, HBr, and HF
- Used as fluorinating agent to produce fluorocarbons, and as oxidizer in rocket propellant systems

Overview of BrF_5 Data

- No human data
- Acute (20-min to 60-min) lethality data in rats exposed to 2 concentrations of BrF_5 (Dost et al., 1968); limited information on toxicity observations
- No other data

PREVIOUS ACTION ON BrF_5

- September, 2007
  - Interim TSD
- May, 2008
  - NAS COT subcommittee review
- April, 2010
  - Response to COT comments

BrF_5 : Summary of AEGLs

Summary of REVISED AEGLs (ppm)						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1 (Non-disabling)	NR	NR	NR	NR	NR	No data
AEGL-2 (Disabling) **Revised:**	3.0 (no change)	2.0 (no change)	1.0 (no change)	*0.50* **0.48**	*0.36* **0.33**	Based on analogy with chlorine pentafluoride PODs = 30, 20, and 10 ppm; UF=10, *n=2* **n=1.9**
AEGL-3 (Lethal)	79	55	33	8.3	4.2	Highest non-lethal BrF_5 concentration in rats (Dost et al. 1970) POD = 500 ppm; UF=10; n = defaults

COT COMMENT/RESPONSE

- Change AEGL-2 values to reflect changes in ClF_5 AEGL-2 values
  - 4- and 8-hour AEGL-2 and AEGL-3 values for ClF_5 recalculated using n=1.9 instead of n=2
  - AEGL-2 values for BrF_5 set equal to those for ClF_5
  - 4- and 8-hour AEGL-2 values for BrF_5 were changed to reflect revised value of n.

Development Team Discussion Points

- TBA

END

REVISIT AEGL FOR CHLOROACETONE (CAS Reg. No. 78-95-5)

NAC/AEGL Meeting 50
San Francisco, CA
April 13-15, 2010

Chemical Manager: Susan Ripple
Chemical Reviewers:
SRC Staff Scientist: Gary Diamond
Author and ORNL Staff Scientist: Cheryl Bast

Chloroacetone

Overview

- Uses:
  - Used in manufacture of couplers for color photography, photosensitizer for polyester-vinyl polymerization, fungicide/bactericide, and intermediate in the production of perfumes, antioxidants, and pharmaceuticals
  - Historically used as a warfare agent gas
- Chemistry:
  - Colorless or amber liquid at room temperature
  - Vapor pressure: 12 mm Hg (25°C)
  - Pungent odor, similar to HCl

Chloroacetone

Data Overview: Humans

- Acute exposures in humans:
  - Anecdotal information about use as a warfare agent
  - Eye and dermal irritation in workers (Sargent et al. 1986)
  - Case of accidental exposure to 4.7 ppm vapor resulted in severe irritation above AEGL-1 severity level (immediate lacrimation and upper respiratory tract irritation, blistering of skin, red, swollen, and painful eyelids)

Chloroacetone

Data Overview: Animals

- Inhalation exposures
  - Lethality studies in rats
  - Respiratory tract irritation (pulmonary edema at death)
- Ingestion exposures
  - Lethality studies in mice, rabbits, rats
  - Gastric irritation, necrosis and perforation
- Acute dermal exposures
  - Dermal irritation (guinea pigs, rabbits)

Chloroacetone

TSD History (1)

- Draft 1 prepared by Cheryl Blast (ORNL) was reviewed at NAC/AEGL-47 (12/2008)
- Response to comments prepared and TSD was revised accordingly (03/2010)
- Response to comments and revised TSD distributed to NAC/AEGL (03/2010)

Chloroacetone

TSD History (2)

- Revised:
  - Time-scaling of 10-min and 8-hr AEGL-2
  - Time-scaling of 8-hr AEGL-3
  - TSD text
- Not revised:
  - POD for derivation of AEGL
  - Basis for POD
  - UFs applied to POD

Summary of Proposed AEGL Values for Chloroacetone [ppm (mg/m³)]						
	10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**
AEGL-1	NR	NR	NR	NR	NR	Insufficient Data
AEGL-2	*8.0 (30)*	5.5 (21)	4.4 (17)	1.1 (4.2)	*1.1 (4.2)*	⅓ of AEGL-3 values
Revised	**5.5 (21)**[a]				**0.53 (2.0)**[b]	
AEGL-3	24 (91)	17 (65)	13 (49)	3.3 (13)	*3.3 (13)*	1-hr Lethality $BMCL_{05}$ (113 ppm) for male rats (Arts and Zwart, 1987) UF= 3 x 3
Revised					**1.6 (6.1)**[c]	

[a] Original value was based on 1/3 of 10-min AEGL-3; however, this resulted in a value above reported adverse levels in humans (4.7 ppm, Sargent et al., 1986); therefore, the revised value adopted the 30-min AEGL-2 as the value for the 10-min AEGL-2.

[b] 1/3 of revised AEGL-3

[c] Original value adopted 4-hr value for 8-hr AEGL-3. The revised values for 8-hr AEGL-3 was extrapolated from 1-hr AEGL, assuming n=1.

Chloroacetone

COT Comment/Response (1)

- Derive AEGL-1 based on POD for irritation in humans (Sargent et al. 1986)
  - NAC concluded that data are not sufficient for derivation of AEGL-1 values
  - NAC concluded that the effects noted in Sargent et al. (1986) are above the definition of AEGL-1 (immediate lacrimation and upper respiratory tract irritation, blistering of skin, red, swollen, and painful eyelids). Value for 10-min AEGL-2 was derived to protect against these effects
  - AEGL-1 was not derived

Chloroacetone

COT Comment/Response (2)

- Provide better justification for establishing 4-hr and 8-hr AEGL values at the same level
  - Revised 8-hr AEGL-3 value was derived based on time scaling from 1-hr $BMCL_{05}$ for lethality (consistent with 4-hr AEGL-3 value)
  - Revised 8-hr AEGL-2 value was derived as 1/3 of corresponding 8-hr AEGL-3 value (consistent with 4-hr AEGL-3 value)

Chloroacetone

Development Team Discussion Points

- TBD

END

REVISIT AEGL FOR Selenium Hexafluoride (CAS Reg. No. 7783-79-1)

NAC/AEGL Meeting 50
San Francisco, CA
April 13-15, 2010

Chemical Manager: George Rusch
Chemical Reviewers:
SRC Staff Scientist: Gary Diamond
Author and ORNL Staff Scientist: Cheryl Bast

SeF_6
Overview

- Use: gaseous electric insulator
- Chemistry:
  - Colorless gas
  - decomposes in moisture to form hydrogen fluoride and selenium oxide
  - Vapor pressure: 651.2 mm Hg (-48.7°C)
- Effects: Severely irritating and corrosive to skin, eyes, and respiratory tract

SeF_6
Data Overview

- Acute exposures in humans: no data
- Animals: inhalation
  - Acute (1-4 hr) study in guinea pigs, mice, rabbits, rats (Kimmerle, 1960)
  - Pathology: lung edema

SeF_6
TSD History (1)

- Draft 1 prepared by Cheryl Bast (ORNL) was reviewed at NAS-COT (5/2008)
- Comments received were responded to and the TSD was revised (03/2010)
- Response to comments and revised TSD were distributed to NAC/AEGL 03/2010)

SeF_6
TSD History (2)

- **Revised:**
  - Reviewers commented on weakness of discussion of selenium and selenium oxide toxicity and the relevance of these topics to mechanisms of action. This has been addressed in the revised TSD with statements referenced to secondary sources (e.g., HSDB, ATSDR, and IPCS)
  - UFs changed from 3 x 1 x 10 = 30 to ***3 x 3 x 3 =30*** (interspecies x intraspecies x modifying factor for data gaps regarding contribution of Se moiety to toxicity); since the product of UFs and MF did not change, the AEGL values did not change
- **Not revised:**
  - PODs for derivation of AEGL values
  - Bases for PODs
  - AEGL values

SeF_6 COT Comment (1)

- There are few data on SeF_6 and apparently no human data at all, but the interspecies differences in toxicity seem small. There is some potential for a sensitive human subpopulation (TSD, Section 4.4.2), and there is some uncertainty as to the exact nature of the reactive species of SeF_6 that produces the observed toxic effects (see above). Given this degree of uncertainty, an interspecies UF of 3, an intraspecies UF of 3, and a modifying factor of 3 may express this range of uncertainty more appropriately. Therefore, the AEGL-1 and AEGL-3 derivation paragraphs should be modified. An issue to be addressed is distinguishing between "irritation effects" and "corrosive effects"; because concentrations increase from below AEGL-1 to AEGL-3, irritation may predominate at lower concentrations and corrosive effects at higher concentrations. Selection of the UFs should be based on the specific effect of concern at the level of concern. See the discussion in SOP Section 2.5.3.3.4, especially the top half of page 87, and Sections 2.5.3.2.3 and 2.5.3.4.4 on pages 72 and 90. Additional support for lowering the modifying factor from 10 to 3 can be provided by having more information on selenium moiety.

SeF_6 Response to Comment (1)

AEGL-1: ~~An intraspecies uncertainty factor of 3 will be applied because selenium hexafluoride is highly irritating and corrosive, and much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of port -of-entry effect is not expected to vary greatly among individuals. An interspecies uncertainty factor of 1 will also be applied because the limited data suggest that the guinea pig, rabbit, rat, and mouse are similarly sensitive to the acute effects of selenium hexafluoride. A modifying factor of 10 will also be applied to account for potential effects of the selenium moiety and the sparse database.~~ ***Interspecies and intraspecies uncertainty factors of 3 each will be applied because selenium hexafluoride is highly irritating and corrosive (effect at AEGL-1 concentrations is most likely to be minor irritation), and much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals. The limited data suggest that the guinea pig, rabbit, rat, and mouse are similarly sensitive to the acute effects of selenium hexafluoride, further supporting the interspecies UF of 3. The intraspecies UF of 3 is further supported by the steep concentration response curve (no effects in rabbit, guinea pig, rat, or mouse for 4-hour exposures at 1 ppm, difficulty breathing and pulmonary edema, but no mortality at 5 ppm, and 100% mortality at 10.***

SeF_6 Response to Comment (1)

AEGL-3: The highest concentration causing no mortality in the guinea pig, rabbit, rats, and mice (5 ppm for 4-hours) (Kimmerle, 1960) will be used to derive AEGL-3 values. ~~An intraspecies uncertainty factor of 3 will be applied because selenium hexafluoride is highly irritating and corrosive, and much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of port~~ portal ~~-of-entry effect is not expected to vary greatly among individuals. An interspecies uncertainty factor of 1 will be applied because the limited data suggest that the guinea pig, rabbit, rat, and mouse are similarly sensitive to the acute effects of selenium hexafluoride. A modifying factor of 10 will also be applied to account for potential effects of the selenium moiety and the sparse database.~~ ***Interspecies and intraspecies uncertainty factors of 3 each will be applied because selenium hexafluoride is highly irritating and corrosive (effects at AEGL-3 concentrations are most likely to be severe irritation/corrosion), and much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals. The limited data suggest that the guinea pig, rabbit, rat, and mouse are similarly sensitive to the acute effects of selenium hexafluoride, further supporting the interspecies UF of 3. The intraspecies UF of 3 is further supported by the steep concentration response curve (no effects in rabbit, guinea pig, rat, or mouse for 4-hour exposures at 1 ppm, difficulty breathing and pulmonary edema, but no mortality at 5 ppm, and 100% mortality at 10 ppm) which implies limited intraindividual variability. A modifying factor of 3 will be applied to account for potential effects of the selenium moiety and the sparse database.*** Thus, the total adjustment is 30.

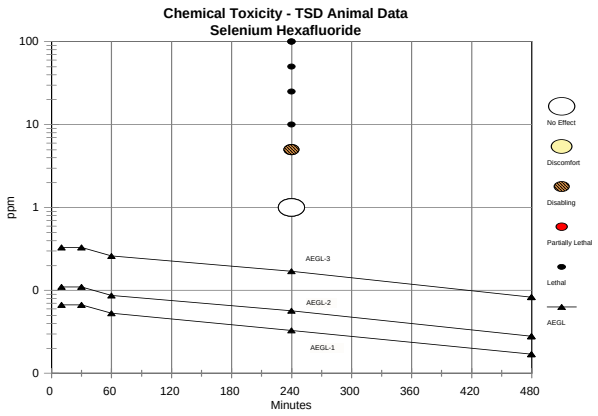
Summary of Proposed AEGL Values for SeF_6 [ppm (mg/m^3)]					
	10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL 1	0.067 ppm (0.53 mg/m^3)	0.067 ppm (0.53 mg/m^3)	0.053 ppm (0.42 mg/m^3)	0.033 ppm (0.26 mg/m^3)	0.017 ppm (0.13 mg/m^3)
AEGL 2	0.11 ppm (0.87 mg/m^3)	0.11 ppm (0.87 mg/m^3)	0.087 ppm (0.69 mg/m^3)	0.057 pm (0.45 mg/m^3)	0.028 ppm (0.22 mg/m^3)
AEGL 3	0.33 ppm (2.6 mg/m^3)	0.33 ppm (2.6 mg/m^3)	0.26 ppm (2.1 mg/m^3)	0.17 ppm (1.3 mg/m^3)	0.083 ppm (0.66 mg/m^3)

UFs revised from 3 x 1 x 10 = 30 to ***3 x 3 x 3 =30*** (interspecies x intraspecies x modifying factor for data gaps regarding contribution of Se moiety to toxicity); since the product of UFs and MF did not change, the AEGL values did not change.

AEGL-1: Based on NOEL for irritation in rabbit, guinea pig, rats, and mice (1 ppm, 4-hrs) (Kimmerle, 1960)

AEGL-2: One-third of the AEGL-3 values

AEGL-3: Highest concentration causing no mortality in rabbit, guinea pig, rats, and mice (5 ppm, 4-hrs) (Kimmerle, 1960)



Extant Standards and Guidelines for Selenium Hexafluoride

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

SeF_6

Development Team Discussion Points

- General agreement that COT comments have been addressed
- Agreement on adjustment of UF and MF, as per NAS comment
- AEGL values unchanged

SeF_6

Development Team Discussion Points (2)

- Suggested revisions (beyond those proposed by ORNL):
  - Expand rationale for basing AEGL-2 as 1/3 of AEGL-3 to include: The two lowest ECs in the study spanned the AEGL-1 (1 ppm) and AEGL-3 (5 ppm), therefore, a value between the AEGL-2 was and AEGL-3 was assigned to the AEGL-2.

SeF_6

Development Team Discussion Points (3)

- Emphasize in appropriate places in the TSD:
  - toxic potency cannot be explained solely by HF
  - SeH_6 slowly hydrolyzes in moist air
  - the exact composition of the SeF_6 aerosol in the respiratory tract is unknown
  - contributions of various reactive species (parent compound and hydrolysis products) to toxicity are not known
  - mechanisms of respiratory tract toxicity of the Se hydrolysis products (e.g. Se oxide) are unknown

END

Methyl isothiocyanate

-Comments on August 19, 2009 FR Notice requesting public comment

-One public comment from:

Amvac Chemical Corporation (AMVAC), Taminco, Inc. (Taminco), and Tessenderlo Kerley, Inc. (TKI) (hereafter the Metam Sodium Alliance or Alliance)

-Summary statement: "The available data and science strongly support the proposed AEGL-1 for MITC of 0.80 ppm (800 ppb). This proposed level is well rationalized and is consistent with the best available science concerning the ocular effects of MITC and the mode of action (MOA) by which such ocular effects are induced."

COMMENT:

The NAC/AEGL Committee correctly concluded that the ocular effects at a MITC concentration of 0.80 ppm were so slight and transient that this level should be considered a no observed effect level (NOEL).

RESPONSE:

-This is incorrect. Exposures to 0.80 ppm were considered a LOAEL for slight eye irritation.

-The exposure of 0.80 ppm was considered a "NOAEL for the AEGL-1". The AEGL-1 is a threshold for "notable" discomfort. As such it allows for mild irritant effects to occur below that threshold.

COMMENT:

The NAC/AEGL Committee also correctly determined that the intraspecies uncertainty factor for the ocular effects of MITC should be set at one.

RESPONSE:

The Technical Support Document states as a rationale that an intraspecies UF of 1 is justified because "considered sufficient to account for the response of the sensitive population to a direct-acting irritant" and in another section "sufficient for NOAEL with direct-acting eye irritant; the endpoint was extremely sensitive (no tearing or redness)". No change needed.

COMMENT:

Toxicology for Excellence in Risk Assessment (TERA) has determined that the mechanism for ocular sensations induced by MITC is reversible binding to specific receptors in free endings of the trigeminal nerve.

RESPONSE:

The comment supports the AEGL-1 derivation. No further response is needed.

COMMENT:

An uncertainty factor for human variability greater than one is unwarranted for MITC because the mode of action (MOA) for ocular effects is a surface reaction with the trigeminal nerve, human variability in sensitivity to ocular irritants is limited, and the human subjects studied represent a sensitive subset of the population.

RESPONSE:

As indicated above, the endpoint was "extremely sensitive" for an AEGL-1 endpoint that would allow for some irritation. This, and the fact that there is little to no pharmacokinetic variability to eye exposures justifies the use of an UF of 1.

COMMENT:

If the benchmark concentration level (BMCL) for the non-adverse ocular effects in the Russell and Rush study was used as a point of departure (POD), use of an uncertainty factor for human variability greater than one would be particularly inappropriate.

RESPONSE:

-The AEGL Program did not use benchmark dose modeling for AEGL-1 type effects.

-In fact it is almost always used only for the AEGL-3, the threshold for lethality.

-Lethality is a clearly dichotomous effect and the AEGL SOP has documented that the BMC01 and BMCL05 are reasonable indicators for the threshold for lethality.

-Such an analysis of the effects observed in the Russell and Rusch study is problematic. The response reported (subjective eye irritation) is really a continuous response where the severity of response can easily vary in a non-measurable manner from individual to individual and the response level to utilize to estimate the threshold has not been well characterized.

-Since the AEGL used an UF of 1 and the commenter agrees with the approach taken, there is no need for a further response.

COMMENT:

The MOA information, human incident data, and animal data all show that ocular effects will occur at MITC concentrations lower than any potential respiratory effect.

RESPONSE:

-Respiratory effects relevant to AEGL-1 or AEGL-2 derivation were not identified in the AEGL document.

-Since the comment does not impact the derivation of the AEGL-1 value, no further comment is necessary.

RECOMMENDATION:

The commenter agrees with the AEGL-1 values and the methodology used to derive the AEGL-1 values.

Recommendation is to elevate methyl isothiocyante from Proposed to Interim Status.

AEGLs FOR CARBON DIOXIDE (CAS Reg. No. 124-38-9)

NAC/AEGL Meeting 50
San Francisco, CA
April 13-15, 2010

Chemical Manager: Marcel van Raaij
Chemical Reviewers: David Freshwater
SRC Staff Scientist: Gary Diamond
Author and ORNL Staff Scientist: Robert Young

Carbon Dioxide Overview

- Colorless, odorless gas
- Naturally occurring; typical ambient air concentrations are 0.03% (300 ppm)
- Product of combustion of carbonaceous materials and oxidative metabolism of hydrocarbons
- Used in manufacturing, fire prevention, beverage carbonation, oil and gas recovery, cooling of food
- Underground sequestration

Carbon Dioxide Physiology

- Major physiological acid that establishes HCO_3^-/H_2CO_3 buffering of extracellular and intracellular pH
- Normal arterial PCO2 is ~40 mmHg (~5%, 50,000 ppm)
- Increasing arterial PCO_2 decreases pH, and triggers complex physiological responses to restore pH (ventilation/perfusion, ICF-ECF H^+ exchange; urine acidification which promotes conservation of bicarbonate, excretion of acid)

CO_2 - Lethality - Humans

- Deaths have occurred in humans exposed to approximately to 11-20% (110,000 – 200,000 ppm) (Hamilton and Hardy, 1974).
- Cases include fishing boats (e.g., Daalgard et al 1972) and fermentation rooms (e.g., Zink and Reinhardt (1975); and involved mixed exposures and uncertain CO_2 exposure levels.
- Natural disaster in Cameroon, in which a large quantity of CO_2 was released from Lake Nyos (Kling et al. 1986) resulted in 1700 deaths. Exposure levels are highly uncertain; however, oil lamps were extinguished suggesting that levels exceeded 8-10% (80,000 – 100,000 ppm).

CO_2 - Lethality - Animals

- Deaths occurred in monkeys when exposures were increased to 60% (600,000 ppm) at rates of 75,000 ppm/hr (~8 hr), 150,000 ppm/hr (~4 hr) or 300,000 ppm/hr (~2 hr) and PO_2 was maintained at 21% *(Stinson and Mattsson, 1970)*
- Rats survived exposures to 40% (400,000 ppm) and ~12% O_2 for 10 min – 6 hr); all rats exposed to higher levels died *(TNO, 2010)*
- Deaths occurred in dogs during 10-min exposure to 80% (800,000 ppm) and 20% O_2 (Ikeda et al. (1989)

CO_2 – Disabling - Humans

- Exposures to >5% (50,000 ppm) in humans resulted in dyspnea, nausea, dizziness, unconsciousness, ECG and EEG anomalies, and anxiety

CO_2 – Disabling – Humans (selected studies)

Exposure Concentration	Exposure Duration	Oxygen	Outcomes	Reference
•2% (20,000 ppm) •4% (40,000 ppm) •5% (50,000 ppm)	5-12 hrs 5-12 hrs 5-12 hrs	14-16%	•slight effect on respiration •mild ventilatory distress ("panting") •dyspnea, nausea, chills	**Brown, 1939b**
•7% (70,000 ppm) •10% (100,000 ppm)	40-90 min 15-25 min	21%	•mild headache, burning eyes •extreme hyperventilation, confusion, restlessness, progressive listlessness	Brackett et al., 1965
7.6% (76,000 ppm)	2.5-8.5 min (5.8 min av.)	NR	headache, dizziness, dyspnea, sweating unconsciousness in some subjects during inhalation period	Dripps and Comroe, 1946.
7-14% (70,000 – 140,000 ppm)	10-20 min	NR	extreme anxiety, unconsciousness, vomiting, sever headache, auditory and visual disturbances, tachycardia, increased pulse pressure	Sechzer et al., 1960
•5% (50,000 ppm) •7.5% (75,000 ppm)	15 min	21%	•anxiogenic effects in panic disorder patients •no effect in normal subjects •anxiogenic in normal subjects	**Woods et al., 1988**
30% (300,000 ppm)	38 sec	70%	unconscious; altered atria or ventricular activity and abnormal cardiac rhythms; health compromised subjects	MacDonald and Simonson, 1953
30% (300,000 ppm)	24-28 sec	70%	unconscious; EEG alterations in health-compromised subjects	Friedlander and Hill, 1954

CO_2 – Woods et al 1988

- Healthy adults (N=11, 7 F, age 19-49 yr)
- Patients diagnosed with panic anxiety disorder (N=14, 9 F, age 28-47 yr)
- Inhalation of 5% CO_2 (21% O_2) for 15 min caused 8/14 panic disorder patients and 0/11 healthy subjects to experience anxiety characterized as panic attacks (p=0.005).
- 3/8 healthy subjects experienced anxiety after inhalation of 7.5% carbon dioxide.

CO_2 – Brown et al 1939b

- Healthy adults males (N=10, age 19-30 yr)
- Inhalation of 2%, 4% or 5% CO_2 (14-16% O_2) for ~ 8 hr
- Increased ventilation observed at 2% CO_2 (20,000 ppm); panting at 4% CO_2 (40,000 ppm); and dyspnea, nausea, and chilliness at 5% CO_2 (50,000 ppm).

CO_2 – Disabling – Animals

- Cardiac arrhythmia occurred in monkeys when exposures were increased to 20% over a period of 1-3 hours and PO_2 was maintained at 21% *(Stinson and Mattsson, 1970)*
- Subpleural atelectasis (lung collapse) occurred in guinea pigs exposed to 15% for 1 or 6 hours (Schaefer et al.,1964)

CO_2 Data Overview – Non-disabling

- Impaired visual performance (reduced depth perception and motion detection) occurred in humans exposed to 2.5% (25,000 ppm) for 1-hour

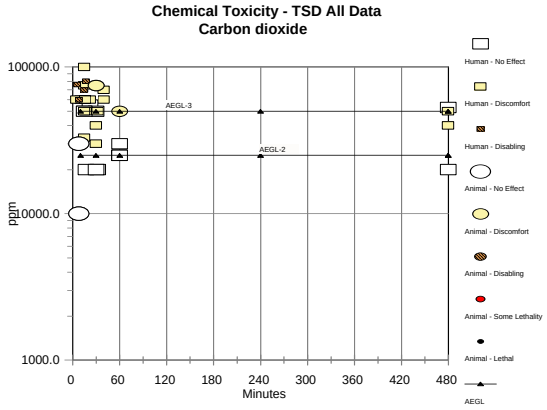
CO_2 – Non-disabling – Humans (selected studies)

Exposure Concentration	Exposure Duration	Oxygen	Outcomes	Reference
2.5% (25,000 ppm)	~1 hr	20.5%	reversible reduction in stereoacuity (depth) perception	**Sun et al., 1996**
2.5% (25,000 ppm)	~1 hr	20.5%	reversible effect on motion detection threshold	**Yang et al., 1997**
3% (30,000 ppm)	5 days	18%	normal adaptive acid-base balance responses; no effect on pulmonary function or behavioral indices in healthy young males	Glatte et al., 1967
3% (30,000 ppm)	1 hr	NR	normal compensatory physiological responses to increased CO_2 in healthy young exercising subjects	Sinclair et al., 1971
3-3.5% (21-25 mm Hg)	2 mo	15-17%	skin flushing, decreased blood pressure, impaired attentiveness; all reversible	Schaefer, 1959
•1% (10,000 ppm) •2% (20,000 ppm) •3% (30,000 ppm) •4% (40,000 ppm)	30 min	17.4-19%	•no effect on ability to exercise •no effect on ability to exercise •dyspnea, intercostal muscle pain but completed exercise •dyspnea, intercostal muscle pain but completed exercise	Menn et al., 1970

CO_2 AEGL-1 Sun et al. 1996, Yang et al. 1997

- Healthy adults (N=3, 1 F, age ~34 yr)
- Exposed to 2.5% CO_2 (PO_2 uncontrolled, ~20.5%) for ~ 1 hr
- Subjects exposed to 2.5% CO_2(25,000 ppm) showed reversible decrease in threshold for visual detection binocular disparity (depth perception)
- And decrease in threshold for visual detection of coherent motion (perception of movement of objects in visual field).

Proposed AEGL Values for Carbon Dioxide (ppm)						
Class	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	25,000	25,000	25,000	25,000	25,000	subclinical effects on vision; 1-hr exposure of human subjects to 2.5% (25,000 ppm) CO_2 (Sun et al. 1996; Yang et al., 1997). UF=1x1; no time scaling
AEGL-2 (Disabling)	50,000	50,000	50,000	50,000	50,000	dyspnea, nausea, chills (anxiety in a sensitive subgroup) exposed to 5% (50,000 ppm) CO_2; exposure durations up to 12 hrs; little or no effect in some individuals; Brown, 1930b; Woods et al., 1988. UF=1x1; no time scaling.
AEGL-3 (Lethality)	NR	NR	NR	NR	NR	not recommended: insufficient data with which to estimate a lethality threshold or exposure concentration-duration relationship



Extant Standards and Guidelines for Carbon Dioxide					
	Exposure Duration				
Guideline	**10 min**	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	25,000	25,000	25,000	25,000	25,000
AEGL-2	50,000	50,000	50,000	50,000	50,000
AEGL-3	NR	NR	NR	NR	NR
ERPG-1 (AIHA)[a]					
ERPG-2 (AIHA)					
ERPG-3 (AIHA)					
EEGL (NRC)[b]			25,000 ppm (2.5%)		
PEL-TWA (OSHA)[c]					5,000 ppm (0.5%)
PEL-STEL (OSHA)[d]					
IDLH (NIOSH)[e]		50,000 ppm (5%)			
REL-TWA (NIOSH)[f]					
REL-STEL (NIOSH)[g]					
TLV-TWA (ACGIH)[h]					5,000 ppm (0.5%)
TLV-STEL (ACGIH)[i]	30,000 ppm (3%)				
MAK (Germany)[j]					5,000 ppm (0.5%)
MAK Spitzenbegrenzung (Germany)[k]					
Einsaztoleranzwert (Germany)[l]					
MAC-Peak Category (The Netherlands)[m]					5,000 ppm (0.5%)
SMAC[n]			13,000 ppm (1.3%)		

CO_2 AEGL-1 Intraspecies UF

- A value of 1 was assigned
- Available studies do not identify or imply a sensitive population
- AEGL-1 values are consistent with the report by Menn et al. (1970) where healthy adults easily completed heavy exercise during 30-minute exposure to 1-2 % (10,000-20,000 ppm) CO_2
- Further, reduction of the AEGL-1 values was not justified due to the subtly of the critical effect (subclinical visual impairment)

CO_2 AEGL-1 Time Scaling

- Time scaling was not performed because longer exposures to CO2 concentrations of 2-3.5% did not produce effects of greater severity; Glatte et al., (1967) reported only normal physiological responses following 5-day exposure to 3% CO2, and Schaefer et al. (1959) reported only minor reversible effects following 2-month exposure to 3-3.5% CO2. Additionally, Stein et al. (1959) showed that continuous exposure of a nonhuman primate to 3% CO2 for up to 93 days was without notable effect.

CO_2 AEGL-2 Intraspecies UF

- A value of 1 was assigned
- With the possible exception of individuals with panic disorders, which was accounted for in one of the key studies, *a sensitive population was not identified with the available data*
- Other possible sensitive populations may include (no direct evidence):
  - People who have limitations in CO_2 elimination (e.g., COPD). These individuals would be prone to hypercapnia and have muted ventilatory response to CO_2 and would be expected to increase CO2 body burden (Dempsey, 2002; O'Donnell et al. 2002; Tenney et al. 1954).

CO_2 AEGL-2 Time Scaling

- Data were insufficient for empirical derivation of a time scaling exponent. Justification may be made for not time scaling from either POD (Brown et al. 1930b, Woods et al. 1988).
- The 15-minute POD was not time scaled (default n = 3) to 1-hour because data from other reports showed that 1-hour exposure to 5% (50,000 ppm) CO2 did not necessarily result in effects severity exceeding that of the AEGL-2 tier.
- Time scaling to 10 minutes was not performed because some reports showed that the resulting exposure concentration (57,000 ppm) would approach that causing ECG alterations as reported by (Okajima and Simonson, 1962).
- Data from Brown (1930b) indicate that the response to 5% (50,000 ppm) CO2 did not vary perceptibly over 5-12 hours (average 8 hours) so the 4-hour and 8-hour AEGL-2 are equivalent. Although the available data imply that exposure to 5% CO2 for several minutes to several hours may not result in life-threatening effects, human data also suggest that exposure to 7-10% may result in notably more severe effects including unconsciousness .

CO_2 AEGL-3

- Due to the lack of data at the time the TSD was prepared with which to adequately estimate a lethality threshold and uncertainties regarding the exposure concentration-duration relationship, AEGL-3 values were not developed and were not recommended.
- Data pertinent to the AEGL-3 has been provided from TNO (2010)
  - rats survived exposures to 40% (400,000 ppm) and ~12% O_2 for 10 min – 6 hr); all rats exposed to higher levels died *(TNO, 2010)*
- Sensitive populations:
  - COPD?
  - IHD?

CO_2 AEGL-3 (2)

- If 40% (400,000 ppm) were adopted as the POD:

Proposed AEGL Values for Carbon Dioxide (ppm)						
Class	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-3 (Lethality)	130,000	130,000	130,000	130,000	130,000	Highest exposure (400,000 ppm, 10 min – 6 hr) that did not produce lethality in rats (TNO, 2010)

UF = 3 x 1 (interspecies x intraspecies) = 3

- AEGL-3 of 130,000 ppm (13%) is in the range of observations of extreme discomfort, anxiety, listlessness, and loss of consciousness in health adults (e.g., Brackett et al. 1965; Sechzer et al. 1960)

Proposed and *Alternative* AEGL Values for Carbon Dioxide (ppm)						
Class	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	25,000	25,000	25,000	25,000	25,000	subclinical effects on vision; 1-hr exposure of human subjects to 2.5% (25,000 ppm) CO_2 (Sun et al. 1996; Yang et al., 1997). UF=1x1; no time scaling
AEGL-2 (Disabling)	50,000	50,000	50,000	50,000	50,000	dyspnea, nausea, chills (anxiety in a sensitive subgroup) exposed to 5% (50,000 ppm) CO_2; exposure durations up to 12 hrs; little or no effect in some individuals; Brown, 1930b; Woods et al., 1988. UF=1x1; no time scaling.
AEGL-3 (Lethality)	NR	NR	NR	NR	NR	not recommended: insufficient data with which to estimate a lethality threshold or exposure concentration-duration relationship
AEGL-3 (Lethality)	***130,000***	***130,000***	***130,000***	***130,000***	***130,000***	Highest exposure (400,000 ppm, 10 min – 6 hr) that did not produce lethality in rats (***TNO, 2010***) UF=3 x 1, no time scaling.

Development Team Discussion Points

- General:
  - revise and revisit TSD
  - include discussion of asphyxiation
  - review and strengthen justification for time scaling to 8 hours
  - review more recent review of Navy studies (Sinclair et al)
  - search for relevant data from clinical medicine (e.g., anesthesiology)
  - circulate action item list

Development Team Discussion Points (2)

- AEGL-3:
  - Include discussion of asphyxiation
  - Consider proposing AEGL-3 values for controlled (i.e., 21%) and uncontrolled O_2 (21%) scenarios
  - Consider basing POD on TNO, 2010
  - Consider establishing an empirical basis for UFs/adjustment factors for intraspecies and interspecies
  - Carefully check case literature of deaths below proposed AEGL-3

Development Team Discussion Points (2)

- AEGL-2:
  - not much controversy with proposed value
  - reconsider use of Woods et al. 1988 as key study (panic anxiety patients)
  - review and justify time scaling to 8 hours (e.g., stress of prolonged increase work of ventilatory/cardiovascular response)
  - review more recent review of Navy studies (Sinclair et al)

Development Team Discussion Points (1)

- AEGL-1:
  - not much controversy with proposed value

END

AEGLs FOR RED PHOSPHORUS/BUTYL RUBBER (CAS Reg. No. 7723-14-0)

NAC/AEGL Meeting 50
San Francisco, CA
April 13-15, 2010

Chemical Manager: Glenn Leach
Chemical Reviewers: Richard Niemeier, Alan Woolf
SRC Staff Scientist: Julie Klotzbach
Author and ORNL Staff Scientist: Bob Young

RP/BR

Chemistry and Use

- RP/BR combustion products (phosphoric oxyacids and phosphine) used as a military smoke screen/obscurant
- RP:BR ≈ 95:5; also may contain small amounts of insulating oil and talc or silica.
- Polymeric $(P_4)_n$ for red phosphorus component
- Properties:
  - Vapor pressure: 0.05 mm Hg at 25°C
  - Solubility in water: negligible
  - Sublimes at 416°C for red phosphorus

RP/BR

Human Data

- Limited human inhalation data
  - Estimated that death may occur in humans exposed to 2000 mg/m^3 for >15 min (Mitchell and Burrows 1990)
    - Note: estimate apparently based on LC_{50} values in animals
  - Occupational exposure to 100-700 mg/m^3 for <15 min produced significant, reversible respiratory distress and irritation of eyes and mucous membranes (Berkowitz et al. 1981)
    - Workers also had concurrent exposure to methylene chloride (Uhrmacher et al. 1985)

RP/BR

Animal: Mortality Overview

- **Rats**
  - 1-hr dose-response data
    - Burton et al. (1982)
    - Aranyi (1983)
  - Point estimates at various times
    - 30-min (Marrs 1983)
    - 1-hr (Weimer et al. 1977)
    - 2- to 4-hr (Weimer et al. 1977; Burton et al. 1982; Aranyi et al. 1983)
- **Guinea pigs**
  - Point estimates: 5- to 150-min (Weimer et al. 1977)

RP/BR

Animal: Mortality D-R (1)

- Burton et al. (1982)
  - 1-hr; single exposure
  - Exp. conc. measured as phosphoric acid
  - Sprague-Dawley rats (10/group; 5M and 5F, or 10 M)
  - Effects: respiratory tract (larynx, trachea, lungs)

Exp. Conc. (mg/m^3)	Mortality	Summary
2720	2/10	NOAEL (not identified) LOAEL = 2720 mg/m^3 $BMCL_{05}$ = 941 mg/m^3 BMC_{01} = 1521 mg/m^3
4030	5/10	
4410	7/10	
6420	9/10	

RP/BR

Animal: Mortality D-R (2)

- Aranyi 1983
  - ~1-hr exposure (1.0 to 1.2 hr); single exposure
  - Exp. conc. measured as total phosphorus
  - Rats: Sprague-Dawley (age and group size varied)
  - Effects: not reported

Exp. Conc. (mg/m^3)	Exp. Time (hr)	Age (wks) [M/F]	Lethality	Summary
2000	**1.0**	6 [10M/10F]	0/20	NOAEL = 2220 mg/m^3 LOAEL = 2620 mg/m^3 All Data: *$BMCL_{05}$ = 2281 mg/m^3 BMC_{01} = 2347 mg/m^3 1-hr data only: $BMCL_{05}$ = 2071 mg/m^3 BMC_{01} = 2298 mg/m^3
2220	1.1	12-13 [9M/9F]	0/18	
2620	**1.0**	12-13 [9M/9F]	1/18	
3090	**1.0**	6 [10M/10F]	5/20	
3150	1.2	7 [5M/5F]	2/10	

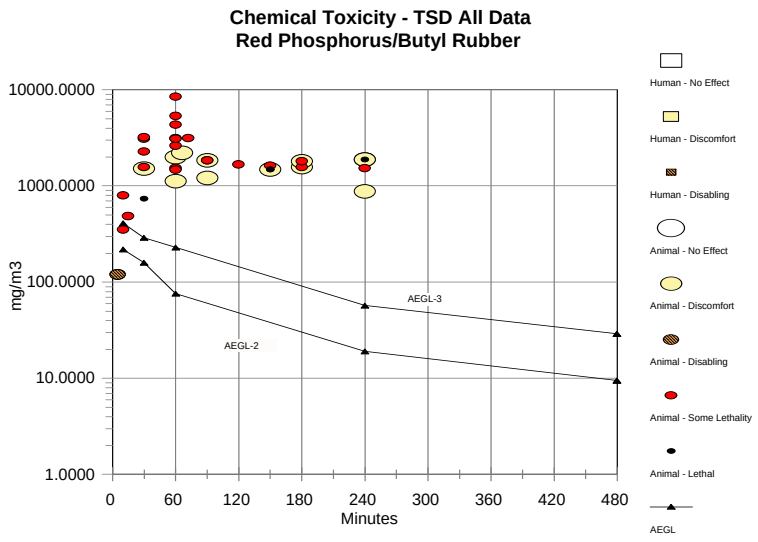
*POD for AEGL-2; includes a "theoretical" 0-response control group

RP/BR: Animal Lethality Point-Estimates in Rats

Exp. Conc. (mg/m^3)	Time (hr)	Mortality	Summary	Reference
680	0.5	1/5	NOAEL (lethality)(30-min) = not identified LOAEL = **680 mg/m^3**	Marrs 1984
1128 1537	1	0/10 1/10	NOAEL (lethality) (1-hr) = 1128 mg/m^3 LOAEL (1-hr)= **1537 mg/m^3**	Weimer et al. 1977
1846	1.5	0/10	NOAEL (lethality) (1.5-hr) = 1846 mg/m^3 LOAEL (1.5-hr) = not identified	
1625 to 1882	2 to 4	4/10 to 10/10	NOAELs (lethality) = not identified (40-100% lethality)	
1210	4	2/10	NOAEL (lethality) = not identified LOAEL (4-hr) = 1210 mg/m^3	Burton et al. 1982
880	4	0/10	NOAEL (lethality)(4-hr) = 880 mg/m^3 LOAEL (4-hr) = not identified	Aranyi 1983
Dose-Response Results: 1-hr $BMCL_{05}$: **2281** mg/m^3 (Aranyi 1983; POD for AEGL-3) 1-hr $BMCL_{05}$: 941 mg/m^3 (Burton et al. 1982)				

Values in **red** are <POD for AEGL-3

RP/BR

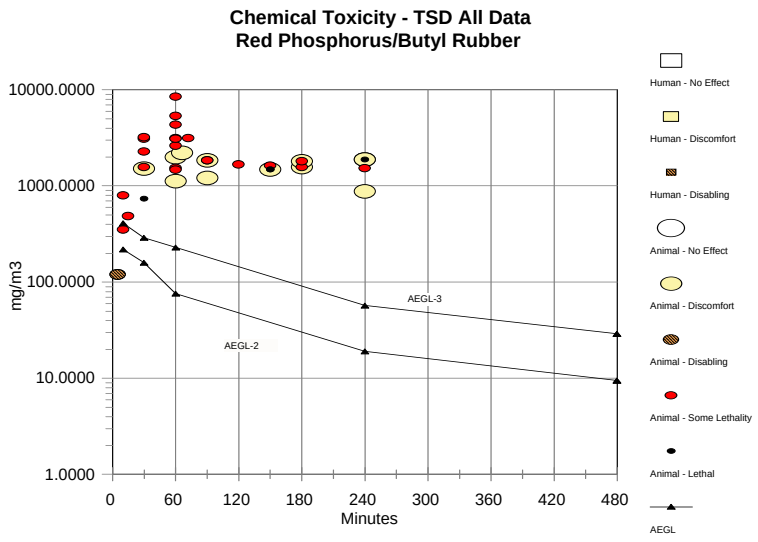


RP/BR

Animal: Guinea Pig Acute Lethality

- Weimer et al. 1977
  - NOAEL (5-min) = 120 mg/m^3
  - Exposure to 352 mg/m^3 for 10 to 1483 for 150 min
    - o Lethality 40 to 100%
    - o Effect:
      - ❑Respiratory distress
      - ❑Severity increased with increasing *C x t* product
  - 1-hr exposure to 1479 mg/m^3 → 90% lethality

RP/BR



RP/BR

Animal: Nonlethal Toxicity – Overview

- **Single Exposure**
  - Dogs (Weimer et al. 1977)
  - Rats (Weimer et al. 1977; Aranyi 1983; Aranyi et al. 1988)
  - Rabbits (Marr 1984)
  - Guinea Pigs (Weimer et al. 1977)
- **Repeated Exposure**
  - Rats (Aranyi 1983, 1984, 1986)

RP/BR

Animal: Nonlethal Toxicity Single Exposure (1)

- Dogs (Weimer et al. 1977):
  - 1519 mg/m^3 (30 min) to 1882 mg/m^3 (4 hr)
  - Effects:
    - No treatment-related deaths
    - Respiratory distress in all groups
    - Conjunctivitis in highest exposure group
  - NOAEL: not identified
  - LOAEL (respiratory distress): 1519 mg/m^3 (30 min)
  - LOAEL (conjunctivitis): 1882 mg/m^3 (4 hr)

RP/BR

Animal: Nonlethal Toxicity Single Exposure (2)

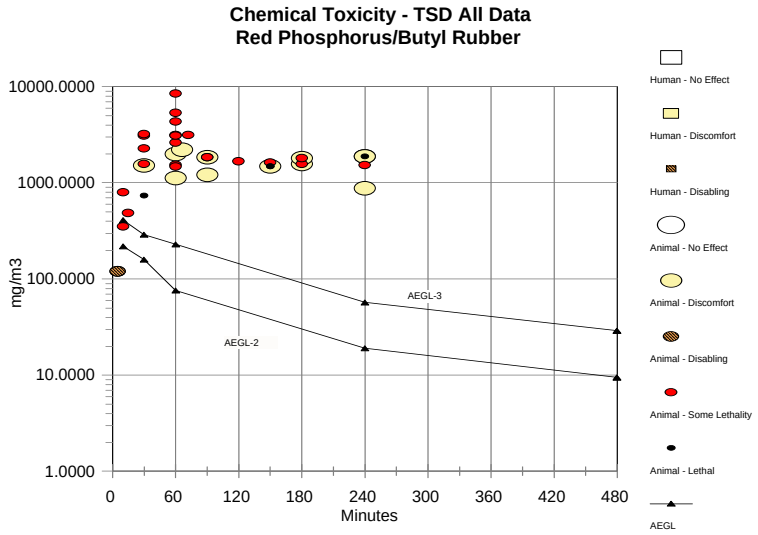
- Rats (Sprague-Dawley)
  - Weimer et al. 1977
    - Exposure: 1128 mg/m^3 (1 hr) to 1882 mg/m^3 (4 hr)
    - Effect: Respiratory distress at sublethal exp to 1128 mg/m^3 (1 hr)
    - NOAEL: not identified; LOAEL: 1128 mg/m^3 (1 hr)
  - Aranyi et al. 1988
    - Exposure: 0 or 1000 mg/m^3 for 3.5 hours
    - Effect: Compromised alveolar macrophage function
    - NOAEL: not identified; LOAEL 1000 mg/m^3 (3.5 hr)
  - Aranyi 1983
    - No deaths at 2000 to 2220 for 1 hr
    - no additional information

RP/BR

Animal: Nonlethal Toxicity Single Exposure (3)

- Rabbits (Marrs 1984)
  - New Zealand white (10F/group)
  - 0 or 680 mg/m^3 (30 min)
  - Sacrificed at 24-hr (n=5) and 14-d (n=5)
  - Effects
    - No lethality; severe respiratory damage
    - At 24-hr:
      - ❑Laryngeal and tracheal inflammation progressing to epithelial necrosis; alveolitis
    - At 14-d:
      - ❑Laryngeal and tracheal inflammation; alveolitis
  - NOAEL: not identified; LOAEL: 680 mg/m^3 (30 min)

RP/BR

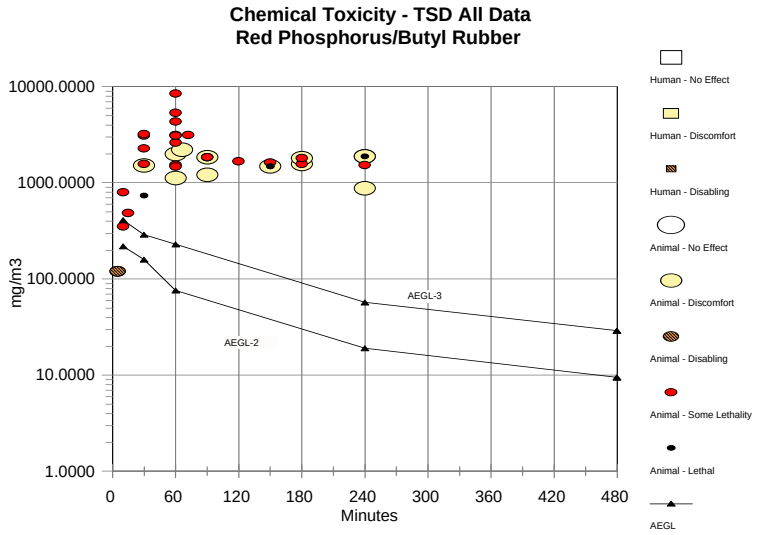


RP/BR

Animal: Nonlethal Toxicity Single Exposure (4)

- Guinea pigs (Weimer et al. 1977)
  - Hartley; 5M/5F per group
  - Exposure: 120 mg/m^3 for 5-min to 1483 mg/m^3 for 150=min
  - No lethality at 120 mg/m^3 for 5 min
  - Respiratory distress in all groups
    - NOAEL: not identified
    - LOAEL (respiratory distress): 120 mg/m^3 for 5 min

RP/BR



RP/BR

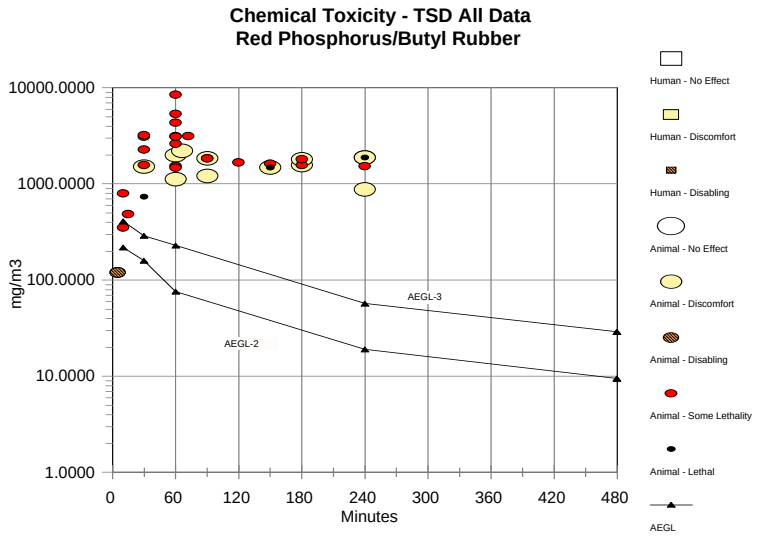
Animal: Nonlethal Toxicity Multiple Exposure

- Rats (Aranyi 1983, 1984, 1986)
  - Exposure periods range:
    - 1-3.5 hr/day for 4 days
    - 2.25 hr/day, 4 day/wk for 13 weeks
  - Most exposure concentrations were sublethal
  - Effects:
    - At shorter durations: minor pulmonary irritation; decreased (transient) body weight gain
    - At longer durations: wheezing; labored breathing; pulmonary atelectesis, hemorrhage and congestion; terminal bronchiolar fibrosis; decreased body weight gain; kidney and liver congestion; liver necrosis.

RP/BR: Summary Acute Sublethal Toxicity

Species	NOAEL/LOAEL (Effect)	Reference
Dogs	NOAEL: not identified *LOAEL: **1519 mg/m^3 for 30 min** (respiratory distress)	Weimer et al. 1977
Rats	NOAEL: not identified LOAEL: **1128 mg/m^3 for 1 hr** (respiratory distress)	Weimer et al. 1977
	NOAEL: 2000-2220 mg/m^3 for 1 hr LOAEL: no information on sublethal toxicity	Aranyi 1983
	NOAEL: not identified LOAEL: 1000 mg/m^3 for 3.5 hr (compromised alveolar macrophage function)	Aranyi et al. 1988
Rabbits	NOAEL: not identified LOAEL: **680 mg/m^3 for 30 min** (severe respiratory tract damage)	Marrs 1984
Guinea pigs	NOAEL: not identified LOAEL: 120 mg/m^3 for 30 min (respiratory distress)	Wiemer et al. 1977
*POD for AEGL-2 values Values in **red** are <POD for AEGL-2		

RP/BR



RP/BR

- **Mechanistic information**
  - Direct contact irritant due to phosphoric acid
  - Cellular toxicity likely due to reducing activity, disrupting oxidative processes
- **Species Variability**
  - Guinea pigs uniquely sensitive (death due to larnygospasm)
  - Respiratory effects in dogs, rats, and rabbits varied ~3-fold
- **Susceptible populations**
  - Pre-existing respiratory diseases
  - As a direct-acting irritant, individual variability may be related to dosimetric factors

RP/BR

AEGL-1 Values

DRAFT PROPOSED AEGL-1 VALUES (mg/m^3)				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
NR	NR	NR	NR	NR

NR: not recommended

- Only AEGL-1 effect: conjunctivitis in some rats and dogs; however lethality occurred at these doses and/or lower doses in rats
- Therefore, available data does not permit identification of a threshold for AEGL-1 severity effects

RP/BR

AEGL-1 Values: Considerations

- Consider development of AEGL-1 values
- Approach used to develop AEGL-1 values for Red Phosphorus
  - 3-fold reduction on AEGL-2 values
  - Rationale: continuum of same MOA (contact irritation)

RP/BR

AEGL-2 Values

DRAFT PROPOSED AEGL-2 VALUES (mg/m^3)				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
220	150	76	19	9.5

- Key study: Weimer et al. 1977
- Species: dogs
- Critical effect: respiratory distress
- POD: 1519 mg/m^3 for 30 minutes
- Time scaling: $C^n \cdot t = k$
  - n = 3 extrapolating to shorter durations; n = 1 extrapolating to longer durations
- Uncertainty factors: total 10
  - Interspecies UF = 3: respiratory effects in dogs, rats, and rabbits varied ~3-fold
  - Intraspecies UF = 3: variability in response would be due to toxicodynamics, rather that toxicokinectics

RP/BR

AEGL-2 Values Considerations

1) A different key study?

Study	Species	NOAEL	LOAEL (Effect)
Weimer et al. 1977	Dogs	Not identified	*1519 mg/m^3 for 30-min (respiratory distress)
Marrs 1984	Rabbits	Not identified	**680 mg/m^3** for 30-min (severe respiratory damage)

*AEGL-2 POD
Value in **red** is <POD for AEGL-2

2) Test substance in key study (Weimer et al. 1977) also contains ~4% black powder.

RP/BR

AEGL-3 Values

DRAFT PROPOSED AEGL-3 VALUES (mg/m^3)				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
410	290	230	57	29

- Key Study: Aranyi 1983
- Species: rats
- POD: $BMCL_{05}$ = 2281 mg/m^3 (1-hr)
- Time scaling: $C^n \cdot t = k$
  - n = 3 extrapolating to shorter durations; n = 1 extrapolating to longer durations
- Uncertainty factors: total 10
  - Interspecies UF = 3: respiratory effects in dogs, rats, and rabbits varied ~3-fold
  - Intraspecies UF = 3: variability in response would be due to toxicodynamics, rather that toxicokinectics

RP/BR: AEGL-3 Values Considerations

1) A different key study for POD?

Study	NOAEL(lethality) mg/m³)	LOAEL (mg/m³)	$BMCL_{05}$ (mg/m³)	BMC_{01} (mg/m³)
Aranyi 1983	2220 (1-hr)	2620 (1-hr)	***2281**	2347
Burton et al. 1982	Not identified	2720 (1-hr)	**941**	1521
Wiemer et al. 1977	1128 (1-hr)	**1537** (1-hr)	NA	NA
Marrs 1984	Not identified	**680** (30-min)	NA	NA

*AEGL-3 POD
Values in **red** are <POD for AEGL-3

2) BMD modeling issues for Aranyi (1983) data set

Data Included in BMD Analysis	$BMCL_{05}$ (mg/m³)	BMC_{01} (mg/m³)
All groups + 0% response "theoretical control"	**2281 (POD)**	2347
All doses ≥NOAEL for lethality (≥2220 mg/m³)	1899	2226
Only 1-hr exposures (not 1.1- or 1.2-hr exp.)	2071	2298

Note: age of rats varied between groups

RP/BR

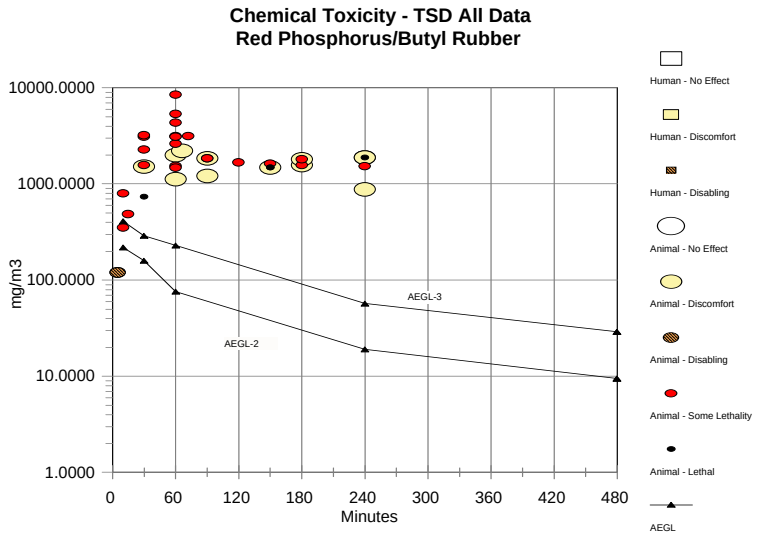
Summary of Draft Proposed AEGL Values for Red Phosphorus/Butyl Rubber (mg/m³)					
	10-min	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1 (Non-disabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	220	150	76	19	9.5
AEGL-3 (Lethal)	410	290	230	57	29

NR: not recommended

RP/BR

Extant standards and guidelines for red phosphorus/butyl rubber (mg/m^3)					
	Exposure Duration				
Guideline	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	220	150	76	19	9.5
AEGL-3	410	290	230	57	29
EEGL	40 (15-min)		10	2 (6-hrs)	
PEGL					1.0
SPEGL	4.0 (15-min)		1.0	0.2 (6-hrs)	
PPEGL					0.1
NR: not recommended due to insufficient data; absence of AEGL-1 values does not imply that exposure below AEGL-2 values are without effect.					

RP/BR



Development Team Discussion Points

- TBA

End

AEGLs FOR MONOETHANOLAMINE (CAS Reg. No. 141-43-5)

NAC/AEGL Meeting 50
San Francisco, CA
April 13-15, 2010

Chemical Manager: Lynn Beasley
Chemical Reviewers: Ernest Falke
SRC Staff Scientist: Heather Carlson-Lynch

MONOETHANOLAMINE

- Primary amine with ammonia-like odor
- Used in gas and oil processing, corrosion inhibitors, adhesives, and in surfactants used in a variety of consumer products
- Properties:
  - Vapor pressure: 0.404 mm Hg at 25^{o}C
  - MP = 10.3 ^{o}C; BP = 170.8 ^{o}C
  - 1 ppm = 2.5 mg/m^3 ; 1 mg/m^3 = 0.401 ppm

MONOETHANOLAMINE

- Limited human inhalation data
  - Case reports of asthma
  - Highest occupational exposure level reported = 0.14 ppm
  - MEA is produced endogenously in mammals

MONOETHANOLAMINE: Single exposure animal data

- Kettering Lab (1957)
  - Unpublished; available version limited to selected data tables and figures
  - Lethality and body weight data reported in dogs, rats, mice, guinea pigs, rabbits, and cats
  - Whole-body exposure, conc. measured by titration; possible reaction with CO_2
  - 15-min to 21-hr exposures

MONOETHANOLAMINE Lethality data (Kettering Laboratory 1957)			
Species	**Exposure Time**	**Concentration (ppm)**	**Mortality**
Guinea pigs	0.25	192	0/6
		630	5/6
		762	4/6
	1 hr	**232**	**4/6**
		537	6/6
	1.5	322	6/6
	3.5 hr	750	6/6
	7 hr	585	6/6
	35 hr	86	3/6
	7 hr/d x 5 d	106 - 110	1/12
	7 hr/d x 25 d	51	0/6
Dogs	**7 hr**	**1087**	**0/1**
Rats	**1 hr**	**1023**	**0/10**
	3.5 hr	634	0/10
		1003	7/10
	7 hr	549	2/10
		1087	6/10
Mice	**1 hr**	**1123**	**3/10**
	3.5 hr	634	5/10
		1255	6/10
	7 hr	549	5/10
		1087	2/9

MONOETHANOLAMINE: Repeated exposure animal data

- Weeks et al. (1960)
  - Dogs (3/grp), rats (40-45/grp), and guinea pigs (22-30/grp)
  - 24 hr/d repeated, whole-body exposure
  - Conc. measured by titration; no distinction between free MEA and MEA combined with CO_2
  - Cageside observations in first 24 hr exposure reported
  - Condensation resulted in severe skin irritation
  - Deaths observed after 10 d at highest exposure

MONOETHANOLAMINE: Repeated exposure animal data

Weeks et al., 1960: Effects in all species

- Dogs: 0, 6, 12, 26, or 102 ppm
- Rats: 0, 5, 12, or 66 ppm
- Guinea pigs: 0, 15, or 75 ppm
- In all species:
  - 5-6 ppm: Slight decreases in alertness and activity; skin irritation after 2-3 wks
  - 12-15 ppm: No behavioral effects after 1 or 24 hrs exposure; lethargy and skin irritation after 3 wks
  - 26 ppm: Immediate signs of restlessness and discomfort followed by lethargy and slight leg tremors; skin irritation within 1 wk
  - 66-102 ppm: Immediate behavioral changes, salivation, vomiting, and labored respiration; hypoactivity by 24 hrs; lethargy by 48 hrs; deaths by 10 d; histopathology of multiple organs

MONOETHANOLAMINE

- Mechanistic information
  - MEA is weak inhibitor of acetylcholinesterase in vitro
  - MEA caused bronchoconstriction in guinea pigs when given by tracheal cannula
    - Mediated by histamine H1 and muscarinic receptors; not pH
- Related Compounds
  - Other primary amines (mono-, di-, trimethylamine) act via direct irritation
  - In 2-week and subchronic studies of N,N-diethylethanolamine in rats, there were irritant but no neurobehavioral effects (Hinz et al., 1992).

MONOETHANOLAMINE

- Interspecies Variability
  - Weeks et al. (1960): similar effects at similar continuous exposures
    - no immediate effects at 12-15 ppm in guinea pigs, rats, dogs
    - immediate behavioral changes, then lethargy, tremors, and mortality over time (beginning at 10, 14, and 25 days) at 66-102 ppm
    - Weeks data argue for UF of 1
  - Kettering Laboratory (1957): guinea pigs more sensitive to acute lethality
    - 4/6 guinea pigs died at 232 ppm for 1 hr
    - 0/10 rats died at 1023 ppm for 1 hr
    - 3/10 mice and 1/4 rabbits died at 1123 ppm for 1 hr
    - 1 dog and 1 cat survived 7 hours at 1087 ppm
    - Kettering data argue for UF of 5

MONOETHANOLAMINE

- Challenges in selecting UFs:
  - Available studies inconsistent re: interspecies variability; suggest interspecies UF of 1 or 5
  - Behavioral changes observed cageside by Weeks et al. (1960) may be neurobehavioral or secondary to skin/respiratory irritation
    - For EEGLs, NRC (2007) made conservative assumption that changes were neurobehavioral
  - Very little mechanistic data

MONOETHANOLAMINE

- Interspecies UF of 3 selected
  - Based on related compounds, MEA assumed to act via irritation; little interspecies variability expected for irritants
  - POD for AEGL-3 based on data in guinea pigs (AEGL-1 based on dogs, rats, and guinea pigs); Kettering (1957) data suggest guinea pigs are sensitive species

MONOETHANOLAMINE

- Intraspecies UF of 3 selected
  - Based on related compounds, MEA assumed to act via irritation; little intraspecies variability expected for irritants

MONOETHANOLAMINE

DRAFT PROPOSED AEGL-1 VALUES (ppm)				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
1.2	1.2	1.2	1.2	1.2

Key study: Weeks at al. (1960)
POD: 12 ppm
- At 12 ppm: no behavioral changes in dogs, rats, guinea pigs in 24 hours
- At 26 ppm: immediate signs of discomfort/restlessness in dogs
- NRC (2007): 12 ppm POD used for 1-hour and 24-hour EEGLs

Time Scaling:
- None: effects assumed to result from direct irritation, which is not time-dependent

Total UF: 10 (3x intraspecies and 3x interspecies)

MONOETHANOLAMINE

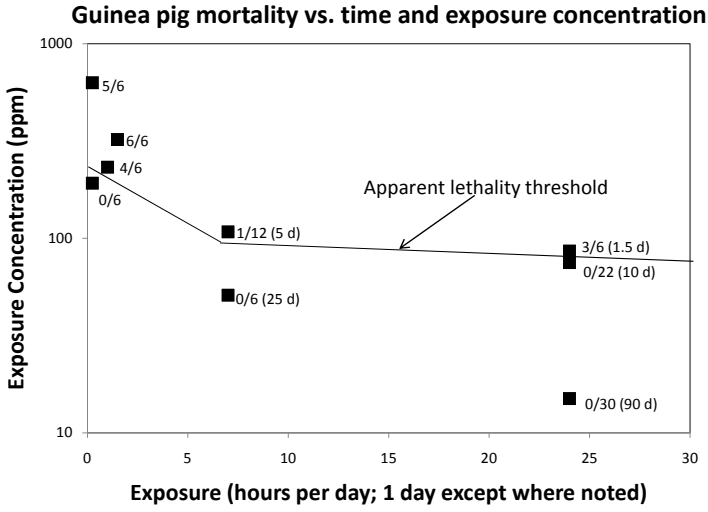
DRAFT PROPOSED AEGL-2 VALUES (ppm)				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
9.4	6.6	5.2	3.3	2.6

Key study: Weeks at al. (1960)
POD: 26 ppm ≈ *threshold for potentially irreversible effects or effects that would impair escape in an 8-hour exposure*
- Dogs were exposed 23.75 hours/day
- At 26 ppm, immediate discomfort and restlessness noted, followed by lethargy (after a few days) and leg tremors (timing not specified)
- At 66 -102 ppm, immediate behavioral changes, vomiting, muscle tremors, labored respiration, and lethargy in guinea pigs, rats, and dogs; deaths after 10, 14, and 25 d (respectively)

Time Scaling: $C^3 \times t = k$
- n=3 (default; inadequate data to estimate)

Total UF:10 (3 x 3 intraspecies x interspecies)

MONOETHANOLAMINE



MONOETHANOLAMINE

- AEGL-3 PODs:
  - 10-min and 30-min AEGL-3 POD = 192 ppm
    - 15-minute observed nonlethal level (Kettering Laboratory, 1957)
  - 1-, 4-, and 8-hour AEGL-3 POD =75 ppm
    - Lower-bound lethality threshold = from continuous exposure study in guinea pigs (Weeks et al., 1960)
    - 1-hr data from Kettering Laboratory (1957) not amenable to modeling (no response near BMR); similar POD calculated if 1-hour LC_{67} 232 ppm/3 (77 ppm)

MONOETHANOLAMINE

DRAFT PROPOSED AEGL-3 VALUES (ppm)				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
22	**9.6**	7.5	7.5	7.5

Key study: Kettering Laboratory (1957)
POD **for *10-min and 30-min* AEGL-3**: 192 ppm
- No deaths in guinea pigs exposed 15 min to 192 ppm
- Guinea pigs most sensitive of 6 species tested
- 15-min data gave divergent $BMCL_{05}$ and BMC_{01} values

Time Scaling: $C^n \times t = k$
- n=3 for 10 min and n=1 for 30 min (defaults; inadequate data to estimate)

Total UF: 10 (3x intraspecies and 3x interspecies)

MONOETHANOLAMINE

DRAFT PROPOSED AEGL-3 VALUES (ppm)				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
22	9.6	***7.5***	***7.5***	***7.5***

Key study: Weeks at al. (1960).
POD **for 1-, 4-, and 8-h AEGL-3**: 75 ppm
- 22 guinea pigs survived 24 hr/d x 10 d exposure to 75 ppm
- Supported by 1-hr LC_{67} of 232 ppm in 6 guinea pigs
- 1-hr data not amenable to modeling (no response near BMR)

Time Scaling: none
- 24 hr/d lethality threshold (75 ppm) ≈ 1-hr lethality threshold estimated from LC_{67} div. by 3 (232/3 = 77 ppm)

Total UF: 10 (3x intraspecies and 3x interspecies)

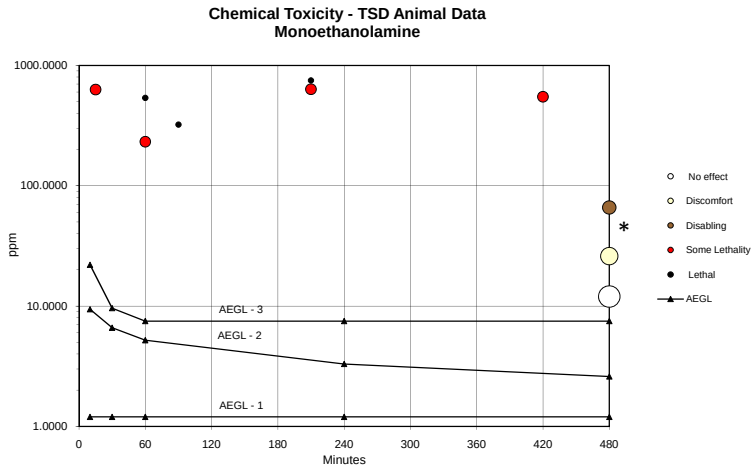
MONOETHANOLAMINE

Summary of Draft Proposed AEGL values					
	10-min	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1 (Non-disabling)	1.2 ppm (3.0 mg/m^3)	1.2 ppm (3.0 mg/m^3)	1.2 ppm (3.0 mg/m^3)	1.2 ppm (3.0 mg/m^3)	1.2 ppm (3.0 mg/m^3)
AEGL-2 (Disabling)	9.4 ppm (24 mg/m^3)	6.6 ppm (17 mg/m^3)	5.2 ppm (13 mg/m^3)	3.3 ppm (8.3 mg/m^3)	2.6 ppm (6.5 mg/m^3)
AEGL-3 (Lethal)	22 ppm (55 mg/m^3)	9.6 ppm (24 mg/m^3)	7.5 ppm (19 mg/m^3)	7.5 ppm (19 mg/m^3)	7.5 ppm (19 mg/m^3)

MONOETHANOLAMINE Standards (ppm)

Standard	**10 min**	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	1.2	1.2	1.2	1.2	1.2
AEGL-2	9.4	6.6	5.2	3.3	2.6
AEGL-3	22	9.6	7.5	7.5	7.5
EEGL (NRC)			4		
PEL-TWA (OSHA)					3
IDLH (NIOSH)		30			
REL-TWA (NIOSH)					3
TLV-TWA (ACGIH)					3
TLV-STEL (ACGIH)	6				
OEL-TWA (EU)					1
OEL-STEL (EU)	3				
MAK (Germany)					2
MAC (Netherlands)					3

MONOETHANOLAMINE



*Effect levels shown at 480 minutes are from Weeks et al. (1960) continuous (23.75 hr/d) exposure study

Development Team Discussion Points

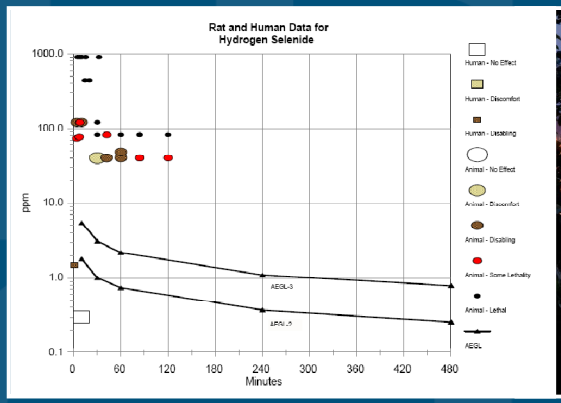
- TBA

END

EPA United States Environmental Protection Agency

Review of Hydrogen Selenide: Calculation of LC_{01} and Value of *n*

George M. Woodall, PhD



Office of Research and Development
National Center for Environmental Assessment - RTP

NAC/AEGL-50
San Francisco, CA
April 14, 2010

United States Environmental Protection Agency

A Minor Discrepancy – Calculation of ppm from mg/m^3

- The conversions factor in Table 1 on page 9 may be slightly incorrect, which might lead to changes in the reported AEGL levels.
- The MW of H_2Se is 80.98, therefore using the conversion formula

$$\frac{[80.98 \times (\text{Observation in mg/m3})]}{24.45}$$

  the correct conversion factors should be: 1 mg/m3 = 0.3 ppm; and 1 ppm = 3.3 mg/m3.
- The values reported for Zwart et al. (Table 3 on page 16) would then change as follows:

Current TSD	Revised Value
Study 1	
40 ppm	39 ppm
81 ppm	78 ppm
121 ppm	117 ppm
437 ppm	425 ppm
898 ppm	875 ppm
Study 2	
48 ppm	47 ppm
73 ppm	71 ppm
76 ppm	74 ppm

United States Environmental Protection Agency

Status at the end of NAC/AEGL-49 (1)

Currently in interim status - can be finalized.

……

AEGL-1 – NR

AEGL-2 – 1/3 AEGL-3

AEGL-3 – POD – LC01 for 60 minutes = 66 ppm

Intraspecies UF = 3

Interspecies UF =10

n = 2

United States Environmental Protection Agency

Status at the end of NAC/AEGL-49 (2)

Derivation of n

The value of n was derived from the data set below by Zwart using the ten Berge equation.

TABLE 3. Lethality of Rats Exposed to H_2Se (No. Dead/No. Exposed)

Concentration	4-20 min	30 min	60 min	120 min
Study 1				
40 ppm	N/A	0/2	0/2	1/2
81 ppm	N/R	2/2	2/2	2/2
121 ppm	1/6	2/2	2/2	n/r
437 ppm	10/10	N/R	N/R	N/R
898 ppm	8/8	2/2	N/R	N/R
Study 2				
48 ppm	N/R	N/R	0/10	N/R
73 ppm	N/R	N/R	2/10	N/R
76 ppm	N/R	N/R	6/10	N/R

Data from Zwart and Arts 1989 and Zwart et al. 1992.
n/r: data not recorded for these concentration-time values

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Status at the end of NAC/AEGL-49 (3)

- LC01 for 60 minutes = 66 ppm
  - LC01 calculated for 120 minutes using an n of 2 = 47 ppm
  - LC01 calculated for 120 minutes using an n of 1 = 33 ppm

- At 40 ppm with 120 minutes of exposure 1/2 animals died
  - An n of 2 predicts that 0/2 should have died at 47 ppm, yet 1/2 died at the lower concentration of 40 ppm
  - Therefore an n of 2 is incorrect.

- SHOULD WE RECONSIDER THE DERIVATION?

- Charge at the end of the discussion (from NAC/AEGL-49 Summary): *"George Woodall, Marcel van Raaij, and Ernie Falke agreed to look at different ways to analyze the Zwart data as it applies to the $C \times t$ protocol."*

United States Environmental Protection Agency

Background: Zwart et al., 1989 Report

- Report includes two “studies” with differences only in duration.
  - Study 1 – follows the C × t protocol [revised TG403] (one animal/sex per group, with groups across multiple concentration/duration combinations)
  - Study 2 – follows a more classical LC_{50} type study (5 animals/sex per group by several concentrations, all for 1-hour)

- Both studies use nose-only exposure protocol, on the same equipment in the same lab using the same species/strain
  - These data could be combined into a single analysis

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Revisiting the Derivations (Value of *n* and LC_{01})

- Currently in the TSD
  - Value of n = 2
  - LC_{01} at 60-minutes = 66 ppm
- Analysis 1 – Using all available data in a single analysis
  - Value of n = 2.6
  - LC_{01} at 60-minutes = 33 ppm
- Analysis 2 – Using only the C × t protocol data in the analysis
  - Value of n = 1.98 (same as in the Zwart et al. report)
  - LC_{01} at 60-minutes = 29 ppm
  - Same results if the highest exposures (100% lethality) dropped from analysis

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Revisiting the 1-hour LC_{01} Calculation

- Analysis 3 – LC_{50} Protocol data (3 concentrations) only in the analysis
  - LC_{01} at 60-minutes = 66 ppm

- Analysis 4 – Using all available data at 1-hour (5 concentrations) in a single analysis
  - LC_{01} at 60-minutes = 67 ppm

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Another Wrinkle to Consider

- From Zwart et al. report:
  "Although the OECD guidelines do allow extension of the observation period which would certainly have increased the observed mortality rates, we did not find such procedure ethically allowed with respect to the animals. Declaring all animals dead which lost weight during the second week of the observation period would result in a LC50 of well below 0.155 g/m3 in study (B) and although no formal solution was obtained in study (A) with such data, the estimated LC50 value, plotted graphically, would be about 0.06-0.07 g/m3."

- Analysis 5 – Using Study 2 data re-scored as suggested by Zwart et al. (count drastic weight loss as mortality)
  - LC_{01} at 60-minutes = 10 ppm

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Main Questions

- Should the C × t protocol data only be used for establishing a value of n?
  - Evaluation with C × t protocol data only: n = 1.98
  - Much different value derived when LC_{50} protocol data added to analysis: n = 2.67

- Which estimate of the LC_{01} is preferable, considering all the evidence:
  - Result from using 1-hour data only – either combined data or only using the Traditional LC_{50} protocol provides a similar result (LC_{01} = 66 ppm)
  - Result from All Data Combined – More data, from across multiple durations and more concentrations used in C × t protocol in combination with LC_{50} protocol data (LC_{01} = 33 ppm)
  - Evidence for continuing mortality after the 2-week observation period from the Zwart et al report statement, analysis of LC_{50} protocol data only (LC_{01} = 10 ppm)

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Options for Consideration

Alternatives for AEGL-3					
	10-min	**30-min**	**1-hour**	**4-hour**	**8-hour**
Current TSD - 66 ppm; n = 2	5.4	3.1	2.2	1.1	0.78
All Data - 33 ppm; n = 2.6	2.2	1.4	1.1	0.65	0.49
C x t data only - 29 ppm; n = 2	2.4	1.4	0.97	0.48	0.34
Projected Mortality - 10 ppm; n = 2	0.82	0.47	0.33	0.17	0.12
Study 2 LC01 with revised n - 66 ppm; n = 2.6	4.4	2.9	2.2	1.3	0.99
Alternatives for AEGL-2					
Current TSD - 1/3 of AEGL-3	Revise (or not) based on choice of AEGL-3				
Weight Loss & Mortality - 10 ppm; n = 2	0.82	0.47	0.33	0.17	0.12
Weight Loss & Mortality - 10 ppm; n = 2.6	0.66	0.44	0.33	0.2	0.15
Alternative - If POD for AEGL-3 = 66 ppm	Use 1/7 of the AEGL-3 across all time points (66 ppm / 10 ppm)				