National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-47
December 3-5, 2008

Holiday Inn
1355 North Harbor Drive
San Diego, CA

AGENDA

Wednesday, December 3, 2008

10:00 a.m.	*Development team meetings: Nitrogen Trifluoride; Tear Gas; Ricin; Phosphorus pentachloride
11:00	Introductory remarks and approval of NAC/AEGL-46 Highlights (George Rusch, Ernie Falke, and Paul Tobin)
11:15	Status Update/ No Data Chemicals: Aluminum chloride; Antimony pentafluoride; phosphorus pentafluoride; phosphorus pentasulfide (Cheryl Bast/Sylvia Talmage)
11:30	SOP Revision Issues (Iris Camacho/Ernie Falke)
11:50	LOA Discussion (Ernest Falke)
12:10 p.m.	Chemical List (Paul Tobin/Ernie Falke)
12:30	Lunch
1:30	Proposal for Grouping all Chlorosilanes (Ernie Falke/Cheryl Bast)
2:00	Acrylonitrile: Response to FR Comments (Susan Ripple/BobYoung)
2:30	Break
2:45	Review of Tear Gas (Glenn Leach/Cheryl Bast)
4:15	Review of Ricin (Jim Holler /Bob Young)
5:30	Adjourn for the day

Thursday, December 4, 2008

8:30 a.m.	*Development team meetings: Organophosphates (Dichlorvos; Dicrotophos; Fenamiphos; Malathion; Mevinphos); Allyl alcohol; Bromoacetone; Methyl iodide
9:30	Review of Dichlorvos (John Hinz/Jennifer Rayner)
10:30	Break
10:45	Review of Dicrotophos (Bob Benson/Bob Young)
11:30	Review of Fenamiphos (George Woodall/Jennifer Rayner)
12:30 p.m.	Lunch
1:30	Review of Malathion (John Hinz/Carol Wood)
2:30	Review of Mevinphos (Dan Sudakin/Jennifer Rayner)
3:30	Break
3:45	Revisit of Allyl Alcohol: Response to COT comment/New data (Bob Benson/Claudia Troxel)
4:45	Review of Bromoacetone (Roberta Grant/Cheryl Bast)
5:30	Adjourn for the day

Friday, December 5, 2008

8:30 a.m.	Review of Phosphorus Pentachloride (Bob Benson/Carol Wood)
9:30	Review of Nitrogen Trifluoride (Bob Benson/Sylvia Talmage)
11:00	Methyl Iodide- Status Update (Alan Becker/Sylvia Talmage)
11:30	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-47

	Chemical	Staff Scientist	CM	Reviewer	Reviewer	Other Attendees
Wed. 12/3/08 10:00 a.m.						
	Nitrogen Trifluoride	Talmage	Benson*	VanRaaij	Freshwater*	Beasley, Cushmac, Hinz, Sudakin, Willhite
	Tear Gas	Bast	Leach*	Holler*	Woolf	Chapman, Niemeier, Rusch
	Ricin	Young	Holler*	Anderson	Leach*	Becker, Gingell, Ripple, Steele, Woodall
	Phosphorus Pentachloride	Wood	Benson*	Heinz	Freshwater*	Baril, Bernas, Camacho, Grant
Thurs. 12/4/08 8:30 a.m.	Organophosphates:					
	Dichlorvos	Rayner	Hinz*	Anderson	Sudakin	Falke, Woolf
	Dicrotophos	Young	Benson*	Rusch	Beasley	
	Fenamiphos	Rayner	Woodall*	Baril	Willhite	
	Malathion	Wood	Hinz*	Anderson	Sudakin	
	Mevinphos	Rayner	Sudakin	Baril	Niemeier*	
	Allyl alcohol	Troxel	Benson*	Woodall*	Niemeier*	Cushmac, Holler, Steele
	Bromoacetone	Bast	Grant	Becker*	Chapman	Bernas, Gingell, Leach
	Methyl iodide	Talmage	Becker*	Hinz*	Freshwater	Camacho, Heinz, Ripple

At this time, the following chemicals do not have a formal pre-meeting discussion scheduled: Chlorosilanes; Acrylonitrile

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

NAC/AEGL Meeting 47: December 3-5, 2008

RETURN TO PAUL TOBIN

Chemical: ATTENDANCE **CAS Reg. No.:**

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

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson					John Hinz				
Marc Baril					Jim Holler				
Lynn Beasley					Glenn Leach				
Alan Becker	ABSENT				Richard Niemeier	ABSENT			
Robert Benson					Susan Ripple				
Edward Bernas					George Rusch, Chair				
Iris Camacho					Martha Steele	ABSENT			
Gail Chapman					Daniel Sudakin				
George Cushmac					Marcel vanRaaij				
David Freshwater					Calvin Willhite				
Ralph Gingell					George Woodall				
Roberta Grant					Alan Woolf				
Dieter Heinz									
E FALKE	✓				TALLY				
Y TOBIN	YST				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:** 12/3/08

ATTACHMENT 3

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR SELECTED CHLOROSILANES:

PROPOSAL TO INCORPORATE ALL CHLOROSILANES INTO ONE TSD AND USE THE HCL ANALOGY APPROACH FOR CONSISTENCY

NAC/AEGL-47
December 3-5, 2008
San Diego, CA

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Ernest Falke

HCl AEGL document: Published in Volume 4.

At NAC-43 and NAC-44 AEGL values were derived for 21 Chlorosilanes based on analogy to HCl:

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

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

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

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

Dichlorosilane (CAS Reg. No. 4109-96-0)

Diethyl dichlorosilane (CAS Reg. No. 1719-53-5)

Dimethyl chlorosilane (CAS Reg. No. 1066-35-9)

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

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

Ethyl trichlorosilane (CAS Reg. No. 115-21-9)

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

Methylvinyl dichlorosilane (CAS Reg. No. 124-70-9)

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

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

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

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

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

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

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

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

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

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

PRIOR TO NAC-43 and NAC-44:

NAC derived AEGL values for three chlorosilanes based on preliminary chemical-specific data (eventually included in Jean et al., 2006):

Methyltrichlorosilane
Dimethyldichlorosilane
Trimethylchlorosilane

COT reviewed these between April 1999 and January 2007.

Proposal:

Incorporate all chlorosilanes into one TSD and use the HCl analogy approach for consistency

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

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

GLP Protocol:

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

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

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

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

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

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

***Chlorosilane under consideration today.**

CONCLUSIONS (Jean et al., 2006)

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

- **log* log regression analysis of chlorosilane LC_{50} values vs. number of chlorine groups yielded an r^2 value of 0.97**
- **The within-class LC_{50} values were not significantly influenced by the number or type of hydrocarbon R-group(s) present (methyl, ethyl, propyl, vinyl).**

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

- **Cases where the predicted value is less may be attributed to incomplete hydrolysis in the test atmosphere**
- **However, continued hydrolysis and generation of hydrogen chloride would be expected for any remaining chlorosilane when in contact with moist tissues (mucous membranes, lung)**

Dichlorosilane (Nakashima et al., 1996):

4-Hr Mouse LC_{50} = 144 ppm

Hydrogen Chloride (NRC, 2004):

1-Hr Mouse LC_{50} = 1108 ppm

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

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

Predicted 4-hr LC_{50} for dichlorosilane:

277 ppm ÷ 2 = 139 ppm

Agrees with experimentally-derived value of 144 ppm

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

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

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

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

Summary of AEGL Values for Monochlorosilanes							
Compound	**Classification**	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint**
MONOCHLOROSILANE Dimethylchlorosilane ***Trimethylchlorosilane***	AEGL-1	**1.8 ppm** ***1.8 ppm***	**1.8 ppm** ***1.8 ppm***	**1.8 ppm** ***1.8 ppm***	**1.8 ppm** ***1.8 ppm***	**1.8 ppm** ***1.8 ppm***	Hydrogen chloride (HCl) AEGL-1 values adopted as AEGL-1 values for Monochlorosilanes (NRC, 2004)
	AEGL-2	100 ppm ***190 ppm***	43 ppm ***64 ppm***	22 ppm ***32 ppm***	11 ppm ***16 ppm***	11 ppm ***16 ppm***	Hydrogen chloride (HCl) AEGL-2 values adopted as AEGL-2 values for Monochlorosilanes (NRC, 2004)
	AEGL-3	620 ppm ***795 ppm***	210 ppm ***270 ppm***	100 ppm ***130 ppm***	26 ppm ***33 ppm***	26 ppm ***33 ppm***	Hydrogen chloride (HCl) AEGL-3 values adopted as AEGL-3 values for Monochlorosilanes (NRC, 2004)

Summary of AEGL Values for Dichlorosilanes							
Compound	**Classification**	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint**
DICHLOROSILANES Dichlorosilane Diethyl dichlorosilane Diphenyl dichlorosilane Methylvinyl dichlorosilane ***Dimethyldichlorosilane***	AEGL-1	0.90 ppm ***0.90 ppm***	0.90 ppm ***0.90 ppm***	0.90 ppm ***0.90 ppm***	0.90 ppm ***0.90 ppm***	0.90 ppm ***0.90 ppm***	Hydrogen chloride (HCl) AEGL-1 values divided by a molar adjustment factor of 2 adopted as AEGL-1 values for Dichlorosilanes (NRC, 2004)
	AEGL-2	50 ppm ***78 ppm***	22 ppm ***26 ppm***	11 ppm ***13 ppm***	5.5 pm ***6.5 ppm***	5.5 ppm ***6.5 ppm***	HCl AEGL-2 values divided by a molar adjustment factor of 2 adopted as AEGL-2 values for Dichlorosilanes (NRC, 2004)
	AEGL-3	310 ppm ***320 ppm***	110 ppm ***110 ppm***	50 ppm ***53 ppm***	13 ppm ***13 ppm***	13 ppm ***13 ppm***	HCl AEGL-3 values divided by a molar adjustment factor of 2 adopted as AEGL-3 values for Dichlorosilanes (NRC, 2004)

Summary of AEGL Values for Trichlorosilanes							
Compound	**Classification**	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint**
TRICHLOROSILANES Allyl trichlorosilane Amyl trichlorosilane Butyl trichlorosilane Chloromethyl trichlorosilane Dodecyl trichlorosilane	AEGL-1	0.60 ppm *0.60 ppm*	0.60 ppm *0.60 ppm*	0.60 ppm *0.60 ppm*	0.60 ppm *0.60 ppm*	0.60 ppm *0.60 ppm*	HCl AEGL-1 values divided by a molar adjustment factor of 3 adopted as AEGL-1 values for Trichlorosilanes (NRC, 2004)
Ethyl trichlorosilane Hexyltrichlorosilane Nonyl trichlorosilane Octadecyl trichlorosilane Octyl trichlorosilane Propyl trichlorosilane Trichloro(dichlorophenyl) silane	AEGL-2	33 ppm *37 ppm*	14 ppm *12 ppm*	7.3 ppm *6.2 ppm*	3.7 ppm *3.1 ppm*	3.7 ppm *3.1 ppm*	HCl AEGL-2 values divided by a molar adjustment factor of 3 adopted as AEGL-2 values for Trichlorosilanes (NRC, 2004)
Trichlorophenylsilane Trichlorosilane Vinyl trichlorosilane ***Methyltrichlorosilane***	AEGL-3	210 ppm *170 ppm*	70 ppm *56 ppm*	33 ppm *28 ppm*	8.7 ppm *7.0 ppm*	8.7 ppm *7.0 ppm*	HCl AEGL-3 values divided by a molar adjustment factor of 3 adopted as AEGL-3 values for Trichlorosilanes (NRC, 2004)

ACRYLONITRILE FR COMMENTS
Comments from AN Group

- **AN Group commended NAC/AEGL for thoughtful, well documented review**

- **AN Group suggested addition of recent developmental/reproductive toxicity studies to TSD**
  - **will not impact AEGL development**
    - **no effects in absence of maternal toxicity**
  - **multigeneration not applicable for acute single exposure scenario**
  - **gestation exposure study (inhalation) route will be incorporated into TSD for completeness**

- **AN Group noted that genotoxicity and carcinogenicity reviews were in preparation**
  - **will incorporate into TSD**

- **AN Group commented on derivation of AEGL-2 and AEGL-3 values:**
  - **AN Group suggested UF of 7.0 (based on PBPK model assessment of species variability) as opposed to overall UF of 10 (3 x 3) chosen by NAC/AEGL**
    - **AN Group suggested above be used to justify "intraspecies" of 7.0 (? a typo ?; AN Group probably meant interspecies UF should be 7.0)**
      - **NAC/AEGL used PBPK model to show that reactive metabolite formation (toxicokinetic component) was similar between rats and humans; 3 would account for possible toxicodynamic variability**
    - **AN Group suggested intraspecies of UF 1 based on PBPK model results for individual variability in metabolite levels**
      - **NAC/AEGL used intraspecies UF of 3 to account for possible toxicodynamic AND toxicokinetic variability; UF of 1 could not be justified by PBPK kinetics alone**

- **AN Group expressed concerns regarding AEGL-3 being too low with respect to occupational history of exposure to AN; i.e., 8-hr exposure to 19 ppm would not pose risk of lethality (OSHA PEL of 20 ppm; workers exposed to 30 ppm [range of ≥20 to 100 ppm] for 40-hr work week)**
    - **somewhat lower AEGL values are justified due to consideration of sensitive population ("healthy worker" vs a more susceptible population)**
    - **total UF of 7 does not result in appreciable change in AEGL-2 and AEGL-3 values for longer durations**

Summary of AEGL Values for Acrylonitrile (AN)						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	4.6 ppm	4.6 ppm	4.6 ppm	4.6 ppm	4.6 ppm	No effect in volunteer human subjects exposed to 4.6 ppm for 8 hrs; UF=1x1 (Jakubowski et al., 1987)
AEGL-2 (Disabling)	290 ppm **420 ppm**	110 ppm **150 ppm**	57 ppm **82 ppm**	16 ppm **23 ppm**	8.6 ppm **12 ppm**	Slight transient effects in rats exposed for 2 hrs to 305 ppm; UF=3x3; n=1.1 (Dudley and Neal, 1942)
AEGL-3 (Lethality)	480 ppm **690 ppm**	180 ppm **250 ppm**	100 ppm **150 ppm**	35 ppm **50 ppm**	19 ppm **27 ppm**	30-min, 1-hr, and 8-hr, $BMCL_{05}$ lethality threshold estimates in rats; UF=3x3; n=1.1 (Appel et al., 1981a; Dudley and Neal, 1942)

AEGL values based on total UF of 7 as suggested by AN Group are shown in red.

Considerations of UFs in AEGLs

Ginger Moser's thoughts
12-4-08

Interspecies UF

"The interspecies uncertainty factor was limited to 3 because the mechanism of action of organophosphate anticholinesterases is well understood and their effect on cholinergic systems is consistent across species. Variability in responses is primarily a function of varying cholinesterase activity and types of cholinesterase. Humans have been shown to have greater levels of plasma cholinesterase than do other species which allows for greater binding of anticholinesterase compounds such as *(fill in name of chemical)*, thereby decreasing the availability of the compound to critical targets such as brain cholinesterase."

"Mechanism of action is well understood"

- This understanding alone does not provide data to lower UF
- Need to know that the enzyme response is the same at comparable tissue concentrations across species, *e.g.*, *in vitro* relative potencies
  - These data would justify refinement
  - Cannot be assumed just because there are similar mechanisms across species

"More plasma ChE… greater binding of chemical"

- Difference between human and rat BuChE in blood is 4-fold
- Depends on inhibitor affinity for BuChE
- Never been shown that species differences in BuChE alone influences sensitivity at comparable administered doses

OPP analysis

- Data comparing administered doses producing same level of effect in rats and humans
- Concluded 2-, 3-, or 5-fold difference in sensitivity for 3 different *N*-methyl carbamates
- This suggests that UF could be lowered, at least for these pesticides

Interspecies UF Summary

- OPP uses interspecies factor of 10X when using animal data
  - But has supported using 3X for carbamate cumulative risk assessment
- Comparison of BuChE and analysis of carbamates could support 3X
- NAS supported 3X for nerve agents
  - Some based on *in vitro* comparisons
  - Not entirely consistent

Review of Esterases

- Esterases = enzymes that hydrolyze esters
  - A- and B-esterases are important for detoxification of cholinesterase inhibitors
  - Overlapping substrate specificity
  - Phylogenetically well-conserved
  - **Differing sensitivities to inhibitors**
- Pattern of esterase activities determines the impact on each chemical's toxicity

A-esterases

- Arylesterases (AE)
  - **Hydrolyze** some B-esterase inhibitors
  - Follows Michaelis enzyme kinetics
  - Stereospecificity
  - Requires calcium
  - Polymorphisms and genetic variants
    - Genotype does not fully predict enzyme activity
- PON = paraoxonase
  - 3 gene products, PON1 most studied
  - Other A-esterases named for substrate used in assay (DFP-ase, etc) – may or may not be the same as PON

B-esterases

- **Inhibited (acylated)** in a time- and temperature-dependent reaction
  - Acylated enzyme is inactive
  - Stochiometric reaction
- Reactivation (hydrolysis) can be fast or slow
- Divided based on substrate specificity, behavior in excess substrate, and susceptibility to inhibitors
- Population variability based on genetics, sex, age, health and physical conditions

B-esterases cont'd

- Acetylcholinesterase (AChE)
  - Hydrolyzes acetylcholine
  - Cholinergic neurons, RBC
  - Plasma – rat ~50%, human none
- Butyrylcholinesterase (BuChE)
  - Hydrolyzes choline esters including acetylcholine
  - Plasma – ~50% in rat, 100% in human
- Carboxylesterases (CaE)
  - Multi-gene family, many substrates
  - Widely distributed in tissues
  - Rat but not human blood (maybe)

Differing Sensitivity to Inhibitors

- If hydrolyzed by A-esterases
  - Could show different rates based on genetic polymorphism
  - Will show less activity in the young
  - OPP analysis with CPO-ase showed 3-fold difference in adults, 30-fold difference from newborn to adult
  - Includes relatively few inhibitors, so genetic variability does not impact sensitivity to most chemicals

Differing Sensitivity to Inhibitors

- If high affinity for BuChE
  - Serves to remove inhibitor from pool
  - Includes many more inhibitors
  - Affinity varies, so impact on detoxification varies
  - Could show different responses based on genetic polymorphism
    - One variant shows absolutely no activity
  - Genetic differences have never been shown to impact human sensitivity with inhibitors

Differing Sensitivity to Inhibitors

- If high affinity for CaE
  - Serves to remove inhibitor from pool
  - Includes many more inhibitors
    - Possibly most important esterase for detoxification
  - Will show less activity in the young
  - Affinity varies, so impact on detoxification varies
  - Have to depend on animal studies for comparisons

Intraspecies UF Summary

- Should be based on detoxification characteristics of each chemical
  - Not same for all chemicals
- OPP uses UF of 10X plus FQPA factor of 10X to account for sensitivity of the young
  - Can be decreased with supporting data
- If AE involved, consider genetics and age
- If CaE involved, consider age
- Impact of BuChE unknown

Fenamiphos

- Little known about detoxification by esterases
  - *In vitro* studies (my lab) show essentially no liver CaE or AE involvement
- No information about sensitivity of the young
- Blood ChE inhibited much more than brain in rats
  - Could imply much greater affinity to BuChE
- Consider BuChE in UF_H

Dichlorvos

- Human data available for AEGL-1
- McGregor review showed similar response in humans and rats, and in adult and babies
- Metabolized by "AE"
  - Defined by Ca^{+2} requirement
  - Polymorphic?
- OPP lowered FQPA factor to 1
- UF_H and UF_A may be refined knowing human data

Malathion

- Hydrolyzed rapidly by CaE
- Young are more sensitive (>4-28 fold)
  - Shown to be due to immature detoxification
- Consider age sensitivity in UF_H

	Preweanling	Adult	Ratio of Adult:Young
LD50 p.o.	134 mg/kg	3697 mg/kg	~28
LD50 p.o.	209 mg/kg	1806 mg/kg	~9
ED50 brain AChE p.o.	200 mg/kg	>750 mg/kg	>4

Mevinphos & Dicrotophos

- Little known about esterase detoxification
- No available information about sensitivity of the young
- OPP lowered dicrotophos FQPA factor to 1.7
- Little data for refinement

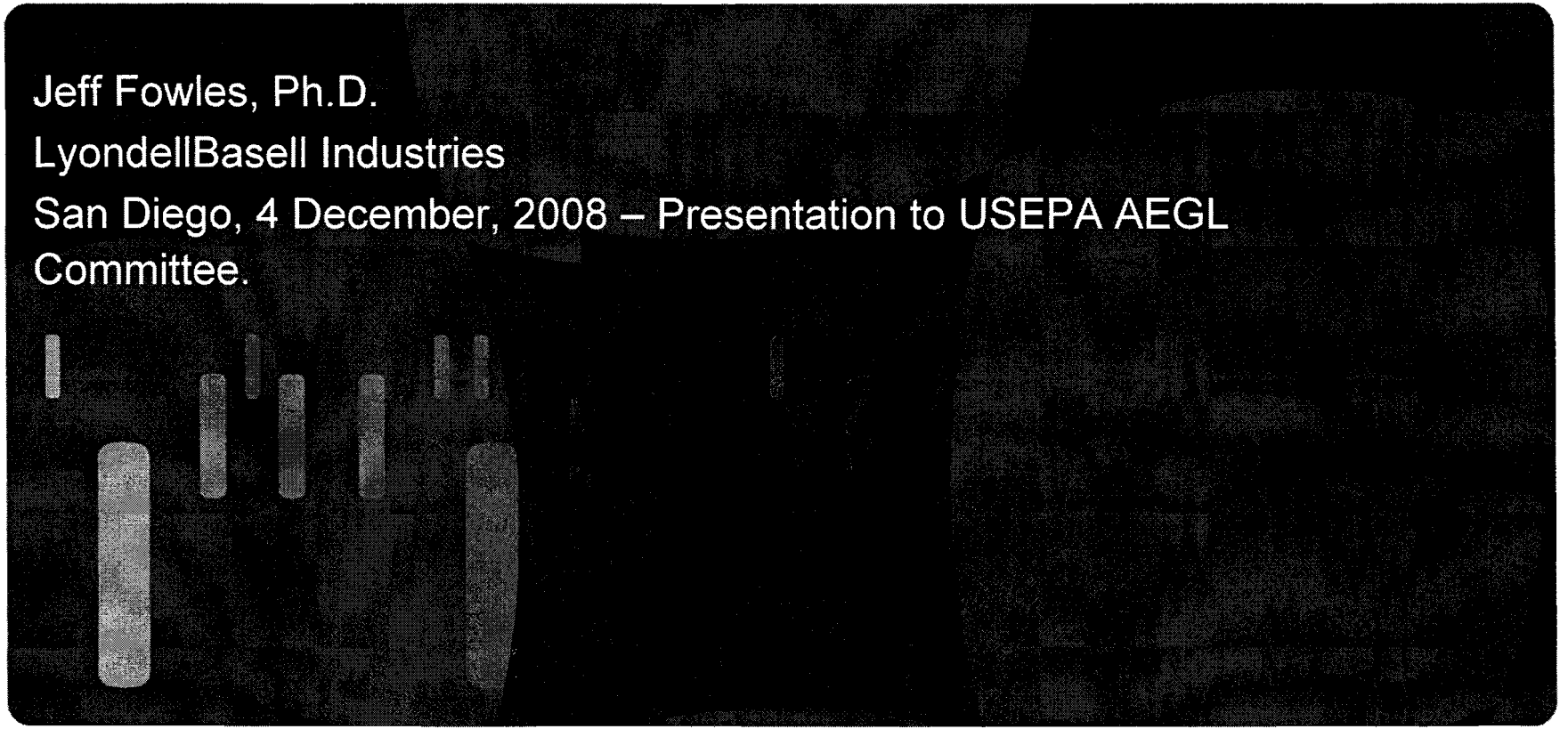
Parathion

- Hydrolyzed by AE (PON)
- High affinity for CaE
- Young are more sensitive (5-9 fold)
  - Shown to be due to immature detoxification
- Consider age and genetics in UF_H

	Young	Adult	Ratio of Adult:Young
Maximally tolerated dose s.c.	2.1 mg/kg	18 mg/kg	~9
LD50 p.o.	0.3 mg/kg	1.4 mg/kg	~5
LD50 i.p.	1.8 mg/kg	8.8 mg/kg	~5
LD50 i.p.	0.8 mg/kg	4.0 mg/kg	~5
ED50 brain AChE s.c.	1.2 mg/kg	6.9 mg/kg	~6

lyondellbasell

Allyl Alcohol – Special Study: Rat Acute Inhalation Toxicity to Inform AEGL Development



Overview

- Background for Acute Inhalation Study (Kirkpatrick, 2008)
- Experimental Design
- Key Results

Background

- Previous Interim AEGL Values (July, 2005)
  - AEGL-1 Slight to moderate irritation in humans at 6.25 ppm for 5 min (UF=3)
  - AEGL-2 NOAEL for severe eye irritation in humans at 12.5 ppm for 5 min (UF=3)
  - AEGL-3 no mortality at 200 ppm for 1 hour in mice, rats and rabbits

AEGL	10-min	30-min	1 hr	4 hr	8 hr
AEGL-1	2.1	2.1	2.1	2.1	2.1
AEGL-2	4.2	4.2	4.2	4.2	4.2
AEGL-3	36	25	20	10	10

Background (continued)

- National Research Council Committee on Toxicology (COT) comments
  - Use of same level for longer duration based on 5-minute human results may not be protective of systemic toxicity to liver and kidney.
  - AEGL-3 values: uncertainty about adjustment and modifying factors
    - COT concluded that total UF =10 is appropriate (Intraspecies UF of 3 and interspecies UF of 3)

Background (continued)

- *"After considerable discussion … with no clear resolution at hand because of some conflicting data, the industry observer (Dr. Marcy Banton, Lyondell Chemical) stated . . .she would ask Lyondell Chemical to conduct additional studies to resolve some of the conflicting data."* -- Review of COT Comments Dec 2006

Study Purpose (hypotheses)

- 1) proposed AEGL-1 and AEGL-2 values are protective of irreversible histopathology in liver, kidney and olfactory epithelium.
- 2) proposed AEGL-3 values are protective of lethality

Actual (measured) Exposure Levels (ppm)

1-hr	0	50 (50.9)	200 (220.3)	400 (402.9)
4-hrs	0	20 (21.9)	50 (52.2)	100 (102.4)
8-hrs	0	10 (10.2)	20 (21.1)	50 (51.7)

Experimental Design

- 5 males and 5 females / dose group
- Sacrifice animals 14 days after exposure
- Clinical observations during exposure (limited)
  - 1 hr: 30 min, 1 hr
  - 4 hr: 30 min, 1 hr, 4 hr
  - 8 hr: 30 min, 1 hr, 4 hr, 8 hr
- Novel stimulus/ arousal towards end of exposure
  - 3 technicians, less reliable

Experimental Design (continued)

- Clinical observations within 22-71 minutes after exposure terminated (reliable)
  - Random order with respect to exposure level
  - Observations made while handling and on an open field arena
  - Technician trained on Functional Observational Battery
- Clinical observations during recovery period (reliable)
  - 18-19 hr and 24-25 hr after exposures terminated
  - Same technician during exposure, immediately after and for first 5-7 days after exposure

Experimental Design (continued)

- Termination
  - Clinical pathology
  - Organ weights: Kidneys, lungs, liver
  - Histopathology: Kidney, liver, Larynx, Trachea, Lungs, Gross lesions (when possible)
- Nasal Pathology
  - 6 nasal levels
  - 5 severity grades including severe-irreversible
  - Irreversible: Opinion of study pathologist that changes would not likely completely recover to the original normal mucosa/submucosa at the microscopic level
  - Confirming independent assessment by Dr Jack Harkema

Key results

- No clinical chemistry, hematology, liver and kidney pathology at any exposure duration and concentration.
- Respiratory effects at higher doses for all exposures recovered fully by next day in all but one animal
  - one male exposed to 50 ppm for 8 hours died next day

Key results (continued)

- Serious, irreversible pathology (olfactory epithelium) limited to two 50 ppm group males exposed for 8 hours
- One death at 50 ppm / 8 hours of exposure

- Dr Harkema's (draft) assessment:
  - Very consistent with WIL Labs pathology report – same overall conclusions with respect to no NOAELs at any timepoint. Nature and extent of lesions verified.
  - The animal that died was not examined due to excessive autolysis.
  - Some areas of focal metaplasia in olfactory epithelium likely irreversible at 1 hour. However – lesion not seen at 4 hours.
  - The impact of this minimal/mild lesion on longterm wellbeing of the animal in some question (less than 5% of total olfactory area was affected). WIL pathologist did not call these lesions irreversible/severe.

Summary of Key Histopathology Lesions

n = 10

PPM Time/Lesion	0	10	20	50	100	200	400
1 hr							
Olfactory Degeneration	0			2		1	3
Chronic Inflammation	3			2		4	9
Olfactory Metaplasia	0			1		0	0
4 hrs							
Olfactory Degeneration	0		0	2	10		
Chronic Inflammation	0		7	7	8		
Olfactory Metaplasia	0		0	0	0		
8 hrs							
Olfactory Degeneration	0	4	6	9			
Chronic Inflammation	3	7	9	10			
Olfactory Metaplasia	0	0	0	1			

Abnormal Respiration Incidence

		10	20	50	100	200	400
1hr	During 1 hr post Next day	N.T.	N.T.	0 0 0	N.T.	0 0 0	1 0 0
4hr	During 1 hr post Next day	N.T.	0 0 0	0 1 0	0 5 0	N.T.	N.T.
8hr	During 1 hr post Next day	0 0 0	0 1 0	4 7 1 (died)	N.T.	N.T.	N.T.

Lack of Response to Stimulus

	0	10	20	50	100	200	400
1hr	2	N.T.	N.T.	0	N.T.	6	3
4hr	0	N.T.	0	2	4	N.T.	N.T.
8hr	0	0	3	4	N.T.	N.T.	N.T.

Acknowledgements

1. Dr Dan Kirkpatrick (WIL Laboratories) – Study Director
2. Dr Abby Li (Exponent) – Study Monitor and PP presentation
3. Dr Jack Harkema (Michigan State University) – Independent respiratory tract pathologist
4. Dr Marcy Banton (Lyondellbasell)

lyondellbasell

Thank you for your attention

Allyl Alcohol

Response to COT Comments on Interim 4 TSD

Claudia Troxel
Bob Benson
Richard Niemeier
George Woodall

- Interim 1: 7/2001
  Interim 2: 3/2003
  Interim 3: same as Interim 2; could be finalized
  Interim 4: 7/2005

- Due to the continuing difficulties encountered in deriving AEGL values using a very limited data set, Lyondell Chemical Company sponsored an additional toxicity study in rats.

- AEGL derivations based on the new data

General information:

- Colorless liquid with pungent mustard-like odor
- Used in production of allyl esters (resins and plasticizers); as intermediate in production of pharmaceuticals and organic chemicals; as fungicide or herbicide; as flavoring agent; in production of glycerol and acrolein
- Production: only one producer so data not available

Human Data

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

Signs/symptoms: Acutely exposed individuals may develop lacrimation, retrobulbar pain, blurred vision, severe irritation of mucous membranes with edema and excessive secretions

Torkelson et al. (1959b): 10 volunteers exposed to 2 ppm for 1-3 minutes reported distinct odor but no irritation

Dunlap et al. (1958): 5 minute exposures; not stated if nominal or measured concentrations (in Table: ≥Mod. = Moderate or greater)

Conc. (ppm)	n	Eye Irritation		Nose Irritation		Olfactory Recog.	
		Slight	≥Mod.	Slight	≥Mod.	Slight	≥Mod.
0.78	6	0	0	2	0	5	1
6.25	6	1	0	3	1	4	2
12.5	7	1	0	3	4	6	1
25	5	0	5	0	5	3	1

Animal Data

- Acute lethality data in rats, mice, rabbits
- Acute nonlethal toxicity in rats
- Repeat-exposure data

Rat Lethality Data (ten Berge n=0.95)			
Conc. (ppm)	**Time (h)**	**Effect**	**Reference**
51, 220, 403	1	No death (n=10)	Kirkpatrick, 2008
22, 52, 102	4	No death (n=10)	
10, 21 52	8	No death (n=10) 1/10 died	
423, 638 114 52	1 4 8	No death (n=6) No death (n=6) No death (n=6)	
200	1	0/10 died	Union Carbide, 1951
1000	0.5 1 2	1/6 died 4/6 died 6/6 died	
1000	1	4/6 died	Smyth and Carpenter, 1948
1000	3	6/6 died	McCord, 1932
1060 *165* *76*	*1* *4* *8*	LC_{50}	*Dunlap et al. (1958)*

Other Lethality Data				
Species	**Conc (ppm)**	**Time (h)**	**Effect**	**Reference**
Monkey	1000	4	1/1 died	McCord, 1932
Mouse	200	1	0/10 died	Union Carbide, 1951
	500	0.5 1	0/10 died 4/10 died	
	1000	1 2 4	6/10 died 8/10 died 10/10 died	
Rabbit	500	2 4	0/4 died 4/4 died	Union Carbide, 1951
Rabbit	1000	3.5 4.25	1/1 died 1/1 died	McCord, 1932

Kirkpatrick, 2008: Acute inhalation in rats

Preliminary study; 3 rats/sex/group

- **1 hr**

  423 ppm: gasping; material around mouth/nose

  638 ppm: gasping; alcohol flushing, material around mouth/nose

- **4 hr**

  114 ppm: gasping; all had flushing; material around nose/mouth

- **8 hr**

  52 ppm: gasping, labored respiration, alcohol flushing, material around nose/mouth

Main study; 5 rats/sex/group; clinical signs and nasal histopathology

- **1 hr**

  0 ppm: 3/10 nasal inflammation

  51 ppm: alcohol flushing

  2/10 olfactory epithelium degeneration; 2/10 inflammation; 1/10 metaplasia

  220 ppm: alcohol flushing; material around mouth

  1/10 olfactory epithelium degeneration; 4/10 inflammation

  403 ppm: gasping; alcohol flushing; material around mouth

  3/10 olfactory epithelium degeneration; 9/10 inflammation

- **4 hr**

  0 ppm: no effects

  22 ppm: material around mouth

  7/10 inflammation

  52 ppm: gasping; alcohol flushing; material around mouth; ↓ reaction

  2/10 olfactory 1/10 respiratory epithelium degeneration; 7/10 inflammation

  102 ppm: gasping; alcohol flushing; material around mouth; ↓ reaction

  10/10 olfactory 2/10 respiratory epithelium degeneration; 8/10 inflammation

Main study; 5 rats/sex/group; clinical signs and nasal histopathology

- **8 hr**

0 ppm: 3/10 nasal inflammation

10 ppm: alcohol flushing; material around mouth

4/10 olfactory epithelium degeneration; 7/10 inflammation

21 ppm: ↑ respiration; alcohol flushing; material around mouth; ↓ reaction

6/10 olfactory epithelium degeneration; 9/10 inflammation

52 ppm: 1/10 died (severe ulceration of respiratory and olfactory epithelium); gasping; ↑ respiration; alcohol flushing; material around mouth; ↓ reaction

9/10 olfactory 2/10 respiratory epithelium degeneration; 10/10 inflammation; 1/10 metaplasia

Severe, irreversible nasal lesions [2/10 severe irreversible olfactory epithelium degeneration; 2/10 severe, irreversible ulceration; 1/10 severe erosion of olfactory epithelium]

Dunlap et al., 1958: Repeat exposure in rats

Rats exposed for 7 h/d, 5 d/wk for 12 wk (60 exposures)

- 1, 2, 5 ppm: No observable adverse effects
- 20 ppm: ↓ bw
- 40 ppm: Irritation (gasping, eye irritation, nasal discharge) disappeared after first few exposures; ↑ lung wt
- 60 ppm: 1/10 died after 4th exposure; Irritation (transient gasping and muzzle rubbing; persistent eye discharge; ↑ lung and kidney wts
- 100 ppm: 6/10 died during first 46 days; similar signs of irritation
- 150 ppm: 10/10 died by 10 exposures;
  Necropsy – hemorrhagic livers, pale and spotted lungs, bloated GI tract, slight liver and lung congestion

Torkelson et al., 1959a

Rats, guinea pigs, rabbits, dogs exposed for 7 h/d, 5 d/wk:

- 2 ppm for 28 exposures: No effects in rats, guinea pigs, rabbits, dogs
- 7 ppm for 134 exposures: Reversible liver and kidney damage

AEGL 3:

- **Key Studies:** Kirkpatrick (2008); Union Carbide (1951); McCord (1932); Smyth and Carpenter (1948)
- **Endpoint:** calculated LC_{01} values; ten Berge software (n=0.95)
  10 m = 2608 ppm
  30 m = 823 ppm
  1 hr = 398 ppm
  4 hr = 93 ppm
  8 hr = 45 ppm
- **Total UF of 10:**
  - **UF_H = 3:** Irritation is not expected to vary greatly within species
  - **UF_A = 3:** Irritation is not expected to vary greatly among species

Summary of AEGL-3 Values				
10 min	30 min	1 hr	4 hr	8 hr
260	82	40	9.3	4.5

AEGL-2

Two rats exposed to 51 ppm for 8 h developed severe, irreversible lesions (Kirkpatrick, 2008); AEGL-2 values could be based on highest NOEL for irreversible nasal histopathological lesions at:

403 ppm for 1 h, 102 ppm for 4 h, 21 ppm for 8 h;

however, these concentrations are similar to the calculated LC_{01} values used for the AEGL-3 derivations:

398 ppm for 1 h; 93 ppm for 4 h; 45 ppm for 8 hr

The data for irreversible nasal lesions were insufficient for analyses by ten Berge software or by benchmark dose because there is only 1 data point with a non-zero response.

No other empirical data meeting the definition of an AEGL-2 endpoint were available; therefore, the AEGL-3 values are ÷ 3 to provide a reasonable estimate for AEGL-2 values.

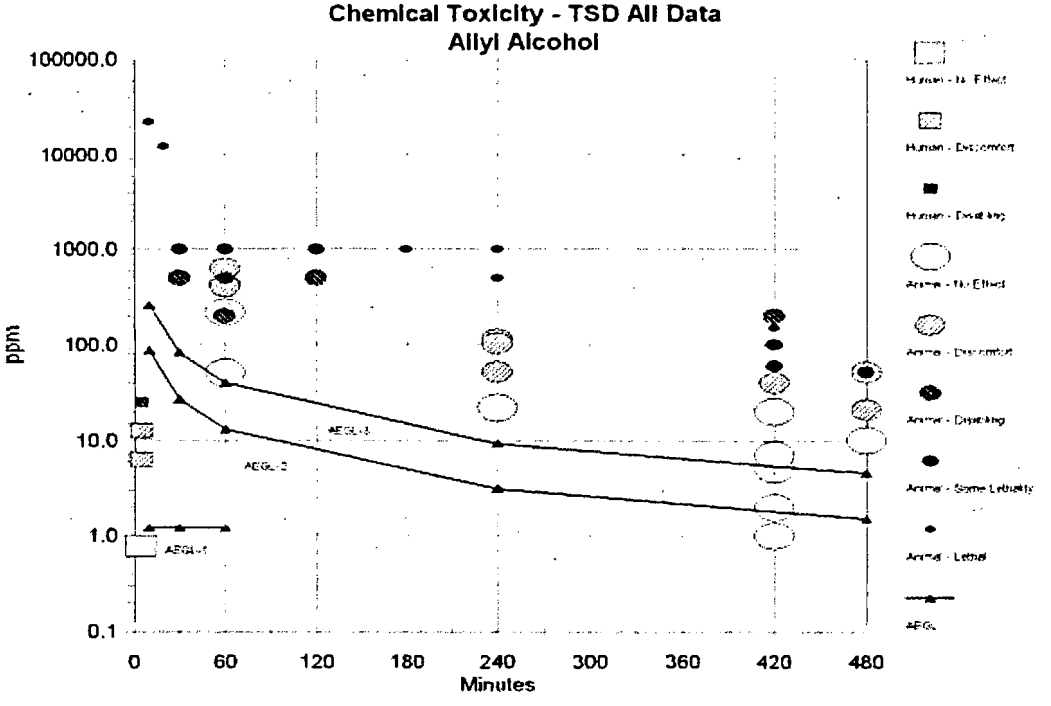
Summary of AEGL-2 Values				
10 min	30 min	1 hr	4 hr	8 hr
87	27	13	3.1	1.5

AEGL 1:

- **Key Study:** Dunlap et al. (1958)
- **Endpoint:** Slight or moderate nose irritation in 3/6 or 1/6 volunteers, respectively, exposed to 6.25 ppm allyl alcohol for 5 min
- **Total UF of 3:**
  - **UF_H = 3:** Irritation is not expected to vary greatly within species
  - **UF_A = 1:** Human data
- **Time scaling:** same 2.1 ppm value was applied across the 10- and 30-min and 1h durations since irritation is a threshold effect and prolonged exposure is not likely to result in a greatly enhanced effect; value not applied to 4- or 8-h durations because of uncertainty in extrapolating from 5 min to 4 or 8 h.
- Insufficient data were available to derive a 4- or 8-h AEGL-1; therefore, no values are recommended for these time points.

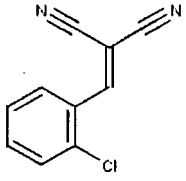
Summary of AEGL-1 Values				
10 min	30 min	1 hr	4 hr	8 hr
2.1	2.1	2.1	NR	NR

Summary of AEGL Values (ppm)						
AEGL	**10 m**	**30 m**	**1 h**	**4 h**	**8 h**	**Endpoint**
1	2.1	2.1	2.1	NR	NR	Slight to moderate irritation in humans at 6 ppm for 5 min (Dunlap et al., 1958)
2	87	27	13	3.1	1.5	AEGL 3 ÷ 3
3	260	82	40	9.3	4.5	Calculated rat LC_{01} values using ten Berge software



ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

TEAR GAS (CS)



NAC/AEGL-47
December 3-5, 2008
San Diego, CA

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Glenn Leach

Chemical Reviewers: Jim Holler and Alan Woolf

White crystalline solid with a pepper-like odor

Hydrolysis of CS produces malononitrile and *o*-chlorobenzaldehyde (t1/2 of ~15 min at pH 7)

First synthesized by Corson and Stoughton in 1928

Abbreviation "CS"

Developed in 1950s as replacement for chemical incapacitant CN (1-chloroacetophenone)

CS is much more potent irritant than CN, but is significantly less toxic

Reported that aerosol concentration of 4 mg/m^3 will disperse majority of rioters within 1 minute, and 10 mg/m^3 will deter trained troops

Because CS is stable when heated and has a low vapor pressure, requires a means of dispersement:

- **Combined w/ pyrotechnic compound in grenade or canister**
- **Generating a smoke or fog**
- **Dispersement of a fine powder as an aerosol**

AEGL-1 Values for Tear Gas				
10-min	30-min	1-h	4-h	8-h
NR	NR	NR	NR	NR

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

Although several studies describe irritation in humans, the severity of effects is above the definition of AEGL-1.

AEGL-2 Values for Tear Gas				
10-min	30-min	1-h	4-h	8-h
0.5 mg/m^3	0.5 mg/m^3	0.5 mg/m^3	0.5 mg/m^3	0.5 mg/m^3

Species: Human
Concentration: 1.5 mg/m^3
Time: 90 min.
Endpoint: Eye and nose irritation; headache. Exposure tolerated.
Reference: Punte et al., 1963

Time Scaling: None. Irritation is a function of direct contact and is not likely to increase with duration of exposure at this level of severity.

Uncertainty Factors:

Intraspecies: 3- Contact irritation is a portal-of-entry effect and is not expected to vary widely among individuals.

Supported by the fact that responses of volunteers with jaundice, hepatitis, or peptic ulcer or those that were 50-60 years old were similar to those of "normal" volunteers when exposed to a highly irritating concentration of CS for short durations (Punte et al., 1963; Gutentag et al., 1960).

Interspecies: 1- Human data.

Support for AEGL-2 Values:

35 subjects exposed for 60 minutes to 0.31-2.3 mg/m^3 (Beswick et al., 1972):

1 subject left at 5 minutes due to vomiting but returned for the duration of the exposure, and another vomited at 55 minutes of exposure (vomiting in both cases ascribed to swallowing large amounts or saliva).

1 subject voluntarily left the exposure at 8 minutes due to irritation; exposed in the range of 0.56-0.86 mg/m^3.

Irritation noted in five subjects exposed to a constant 0.78 mg/m^3 CS for 60 min; all remained in the chamber for the entire exposure.

AEGL-3 Values for Tear Gas				
10-min	30-min	1-h	4-h	8-h
140 mg/m^3	29 mg/m^3	11 mg/m^3	1.5 mg/m^3	1.5 mg/m^3

Species: Rat
Concentration: Range of 37 to 5176 mg/m^3
Time: Range of 5 to 300 minutes
Endpoint: Lethality threshold (LC_{01}) calculated using probit-analysis dose-response ten Berge program*
Reference: McNamara et al.(1969); Ballantyne and Calloway (1972); Ballantyne and Swantson (1978)

Time Scaling: $c^n \times t = k$, where the exponent, n, is 0.70, as determined by analysis of rat lethality data using ten Berge (2006) software. 4-hour value adopted as 8-hour value; time scaling yielded an 8-hour value inconsistent with the AEGL-2 values derived from a rather robust human data set.

Uncertainty Factors:
Intraspecies: 3: Clinical signs are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly among individuals.

Responses of volunteers with jaundice, hepatitis, or peptic ulcer or those that were 50-60 years old were similar to those of "normal" volunteers when exposed to a highly irritating concentration of CS for short durations (Punte et al., 1963; Gutentag et al., 1960).

Interspecies: 3: Clinical signs are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly between species.

LCT_{50} values of 88,480 mg min/m^3 for rats; 67,200 mg min/m^3 for guinea pigs; 54,090 mg min/m^3 for rabbits; and 50,010 mg min/m^3 for mice (Ballantyne and Swantson, 1978), values all well within a factor of two.

The AEGL-3 values are considered protective.

No mortality- 10-min exposures:

Rats - 1802 mg/m^3 (Ballantyne and Swantson, 1978)

Rabbits- 1434 mg/m^3 (Ballantyne and Swantson, 1978)

Mice or rabbits- 4250 mg/m^3 (Ballantyne and Calloway, 1972)

Applying a UF of 10 to these concentrations, yields values ranging from 143-425 mg/m^3, suggesting that the derived 10-min AEGL-3 of 140 mg/m^3 is appropriate.

No mortality- 5-hr exposures:

Guinea pigs- 44.7 mg/m^3 (Ballantyne and Calloway, 1972)

Mice - 40 mg/m^3 (Ballantyne and Calloway, 1972)

Applying a UF of 10 to these concentrations, yields a value of approximately 4.0 mg/m^3 for 5-hours.

1/10 mortality- 5-hr exposure:

Rats- 37 mg/m^3 for 5-hr (Ballantyne and Calloway, 1972)

Dividing 37 mg/m^3 by 2 to obtain an approximate threshold for lethality, yields 18.5 mg/m^3; application of a total UF of 10, yields a value of 1.9 mg/m^3 for 5-hr.

The values derived from the 5-hr data show that the 4- and 8-hr AEGL-3 values are of 1.5 mg/m^3 are appropriate.

***AEGL-3 values using the L_{05} would be:**

10 min	**111 ppm**
30 min	**24 ppm**
1 hr	**7.9 ppm**
4 hr	**0.75 ppm**
8 hr	**0.22 ppm**

Less consistent with human data

TABLE 1. Standards and Guidelines for Tear Gas

Guideline	Exposure Duration				
	10-min	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.5 mg/m^3	0.5 mg/m^3	0.5 mg/m^3	0.5 mg/m^3	0.5 mg/m^3
AEGL-3	140 mg/m^3	29 mg/m^3	11 mg/m^3	1.5 mg/m^3	1.5 mg/m^3
ERPG-1 (AIHA)[a]			0.005 mg/m^3		
ERPG-2 (AIHA)[a]			0.1 mg/m^3		
ERPG-3 (AIHA)[a]			25 mg/m^3		
IDLH (NIOSH)[b]		2 mg/m^3			
REL-TWA (NIOSH)[c]					0.4 mg/m^3
PEL-TWA (OSHA)[d]					0.4 mg/m^3
TLV-STEL (ACGIH)[e]	0.005 ppm (0.4 mg/m^3)				
MAC (The Netherlands)[f]					0.4 mg/m^3

24-hr PAL-1: 0.04 mg/m^3

Eye irritation in mice and rats at 0.4 mg/m^3 for 6 h/d, 5 d/wk for 13 wk:
Interspecies UF = 3
Intraspecies UF = 3

NTP (1990) studies showed similar results at longer times indicating that effects do not progress.

24-hr PAL-2: 0.5 mg/m^3

Same POD and UF as AEGL-2. No time scaling.

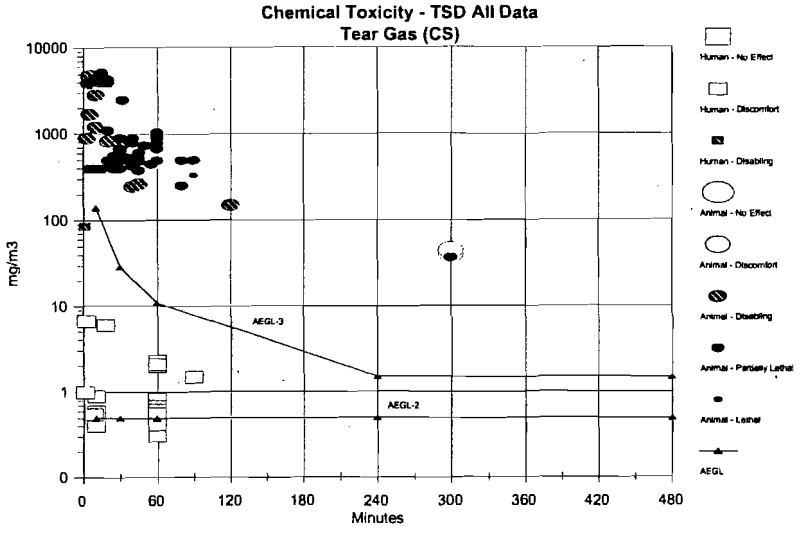
24-hr PAL-3: 1.2 mg/m^3:

37-45 mg/m^3 for 5 hr: 1/10 rats died; 0/10 mice died; 0/5 GP died

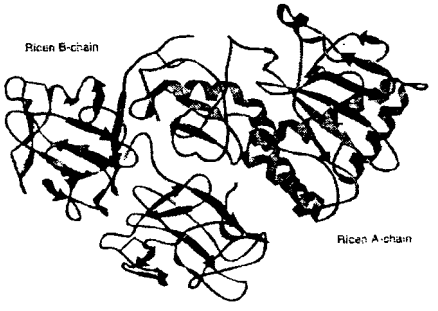
POD: 37 mg/m^3 ÷ 3 = 12 mg/m^3 (estimated threshold for lethality)

Interspecies UF = 3
Intraspecies UF = 3

No time scaling


Chemical Toxicity - TSD All Data
Tear Gas (CS)
10000
1000
100
10
1
0
mg/m3
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Partially Lethal
Animal - Lethal
AEGL

AEGLs for RICIN
(CAS Reg. No. 9009-86-3)



NAC/AEGL Meeting 47
San Diego, CA
December 3-5, 2008

RICIN AEGL

- **Ricin is a heterodimeric glycoprotein found in castor beans**
- **The glycoprotein consists of an A-chain (RTA) and B-chain (RTB) linked by a disulfide bond**
- **Inhibition of protein synthesis results in cell death**
- **Latency period (approximately 18-24 hours) between exposure and death**
- **Limited inhalation toxicity data**
  - **highly variability toxicity**

Human Data

- **No inhalation toxicity data**
- **Oral toxicity (accidental and intentional poisonings)**
  - **latency of 1 hour to 2-14 days**
  - **weakness/prostration; more severe case showed nausea, vomiting, cramps, abdominal pain, fever; lethality preceded by convulsions**

Animal Data

- **10-min exposure (nose-only) of monkeys to 128-353 mg•min/m^3 was lethal (Wilhelmsen and Pitt, 1996)**
  - **time to death: 36 to 48 hours**
  - **no signs of toxicity during the first 20-24 hrs postexposure**
  - **clinical observations after the latency period included abrupt onset and rapidly progressing dyspnea.**

- **LCt_{50} value of 5.8 mg•min/m^3 for male and female rats Bide et al. (1997)**

Animal Data

- 6.25-min exposure to 11.21 mg/m^3 was approximately equivalent to an LCt_{30} (Brown and White, 1997)
  - 3 rats killed at 3, 6, 9, 12, 15, 24, 36, and 48 hours
  - 12-15 hrs post exposure: damage to alveolar wall cells was observed that progressed to intra-alveolar edema
  - 24 and 36 hrs post exposure: intra-alveolar edema
  - 48 hours post exposure: intra-alveolar edema somewhat reduced, generalized type II pneumocytes hyperplasia
  - No rats died during the 48-hr course of the experiment.

- Effect of particle size on toxicity of inhaled ricin (Roy et al., 2003)
  - target concentration of 2.5 mg/m^3 for durations of 10 minutes for small particles (1 µm) and 30 minutes for large particles (5 or 12 µm)
  - 1-µm particles: mice not sacrificed at scheduled times died within 72-hours after exposure
  - particles > 3 µm (even when the exposure was equivalent to a supralethal exposure when delivered as 1-µm particles): all mice survived; none showed signs of toxicity

Animal Data

- nose-only exposure of rats to ricin aerosol at 82.1 mg/min/m^3 (lethal concentration), 16.7 mg•min/m^3 (sublethal concentration; ≈LC_{25}), or phosphate-buffered saline aerosol (Kokes et al., 1994)

Acute lung injury in rats exposed to ricin aerosol			
Parameter	Exposure concentration		
	Control	16.7 mg-min/m^3	82.1 mg-min/m^3
Water content (mL/g dry wt.)	3.6 ± 0.2	3.6 ±0.1	6.2 ± 0.3
Bronchoalveolar lavage			
Total protein (mg/dL)	2.4 ± 0.2	19.4 ± 5.5	320 ± 66
Albumin (mg/dL)	0.8 ± 0.05	2.3 ± 0.7	78 ± 18
LDH (U/L)	129 ± 9	469 ± 68	641 ± 51
Total cell count (×10^4)	57 ± 7	113 ± 30	163 ± 17
Neutrophils (%)	1.0 ± 0.3	65 ± 7	94 ± 3
P_aO_2 (mm Hg)	90 ± 5	83 ±3	48 ± 11
Hematology			
Neutrophils (%)	28 ± 2	44 ± 6	86 ± 3
Fibrinogen (mg/dL)	277 ± 19	430 ± 56	891 ± 15
Kokes et al., 1994			

Animal Data

- **rats were exposed (head-only) to ricin (2.0-mg/mL in phosphate buffered saline (Griffiths et al., 1993; 1995a)**
  - **commercial (Sigma Chemical Corp.)**
  - **in-house ricin purified from seeds of *Ricinus communis* var. *zanzibariens***

- **preparation/source-dependent toxicity**

- **steep exposure response**

Mortality in rats following exposure to ricin aerosol.				
Exposure time (min)	**Aerosol conc. (µg/L)**	**Ct (mg-min/m^3)**	**Inhaled dose (µg/kg bw)**	**Mortality**
Commercial ricin				
2	0.57	1.51	1.05	0/6
2	1.48	3.01	2.02	0/6
3	1.48	4.54	3.55	1/6
2	2.98	5.96	3.83	4/6
4	2.98	11.93	7.67	6/6
40	2.98	119.3	85.77	5/5
LCt_{50}= 4.54-5.96 mg-min/m^3				
In-house purified ricin				
6	1.71	10.2	7.8	1/6
7.5	1.49	11.2	7.6	1/6
6.5	1.99	12.9	9.8	3/6
7.3	1.82	13.3	10.5	4/6
8	1.85	14.8	9.9	6/6
12	1.74	20.9	16.2	6/6
LCt_{50}= 12.5 mg-min/m^3				

AEGL-1

Not recommended: insufficient data

AEGL-2

AEGL-2 values for ricin (mg/m^3)					
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-2	0.021	0.0070	0.0035	NR	NR

Key Study: Kokes, J., Assaad, A., Pitt, L., Estep, J., McAnuity, E., and Parker, G. 1994. Acute pulmonary response of rats exposed to a sublethal dose of ricin aerosol. Experimental biology 94, parts I and II, Anaheim, California, USA, April 24-28, 1994. FASEB Journal; 8 (4-5):A144.

Critical Effect/POD: nonlethal pulmonary effects in rats Ct of 16.7 $mg \cdot min/m^3$. Because the exposure was noted as being an LC_{25} it was reduced 3-fold (to 5.6 $mg \cdot min/m^3$). Griffiths et al. (1995a) noted up to a 2.7-fold potency difference for two ricin preparations. Therefore, the 5.6 $mg \cdot min/m^3$ Ct product was further reduced 2.7-fold to 2.1 $mg \cdot min/m^3$.

Time Scaling: ten Berge analysis of lethality data indicated a point estimate of 0.95 for the ln(conc) – ln(minutes) relationship. AEGL values determined as the concentration required to produce the Ct product of 16.7 $mg \cdot min/m^3$ at the respective AEGL exposure duration. Experimental exposures were of vey short duration, therefore 4-hour and 8-hour AEGL values are not recommended.

Uncertainty Factors: Total UF = 10

Interspecies: 3; . The mechanism of action of ricin is dependent upon cellular and subcellular events that would be common across species. Variability due to species differences in respiratory tract anatomy and deposition of ricin aerosols justifies an interspecies uncertainty factor of 3

Intraspecies: 3; the mechanism for ricin-induced toxicity would not vary significantly among individuals. Individual variability in ventilatory parameters and subsequent variability of deposition of ricin aerosols justifies an intraspecies uncertainty factor of 3.

AEGL-3

AEGL-3 values for ricin (mg/m^3)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	0.033	0.010	0.0048	NR	NR

NR: not recommended; insufficient data for derivation of AEGL-3 values for these exposure durations.

Key Study: Griffiths, G.D., Rice, P., Allenby, A.C., Bailey, S.C., Upshall, D.B. 1995a. Inhalation toxicology and histopathology of ricin and abrin toxins. Inhal. Toxicol. 7:269-288.

Critical Effect/POD: estimated lethality thresholds (LC_{01}) for rats (ten Berge software). Griffiths et al. (1995a) noted up to a 2.7-fold potency difference for two ricin preparations

Time Scaling: ten Berge analysis of lethality data indicated a point estimate of 0.95 for the ln(conc) - ln(minutes) relationship.

Uncertainty Factors: Total UF = 10

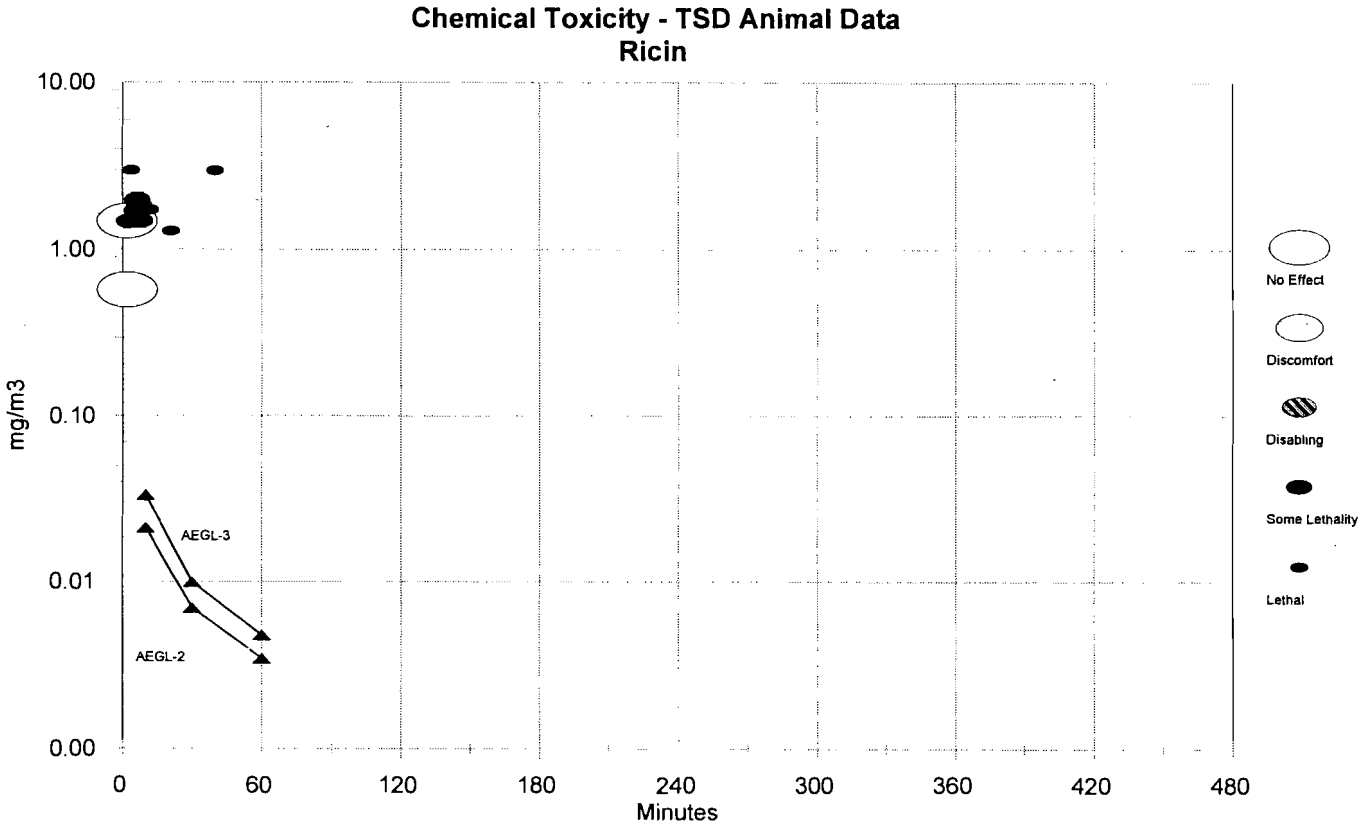
Interspecies: 3; The mechanism of action of ricin is dependent upon cellular and subcellular events that would be common across species. Variability due to species differences in respiratory tract anatomy and deposition of ricin aerosols justifies an interspecies uncertainty factor of 3

Intraspecies: 3; the mechanism for ricin-induced toxicity would not vary significantly among individuals. Individual variability in ventilatory parameters and subsequent variability of deposition of ricin aerosols justifies an intraspecies uncertainty factor of 3.

SOME POINTS TO CONSIDER

- **ricin is a biological with highly variable toxicity due to multiple factors: aerosol size, extraction procedure, source variability**
  - **how meaningful are the available data ???**

- **currently available experimental data are for very short exposure durations**
  - **most experimental durations are for a few minutes**
  - **extrapolation to 4 and 8 hours ??????**


Chemical Toxicity - TSD Animal Data
Ricin
10.00
1.00
0.10
0.01
0.00
mg/m3
AEGL-3
AEGL-2
0
60
120
180
240
300
360
420
480
Minutes
No Effect
Discomfort
Disabling
Some Lethality
Lethal

ACUTE EXPOSURE GUIDELINE LEVELS
(AEGLs)
FOR
DICHLORVOS
(CAS Reg. No. 62-73-7)

NAC/AEGL-47
December 3-5, 2008

ORNL Staff Scientist: Jennifer Rayner

Chemical Manager: John Hinz

Chemical Reviewers: Henry Anderson, Daniel Sudakin

Dichlorvos

Common Synonyms: DDVP, Novatox, Vapona, 2,2-dichloroethenyl dimethylphosphate

Conversion
1 ppm= 9.17 mg/m^3
1 mg/m^3= 0.111 ppm

Physical Characteristics:
- Liquid-colorless to amber

Uses:
- Internal and external organophosphate pesticide
- As a metabolite of metrifonate to treat Alzheimer's disease

Absorption, Distribution, Metabolism, Elimination

- Absorbed rapidly by all routes of exposure (inhalation, oral, dermal)
- Rapid absorption confirmed by evidence of toxicity
- Distributed to major organs: liver & kidney depending on concentration
- Liver is major site of metabolism
- Eliminated primarily in expired air or urine
- Metabolized by two pathways
  - Glutathione-dependent pathway (minor pathway)
    - Produces desmethyl dichlorvos, monomethyl phosphate, and dichloroacetaldehyde
  - Glutatione-independent (major pathway)
    - Catalyzed by "A"-esterases, produces dimethyl phosphate and dichloroacetaldehyde

Other Information

- Mechanism of toxicity: cholinesterase (ChE) inhibition, specifically acetylcholinesterase activity.
- Sensitive population:
  - None identified;
  - seriously ill could be more sensitive than healthy individuals,
  - renal dysfunction does not increase sensitivity
  - Debilitated patients with severe intestinal parasite infections or severe anemia do not appear more sensitive
- Species susceptibility: dogs appear more sensitive than rats & rats appear more sensitive than mice
- Humans appear no more sensitive than rats
- Humans appear less sensitive than dogs

Species Susceptibility
Rationale for Interspecies UF = 1

- MacGregor et al., 2005
  - Reviewed pharmacokinetics & toxicity data in multiple species: humans, rats, mice, dogs, and monkeys, both sexes, all age groups
  - Data sets: oral and inhalation studies from published and unpublished sources, acute-chronic studies
  - Erythrocyte ChE (eChE) activity was the critical endpoint for species comparison
  - MacGregor et al. conclusions
    - Lowest dose causing greater than 10% inhibition of eChE was 0.02 mg/kg for 90 days in animals compared with 0.03 mg/kg in humans for 120 days
    - Lowest and next lowest dose causing greater than 20% eChE inhibition was 0.1 mg/kg and 0.19 mg/kg, respectively, in animals and 0.3 mg/kg and 1.0 mg/kg, respectively, in humans.
  - Overall conclusion: within the dose range and durations of exposure investigated, humans appeared no more sensitive than laboratory animals to eChE inhibiting effects of DDVP.

- Humans dosed with 32 mg/kg of DDVP (Hine and Slomka 1970)
  - No treatment-related clinical signs
  - eChE inhibition: 25-45%

- Rats dosed with 35 mg/kg (Twomey 2002a,b,c)
  - 4/9 males killed 1 hour after dosing for humane reasons
  - 1/5 females died
  - Surviving animals showed severe cholinergic signs of toxicity:
    - decreased activity, lacrimation, miosis, irregular breathing, clonic convulsions, tremors/fasciculation, prostration, decreased righting and splay reflexes, and salivation

- Humans dosed with up to 12 mg/kg (Cervoni et al., 1969; Pena-Chavarria et al., 1969)
  - Over 800 subjects suffering from intestinal parasites included in 2 studies
  - Some were in debilitated state: malnutrition, 40% with severe anemia (hemoglobin: 3.0-9.9 g/dL)
  - No cholinergic signs of toxicity
  - eChE inhibition: 75% or less

- Greyhound dogs dosed with 11 or 22 mg/kg (Snow and Watson 1973; Snow 1973)
  - Death at 22 mg/kg
  - Severe signs of toxicity at 11 mg/kg

- Interspecies UF = 1

Intraspecies Variability Rationale for UF = 10

The default intraspecies uncertainty factor of 10 was maintained for dicrotophos AEGL-3 values. The underlying mechanism of organophosphates is inhibition of cholinesterase by phosphorylation of the esteratic site of the enzyme. Cholinesterases in the blood and tissues are known to be instrumental in limiting the amount of organophosphate compounds reaching critical targets such as brain ChE and acetylChE at cholinergic synapses. Genetic polymorphism has been shown for A-esterases (paraoxonase/arylesterase) in blood and liver of humans. Individuals expressing forms with low hydrolyzing activity are considered to be more susceptible to organophosphate anticholinesterase poisoning. About Evidence for gender and age-related variability in the toxic response to organophosphates has been reported for humans (summarized in NRC, 2003). In the absence of chemical-specific data showing that dicrotophos would act contrary to other organophosphate cholinesterase inhibitors, an intraspecies uncertainty factor of 10 was retained.

HUMAN INHALATION DATA

Concentration	Duration	Effects	Ref.
1-52 mg/m^3 (0.11-5.8 ppm)	10 min-4 hr	Nose and throat irritation; substernal discomfort at the highest concentrations	Hunter 1970a
1 mg/m^3 (0.11 ppm)	2-7 hr	Plasma cholinesterase activity inhibited after 6-7 hours of exposure; no clinical symptoms	Hunter 1970b
0.5 mg/m^3 (0.056 ppm)	5 hr/night, 4 nights/week for 2 weeks	No signs of toxicity; plasma ChE activity inhibited by 34%; erythrocyte ChE activity unaffected;	IPCS 1978
0.7 mg/m^3 (0.078 ppm) (avg.)	8 months	Plasma ChE inhibited by 60% and erythrocyte ChE inhibited by 35%; no clinical symptoms	Menz et al. 1974
1.15 mg/m^3 (0.13 ppm)	Several days, concurrent with dermal exposure	Minor flu-like symptoms, tiredness, wheezing, tightness of chest, plasma and erythrocyte ChE inhibited by 30%	Mason et al. 2000

ACUTE ANIMAL DATA

Species	Concentration	Duration	Effect	Ref.
Rat	1 mg/m^3 0.11 ppm 2 mg/m^3 0.22 ppm 5 mg/m^3 0.56 ppm 10 mg/m^3 1.1 ppm 15 mg/m^3 1.7 ppm	45 min	Shorter trachea epithelial cells; loss of cell cilia Shorter trachea epithelial cells; loss of cell cilia Alveolar interstitial thickening, capillary congestion ≥ 1.1 ppm- dyspnea; ↑ salivation; excessive urination and defecation; alveolar degeneration	Atis et al. 2002
Mouse	64 mg/m^3 7.1 ppm 72 mg/m^3 8.1 ppm	16 hr	Signs of organophosphate intoxication	Dean and Thorpe 1972a
Mouse	30 mg/m^3 3.1 ppm 55 mg/m^3 6.1 ppm	16 hr	No cholinergic effects	Dean and Thorpe 1972b
Guinea Pig	35 mg/m^3 3.9 ppm 55 mg/m^3 6.1 ppm 75 mg/m^3 8.3 ppm	20 min	Miosis; salivation; lacrimation; AChE ↓24.7%, BChE ↓48% Miosis; salivation; lacrimation; AChE ↓46%, BChE ↓69% Miosis; salivation; lacrimation; AChE ↓41%, BChE↓66%	Taylor et al. (2008)

ANIMAL DATA- Reproductive/Developmental

Species	Concentration	Duration	Effect	Ref.
Rabbit	4 µg/L 0.44 ppm	7 hr/d, GD 6-18	No treatment-related effects	Schwetz et al. 1979
Rabbit	0.25 mg/m^3 0.028 ppm 1.25 mg/m^3 0.14 ppm 2 mg/m^3 0.22 ppm 4 mg/m^3 0.44 ppm 6.25 mg/m^3 0.69 ppm	23 hr/d, 7/d wk, GD1-28	No effects Plasma ChE activity ↓35%, Erythrocyte ChE activity ↓68%, brain ChE activity ↓56% 1/20 deaths; death on day 23 of study 6/20 deaths; severe intoxication 16/20 deaths; anorexia; lethargy; muscular tremors	Thorpe et al. 1972
Rat	0.25 mg/m^3 0.028 ppm 1.25 mg/m^3 0.14 ppm 6.25 mg/m^3 0.69 ppm	23 hr/d, 7/d wk, GD1-20	No effects Plasma ChE activity ↓33%, Erythrocyte ChE activity ↓29%, brain ChE activity ↓28% Plasma ChE activity ↓73%, Erythrocyte ChE activity ↓88%, brain ChE activity ↓83%; less activity	Thorpe et al. 1972
Mouse	1.9 mg/m^3 0.21 ppm 3.0 mg/m^3 0.33 ppm 4.6 mg/m^3 0.51 ppm	4 d	Plasma ChE ↓90% day 4, 38% day 7, 75% day 14 Plasma ChE ↓93% day 4, 37% day 7 Plasma ChE ↓94% day 4, 28% day 7, 5% day 14 No cholinergic signs, no developmental effects	Case-bolt et al. 1990
Mouse	4 µg/L 0.44 ppm	7 hr/d, GD6-15	No treatment-related effects	Schwetz et al. 1979
Mouse	30 mg/m^3 3.3 ppm 55 mg/m^3 6.1 ppm 2.1 mg/m^3 0.23 ppm 5.8 mg/m^3 0.64 ppm	16 hr/d or 23 hr/d for 4 wk	No effect on reproductive parameters	Dean and Thorpe 1972b

ANIMAL DATA- Genotoxicity

Species	Concentration	Duration	Effect	Ref.
Mouse	2 mg/m^3 0.22 ppm 8 mg/m^3 0.89 ppm	~ 7 wk	No effect on dominant lethality	Dean and Blair 1976
Mouse	64 mg/m^3 7.1 ppm 72 mg/m^3 8.1 ppm 5 mg/m^3 0.56 ppm	16 hr/d or 23 hr/d for 21 d	For all concentrations: No ↑ in chromatid aberrations in bone marrow cells; similar frequency of chromosome aberrations in meiotic testicular cells compared to control mice	Dean and Thorpe 1972a
Mouse	30 mg/m^3 3.3 ppm 55 mg/m^3 6.1 ppm 2.1 mg/m^3 0.23 ppm 5.8 mg/m^3 0.64 ppm	16 hr/d or 23 hr/d for 4 wk	No effect on dominant lethality	Dean and Thorpe 1972b

AEGL-1 Values for Dichlorvos

10-minute	30-minute	1-hour	4-hour	8-hour
0.011 ppm 0.10 mg/m^3	0.011 ppm 0.10 mg/m^3	0.011 ppm 0.10 mg/m^3	0.011 ppm 0.10 mg/m^3	0.011 ppm 0.10 mg/m^3

Key Study: Hunter, C.G. (1970a) Dichlorvos: inhalational exposures with human subjects. Part 1. Report No. TLGR.0061.70. Sittingbourne, Shell Research Ltd.
Menz, M., H. Luetkmeier, and K. Sachsse. 1974. Long-term exposure of factory workers. Arch. Environ. Health. 28:72-76.

Toxicity endpoint: The AEGL-1 values were based upon the Hunter (1970a) report in which human volunteers were exposed to 0.11 ppm (1 mg/m^3) for 2-7 hours and had no adverse health effects. This is supported by Menz et al. (1974) in which workers were exposed to an average concentration of 0.078 ppm (0.7 mg/m^3) dichlorvos for 8 months and experienced no adverse health effects.

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

Uncertainty factors: A total uncertainty factor of 3 was applied to
Interspecies: 1; Human data were used.
Intraspecies: 10; Documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases

AEGL-2 Values for Mevinphos

10-minute	30-minute	1-hour	4-hour	8-hour
0.092 ppm 0.83 mg/m^3	0.064 ppm 0.58 mg/m^3	0.042 ppm 0.38 mg/m^3	0.042 ppm 0.38 mg/m^3	0.042 ppm 0.38 mg/m^3

Key Study: Atis, S., U. Comelekoglu, B. Coskun, A. Ozge, Ersoz, and D. Talas. 2002. Electrophysiological and histopathological evaluation of respiratory tract, diaphragm, and phrenic nerve after dichlorvos inhalation in rats. Inhal. Toxicol. 14: 199-215.

Toxicity endpoint: The AEGL-2 values were based upon the highest experimental exposure (0.56 ppm, 5 mg/m^3) lasting 45 minutes in rats without an AEGL-2 effect.

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

Uncertainty factors: A total uncertainty factor of 3 was applied to Interspecies: 1; No mechanistic differences in dichlorvos poisoning in animals and humans. Humans are no more sensitive and possibly less sensitive than laboratory species to DDVP. Intraspecies: 10; Documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases

The 4-hour and 8-hour AEGL-2 values were held constant from the 60-min AEGL-2 because they would have been inconsistent with human exposure data (Hunter 1970a; Menz et al. 1974) and AEGL-1 values. Below the values are shown with time scaling.

AEGL-3 Values for Dichlorvos

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

AEGL-3 values were not derived due to insufficient data.

Summary of AEGL Values for Dichlorvos

	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Non-disabling)	0.011 ppm 0.10 mg/m^3	0.011 ppm 0.10 mg/m^3	0.011 ppm 0.10 mg/m^3	0.011 ppm 0.10 mg/m^3	0.011 ppm 0.10 mg/m^3
AEGL-2 (Disabling)	0.092 ppm 0.83 mg/m^3	0.064 ppm 0.58 mg/m^3	0.042 ppm 0.38 mg/m^3	0.042 ppm 0.38 mg/m^3	0.042 ppm 0.38 mg/m^3
AEGL-3 (Lethal)	NR	NR	NR	NR	NR

NR: Not Recommended due to insufficient data.

Extant Standards and Guidelines

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	0.011 ppm 0.10 mg/m^3	0.011 ppm 0.10 mg/m^3	0.011 ppm 0.10 mg/m^3	0.011 ppm 0.10 mg/m^3	0.011 ppm 0.10 mg/m^3
AEGL-2	0.092 ppm 0.83 mg/m^3	0.064 ppm 0.58 mg/m^3	0.042 ppm 0.38 mg/m^3	0.042 ppm 0.38 mg/m^3	0.042 ppm 0.38 mg/m^3
AEGL-3	NR	NR	NR	NR	NR
PEL-TWA (OSHA)[a]					0.11 ppm 1 mg/m^3 (skin)
IDLH (NIOSH)[a]		11 ppm 100 mg/m^3			
REL-TWA (NIOSH)[a]					0.11 ppm 1 mg/m^3 (skin)
TLV-TWA (ACGIH)[a]					0.011 ppm 0.1 mg/m^3 (skin)
MAK (Germany)[a]					0.11 ppm 1 mg/m^3 (skin)
MAC-Peak Category (The Netherlands)[a]					0.11 ppm 1 mg/m^3 (skin)

24-hr PAL-1: 0.047 ppm (0.42 mg/m^3)

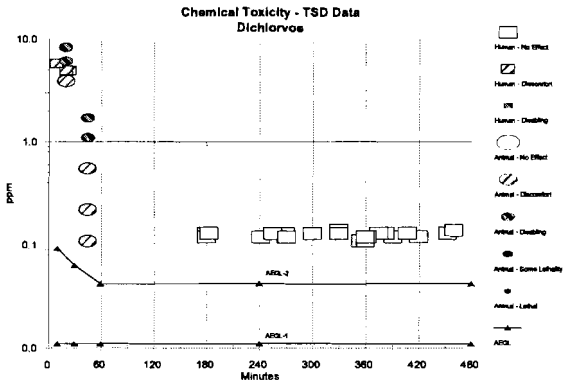
Plasma, erythrocyte, and brain ChE activity was inhibited by 35%, 68%, and 56%, respectively, in rabbits exposed to 0.14 ppm (1.3 mg/m^3) for 23 hr/d, 7 d/wk GD1-28;
Interspecies UF = 1 Humans are no more sensitive and possibly less sensitive than laboratory species to DDVP.
Intraspecies UF = 3 Documented lack of variability in sensitivity among different age groups and genders, and no known genetic polymorphisms in DDVP-ase in the population.

24-hr PAL-2: 0.23 ppm (2.1 mg/m^3)

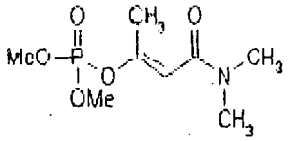
1day exposure in rabbits to 0.69 ppm (6.2 mg/m^3) for 23 hr/d. Rabbits exposed for7 d/wk GD1-28. After 6 days rabbits experienced anorexia, lethargy, muscular tremors.
Interspecies UF = 1
Intraspecies UF = 3

24-hr PAL-3: NR:

NR due to insufficient data



AEGLs for DICROTOPHOS
(CAS Reg. No. 141-66-2)



NAC/AEGL Meeting 47
San Diego, CA
December 3-5, 2008

DICROTOPHOS

- organophosphate insecticide; cholinesterase (ChE) inhibitor
- ~550,000 pounds of dicrotophos are used annually in the United States,

Human Data

- **No inhalation toxicity data**

Animal Data

- **Kettering Laboratory (1965)**
  - **5 rats/group**
  - **whole-body exposure, no MMAD data, no analytical measurements**
  - **dicrotophos technical (84%)**
    - **1-hr exposure to 0.72 mg/L (720 mg/m^3) killed 4 of 5 rats**
    - **1-hr exposure to 0.48 mg/L (equivalent to 480 mg/m^3) was not lethal**
  - **dicrotophos commercial (38.2 %)**
    - **1-hr exposure to 0.86 mg/L (equivalent to 860 mg/m^3) killed 1 of 5 rats**
    - **1-hr exposure to 0.81 mg/L (equivalent to 810 mg/m^3) was not lethal**

Animal Data

- **Sachsse et. al. (1974)**
  - **9 ♂ and 9 ♀ rats/group, exposed 1 or 4 hrs**
  - **7-day post exposure period**
  - **Cascade impactor and gravimetric techniques; MMAD 2-7 µm**
  - **1-hr and 4-hr LC_{50}: 90 mg/m^3**

AEGL 1

AEGL-1 values for dicrotophos					
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.

AEGL-2

AEGL-2 values for dicrotophos (mg/m^3)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	0.17	0.17	0.17	0.17	0.083

- Exposure-response data are insufficient regarding an AEGL-2 critical effects and POD
- Limited data (Kettering Laboratory, 1965) suggest steep dose-response relationship
- AEGL-2 values derived as 3-fold reduction of AEGL-3 values

AEGL-3

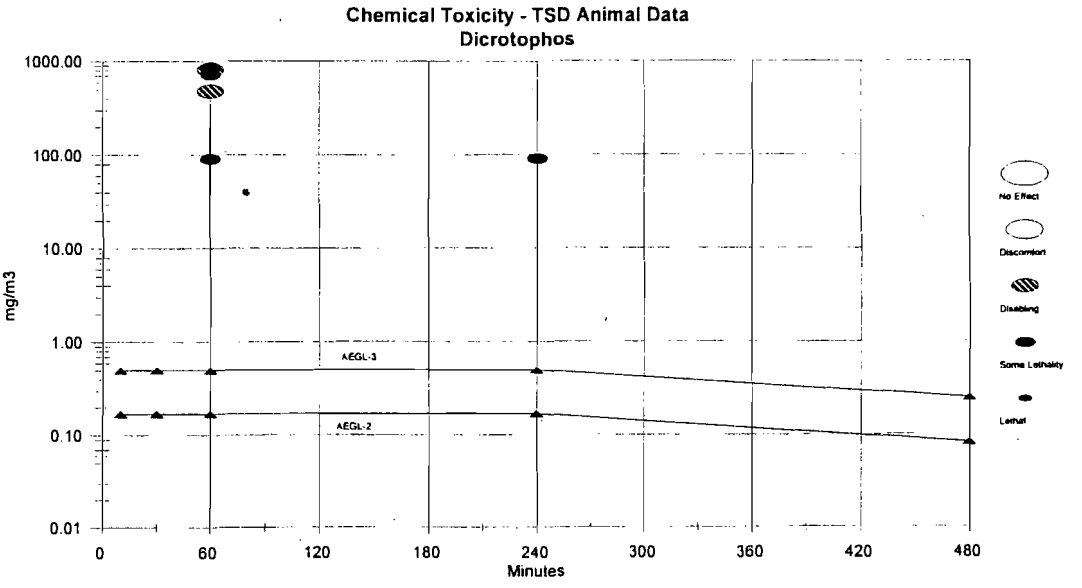
AEGL-2 values for dicrotophos (mg/m^3)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	0.50	0.50	0.50	0.50	0.25

Key Study: Sachsse, K., Ullmann, G., Voss, G., Hess, R. 1974. Measurement of inhalation toxicity of aerosols in small laboratory animals. In: Duncan,W.A.M., ed. Experimental Model Systems in Toxicology and Their Significance in Man. Proceedings of the European Society for the Study of Drug Toxicity. XV: 239-251.

Critical Effect/POD: 1-hr and 4-hr rat LC_{50} values of 90 mg/m^3; steep exposure-response relationship justified 3-fold reduction to 30 mg/m^3 as an estimate of the lethality threshold.

Time Scaling: Due to data deficiencies and the equivalent 1-hour and 4-hour LC_{50} values, a protective approach was applied in which the 10-minute, 30-minute, and 1-hour AEGLs value were set equivalent to the 4-hour value rather than the default time scaling methodology. The 8-hour AEGL-3 was derived using an n = 1 as per the default approach (NRC, 2001).

Uncertainty Factors: Total UF = 30
Interspecies: 3; The underlying mechanism of toxicity is similar across species; additionally, humans may have some protective advantage regarding plasma ChE and red blood cell ChE activity which are less critical targets and serve as a buffer against cholinergic-mediated adverse effects.
Intraspecies: 10; due to known genetic polymorphisms in activity levels of enzymes involved in deactivation of OPs as well as gender and age-related variability in the toxic response to organophosphates.


Chemical Toxicity - TSD Animal Data
Dicrotophos
1000.00
100.00
10.00
1.00
0.10
0.01
mg/m3
AEGL-3
AEGL-2
0
60
120
180
240
300
360
420
480
Minutes
No Effect
Discomfort
Disabling
Some Lethality
Lethal

ACUTE EXPOSURE GUIDELINE LEVELS
(AEGLs)
FOR
FENAMIPHOS
(CAS Reg. No. 22224-92-6)

NAC/AEGL-47
December 3-5, 2008

ORNL Staff Scientist: Jennifer Rayner

Chemical Manager: George Woodall

Chemical Reviewers: Marc Baril, Calvin Willhite

Fenamiphos

Common Synonyms: Nemacur, Phenamiphos,

Conversion
1 ppm= 12.4 mg/m^3
1 mg/m^3= 0.08 ppm

Physical Characteristics:
- Solid-white crystals,

Uses:
- Organophosphate pesticide

Absorption, Distribution, Metabolism, Elimination

- **Absorption**
  - Absorbed following inhalation, ingestion, and dermal contact with skin

  Distribution
  - Distributed to body tissue through the blood
- **Metabolism**
  - Oxidation- major pathway
- **Elimination**
  - Primarily in urine and feces, some exhalation

Mechanism of Toxicity

- Cholinesterase (ChE) inhibition, specifically acetylcholinesrase activity.

ANIMAL DATA- Inhalation

Species	Concentration (ppm)	Exposure Time	Effect	Ref.
Rat male	2.32 6.00 6.96 8.24 11.2 13.2 14.96	1 hr	No effect 5% mortality; (1/20) 30% mortality, (6/20) 60% mortality; (12/20) 65% mortality; (13/20) 95% mortality; (19/20) 100% mortality; (20/20)	Kimmerle 1972
Rat female	2.32 5.60 8.40 9.36 11.84 13.6 14.8 15.6 25.6	1 hr	No effect Cholinesterase activity inhibition 5% mortality; (1/20) Cholinesterase activity inhibition 35% mortality; (7/20) 60% mortality; (12/20) 90% mortality; (18/20) 90% mortality; (18/20) 100% mortality; (20/20)	Kimmerle 1972
Rat	10.5 male 10.4 female	1 hr	LC_{50}	Thyssen 1979a
Rat	8	4 hr	LC_{50}	Thyssen 1979a
Rat	8	4 hr	Less than the LC_{50}	U.S. EPA 1999
Rat	0.0024 0.02 0.28	6 hr/d, 5 d/wk for 21 days	↓Plasma and RBC cholinesterase activity	

ANIMAL DATA- Developmental/Reproductive Toxicity

Species	Concentration (mg/kg)	Exposure Time	Effect	Ref.
Rabbit oral gavage	0.1 0.3 1.0	GD 6-18	Not fetotoxic or embryotoxic, No effect on maternal reproductive parameters 0.3 and 1.0 mg/kg: ↓body weight gain	Hazleton Raltech 1982
Rabbit oral gavage	0.1 0.5 2.5	GD 6-18	No effects 2.5: 25% maternal mortality, ↓weight gain and food consumption, cholinergic effects	Becker 1986; U.S. EPA 1999
Rat oral gavage	0.3 1.0 3.0	GD 6-15	No effects 3.0: cholinergic signs observed within 30 min of treatment	Schlueter 1981
Rat oral gavage	0.25 0.85 3.0	GD 6-15	No effects 3.0: Tremors, 6 deaths, ↓weight gain and food consumption	Astroff and Young 1998
Rat feed	0.15 1 1.5	3-gen study	No effects 1.5: ↓weight gain in F2 males	U.S. EPA 1999
Rat feed	0.17 0.2 0.64 0.73 2.8 3.2	2-gen study	No effects 0.73: ↓RBC cholinesterase activity in 4-day old pups and adults 2.8, 3.2: F1 pup ↓weight gain, F0 and F1 ↓weight gain during lactation, ↓adult plasma and brain cholinesterase	Eigenberg 1991

AEGL-1 Values for Fenamiphos

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

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

AEGL-2 Values for Fenamiphos

10-minute	30-minute	1-hour	4-hour	8-hour
0.087 ppm (1.1 mg/m^3)	0.060 ppm (0.74 mg/m^3)	0.047 ppm (0.58 mg/m^3)	0.012 ppm (0.15 mg/m^3)	0.0060 ppm (0.074 mg/m^3)

Key Study: Kimmerle, G. 1972. Acute inhalation toxicity study with Nemacur active ingredient on rats. Unpublished report. Bayer AG, Wuppertal, Germany.

Organophosphate poisoning exhibits a steep exposure-response curve (NRC 2003). One of twenty male rats died after exposure to 6.0 ppm, 6/20 died after exposure to approximately 7.0 ppm, and 12/20 died after exposure to 8.24 ppm. All 20 rats died after exposure to 14.96 ppm (Kimmerle 1972).

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

AEGL-3 Values for Fenamiphos

10-minute	30-minute	1-hour	4-hour	8-hour
0.26 ppm (3.2 mg/m^3)	0.18 ppm (2.2 mg/m^3)	0.14 ppm (1.7 mg/m^3)	0.036 ppm (0.45 mg/m^3)	0.018 ppm (0.22 mg/m^3)

Key Study: Kimmerle, G. 1972. Acute inhalation toxicity study with Nemacur active ingredient on rats. Unpublished report. Bayer AG, Wuppertal, Germany.

Toxicity endpoint: The AEGL-3 values were based upon the 1-hr BMC_{01} of 4.3 ppm (53 mg/m^3) in rats.

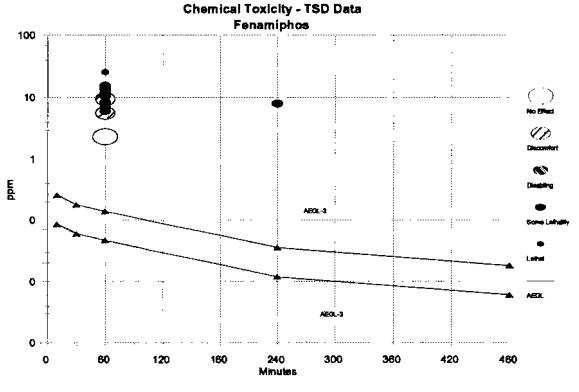
Time scaling: $C^n \times t = k$, temporal scaling, using n = 3 when extrapolation to shorter time points and n = 1 when extrapolating to longer time points due to lack of data to derive the value of n (NRC 2001).

Uncertainty factors: A total uncertainty factor of 30 was applied to
Interspecies: 3; variability in the toxic response 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 mevinphos than do other species. This decreases the dose to critical targets. Therefore, the interspecies uncertainty factor is limited to 3.
Intraspecies: 10; the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justify retention of the intraspecies uncertainty factor of 10.

Summary of AEGL Values for Fenamiphos

	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 Non-disabling	NR	NR	NR	NR	NR
AEGL-2 Disabling	0.087 ppm 1.1 mg/m^3	0.060 ppm 0.74 mg/m^3	0.047 ppm 0.58 mg/m^3	0.012 ppm 0.15 mg/m^3	0.0060 ppm 0.074 mg/m^3
AEGL-3 Lethal	0.26 ppm 3.2 mg/m^3	0.18 ppm 2.2 mg/m^3	0.14 ppm 1.7 mg/m^3	0.036 ppm 0.45 mg/m^3	0.018 ppm 0.22 mg/m^3

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



Extant Standards and Guidelines

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.087 ppm 1.1 mg/m^3	0.060 ppm 0.74 mg/m^3	0.047 ppm 0.58 mg/m^3	0.012 ppm 0.15 mg/m^3	0.0060 ppm 0.074 mg/m^3
AEGL-3	0.26 ppm 3.2 mg/m^3	0.18 ppm 2.2 mg/m^3	0.14 ppm 1.7 mg/m^3	0.036 ppm 0.45 mg/m^3	0.018 ppm 0.22 mg/m^3
REL-TWA (NIOSH)[f]					0.008 ppm 0.1 mg/m^3 (skin)
TLV-TWA (ACGIH)[b]					0.004 ppm 0.05 mg/m^3 (IFV, skin)
MAC-Peak Category (The Netherlands)[g]					0.008 ppm 0.1 mg/m^3

24-hr PAL-1: 0.021 mg/m^3 (0.0017 ppm)

No effects in rats exposed to 3.5 mg/m^3 for 6 hr/d, 5 d/wk for 3 wk:
Interspecies UF = 3 do not have data to support if systemic neurological effect is same among species
Intraspecies UF = 10 to protect potentially sensitive subpopulations from systemic effects
Extrapolated to 24 hours

24-hr PAL-2: 0.056 mg/m^3 (0.0045 ppm)

PAL 3/3.

24-hr PAL-3: 0.17 mg/m^3 (0.014 ppm):

Rat 4 hr LC_{50} of 91 mg/m^3 / 3 to estimate threshold of lethality (ACGIH)
Interspecies UF = 3
Intraspecies UF = 10
Extrapolated to 24 hours

AEGLs for MALATHION

NAC-AEGL #47
[3-5 Dec 08]

Chemical manager	John Hinz
Chemical Reviewers	Henry Anderson
	Daniel Sudakin
Principal Author	Carol Wood

Malathion

- Broad-spectrum OP insecticide
- Used on crops, flowering plants, pest eradication programs, ectoparasites on humans and cattle
- Degraded in water by hydrolysis and microbial action; half-life 0.5-10 day; pH dependent
- Low vapor pressure; removed from atmosphere by wet deposition

UF application in PAL derivation for Malathion (NRC 2003)

- UF_H: 10: (intraspecies) to account for cholinesterase variability in the population.
- UF_A = 3: (interspecies) to account for the difference in serum carboxylesterase levels between humans and rats.

Inhalation Toxicity Data for Malathion

- Humans
  - Monitoring studies of agricultural workers measured urinary metabolites to assess exposure
  - No lethality
- Animals
  - Three acute and one subchronic studies
  - No lethality

Summary of inhalation toxicity data in laboratory animals

Species	Concentration	Duration	Effects	Reference
Rabbit	123 mg/m³ (MMAD = 12 µm)	6 hr	No deaths; ChEI: 38-41% plasma; 38-49% RBC	Weeks et al., 1977
Rat	5200 mg/m³	4 hr	No deaths	US EPA 2000
Mice	6900 mg/m³ (MMAD = 1.5-2.0 µm)	5 hr	ChEI plasma: up to 45%, highly variable	Berteau et al., 1976
Rat	100 mg/m³ 450 mg/m³ 2010 mg/m³ (MMAD = 1.6-1.7 µm)	6 hr/d, 5 d/wk, 13 weeks	ChEI: plasma 2-16%; RBC 9-11%, brain 4-5% ChEI: plasma 7-30%; RBC 22-27%, brain 3-8% Clinical signs; ChEI: plasma 18-70%; RBC 43-44%, brain 17-41%	US EPA, 2000b

AEGL-1 Values for Malathion

10-min	30-min	1-hr	4-hr	8-hr
15 mg/m³	15 mg/m³	15 mg/m³	15 mg/m³	15 mg/m³

- Key Study: US EPA 2000
- Exposure: rats; 450 mg/m³ for 6 hr/d, 5 d/wk, 13 wks
- Effect: ChEI: plasma 7-30%; RBC 22-27%, brain 3-8%
- Scaling: none
- UFs: 30 — 10 intra- to account for cholinesterase variability between individuals
  3 inter- to account for the difference in serum carboxylesterase levels between humans and rats

AEGL-2 Values for Malathion

10-min	30-min	1-hr	4-hr	8-hr
150 mg/m³	150 mg/m³	120 mg/m³	77 mg/m³	50 mg/m³

- Key Study: US EPA 2000
- Exposure: rats; 2010 mg/m³ for 6 hr/d, 5 d/wk, 13 wks
- Effect: Clinical signs; ChEI: plasma 18-70%; RBC 43-44%, brain 17-41%
- Scaling: $C^n \times t = k$; where n = 1 or 3
- UFs: 30 10 intra- to account for cholinesterase variability between individuals
  3 inter- to account for the difference in serum carboxylesterase levels between humans and rats

AEGL-3 Values for Malathion

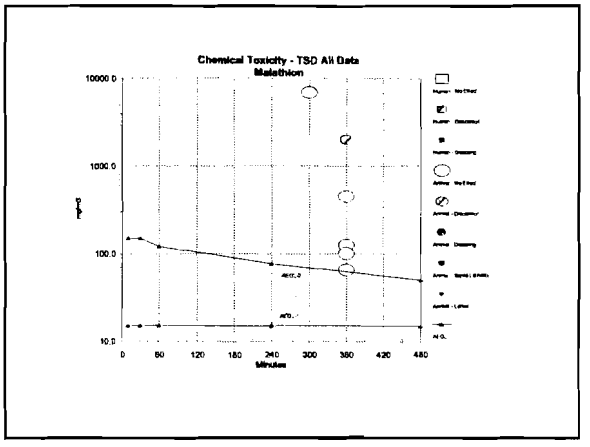
10-min	30-min	1-hr	4-hr	8-hr
NR	NR	NR	NR	NR

- Key Study: none
- Effect: no lethality data were found
  - 2010 mg/m³ for 6 hr/d, 5 d/ wk, 13 wks to rats
  - 6800 mg/m³ for 5 hr to mice
  - 5200 mg/m³ for 4 hr to rats

Summary of AEGL values for Malathion

AEGL	10-min	30-min	1-hr	4-hr	8-hr
1	15 mg/m³	15 mg/m³	15 mg/m³	15 mg/m³	15 mg/m³
2	150 mg/m³	150 mg/m³	120 mg/m³	77 mg/m³	50 mg/m³
3	NR	NR	NR	NR	NR

24-hr PAL 1 = 8.5 mg/m³ based on human data
24-hr PAL 2 and 3 = NR


Chemical Toxicity - TSD All Data
Malathion
10000.0
1000.0
100.0
10.0
0
60
120
180
240
300
360
420
480
Minutes

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR MEVINPHOS (CAS Reg. No. 7786-34-7)

NAC/AEGL-47
December 3-5, 2008

Mevinphos

Common Synonyms: Phosdrin, Crotonic acid,

Conversion
1 ppm= 9.17 mg/m^3
1 mg/m^3= 0.11 ppm

Physical Characteristics:
- Liquid-pale yellow-orange

Uses:
- Organophosphate pesticide

ORNL Staff Scientist: Jennifer Rayner

Chemical Manager: Daniel Sudakin

Chemical Reviewers: Marc Baril, Richard Niemeier

Absorption, Distribution, Metabolism, Elimination

- **Absorption**
  - Absorbed following inhalation, ingestion, and dermal contact with skin

  Distribution
  - Distributed to body tissue through the blood
- **Metabolism**
  - Oxidation and hydrolysis
- **Elimination**
  - Primarily in urine and feces, some exhalation

Mechanism of Toxicity

- Cholinesterase (ChE) inhibition, specifically acetylcholinesrase activity.

ANIMAL DATA

Species	Concentration (ppm)		Exposure Time	Effect	Ref.
Rat	0.012 mg/L 0.0073 mg/L 0.0098 mg/L	0.32 ppm 0.80 ppm 1.08 ppm	4 hr	Male LC_{50} Female LC_{50} Combined LC_{50}	U.S. EPA 1999
Rat	9.8 mg/m^3 8-10 ppm	1.078 ppm	1 hr	LC_{50}	ACGIH 2003
Rat	0.053 mg/L 0.087 mg/L 0.130 mg/L 0.173 mg/L 0.346 mg/L	5.83 ppm 9.57 ppm 14.3 ppm 19 ppm 38 ppm	1 hr	17% mortality 33% mortality 50% mortality 50% mortality 100% mortality	Kodama et al. 1954
Rat	0.24 mg/L	26.64 ppm	Up to 1 hr	10-15 min- miosis, ear twitching, ↑ chewing 15-40 min- lacrimation, salivation, tremors 40-60 min- respiratory distress, convulsions, death	Kodama et al. 1954

AEGL-1 Values for Mevinphos

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

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

AEGL-2 Values for Mevinphos

10-minute	30-minute	1-hour	4-hour	8-hour
0.017 ppm (0.16 mg/m^3)	0.012 ppm (0.11 mg/m^3)	0.0097 ppm (0.089 mg/m^3)	0.0024 ppm (0.022 mg/m^3)	0.0012 ppm (0.011 mg/m^3)

Key Study: Kodama, J.K., M.S Morse, H.H. Anderson, M.K. Dunlap, and C.H. Hine. 1954. Comparative toxicity of two vinyl-substituted phosphates. Arch. Ind. Hyg. Occup. Med. 9: 45-61

Organophosphate poisoning exhibits a steep exposure-response curve (NRC 2003). One of six rats died after a 1 hour exposure to 5.83 ppm, and all rats died after exposure to 38 ppm of mevinphos (Kodama et al. 1954).

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

AEGL-3 Values for Mevinphos

10-minute	30-minute	1-hour	4-hour	8-hour
0.052 ppm (0.48 mg/m^3)	0.036 ppm (0.33 mg/m^3)	0.029 ppm (0.27 mg/m^3)	0.0072 ppm (0.066 mg/m^3)	0.0036 ppm (0.033 mg/m^3)

Key Study: Kodama, J.K., M.S Morse, H.H. Anderson, M.K. Dunlap, and C.H. Hine. 1954. Comparative toxicity of two vinyl-substituted phosphates. Arch. Ind. Hyg. Occup. Med. 9: 45-61

Toxicity endpoint: The AEGL-3 values were based upon the 1-hr BMC_{01} of 0.865 ppm (7.9 mg/m^3) used as an estimate of lethality threshold in rats.

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

Uncertainty factors: A total uncertainty factor of 30 was applied to
Interspecies: 3; variability in the toxic response 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 mevinphos than do other species. This decreases the dose to critical targets. Therefore, the interspecies uncertainty factor is limited to 3.
Intraspecies: 10; the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justify retention of the intraspecies uncertainty factor of 10.

Summary of AEGL Values for Mevinphos

	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 Non-disabling	NR	NR	NR	NR	NR
AEGL-2 Disabling	0.017 ppm 0.16 mg/m^3	0.012 ppm 0.11 mg/m^3	0.0097 ppm 0.089 mg/m^3	**0.0024 ppm 0.022 mg/m^3**	**0.0012 ppm 0.011 mg/m^3**
AEGL-3 Lethal	0.052 ppm 0.48 mg/m^3	0.036 ppm 0.33 mg/m^3	0.029 ppm 0.27 mg/m^3	**0.0072 ppm 0.066 mg/m^3**	**0.0036 ppm 0.033 mg/m^3**

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

Extant Standards and Guidelines

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.017 ppm 0.16 mg/m^3	0.012 ppm 0.11 mg/m^3	0.0097 ppm 0.089 mg/m^3	0.0024 ppm 0.022 mg/m^3	0.0012 ppm 0.011 mg/m^3
AEGL-3	0.052 ppm 0.48 mg/m^3	0.036 ppm 0.33 mg/m^3	0.029 ppm 0.27 mg/m^3	0.0072 ppm 0.066 mg/m^3	0.0036 ppm 0.033 mg/m^3
PEL-TWA (OSHA)					0.01 ppm (skin) 0.1 mg/m^3
PEL-STEL (OSHA)	0.03 ppm (skin) 0.3 mg/m^3				
IDLH (NIOSH)		4 ppm 37 mg/m^3			
REL-TWA (NIOSH)					0.01 ppm (skin) 0.1 mg/m^3
REL-STEL (NIOSH)	0.03 ppm (skin) 0.3 mg/m^3				
TLV-TWA (ACGIH)					0.01 ppm 0.1 mg/m^3 (skin, IFV)
MAK (Germany)					0.01 ppm (skin) 0.1 mg/m^3
MAC- The Netherlands					0.01 ppm 0.1 mg/m^3

24-hr PAL-1: NR

Not recommended due to insufficient data

24-hr PAL-2: 0.0005 ppm (0.0046 mg/m^3)

PAL 3/3.

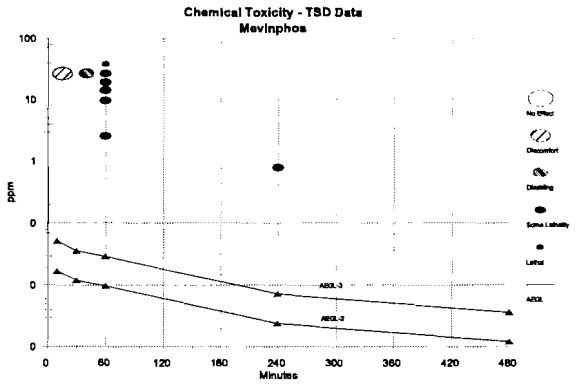
24-hr PAL-3: 0.0015 ppm (0.014 mg/m^3):

Female rat 4 hr LC_{50} of 0.80 ppm (7.3 mg/m^3) to estimate threshold of lethality

Interspecies UF = 3 the variability in the toxic responses is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater percentage of butyryl (plasma) cholinesterase with which to bind anticholinesterases such as mevinphos than do other species. This decreases the dose to critical targets.

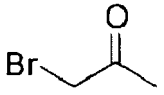
Intraspecies UF = 10 the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases.

Extrapolated to 24 hours



ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

BROMOACETONE



NAC/AEGL-47
December 3-5, 2008
San Diego, CA

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Roberta Grant

Chemical Reviewers: Alan Becker and Gail Chapman

Irritant

Limited data set

<u>Human Data:</u>

0.1 ppm (nominal): Ocular irritation in 2/6 subjects

1.0 ppm (analytical): Ocular irritation in 6/6 subjects

Animal Data:

TABLE 1. Acute inhalation toxicity of bromoacetone in male rats					
Conc (ppm)	Duration (min)	Mortality	Died within indicated number of days	Signs during exposure	Signs post-exposure
17	12	0/5	-	Lacrimation, nasal discharge, labored breathing	None
28	30	2/5	1		Bloody nasal discharge, weight loss
28	60	4/5	14		Gasping, wheezing, bloody nasal discharge, weight loss
28	120	5/5	1		Gasping, wheezing, bloody nasal discharge
48	60	5/5	12	As above, except more rapid onset and more severe	Wheezing, bloody nasal discharge
48	120	5/5	1		Gasping, wheezing, bloody nasal discharge
51	6	0/5	-		Weight loss
51	12	0/5	-		None
51	30	3/5	2		Wheezing, bloody nasal discharge, weight loss
131	10	5/5	11	Much faster onset and more severe	Wheezing, bloody nasal discharge, weight loss
131	30	5/5	3		Gasping, wheezing, bloody nasal discharge

TABLE 2. Acute irritation of bromoacetone in male rats*					
Concentration (ppm)	Duration (min)	Mortality	Signs during exposure	Time-to-response (sec)	Signs post-exposure
0	15	0/4	None	-	None
1.0	15	0/4	Mild blinking (reported as +/-)	101	None
2.0	20	0/4	Blinking	98	None
6.3	74	0/4	Blinking	56	None
10.0	43	0/4	Blinking, lacrimation, sneezing	68	Body weight loss
18.0	87	Not reported	Blinking, lacrimation, sneezing, dyspnea	25	Nasal discharge, body weight loss

*Dow Chemical, 1968

AEGL-1 Values for Bromoacetone				
10-min	30-min	1-h	4-h	8-h
0.011 ppm	0.011 ppm	0.011 ppm	0.011 ppm	0.011 ppm

Species: Human
Concentration: 0.1 ppm
Time: Seconds
Endpoint: Immediate ocular irritation in 2/6 humans. (Considerable ocular irritation noted in 6/6 humans at 1 ppm: next highest concentration)

Reference: Dow Chemical, 1968

Time Scaling: None Applied. Contact irritation.

Uncertainty Factors:

Intraspecies: 3 Contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals.

Interspecies: 1 Human data

Modifying Factor:3

Lack of human data beyond a few seconds
POD was nominal concentration (higher concentration was analytical)

AEGL-2 Values for Bromoacetone				
10-min	30-min	1-h	4-h	8-h
1.4 ppm	0.57 ppm	0.33 ppm	0.11 ppm	0.063 ppm

Endpoint: Three-fold reduction of AEGL-3 values

Approach used even though concentration-response relationship is not particularly steep

Use of rat irritation data as POD (10 ppm; 43 min) yields AEGL-2 values essentially identical to AEGL-3 values calculated from more robust lethality data.

Suggests proposed AEGL-2 values are protective.

10 min	3.2 ppm
30 min	1.3 ppm
1 hr	0.77 ppm
4 hr	0.26 ppm
8 hr	0.15 ppm

AEGL-3 Values for Bromoacetone				
10-min	30-min	1-h	4-h	8-h
4.1 ppm	1.7 ppm	0.98 ppm	0.32 ppm	0.19 ppm

Species: Rat
Concentration: Range of 1 to 131 ppm
Time: Range of 6 to 120 minutes
Endpoint: Lethality threshold (LC_{01}) calculated using probit-analysis dose-response ten Berge program*
Reference: Dow Chemical, 1968

Time Scaling:

$c^n \times t = k$, where the exponent, n, is 1.3, as determined by analysis of rat lethality data using ten Berge (2006) software.

Uncertainty Factors:
Intraspecies: 3
Interspecies: 3:
Considered sufficient because bromoacetone is an irritant (lacrimation, nasal discharge, gasping, wheezing, and labored breathing in rats and ocular irritation in humans; Dow Chemical, 1968) and clinical signs are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly between species or among individuals.

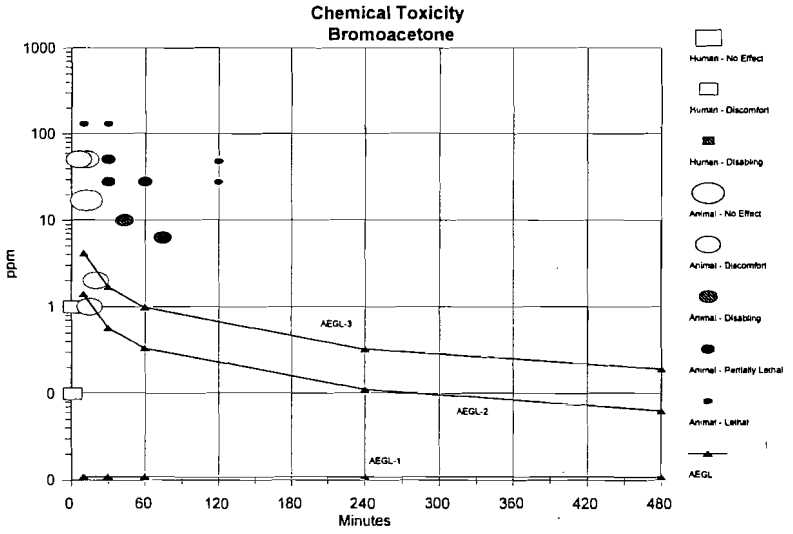
*AEGL-3 values using the L_{05} would be:

10 min	2.5 ppm
30 min	0.94 ppm
1 hr	0.44 ppm
4 hr	0.089 ppm
8 hr	0.039 ppm

These values are inconsistent with human data- ocular irritation at 0.1 or 1 ppm

AEGL Values for Bromoacetone					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	0.011 ppm	0.011 ppm	0.011 ppm	0.011 ppm	0.011 ppm
AEGL-2	1.4 ppm	0.57 ppm	0.33 ppm	0.11 ppm	0.063 ppm
AEGL-3	4.1 ppm	1.7 ppm	0.98 ppm	0.32 ppm	0.19 ppm

There are no other standards or guidelines for bromoacetone!



ATTACHMENT 16

AEGLs for PHOSPHORUS PENTACHLORIDE

NAC-AEGL #47

[3-5 Dec 08]

Chemical manager	Bob Benson
Chemical Reviewers	Dieter Heinz
	David Freshwater
Principal Author	Carol Wood

Phosphorus Pentachloride (PCl_5)

- Non-combustible solid that fumes in moist air; violent hydrolysis
- Sublimes without melting
- Pungent irritating odor
- Used as chlorinating agent and catalyst

PCl_5: Mechanism

- Exact mechanism of toxicity is unknown. The exothermic reaction with water may contribute to localized tissue damage in addition to the effects from hydrogen chloride and phosphoric acid released during the reaction.

- Reaction:

$$PCl_5 + H_2O \rightarrow POCl_3 + 2HCl$$

$$POCl_3 + 3H_2O \rightarrow H_3PO_4 + 3HCl$$

PCl_5: data available

- Human data: case report of industrial accident; workers exposed to mixture of HCl, phosphorus oxychloride, PCl_5, oxalyl chloride, oxalic acid had cough, irritation of eyes and throat, wheezing, rales

- Animal data: one secondary source with no primary reference; one Russian study with limited details

Animal Data: Henderson and Haggard 1927 (secondary)

- 1020 mg/m^3 (122 ppm) is lethal to mice in 10 minutes
- These authors also stated that no known systemic toxicity occurs.

Animal Data: Molodkina 1973 (Russian)

- Lethality: ***Duration not given***
  - LC_{16} = 120 mg/m^3
  - LC_{50} = 205 mg/m^3
  - LC_{84} = 340 mg/m^3

- Clinical signs: restlessness during first 5-15 minutes, followed by decreased motor coordination, jerking, twitching, tremor, depressed respiration, labored breathing. Survivors were apathetic, did not eat and lost weight for several days post-exposure.

- Irritation threshold = 8 mg/m^3 (0.96 ppm)
  - defined as the concentration that resulted in changes in breathing frequency and coloration of the lungs as well as clinical observations

AEGL-1 Values for PCl_5

10-min	30-min	1-hr	4-hr	8-hr
0.80 mg/m^3	0.80 mg/m^3	0.80 mg/m^3	0.80 mg/m^3	0.80 mg/m^3

- Key Study: Molodkina 1973
- Exposure: rats; 8.0 mg/m^3
- Effect: Irritation threshold
- Scaling: none; contact irritation
- UFs: 10 — 3 intra- mechanism of contact irritation is not expected to differ between individuals
  3 inter- mechanism of contact irritation is not expected to differ between rats and humans

AEGL-2 Values for PCl_5

10-min	30-min	1-hr	4-hr	8-hr
NR	NR	NR	NR	NR

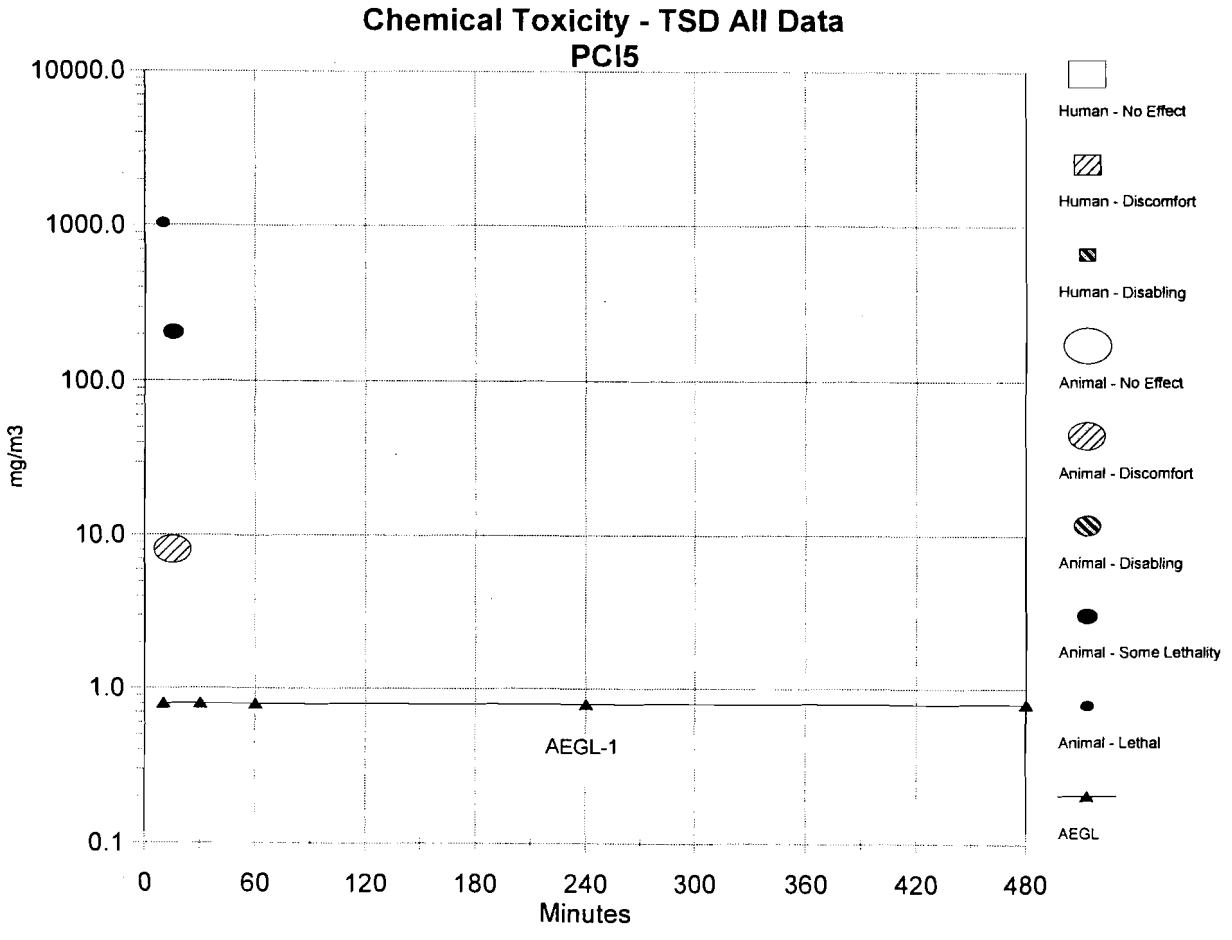
- Key Study: none
- Effect: no data with the appropriate endpoint were found

AEGL-3 Values for PCl_5

10-min	30-min	1-hr	4-hr	8-hr
NR	NR	NR	NR	NR

- Key Study: none
- Effect: no data with the appropriate endpoint were found

Summary of AEGL values for PCl_5					
AEGL	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
1	0.80 mg/m^3 0.096 ppm	0.80 mg/m^3 0.096 ppm	0.80 mg/m^3 0.096 ppm	0.80 mg/m^3 0.096 ppm	0.80 mg/m^3 0.096 ppm
2	NR	NR	NR	NR	NR
3	NR	NR	NR	NR	NR


Chemical Toxicity - TSD All Data
PCl5
10000.0
1000.0
100.0
10.0
1.0
0.1
mg/m3
0
60
120
180
240
300
360
420
480
Minutes
AEGL-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

PCl_5: Structure Activity Relationships

- Phosphorus trichloride

$$PCl_3 + 3H_2O \rightarrow H_3PO_3 + 3HCl, \text{ or}$$
$$3PCl_3 + 8H_2O \rightarrow H_3PO_3 + H_4P_2O_5 + 9HCl$$

- Phosphorus oxychloride

$$POCl_3 + 3H_2O \rightarrow H_3PO_4 + 3HCl$$

- PCl_5:

$$PCl_5 + H_2O \rightarrow POCl_3 + 2HCl$$
$$POCl_3 + 3H_2O \rightarrow H_3PO_4 + 3HCl$$

Summary of AEGL values for HCl, PCl_3, and $POCl_3$					
AEGL	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
HCl (NRC 2004)					
1	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm
2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm
3	620 ppm	210 ppm	100 ppm	26 ppm	26 ppm
PCl_3 (US EPA 2006; interim)					
1	0.34 ppm	0.34 ppm	0.34 ppm	0.34 ppm	0.34 ppm
2	2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	0.83 ppm
3	7.0 ppm	7.0 ppm	5.6 ppm	3.5 ppm	1.8 ppm
$POCl_3$ (US EPA 2008; interim)					
1	NR	NR	NR	NR	NR
2	NR	NR	NR	NR	NR
3	1.1 ppm	1.1 ppm	0.85 ppm	0.54 ppm	0.27 ppm

Comparison of AEGL-1 values for HCl, PCl_3, and PCl_5					
AEGL	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
HCl (NRC 2004)					
1	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm
PCl_3 (US EPA 2006; interim)					
1	0.34 ppm	0.34 ppm	0.34 ppm	0.34 ppm	0.34 ppm
PCl_5					
1	0.096 ppm 0.80 mg/m^3	0.096 ppm 0.80 mg/m^3	0.096 ppm 0.80 mg/m^3	0.096 ppm 0.80 mg/m^3	0.096 ppm 0.80 mg/m^3

Comparison of AEGL-3 values for HCl, PCl_3, and $POCl_3$					
AEGL	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
HCl (NRC 2004)					
3	620 ppm	210 ppm	100 ppm	26 ppm	26 ppm
PCl_3 (US EPA 2006; interim)					
3	7.0 ppm	7.0 ppm	5.6 ppm	3.5 ppm	1.8 ppm
$POCl_3$ (US EPA 2008; interim)					
3	1.1 ppm	1.1 ppm	0.85 ppm	0.54 ppm	0.27 ppm

Ratios of AEGL-1 values for HCl, PCl_3, and PCl_5
HCl : PCl_3 = 1.8 : 0.34 = 5.3
HCl : PCl_5 = 1.8 : 0.096 = 19
PCl_3 : PCl_5 = 0.34 : 0.096 = 3.5

Ratios of 1-hr AEGL-3 values for HCl, PCl_3, and $POCl_3$
HCl : PCl_3 = 100 : 5.6 = 18 (7.4-89)
HCl : $POCl_3$ = 100 : 0.85 = 118 (48-564)
PCl_3 : $POCl_3$ = 5.6 : 0.85 = 6.6 (6.5-6.7)

Phosphorus chlorides not that far apart

Possible AEGL-3 Values for PCl_5

10-min	30-min	1-hr	4-hr	8-hr
31	11	5.0	1.3	1.3
2.0	2.0	1.6	1.0	0.51

- Endpoint:
  - HCl values divided by 20
    - [620, 210, 100, 26, 26 ppm]
  - PCl_3 values divided by 3.5
    - [7.0, 7.0, 5.6, 3.5, 1.8 ppm]

Summary of AEGL values for PCl_5					
AEGL	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
1	0.80 mg/m^3 0.096 ppm	0.80 mg/m^3 0.096 ppm	0.80 mg/m^3 0.096 ppm	0.80 mg/m^3 0.096 ppm	0.80 mg/m^3 0.096 ppm
2	NR	NR	NR	NR	NR
3	NR (2.0 ppm)	NR (2.0 ppm)	NR (1.6 ppm)	NR (1.0 ppm)	NR (0.51 ppm)

Endpoint Selection

- AEGL-1
  - HCl: NOAEL in exercising asthmatics
  - PCl_3: NOAEL in rats
  - PCl_5: irritation threshold
- AEGL-2
  - HCl: mouse RD_{50}; histopath in rats
  - PCl_3: histopath in rats
- AEGL-3
  - HCl: 1/3 of 1-hr LC_{50} in rats
  - PCl_3: 1/3 of 4-hr LC_{50} in rats
  - $POCl_3$: 1/3 of 4-hr LC_{50} in rats

Summary of AEGL values for PCl_5					
AEGL	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
1	0.80 mg/m^3 0.096 ppm	0.80 mg/m^3 0.096 ppm	0.80 mg/m^3 0.096 ppm	0.80 mg/m^3 0.096 ppm	0.80 mg/m^3 0.096 ppm
2	NR	NR	NR	NR	NR
3 (PCl_3/ 3.5)	NR (2.0 ppm)	NR (2.0 ppm)	NR (1.6 ppm)	NR (1.0 ppm)	NR (0.51 ppm)
3 (1-hr LC_{50})	12 mg/m^3 1.4 ppm	8.6 mg/m^3 1.0 ppm	6.8 mg/m^3 0.82 ppm	1.7 mg/m^3 0.20 ppm	0.85 mg/m^3 0.10 ppm
3 (4-hr LC_{50})	20 mg/m^3 2.4 ppm	14 mg/m^3 1.7 ppm	11 mg/m^3 1.3 ppm	6.8 mg/m^3 0.82 ppm	3.4 mg/m^3 0.41 ppm

AEGL values for PCl_5					
	10-min	30-min	1-hr	4-hr	8-hr
AEGL 1					
AEGL 2					
AEGL 3					

ACUTE EXPOSURE GUIDELINE LEVELS FOR NITROGEN TRIFLUORIDE (NF_3)

National Advisory Committee for AEGLs Meeting 47
San Diego, CA
December 3-5, 2008

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Bob Benson

Chemical Reviewers:
Marcel van Raaij
David Freshwater

NITROGEN TRIFLUORIDE

Properties

Practically odorless gas
Water insoluble

Data Base (robust)

Acute lethality studies with four species
- monkey
- dog
- rat
- mouse

Less than a 2-fold difference among species in lethality values at each exposure duration
Exposure durations of 15 minutes to 2 hours

Repeat-exposure and subchronic studies – rat
Developmental/Reproductive toxicity – rat
Genotoxicity studies
No carcinogenicity study

NITROGEN TRIFLUORIDE

Mode of Action

Methemoglobin formation

Inhaled NF_3 reacts with the hemoglobin of the blood to form methemoglobin.

Methemoglobin is unable to carry oxygen to the tissues.

Death is due to tissue anoxia

Methemoglobinemia is reversible

Signs and symptoms of methemoglobinemia

Methemoglobin Concentration (%)	Signs and Symptoms
1.1	Normal level
1-15	None
15-20	Clinical cyanosis (chocolate brown blood); no hypoxic symptoms
30	Fatigue; recovery without treatment
20-45	Anxiety, exertional dyspnea, weakness, fatigue, dizziness, lethargy, headache, syncope, tachycardia
45-55	Decreased level of consciousness
55-70	Hypoxic symptoms: semi-stupor, lethargy, seizures, coma, bradycardia, cardiac arrhythmias
>70	Heart failure from hypoxia; high incidence of mortality
>85	Lethal

NITROGEN TRIFLUORIDE

Data for Derivation of AEGL-1 and AEGL-2

Endpoint of methemoglobin formation

Methemoglobin formation in monkeys and dogs			
Time (minutes)	**Concentration (ppm)**	**Mean methemoglobin (%)**	
		Monkeys	**Dogs**
15	7000[a]	16.5±1.0 (n = 6)	19.2±1.6 (n = 6)
30	3500[a]	15.0±0.5 (n = 6)	10.3±1.0 (n = 6)
60	2000[a]	10.3±2.1 (n = 6)	15.2±1.8 (n = 6)
60	1075[b]	—	9.7 (n = 3)
60	510[c]	—	2.2 (n = 3)
60	290[d]	—	0.0 (n = 3)

[a] Dose of 105,000-120,000 ppm-minutes.
[b] Dose of 64,500 ppm-minutes.
[c] Dose of 31,000 ppm-minutes.
[d] Dose of 17,400 ppm-minutes
Source: Vernot et al. 1973.

NITROGEN TRIFLUORIDE

Lethality data for derivation of AEGL-3

LC_{50} Values in Four Species of Animals (ppm)			
Species	**15 min**	**30 min**	**60 min**
Monkey	24,000	14,000	10,000
Dog	38,000	20,400	9600
Rat	26,700	11,700	6700
Mouse	19,300	12,300	7500

Source: Vernot et al. 1973.

Additional similar rat lethality data from Dost et al. 1970a
e.g., 180-minute exposure to 4000 ppm = 0% mortality

These two studies used analytical concentrations.

NITROGEN TRIFLUORIDE

Uncertainty factors

Uncertainty factors:
Interspecies: 1:

LC_{50} values were similar for four species (monkey, dog, rat, mouse)

Intraspecies; 10:

Infants lack the NADH co-factor for methemoglobin reductase. Methemoglobin reductase reduces methemoglobin to oxyhemoglobin, the active oxygen-carrying form. Some humans may be anemic or deficient in methemoglobin reductase.

Time-scaling ($C^n \times t = k$)

Used the n value of 1.2 from the rat lethality studies ($C^{1.2} \times t = k$)

NITROGEN TRIFLUORIDE

Derivation of AEGL-1:

Point of departure: 1-hour exposure of dogs to 1075 ppm NF_3
9.7% methemoglobin formation
Total uncertainty factor of 10; time-scaled with n value of 1.2 ($C^{1.2} \times t = k$)

AEGL-1 Values for Nitrogen Trifluoride				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
480 ppm (1400 mg/m^3)	190 ppm (550 mg/m^3)	110 ppm (320 mg/m^3)	34 ppm (99 mg/m^3)	19 ppm (55 mg/m^3)

Derivation of AEGL-2:

Point of departure: 1 hour exposure of monkeys and dogs to 2000 ppm NF_3
10-15% methemoglobin formation
Total uncertainty factor of 10; time-scaled with n value of 1.2 ($C^{1.2} \times t = k$)

AEGL-2 Values for Nitrogen Trifluoride

10-min	30-min	1-h	4-h	8-h
890 ppm ($2600\ mg/m^3$)	360 ppm ($1000\ mg/m^3$)	200 ppm ($580\ mg/m^3$)	63 ppm ($180\ mg/m^3$)	35 ppm ($100\ mg/m^3$)

NITROGEN TRIFLUORIDE

Derivation of AEGL-3:

Derived with the ten Berge (2006) regression-analysis dose-response program
Used the rat data because if was the most robust
Rat 60-minute LC_{50} value slightly lower than for other three species
Threshold for lethality set at the 1% response
Applied total uncertainty factor of 10
Values are automatically time-scaled ($C^{1.2} \times t = k$)

AEGL-3 Values for Nitrogen Trifluoride				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
1700 ppm (4900 mg/m^3)	670 ppm (1900 mg/m^3)	380 ppm (1100 mg/m^3)	120 ppm (350 mg/m^3)	69 ppm (200 mg/m^3)

NITROGEN TRIFLUORIDE

Proposed AEGL Values for Nitrogen Trifluoride					
Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	480 ppm	190 ppm	110 ppm	34 ppm	19 ppm
AEGL-2	890 ppm	360 ppm	200 ppm	63 ppm	35 ppm
AEGL-3	1700 ppm	670 ppm	380 ppm	120 ppm	70 ppm

AEGL-1: based on 9.7% methemoglobin formation in dogs, 1075 ppm for 1 hour. Interspecies and intraspecies uncertainty factors of 1 and 10, respectively, were applied.
AEGL-2: based on 10-15% methemoglobin formation in monkeys and dogs, 2000 ppm for 1 hour. Inter- and intraspecies uncertainty factors of 1 and 10, respectively, were applied.
AEGL-3: based on threshold for lethality (1% response from ten Berge program). Inter- and intraspecies uncertainty factors of 1 and 10, respectively, were applied

NITROGEN TRIFLUORIDE

AEGL-3 Values calculated using lower 95% confidence limit of the 5% response; n time-scaling value remains the same, 1.2

AEGL-3 Values for Nitrogen Trifluoride (5% response, 95% LCL)				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
780 ppm	310 ppm	160 ppm	41 ppm	20 ppm

Values are lower than the proposed AEGL-2

NITROGEN TRIFLUORIDE

Category graph of toxicity data and AEGL values