National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-43
June 20-22, 2007

Swedish Seamen's Church
Rotterdam, Netherlands

AGENDA

Wednesday, June 20, 2007

10:00 a.m.	*Development team meetings: Selected Chlorosilanes & Silicon tetrachloride; BZ; Chlorosulfonic acid
11:00	Introductory remarks and approval of NAC/AEGL-42 and Highlights (George Rusch, Ernie Falke, and Paul Tobin)
11:15	AEGL Program Overview (Paul Tobin)
11:45	Revisit of Toluene: PBPK Issues (George Woodall)
12:30 p.m.	Lunch
1:30	Review of Selected Chlorosilanes and Silicon Tetrachloride (Ernie Falke/Cheryl Bast)
3:15	Break
3:30	Review of BZ (Glenn Leach/Bob Young)
5:30	Adjourn for the day

Thursday, June 21, 2007

8:00 a.m.	Development team meetings: Osmium Tetroxide; Pentaborane; Methanesulfonyl chloride
9:30	Review of Chlorosulfonic Acid (Susan Ripple/Sylvia Milanez/Ernie Falke)
10:30	Break
10:45	Review of Chlorosulfonic Acid (continued)
12:00 p.m.	Lunch
1:00	Status Update: Fluorosulfonic acid and Magnesium Diamide (Ernie Falke/George Rusch/Cheryl Bast)
1:15	Developmental Toxicity Update (Marcel van Raaij)
2:30	Review of Methanesulfonyl Chloride (Roberta Grant/Cheryl Bast)
3:30	Break
3:45	Review of Osmium Tetroxide (Dieter Heinz/Bob Young)
5:30	Adjourn for the day

Friday, June 22, 2007

8:00 a.m.	Revisit of Silicon Tetrafluoride (Ernest Falke/ Cheryl Bast)
9:30	Break
9:45	Review of Pentaborane (George Woodall/Sylvia Milanez)
11:45	Administrative matters
12:00 noon	Adjourn meeting

*See page 2.

Pre-meeting Small Discussion Groups: NAC-43

	Chemical	Staff Scientist	CM	Reviewer	Reviewer,	Other Attendees
Wed 6/20 10:00 a.m.	Selected Chlorosilanes and Silicon tetrachloride	Bast	Falke	Tobin	Cushmac	Baril, Bernas, Gingell, Holler
	BZ	Young	Leach*	Niemeier*	Woodall	Benson, Chapman, Sudakin, Willhite, vanRaaij
	Chlorosulfonic acid	Milanez	Ripple	Anderson	Becker	Beasley, Heinz, Rusch, Woolf
Thurs 6/21 8:00 a.m.	Osmium Tetroxide	Young	Heinz	Leach*	Chapman	Anderson, Bernas, Gingell, Holler
	Pentaborane	Milanez	Woodall	Baril	van Raaij	Beasley, Cushmac, Falke, Willhite
	Methanesulfonyl chloride	Bast	Grant*	Rusch	Neimeier*	Becker, Benson, Ripple, Sudakin, Woolf

*Not attending NAC-43

ATTACHMENT 2

NAC/AEGL Meeting 43: June 20-22, 2007

Chemical: Attendee list **CAS Reg. No.:**

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

Cheryl Bast - ORNL
Robert Young - ORNL
Sylvia Milanez - ORNL
Sylvie Tissot - France
Robin fields - UK

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	✓				John Hinz	Absent			
Marc Baril	Absent				Jim Holler	Absent			
Lynn Beasley	✓				Glenn Leach	Absent			
Alan Becker	✓				Richard Niemeier	Absent			
Robert Benson	✓				Susan Ripple	✓			
Edward Bernas	✓				George Rusch, Chair	✓			
Gail Chapman	✓				Martha Steele	Absent			
George Cushmac	✓				Daniel Sudakin	✓			
Ernest Falke	✓				Marcel vanRaaij	✓			
David Freshwater	Absent				Calvin Willhite	✓			
Ralph Gingell	✓				George Woodall	✓			
Roberta Grant	Absent				Alan Woolf	✓			
Dieter Heinz	✓				David Kelly	✓			
Paul Tobin	✓				**TALLY**				
Iris Camacho		✓			**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:** _____

Acute Exposure Guideline Levels

Paul S. Tobin, Ph.D.
U.S. Environmental Protection Agency
Washington, DC
tobin.paul@epa.gov

Human Health Standards

Risk Managers may consider use of a wide range of Human Health Standards (and their derivation basis) for use in chemical emergency planning, depending on:

- Exposure duration (short vs. long term)
- Threshold versus safe end point (emergency versus occupancy situation)
- Exposed population (worker vs. general population)

Definition of Threshold Values

"...adverse effects for each (AEGL) tier are not likely to occur below that level for a specified exposure duration but are increasingly likely to occur at concentrations above that level in a general population, including susceptible individuals. For this reason, the NRC also refers to the (AEGLs) as threhold levels" (NRC 1993)

"...AEGLs are not true effect levels. Rather, they are considered threshold levels that represent an estimated point of transition and reflect the best efforts to establish quantitatively a demarcation between one defined set of symptoms or adverse effects and another defined set of symptoms or adverse effects." (NRC 2001)

AEGL Definitions

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter (ppm or mg/m3)) of a substance above which it is predicted that the general population, including susceptible individuals, could experience **notable discomfort**, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience **irreversible** or other serious, long-lasting adverse health effects or an **impaired ability to escape**.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or **death**.

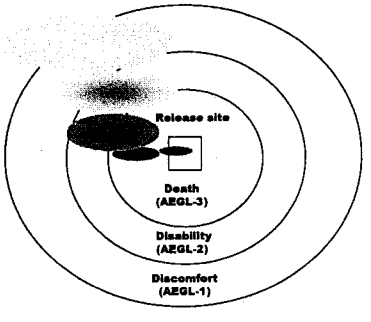
Airborne concentrations **below the AEGL-1** represent exposure levels that can produce **mild** and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, **including susceptible subpopulations**, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

CHARACTERISTICS OF AEGLs

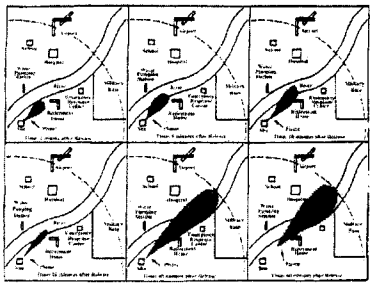
HAZARD ASSESSMENT

Threshold Levels	Effects
DEATH	Increasing likelihood of death
AEGL-3	
DISABLING	• Impairment of ability to escape • Increasing severity of irreversible or other serious long-lasting effects
AEGL-2	
DISCOMFORT	•Increase in **notable** discomfort •Increasing severity of reversible effects (with or without signs/symptoms)
AEGL-1	
DETECTABILITY	Increasing complaints of objectionable odor, taste, sensory irritation or other mild, non-sensory or asymptomatic effects

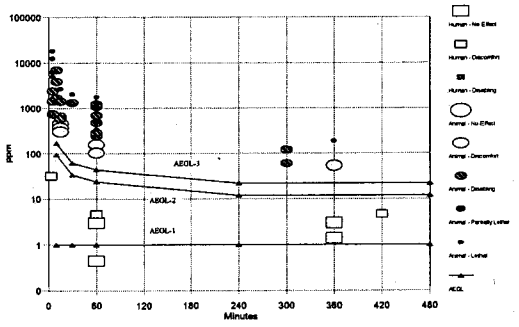
AEGL "Vulnerable"/ "Safe" Zones



Plume Developed and Movement during A Hypothetical Accidental Release

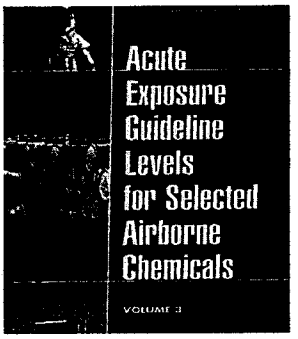


Hydrogen fluoride



AEGL Values for Hydrogen Fluoride (ppm)

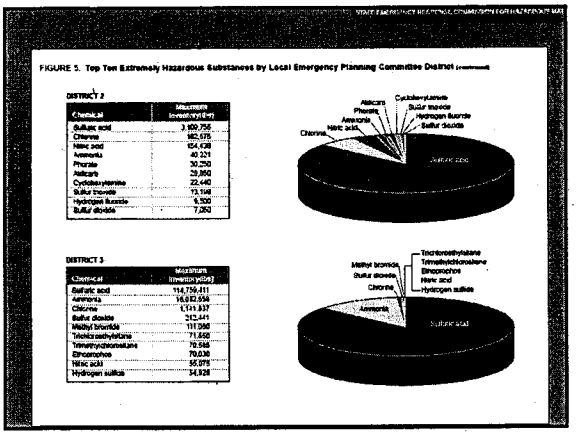
	10 min	30 min	1 hour	4 hours	8 hours
AEGL-1	1.0	1.0	1.0	1.0	1.0
AEGL-2	95	34	24	12	12
AEGL-3	170	62	44	22	22



CHEMICAL CLASSES

285 AEGL CHEMICALS IN 50 CHEMICAL CATEGORIES

ACID HALIDES (10)
ALCOHOLS (2)
ALDEHYDES (8)
ALUMINUM COMPOUNDS (2)
AMINES (15)
ANILINES (1)
ANTIMONY COMPOUNDS (2)
ARSENIC COMPOUNDS (12)
BORON COMPOUNDS (9)
BROMINE COMPOUNDS (4)
CHLORINE, INORGANIC (4)
CHOROFORMATES (11)
CHLOROSILANES (21)
CHROMIUM COMPOUNDS (1)
EPOXIDES (5)
ESTERS (6)
ETHERS (6)
FLUORINES, INORGANIC (4)
GERMANIUM COMPOUNDS (1)
HALOGENS, INORGANIC (22)
HYDRAZINES (4)
HYDROCARBONS, ALIPHATIC (5)
HYDROCARBONS, AROMATIC (11)
IMINES (2)
INORGANIC ACIDS (7)
ISOCYANATES (12)
KETONES (7)
LEAD COMPOUNDS (2)
LITHIUM COMPOUNDS (1)
MERCAPTANS (4)
MERCURY COMPOUNDS (1)
METAL CARBONYLS (2)
METAL PHOSPHIDES (7)
NITRILES (13)
NITRO COMPOUNDS (2)
NITROGEN COMPOUNDS, INORG (6)
ORGANIC ACIDS (5)
ORGANOSULFATES (1)
OSMIUM COMPOUNDS (1)
OXYGEN COMPOUNDS, INORG (1)
PEROXIDES (1)
PHENOLS (1)
PHOSPHONATE ESTERS (5)
PHOSPHORUS COMPNDS, OTHER (12)
SELENIUM COMPOUNDS (1)
SILICON COMPOUNDS (5)
SULFUR COMPOUNDS (14)
TITANIUM COMPOUNDS (1)
TUNGSTEN COMPOUNDS (1)
ZINC COMPOUNDS (1)



Effect of AEGL Value on Vulnerable Zone

Example of 10-factor AEGL difference on vulnerable zone distance

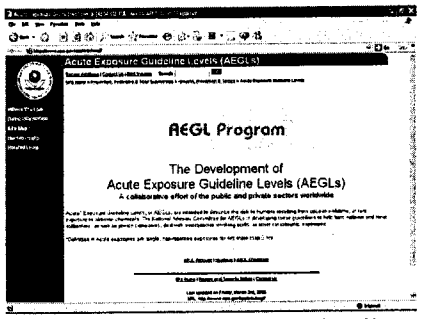
	Hydrogen cyanide (actual)	Hydrogen cyanide ('IF' 10-fold more conservative)
AEGL-2 (30 min)	0.01 mg/l	0.001mg/l
Wind Speed	3.4 mph	3.4 mph
Terrain	rural	rural
Atmospheric stability	F	F
Release	100 lbs	100 lbs
Vulnerable zone	**0.3 miles**	**1.2 miles**

AEGL Chemical Status

STATUS	NUMBER OF CHEMICALS
Final	31
Interim	100
Proposed	61

AEGL Program

AEGL website



http://www.epa.gov/oppt/aegl/

Uncertainty Factors Inter-Species & Intra-Species

"Uncertainty factors between 1 and 10 are applied to account for interspecies and intraspecies variability in the derivation of AEGL values (NRC 1993)."

Interspecies UF

- UF = 10
  - Default UF. Considerations of toxicokinetics and toxicodynamics (or structurally related analongs) may be used to lower UF to 3 or 1
- UF = 3
  - Most susceptible species as toxic end point
  - Biological response closely related to humans
  - Mode of action not expected to vary much among species
- UF = 1
  - Human test data

Intraspecies UF

- "AEGLs are designed to protect almost all people in the general population (NRC 1993)."
- Newborns, infants, children, adults, elderly, infirm, compromised by illness including asthma, compromised pulmonary function, alcoholism, heart disease)

Modifying Factors

- Limited Data Set
- Adverse effects used to set AEGL values are more severe than AEGL definition
- Differential toxicity of chemical isomers

Time Scaling

- When available, use toxicity data from differing exposure durations to set AEGLs
- When not avialable, use Ten Berge (1986)

$$C^n \times t = k \qquad n = 0.8 - 3.5$$

- n = 1-3 includes about 90% of chemicals
- For AEGL derivation, a value of n=1 is used when extrapolating from shorter to longer exposure and a value of n=3 is used when extrapolating from longer to shorter exposure (but for extrapolations from 4 or 8 hr, 10 min is = 30 min value)

AEGL-1 Threshold

- Above AEGL-1 discomfort increases
- Below AEGL-1 "Exposure insufficient to cause discomfort or adverse health effects may be perceived nevertheless by means of smell, taste, or sensations (mild sensory irritation) that are not uncomfortable. The awareness of exposure may lead to anxiety and complaints and constitutes what is termed here 'detectability.'"
- Below AEGL-1 effects = disagreeable odor, taste or other sensations , mild lacrimation, or coughing; or asymptomatic effects such as methemoglobin levels (22%), elevated blood enzymes, or transient altered pulmonary function
- If AEGL-1 is close to or exceeds AEGL-2, then it is noted as "Not Recommended"

AEGL Values for Methyl Isocyanate (ppm)

	10 min	30 min	1 hour	4 hours	8 hours
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.40	0.13	0.067	0.017	0.0080
AEGL-3	1.2	0.40	0.20	0.050	0.025

NR = Not recommended, since AEGL-1 irritation levels would exceed AEGL-2

AEGL-2 Threshold

- Above AEGL-2, there is an increasing likelihood that people may become disabled (i.e. require assistance to prevent more severe effects) or are increasingly likely to experience serious or irreversible health effects.
- Use highest exposure without an AEGL-2 effect as the toxic end point
- A fraction of AEGL-3, usually 1/3, can be used if the dose-response is steep and no other data is available (a factor of less than 3 may be used depending on the total toxicity data profile)

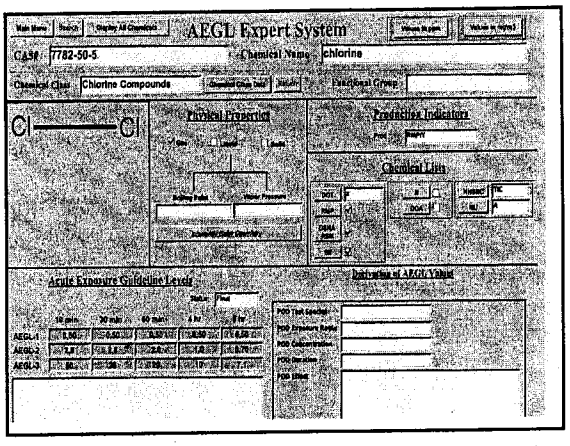
AEGL Values for Methyl chloroformate (ppm)

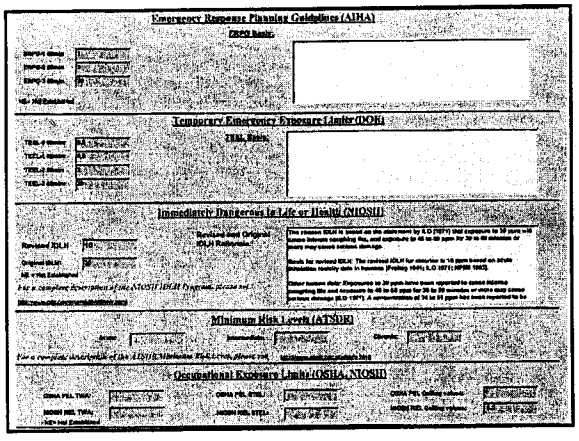
	10 min	30 min	1 hour	4 hours	8 hours
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	4.0	2.8	2.2	1.4	0.70
AEGL-3	12	8.5	6.7	4.2	2.1

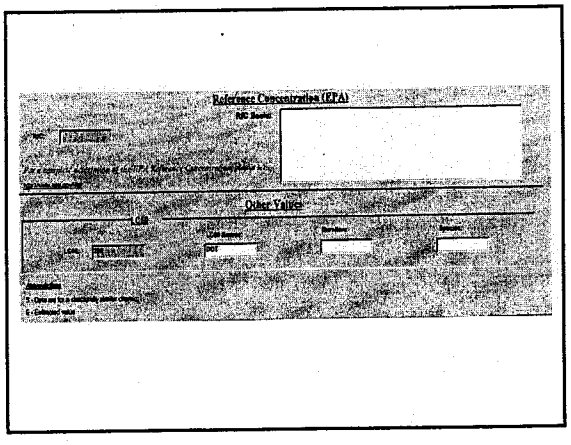
AEGL-2 values = AEGL-3 values divided by 3

AEGL-3 Threshold

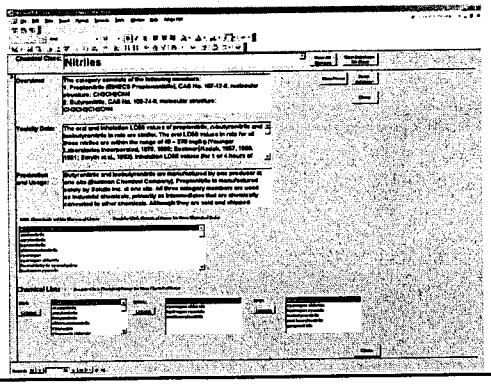
- Above AEGL-3, there is an increasing likelihood of death or life-threatening effects occurring
- Toxic end point is the highest exposure level that does not cause lethality or LC50 divided by 3 (when supported by exposure response)
- Other statistical methods (BMC_{05} etc) may also be used when sufficient information is available

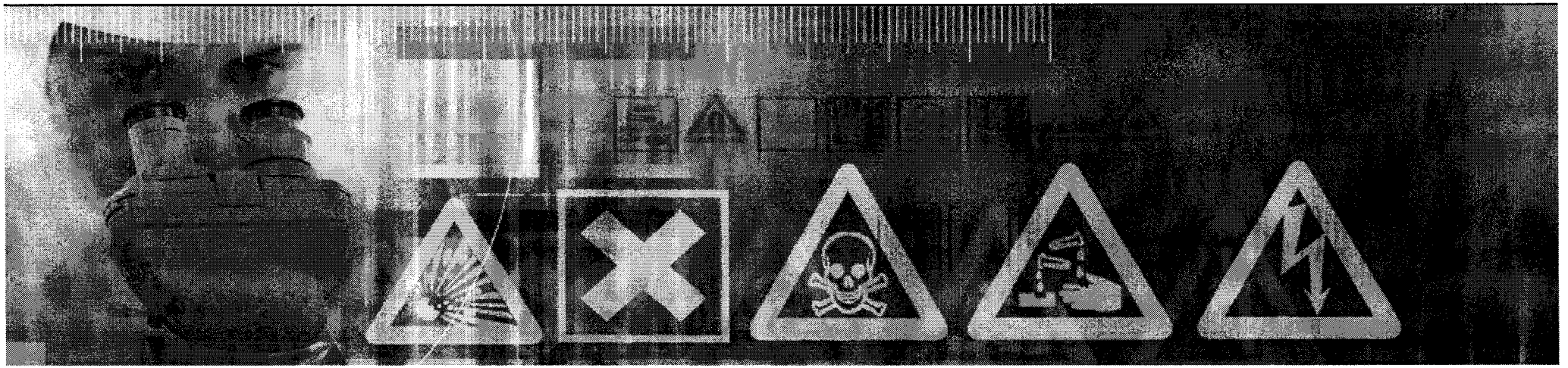






AEGL EXPERT SYSTEM DATABASE: Nitriles





ACUTE EXPOSURE LEVELS
From national program to international collaboration

INERIS

Current situation: national programs

- **USA: AEGLs, ERPGs, TEELs**

- **Europe**
  - ✓ AETLs and ACUTEX methodology
  - ✓ UK: SLOT/SLOD
  - ✓ Dutch values
  - ✓ France: SEL/SEI/SER

INERIS

Comparison AEGL/AETL methodologies

- ✓ Choice of POD
- ✓ PKPB modelling for internal dose for systemic agents
- ✓ Derivation of level 3:
  - ✓ BMC, probit models
  - ✓ POD and Haber's law (n= 1 or 3)
  - ✓ 1/3LC50 as POD in case of lack of individual data
- ✓ Derivation of level 2
  - ✓ POD and Haber's law
  - ✓ 1/3 of level 3 value in case of lack of data
- ✓ Derivation of level 1
  - ✓ POD or not determined
- ✓ Use of inter/intraspecies UF

INERIS

Comparison AEGL/AETL methodologies

BUT

Some differences

- ✓ **Objectives: emergency vs LUP**
- ✓ **Definitions (similarity**
- ✓ **Level 3 split in 3a and 3b depending of the use**
- ✓ **Population of concern: sensitive subpopulations**
- ✓ **Modifying Factors**

INERIS

Towards harmonisation & international values

Future Needs?

- Harmonisation of definitions
- Consensus on main differences: population, MF
  - Relation with uses of the values
- CHERISMA (FP7 delayed 3rd call, focus on emergency, AEGLs as partner)
- Other kind of collaboration? OECD level?

INERIS

TOLUENE – BACKGROUND for NAC-43

At NAC-42, discussions and suggestions among the NAC members prior to and during the toluene presentation led to consideration of several studies for both the AEGL-2 and -3. Jim Dennison of Century Environmental, Inc., was called upon to model the data for the suggested studies. Of two studies considered for development of AEGL-2 values, the study of Oshiro and Bushnell (2004) was chosen. The point of departure was the threshold for narcosis in a 70-minute exposure of Long-Evans rats to 2400 ppm. A single intraspecies uncertainty factor of 3 was applied because modeling accounted for the rat to human extrapolation, and the threshold for narcosis does not differ by more than three-fold among humans. The AEGL-3 point of departure remained the highest non-lethal value of 6250 ppm in a 2-hour rat study by Mullin and Krivanek (1982). Scaling to the other exposure durations was based on modeling. Although these values were accepted at NAC-42, further discussions focused on the AEGL-3. It was decided to have AEGL-3 values modeled based on a rat study that provides a higher NOAEL for lethality, 6030 ppm for 4 hours (Wada et al. 1989). The values based on Wada et al. (1989) are being considered as replacement for the AEGL-3 values accepted at NAC-42.

TOLUENE AEGL VALUES

Classification	Exposure Duration				
	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours
AEGL-1	200 ppm	200 ppm	200 ppm	200 ppm	200 ppm
AEGL-2	3100 ppm	1600 ppm	1200 ppm	790 ppm	650 ppm
*AEGL-3	13,000 ppm	6100 ppm	4500 ppm	3000 ppm	2500 ppm
**AEGL-3	16,000 ppm	7700 ppm	5700 ppm	3800 ppm	3100 ppm

Note: The 10-minute AEGL-3 will be replaced by ** because it is higher than 50% of the LEL of toluene in air (LEL = 14,000 ppm. The 10- and 30-minute AEGL-2 values and the 30-minute through 8-hour AEGL-3 values will have an * because they are higher than 1/10 of the LEL.

*AEGL-2: Mullin and Krivanek (1982)
**AEGL-3: Wada et al. (1989)

TOLUENE - POINTS OF DEPARTURE

AEGL-1: Based on multiple clinical studies of exposure to 200 ppm for several hours. Some protocols included peak exposures to 300 ppm and exercise. Modeling was not used for the endpoint of sensory irritation/notable discomfort.

AEGL-2: Based on the threshold (NOAEL) for narcosis in the rat, a 70-minute exposure to 2400 ppm (Oshiro and Bushnell 2004). Intraspecies UF of 3 applied to the internal dose. Values time-scaled based on modeling. Values accepted by NAC-42.

***AEGL-3:** - Based on a NOAEL for lethality, a 2-hour exposure of rats to 6250 ppm (Mullin and Krivanek 1982). Intraspecies UF of 3 applied to the internal dose. Values time-scaled based on modeling. Values accepted by NAC-42.

****AEGL-3:** Based on NOAEL for lethality, a 4-hour exposure of rats to 6030 ppm (Wada et al. 1989). Intraspecies UF of 3 applied to the internal dose. Values time scaled based on modeling. Values to be considered by NAC-43.

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR SILICON TETRAFLUORIDE

NAC/AEGL-43
June 20-22, 2007
Rotterdam, The Netherlands

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Ernest Falke

Chemical Reviewers: George Rusch and Paul Tobin

Mechanism of Toxicity: **Irritant**

Data Set: **Sparse**

Cannot use Hydrogen Fluoride Molar Equivalence Approach

Unable to obtain Hirose et al., 1993 study

AEGL-1 VALUES: SILICON TETRAFLUORIDE				
10 minute	30 minute	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR

NR: Not Recommended due to insufficient data.

AEGL-2 VALUES: SILICON TETRAFLUORIDE				
10 minute	30 minute	1 hour	4 hour	8 hour
6.3 ppm	4.3 ppm	3.3 ppm	0.87 ppm	0.43 ppm

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

Approach justified by relatively steep concentration-response curve

60% mortality in rats exposed to 100 ppm and 100% mortality at 150 ppm; 6 hours/day for up to 5 days (IRI, 1988)

Values considered protective

Rats exposed to 3.0 or 15 ppm for 6 hours/day, 5 days/week for 4 weeks showed signs of irritation during and after each exposure, and nasal, bone, and tooth pathology at the end of the study period (IRI, 1988)

AEGL-3 VALUES: SILICON TETRAFLUORIDE				
10 minute	30 minute	1 hour	4 hour	8 hour
19 ppm	13 ppm	10 ppm	2.6 ppm	1.3 ppm

Species: Rat
Concentration: 307 ppm
Time: 1 hour
Endpoint: Estimated lethality threshold (⅓ the LC_{50} of 922 ppm)
Reference: Scheel et al., 1968

POD justified by relatively steep concentration-response curve

60% mortality in rats exposed to 100 ppm and 100% mortality at 150 ppm; 6 hours/day for up to 5 days (IRI, 1988)

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

Uncertainty Factors:
Interspecies = 3: Direct-acting irritant
Intraspecies = 3: Direct-acting irritant

Modifying Factor:
Sparse data base = 3

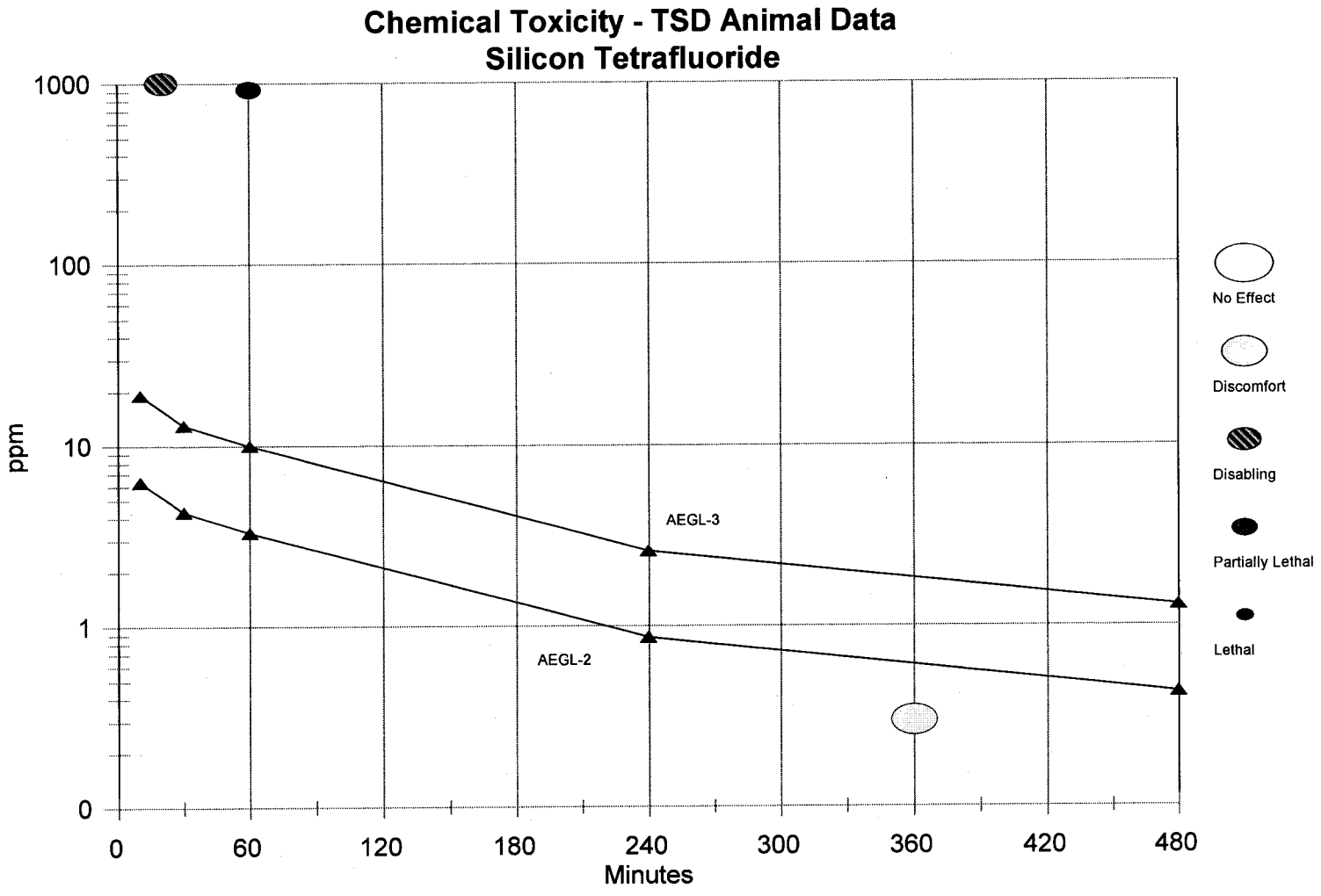
Support for Proposed AEGL-3 values:

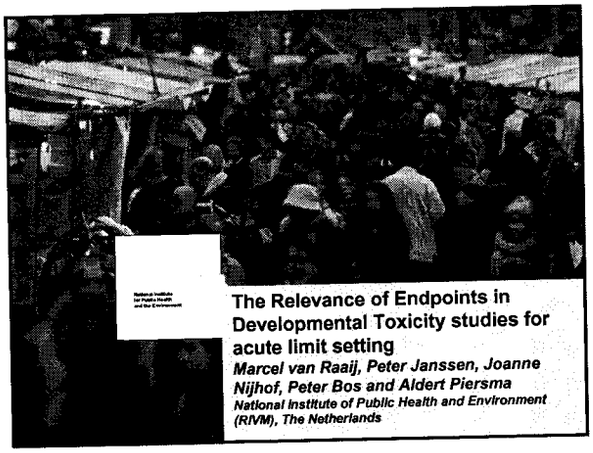
POD: 1000 ppm for 20 min (rats)- Severe irritation , respiratory difficulty, lethargy, no mortality (Gage, 1970)

Same time scaling and UF/MF application.

10 minute	*30 minute*	*1 hour*	*4 hour*	*8 hour*
42 ppm	*22 ppm*	*11 ppm*	*2.7 ppm*	*1.4 ppm*

There are no other standards or guidelines for silicon tetrafluoride!





The Relevance of Endpoints in Developmental Toxicity studies for acute limit setting

Marcel van Raaij, Peter Janssen, Joanne Nijhof, Peter Bos and Aldert Piersma
National Institute of Public Health and Environment (RIVM), The Netherlands

Introduction to the study

- RIVM/SIR participates in limit setting for acute exposures
  - Acute Exposure Guideline Levels (AEGLs)
  - Acute Reference Dose (ARfD)
- RIVM/SIR is consulted when limits are exceeded and in cases of chemical incidents
  - Risk assessment for various substances, often related to short term or acute exposure (both food and non-food related)

Introduction - 2

- About 15-30% of the ARfD's is set on developmental toxicity endpoints
- About 10% of the Dutch Emergency Response values for hazardous substances (similar to AEGLs) is set on developmental toxicity endpoints
- Developmental toxicity is considered a relevant endpoint for acute limit setting
  - Normal guideline-based developmental toxicity study regarded as rather 'acute'
  - Developmental effects are linked to the 'critical window' concept.

Introduction - 3

However.....

- Developmental tox studies: 10-14 days exposure
  - Exposure is about 40% of gestation period
- ARfD is limit for single exposure (< 24h)
- AEGL's are limits for short exposure 10 min - 8h.
  - One day exposure for humans is < 1% of total gestation period

- Is the NOAEL from a standard developmental toxicity study representative for a single day exposure ?
- Are all endpoints observed in developmental toxicity studies equally relevant for acute limit setting ?

4

How to investigate?

- Comparing dose response data (BMD) for single and repeated exposures would be most appropriate
- Most data sets on single dose developmental toxicity do not allow dose response modelling.
- Therefore, effect and no-effect levels will be used.

5

Hypothesis

- When effects are relevant or due to a single exposure then:

  $NOAEL_{single} \approx NOAEL_{repeated}$

  $LOAEL_{single} \approx LOAEL_{repeated}$

- When effects are not / less relevant for a single exposure then:

  $NOAEL_{single} > NOAEL_{repeated}$

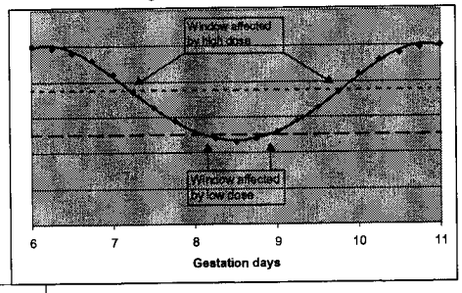
  $LOAEL_{single} > LOAEL_{repeated}$

AND.....

  $NOAEL_{single} > LOAEL_{repeated}$

6

Relation "Dose & Window of Sensitivity"



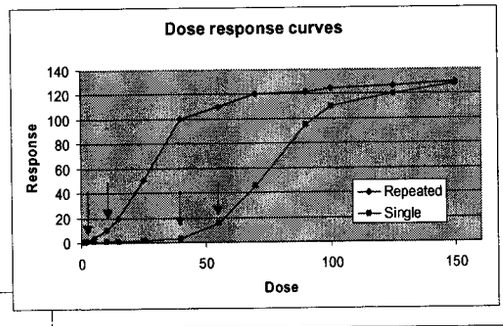
7

Approach

- Identify substances for which single dose studies have been performed
- Indentify 'normal guideline-based' developmental toxicity studies (repeated study) for the same substance - species - route combination.
- Establish NOAEL and LOAEL values for each type of effect reported for both single and repeated studies
- Express the ratio of the $NOAEL_{single}$ and the $NOAEL_{repeated}$
- Calculate the $NOAEL_{single}$ / $LOAEL_{repeated}$ ratio (NLR)
  - When NLR < 1: no difference is shown.

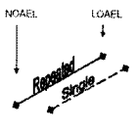
8

Dose Response curves



9

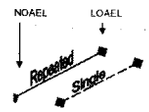
Different dose-response outcomes



Ratio
$NOAEL_{single} / LOAEL_{rep}$

< 1

Different dose-response outcomes



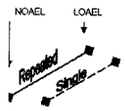
Ratio
$NOAEL_{single} / LOAEL_{rep}$

< 1

Ratio
$NOAEL_{single} / LOAEL_{rep}$

= 1

Different dose-response outcomes



Ratio
$NOAEL_{single} / LOAEL_{rep}$

< 1

Ratio
$NOAEL_{single} / LOAEL_{rep}$

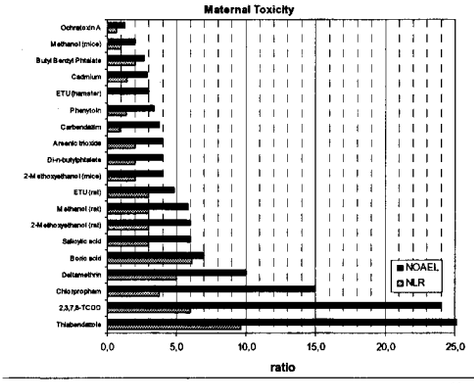
= 1

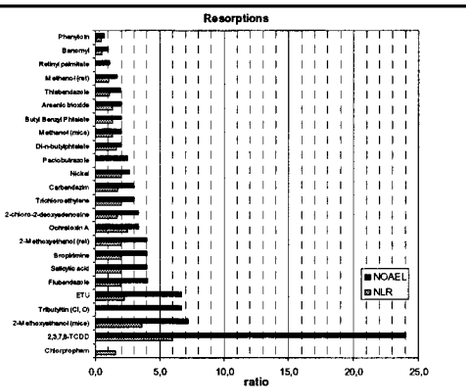
Ratio
$NOAEL_{single} / LOAEL_{rep}$

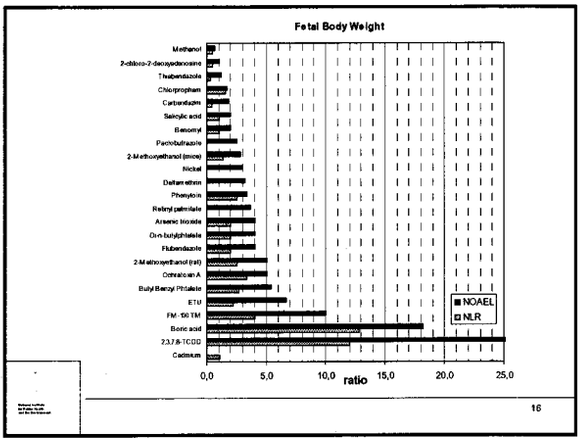
> 1

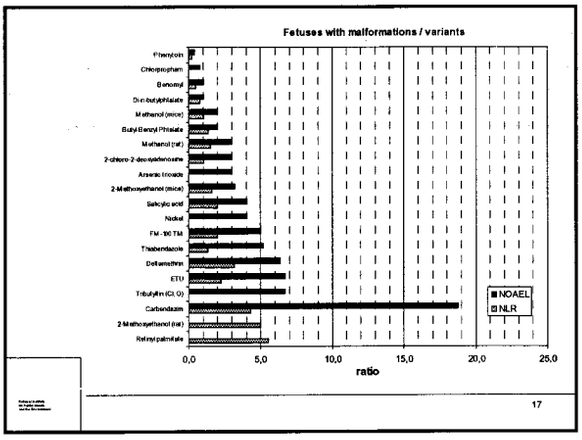
Effects included

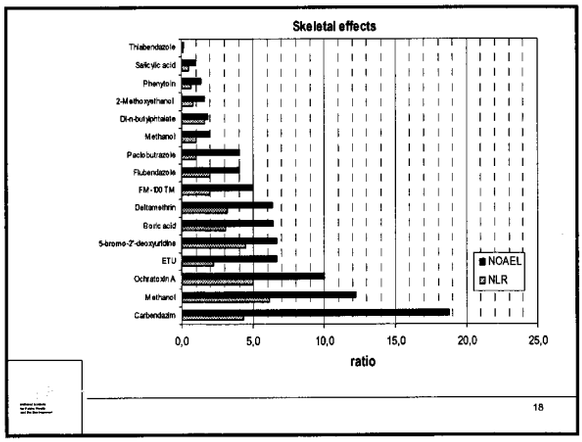
- Maternal toxicity (BW gain, Food Intake, Clinical sings, or organ weights)
- Resorptions
- Fetal body weight
- Number of animals with malformations / variants
- Skeletal effects (e.g. fused sternebrae, fused arches / vertebrae)
- Some specific malformation (cleft palate, dilated renal pelvis)






Fetal Body Weight
Methanol
2-chloro-2-deoxyadenosine
Thiabendazole
Chlorpropham
Carbendazim
Salicylic acid
Benomyl
Paclobutrazole
2-Methoxyethanol (mice)
Nickel
Deltamethrin
Phenytoin
Retinyl palmitate
Arsenic trioxide
Di-n-butylphtalate
Flubendazole
2-Methoxyethanol (rat)
Ochratoxin A
Butyl Benzyl Phtalate
ETU
FM-100 TM
Boric acid
2,3,7,8-TCDD
Cadmium
NOAEL
NLR
0,0
5,0
10,0
15,0
20,0
25,0
ratio
16


Fetuses with malformations / variants
Phenytoin
Chlorpropham
Benomyl
Di-n-butylphtalate
Methanol (mice)
Butyl Benzyl Phtalate
Methanol (rat)
2-chloro-2-deoxyadenosine
Arsenic trioxide
2-Methoxyethanol (mice)
Salicylic acid
Nickel
FM-100 TM
Thiabendazole
Deltamethrin
ETU
Tributyltin (Cl, O)
Carbendazim
2-Methoxyethanol (rat)
Retinyl palmitate
NOAEL
NLR
0,0
5,0
10,0
15,0
20,0
25,0
ratio
17

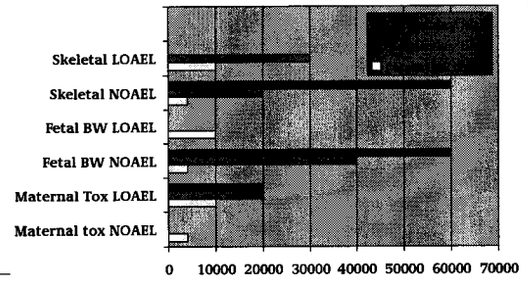

Skeletal effects
Thiabendazole
Salicylic acid
Phenytoin
2-Methoxyethanol
Di-n-butylphtalate
Methanol
Paclobutrazole
Flubendazole
FM-100 TM
Deltamethrin
Boric acid
5-bromo-2'-deoxyuridine
ETU
Ochratoxin A
Methanol
Carbendazim
NOAEL
NLR
0,0
5,0
10,0
15,0
20,0
25,0
ratio
18

Summary results

Endpoint	$NOAEL_{single}/NOAEL_{repeated}$ ratio≤ 3 (%)	NLR-value ≤ 2 (%)
Maternal toxicity	26	50
Resorption	57	81
Fetal body weight	43	60
Malformations/variants	50	69
Skeletal effects	38	56

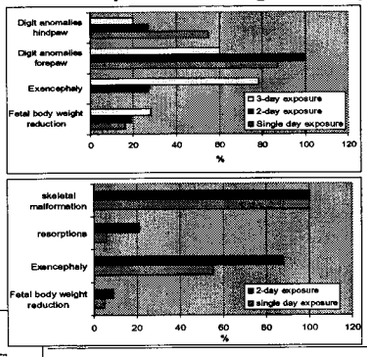
19

FM-100 Flame Retardant



20

Other comparisons single vs. repeated

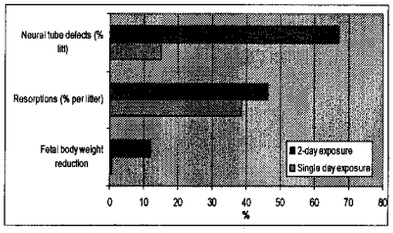


2-Methoxy ethanol

2 studies using 250 mg/kg bw for 1,2, or 3 days

21

Other comparisons single vs. repeated



Methanol-inhalation at 15000 ppm (6h/day) for 1 or 2 days

Conclusions

- The $NOAEL_{repeated}$ especially for the endpoints resorption and malformations, is representative for single exposures.
- In addition, for 50 – 81% of the substance-route-species combinations the NOAEL of the single dose study is close to the LOAEL of the repeated dose study.
- Maternal toxicity appears to be the endpoint showing the largest difference between single and repeated dose studies.

Conclusions-2

- Resorptions appears to be the endpoint showing the smallest difference between single and repeated dose studies.
- Taken together, we conclude that the NOAELrepeated for resorptions and fetal malformation/variants can be regarded as a relevant point of departure for acute limit setting. The relevance of fetal body weight as endpoint for acute limit setting should be evaluated within the total context of effects including maternal toxicity and other fetal effects.

Remarks

- Despite a thorough data search the current study had to be based on a limited number of substances
- For some effects, the NOAEL observed in a repeated dose study may actually be determined by effects that are correlated to a critical window. When the window is small, the NOAELrepeated is predictive for a single day exposure. However, this concept probably is not valid for all types of endpoints determined in developmental toxicity studies.
- Maternal toxicity is an important cause of a range of secondary developmental effects. It is not possible to identify specific effects that are exclusively induced by maternal toxicity.
  However, it is noted that within the framework of AEGL-derivation it is the occurrence of the effect on the unborn in itself that is relevant rather than whether the effect is secondary to maternal toxicity or not.

Remarks

- Route specificity ? Analysis is dominated by oral studies (relevant to ARfD, also relevant for AEGLs ?)
- Bolus / gavage versus diet ? Is gavage-dosing only a worst case type of dosing compared to diet ? Or do we primarily study effects that are based on Cmax rather than AUC ?
  - Oral gavage could implicate something for acute inhalation

Overall Conclusion

- Limited but illustrative analysis
- Gross maternal toxicity in normal 'repeated' developmental studies is not representative for maternal toxicity in single dose experiments
  - Maternal toxicity is not a relevant endpoint for acute limit setting ⇒ what does this mean for effects directly related to maternal toxicity ?
- Using a NOAEL from a normal 'repeated' developmental study will provide a conservative estimation of the NOAEL for single exposures for most developmental toxicants.
- Differences between single and repeated dose NOAELs is mostly modest. For resorptions and malformations, difference is very limited.

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR SELECTED CHLOROSILANES

NAC/AEGL-43
June 20-22, 2007
Rotterdam, The Netherlands

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Ernest Falke

Chemical Reviewers: George Cushmac and Paul Tobin

HCl AEGL document: Published in Volume 4.

NAC has previously derived AEGL values for five chlorosilanes:

Methyltrichlorosilane:	**COT-Approved**
Dimethyldichlorosilane:	**COT-Approved**
Trimethylchlorosilane:	**COT-Approved**
Methyldichlorosilane:	**FR-10**
Methylchlorosilane:	**FR-10**

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

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

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

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

All will be published in the same volume.

Search of U.S. Coast Guard National Response Center Database (www.nrc.uscg.mil):

Yielded many reports of chlorosilane releases:

Dichlorosilanes: 23 incident reports

Trichlorosilanes: 32 incident reports

Equipment failure, Operator Error

Fixed and mobile releases

ppm to mg/m^3 conversion error in TSD

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

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

GLP Protocol:

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

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

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

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

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

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

*Chlorosilane in this TSD for Value Derivation

**AEGL Values Proposed or Interim

CONCLUSIONS (Jean et al., 2006)

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

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

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

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

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

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

Dichlorosilane (Nakashima et al., 1996):

4-Hr Mouse LC_{50} = 144 ppm

Hydrogen Chloride (NRC, 2004):

1-Hr Mouse LC_{50} = 1108 ppm

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

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

Predicted 4-hr LC_{50} for dichlorosilane:

277 ppm ÷ 2 = 139 ppm

Agrees with experimentally-derived value of 144 ppm

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

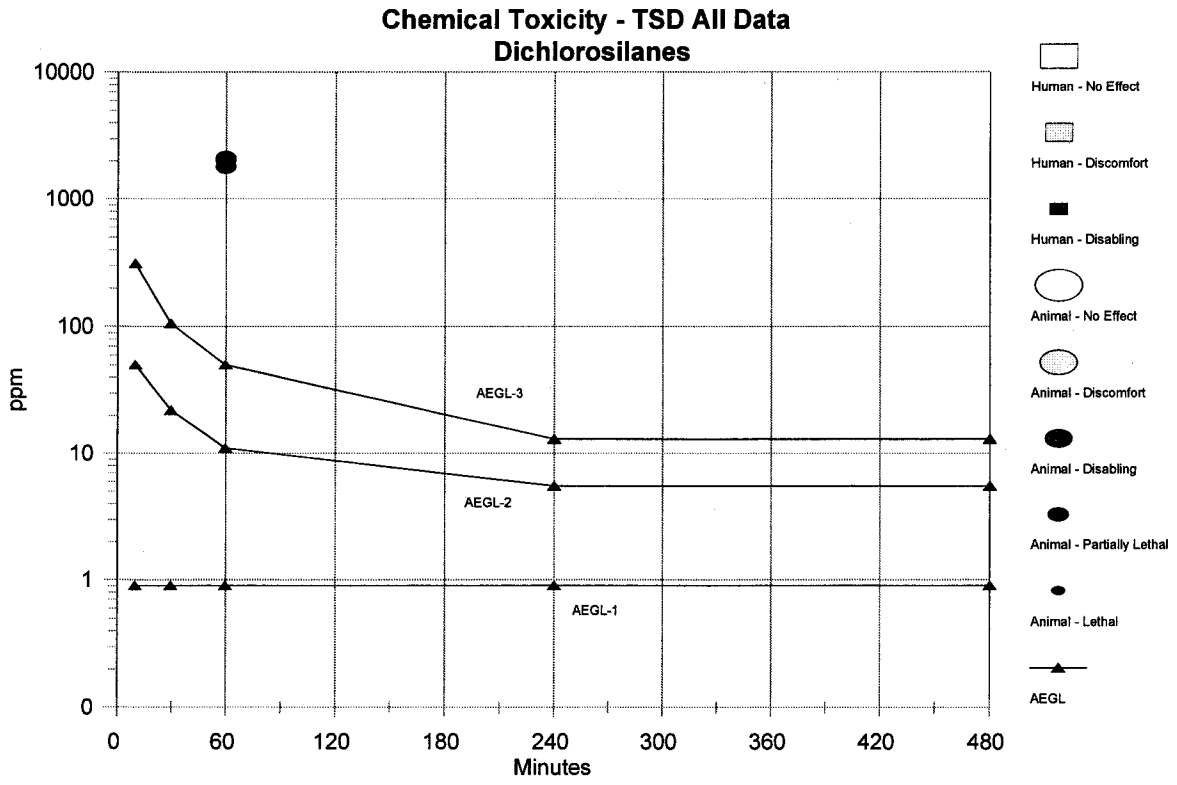
This information taken in conjunction with the observed clinical signs suggests:

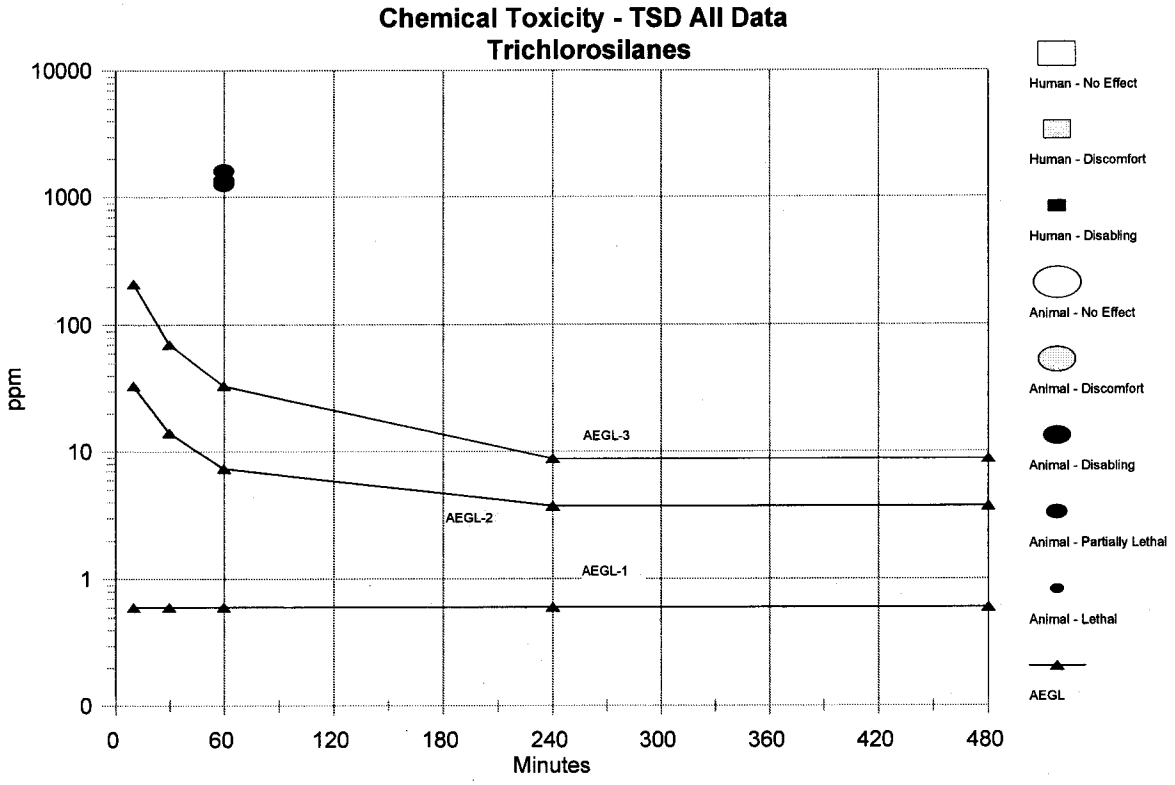
The acute toxicity of the chlorosilanes is both quantitatively and qualitatively similar to hydrogen chloride and therefore, the hydrogen chloride hydrolysis product is responsible for the acute inhalation toxicity of chlorosilanes.

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

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

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 Hexyltrichlorosilane Nonyl trichlorosilane Octadecyl trichlorosilane Octyl trichlorosilane Propyl trichlorosilane Trichloro(dichlorophenyl) silane Trichlorophenylsilane Trichlorosilane Vinyl trichlorosilane	AEGL-1	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm	Hydrogen chloride AEGL-1 values divided by a molar adjustment factor of 3
	AEGL-2	33 ppm	14 ppm	7.3 ppm	3.7 pm	3.7 ppm	Hydrogen chloride AEGL-2 values divided by a molar adjustment factor of 3
	AEGL-3	210 ppm	70 ppm	33 ppm	8.7 ppm	8.7 ppm	Hydrogen chloride AEGL-3 values divided by a molar adjustment factor of 3


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


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

HYDROGEN CHLORIDE AEGL-1 VALUES				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
1.8 ppm	**1.8 ppm**	**1.8 ppm**	**1.8 ppm**	**1.8 ppm**
Key Reference: Stevens, B. et al. 1992. Respiratory effects from the inhalation of hydrogen chloride in young adult asthmatics. JOM. 34: 923-929.				
Test Species/Strain/Number: Human/adult asthmatics/10				
Exposure Route/Concentrations/Durations: inhalation at 0, 0.8, or 1.8 ppm for 45 minutes while exercising: (1.8 ppm was determinant for AEGL-1)				
Effects: No treatment-related effects were observed in any of the individuals tested.				
Endpoint/Concentration/Rationale: The highest concentration tested was a no-effect-level for irritation in a sensitive human population (10 asthmatic individuals tested) and was selected as the basis of AEGL-1. Effects assessed included sore throat, nasal discharge, cough, chest pain or burning, dyspnea, wheezing, fatigue, headache, unusual taste or smell, total respiratory resistance, thoracic gas volume at functional residual capacity, forced expiratory volume, and forced vital capacity. All subjects continued the requisite exercise routine for the duration of the test period.				
Uncertainty Factors/Rationale: Interspecies: 1, test subjects were human; Intraspecies: 1, test subjects were sensitive population (exercising asthmatics)				
Modifying Factor: Not applicable				
Animal to Human Dosimetric Adjustment: Insufficient data				
Time Scaling: The AEGL-1 values for a sensory irritant were held constant across time because it is a threshold effect and prolonged exposure will not result in an enhanced effect. In fact one may become desensitized to the respiratory tract irritant over time. Also, this approach was considered valid since the endpoint (no treatment-related effects at the highest concentration tested in exercising asthmatics) is inherently conservative.				
Data quality and research needs: The key study was well conducted in a sensitive human population and is based on no treatment-related effects. Additionally, the direct-acting irritation response is not expected to vary greatly among individuals. Therefore, confidence in the AEGL values derived is high.				

HYDROGEN CHLORIDE AEGL-2 VALUES				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
100 ppm	**43 ppm**	**22 ppm**	**11 ppm**	**11 ppm**

Key References: Stavert et al. 1991. Relative acute toxicities of hydrogen chloride, hydrogen fluoride, and hydrogen bromide in nose- and pseudo-mouth-breathing rats. Fundam. Appl. Toxicol. 16: 636-655. (30-min, 1-, 4-, and 8-hr)

Barrow, C.S., Alarie, Y., Warrick, M., and Stock, M.F. 1977. Comparison of the sensory irritation response in mice to chlorine and hydrogen chloride. Arch. Environ. Health. 32:68-76. (10-min)

Test Species/Strain/Number: F344 rats/ 8 males/concentration (30-min, 1-, 4-, and 8-hr); Male Swiss Webster mice (10-min)

Exposure Route/Concentrations/Durations: Inhalation: 0, or 1300 ppm/30 minutes (1300 ppm was determinant for 30-min, 1-, 4-, and 8-hr AEGL-2)

Effects (30-min, 1-, 4-, and 8-hr):
0 ppm: no effects
1300 ppm: Nose breathers: severe necrotizing rhinitis, turbinate necrosis, thrombosis of nasal submucosa vessels
1300 ppm: Mouth breathers: severe ulcerative tracheitis accompanied by necrosis and luminal ulceration (determinant for AEGL-2)
RD50 = 309 ppm (determinant for 10-min AEGL-2)

Endpoint/Concentration/Rationale: 1300 ppm for 30 min; severe lung effects (ulcerative tracheitis accompanied by necrosis and luminal ulceration) or nasal effects (necrotizing rhinitis, turbinate necrosis, thrombosis of nasal submucosa vessels histopathology) in pseudo-mouth breathing male F344 rats. (30-min, 1-, 4-, and 8-hr); RD50 of 309 ppm ÷ 3 to estimate irritation (10-min)

Uncertainty Factors/Rationale (30-min, 1-, 4-, and 8-hr):
Total uncertainty factor: 10
Intraspecies: 3- steep concentration-response curve implies limited individual variability
Interspecies: 3- The use of an intraspecies uncertainty factor of 10 would bring the total uncertainty/modifying factor to 100 instead of 30. This would generate AEGL-2 values which are not supported by data on exercising asthmatics; an especially sensitive subpopulation because exercise increases hydrogen chloride uptake and exacerbates irritation; no effects were noted in exercising young adult asthmatics exposed to 1.8 ppm HCl for 45 minutes (Stevens et al., 1992). Using a total UF of 30 would yield 4- and 8-hr values of 3.6 ppm (instead of 11 ppm). It is not supportable to predict that humans would be disabled by exposure for 4- or 8- hours to 3.6 ppm of hydrogen chloride when exercising asthmatics exposed to one-half this level for 45 minutes had no effects. The shorter time points would yield values 4- to 7-fold above 1.8 ppm; however, the confidence in the time scaling for hydrogen chloride is good for times up to 100-min because the value of 'n' was derived from a regression analysis of rat and mouse mortality data with exposure durations ranging from 1 to 100 minutes. The 30 minute value of 43 ppm derived with the total UF of 10 is reasonable in light of the fact that baboons exposed to 500 ppm for 15 minutes experienced only a slightly increased respiratory rate.

Modifying Factor (30-min, 1-, 4-, and 8-hr): 3- based on sparse database for AEGL-2 effects and the fact that the effects observed at the concentration used as the basis for AEGL-2 were somewhat severe
(10-min) : The 10-minute AEGL-2 value was derived by dividing the mouse RD_{50} of 309 ppm by a factor of 3 to obtain a concentration causing irritation (Barrow et al., 1977). One-third of the mouse RD_{50} for hydrogen chloride corresponds to an approximate decrease in respiratory rate of 30%, and decreases in the range of 20 to 50% correspond to moderate irritation (ASTM, 1991).

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^n \times t = k$ where $n = 1$: based on regression analysis of combined rat and mouse LC_{50} data (1 min. to 100 min.) reported by ten Berge et al., 1986. Data point used to derive AEGL-2 was 30 minutes. AEGL-2 values for 1-hr exposure period was based on extrapolation from the 30 minute value. The 4- and 8-hour AEGL-2 values were derived by applying a modifying factor of 2 to the 1-hr AEGL-2 value because time scaling would yield a 4-hour AEGL-2 value of 5.4 ppm and an 8-hour AEGL-2 of 2.7 ppm, close to the 1.8 ppm tolerated by exercising asthmatics without adverse health effects.

HYDROGEN CHLORIDE AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
620 ppm	210 ppm	100 ppm	26 ppm	26 ppm

Key Reference: Vernot, E.H., MacEwen, J.D., Haun, C.C., Kinkead, E.R. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42: 417-423.; Wohlslagel, J., DiPasquale, L..C., Vernot, E.H. 1976. Toxicity of solid rocket motor exhaust: effects of HCl, HF, and alumina on rodents. J. Combustion Toxicol. 3: 61-70.

Test Species/Strain/Sex/Number: Sprague-Dawley rats, 10 males per concentration

Exposure Route/Concentrations/Durations: Inhalation at 0, 1813, 2585, 3274, 3941, or 4455 ppm for 1 hr

Effects:

Concentration	Mortality
0 ppm	0/10
1813 ppm	0/10
2585 ppm	2/10
3274 ppm	6/10
3941 ppm	8/10
4455 ppm	10/10

LC_{50}: reported as 3124 ppm (determinant for AEGL-3)

Endpoint/Concentration/Rationale: 1/3 of the 1-hr LC_{50} (3124 x 1/3 = 1041 ppm) to estimate a concentration causing no deaths.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Intraspecies: 3- steep concentration-response curve implies limited individual variability
Interspecies: 3- **1)** The steep concentration-response curve for lethality observed in the Wohlslagel et al. (1976) study in which 1041 ppm (1/3 of the LC_{50} of 3124 ppm) was lower than the LC_0 of 1813 ppm. This is a conservative selection of the LC_0 and the steep concentration-response curve argues for little inter-individual variability; **2)** AEGL-3 values generated from a total uncertainty factor of 30 would be close to the AEGL-2 values (within a factor of 2) generated above which are reasonable when compared with data on exercising asthmatics; **3)** Sellakumar et al. (1985) exposed rats to 10 ppm of hydrogen chloride for 6 hours a day, 5 days a week for life and only observed increased trachael and laryngeal hyperplasia. The 360 minute AEGL-3 using an intraspecies uncertainty factor of 3 is 17 ppm, close to the level used in the lifetime study in which only mild effects were induced; **4)** Rats exposed to 50 ppm of hydrogen chloride for 6 hours per day, 5 days a week for 90 days (Toxigenics, 1984) exhibited mild rhinitis. This level is already 2-fold above the AEGL-3 value for death. Thus, the total uncertainty factor is 10. It was then time-scaled to the specified 10- and 30-minute and 4-hr AEGL exposure periods using the $c^n \times t = k$ relationship, where n=1 based on regression analysis of combined rat and mouse LC_{50} data (1 min. to 100 min.) as reported by ten Berge et al., 1986. The 4-hour AEGL-3 value was also adopted as the 8-hour AEGL-3 value because of the added uncertainty of time scaling to 8-hours utilizing a value of 'n' derived for exposure durations up to 100 minutes and because the value derived from extrapolation is inconsistent with the total database.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^n \times t = k$ where n = 1, based on regression analysis of rat and mouse mortality data (1 min. to 100 min.) reported by ten Berge et al., 1986. Reported 1-hour data point was used to derive AEGL-3 values. AEGL-3 values for 10-min, 30-min, and 4-hr were based on extrapolation from the 1-hour value. The 4-hr value was adopted as the 8-hr value.

Data quality and research needs: Study is considered appropriate for AEGL-3 derivation since exposures are over a wide range of HCl concentrations and utilize a sufficient number of animals. Data were insufficient to derive a no-effect-level for death. One-third of the LC_{50} has been utilized previously for chemicals with steep concentration-response curves. Also, in the key study, no deaths were observed in rats exposed to 1813 ppm.

ATTACHMENT 9

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR SILICON TETRACHLORIDE (TETRACHLOROSILANE)

NAC/AEGL-43
June 20-22, 2007
Rotterdam, The Netherlands

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Ernest Falke

Chemical Reviewers: George Cushmac and Paul Tobin

Search of U.S. Coast Guard National Response Center Database (www.nrc.uscg.mil):

Yielded 14 reports for Silicon Tetrachloride releases:

Equipment failure, Operator Error

Fixed and mobile releases

ppm to mg/m^3 conversion error in TSD

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

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

The acute toxicity of the mono-, di, and tri-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.

The acute toxicity of silicon tetrachloride appears to be quantitatively similar to the trichlorosilanes.

However:

Rat 1-hr exposure (Jean et al., 2006)			
Concentration	**Mortality**		
	Male	**Female**	**Total**
?????	**Equipment problems prevented monitoring of humidity and maintenance of an acceptable exposure concentration; Data not reported**		
1209 ppm	**1/5**	**2/5**	**3/10**
1497 ppm	**3/5**	**3/5**	**8/10**
3051 ppm	**5/5**	**5/5**	**10/10**
$BMCL_{05}$	**580 ppm**		
BMC_{01}	**912 ppm**		
LC_{50}	**1312 ppm**		

Although the 1-hr rat LC_{50} value for silicon tetrachloride suggests that only three moles of hydrogen chloride were produced, the use of a molar adjustment factor of four is considered appropriate:

Experimental difficulties at lower exposure concentrations in this study

The use of the molar adjustment factor of four will yield protective AEGL values:

Silicon tetrachloride LC_{50} > ¼ of the HCl LC_{50}

Values will be consistent with the overall chlorosilane database.

Therefore, AEGL values for silicon tetrachloride will be derived by applying a molar adjustment factor of 4 to the hydrogen chloride AEGL values

TABLE 1. Summary of Animal Inhalation Toxicity Data				
Species	**Concentration**	**Duration**	**Effects**	**Reference**
Rat	23,400 ppm	1 min	0/3 dead	Union Carbide, 1946
Rat	46,800 ppm	1 min	3/3 dead	Union Carbide, 1946
Rabbit	720 ppm	3 min	Severe eye injury	Union Carbide, 1946
Rat	580 ppm	1 hr	$BMCL_{05}$	Jean et al., 2006; Dow Corning, 1997a
Rat	912 ppm	1 hr	BMC_{01}	Jean et al., 2006; Dow Corning, 1997a
Rat	1209 ppm	1 hr	3/10 dead; eye and nose irritation; respiratory difficulty; lung pathology	Jean et al., 2006; Dow Corning, 1997a
Rat	1312 pm	1 hr	LC_{50}	Jean et al., 2006; Dow Corning, 1997a
Rat	1497 ppm	1 hr	8/10 dead; eye and nose irritation; respiratory difficulty; lung pathology	Jean et al., 2006; Dow Corning, 1997a
Rat	3051 ppm	1 hr	10/10 dead; eye and nose irritation; respiratory difficulty; lung pathology	Jean et al., 2006; Dow Corning, 1997a
Rat	8000 ppm	4 hr	2/6, 3/6, or 4/6 dead	Carpenter et al., 1949

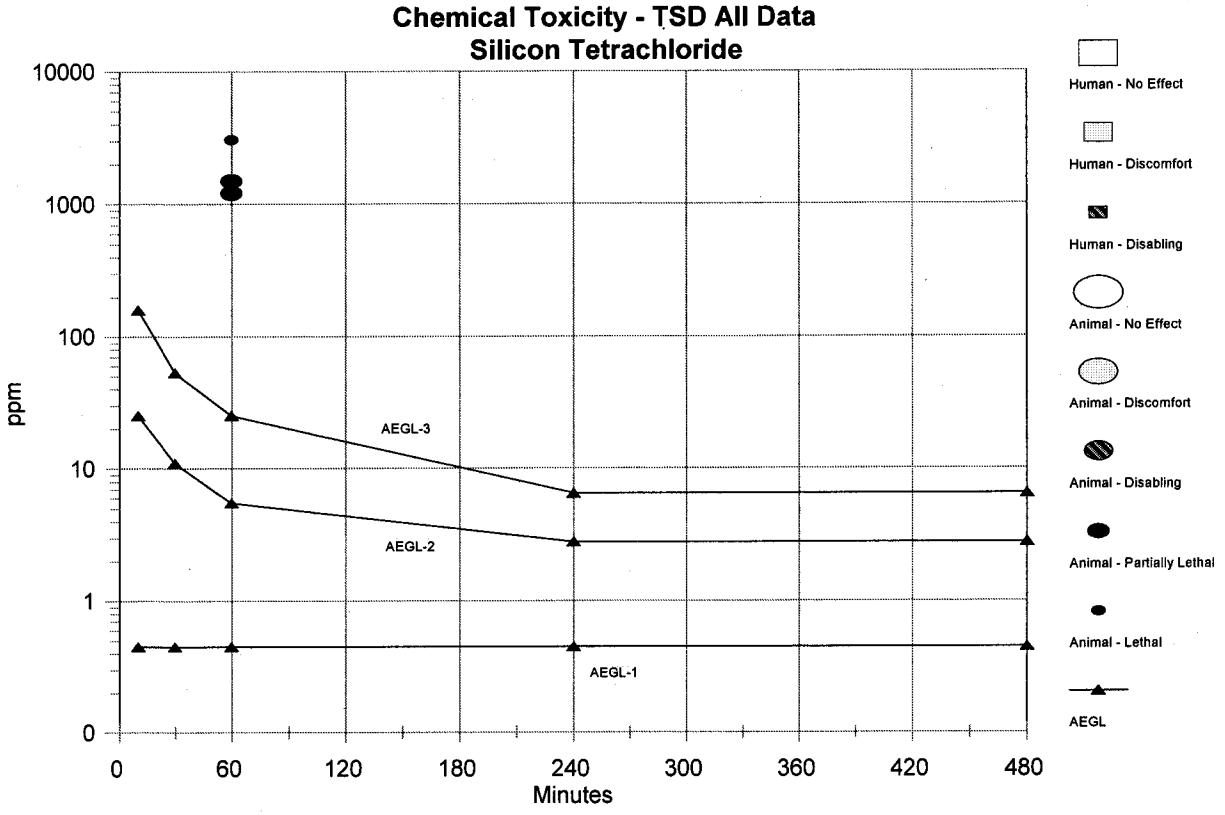
Summary of AEGL Values for Silicon Tetrachloride						
Classification	**10-mim**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	**0.45 ppm (3.1 mg/m^3)***	**0.45 ppm (3.1 mg/m^3)**	**0.45 ppm (3.1 mg/m^3)**	**0.45 ppm (3.1 mg/m^3)**	**0.45 ppm (3.1 mg/m^3)**	**Hydrogen chloride AEGL-1 values divided by a molar adjustment factor of 4 adopted as AEGL-1 values for silicon tetrachloride (NRC, 2004)**
AEGL-2 (Disabling)	**25 ppm (170 mg/m^3)**	**11 ppm (76 mg/m^3)**	**5.5 ppm (38 mg/m^3)**	**2.8 ppm (19 mg/m^3)**	**2.8 ppm (19 mg/m^3)**	**Hydrogen chloride AEGL-2 values divided by a molar adjustment factor of 4 adopted as AEGL-2 values for silicon tetrachloride (NRC, 2004)**
AEGL-3 (Lethal)	**160 ppm (1100 mg/m^3)**	**53 ppm (370 mg/m^3)**	**25 ppm (170 mg/m^3)**	**6.5 ppm (45 mg/m^3)**	**6.5 ppm (45 mg/m^3)**	**Hydrogen chloride AEGL-3 values divided by a molar adjustment factor of 4 adopted as AEGL-3 values for silicon tetrachloride (NRC, 2004)**

***mg/m^3 values corrected in overhead**

TABLE 2. Extant Standards and Guidelines for Silicon Tetrachloride					
Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.45 ppm	0.45 ppm	0.45 ppm	0.45 ppm	0.45 ppm
AEGL-2	25 ppm	11 ppm	5.5 ppm	2.8 ppm	2.8 ppm
AEGL-3	160 ppm	53 ppm	25 ppm	6.5 ppm	6.5 ppm
ERPG-1 (AIHA)			0.75 ppm		
ERPG-2 (AIHA)			5 ppm		
ERPG-3 (AIHA)			37 ppm		
WEEL (AIHA)		1.25 ppm			

The ERPG values were derived by dividing the hydrogen chloride ERPG values by 4.

The WEEL was derived by dividing the hydrogen chloride WEEL by 4.


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

HYDROGEN CHLORIDE AEGL-1 VALUES				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
1.8 ppm	**1.8 ppm**	**1.8 ppm**	**1.8 ppm**	**1.8 ppm**
Key Reference: Stevens, B. et al. 1992. Respiratory effects from the inhalation of hydrogen chloride in young adult asthmatics. JOM. 34: 923-929.				
Test Species/Strain/Number: Human/adult asthmatics/10				
Exposure Route/Concentrations/Durations: inhalation at 0, 0.8, or 1.8 ppm for 45 minutes while exercising: (1.8 ppm was determinant for AEGL-1)				
Effects: No treatment-related effects were observed in any of the individuals tested.				
Endpoint/Concentration/Rationale: The highest concentration tested was a no-effect-level for irritation in a sensitive human population (10 asthmatic individuals tested) and was selected as the basis of AEGL-1. Effects assessed included sore throat, nasal discharge, cough, chest pain or burning, dyspnea, wheezing, fatigue, headache, unusual taste or smell, total respiratory resistance, thoracic gas volume at functional residual capacity, forced expiratory volume, and forced vital capacity. All subjects continued the requisite exercise routine for the duration of the test period.				
Uncertainty Factors/Rationale: Interspecies: 1, test subjects were human; Intraspecies: 1, test subjects were sensitive population (exercising asthmatics)				
Modifying Factor: Not applicable				
Animal to Human Dosimetric Adjustment: Insufficient data				
Time Scaling: The AEGL-1 values for a sensory irritant were held constant across time because it is a threshold effect and prolonged exposure will not result in an enhanced effect. In fact one may become desensitized to the respiratory tract irritant over time. Also, this approach was considered valid since the endpoint (no treatment-related effects at the highest concentration tested in exercising asthmatics) is inherently conservative.				
Data quality and research needs: The key study was well conducted in a sensitive human population and is based on no treatment-related effects. Additionally, the direct-acting irritation response is not expected to vary greatly among individuals. Therefore, confidence in the AEGL values derived is high.				

HYDROGEN CHLORIDE AEGL-2 VALUES				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
100 ppm	**43 ppm**	**22 ppm**	**11 ppm**	**11 ppm**

Key References: Stavert et al. 1991. Relative acute toxicities of hydrogen chloride, hydrogen fluoride, and hydrogen bromide in nose- and pseudo-mouth-breathing rats. Fundam. Appl. Toxicol. 16: 636-655. (30-min, 1-, 4-, and 8-hr)

Barrow, C.S., Alarie, Y., Warrick, M., and Stock, M.F. 1977. Comparison of the sensory irritation response in mice to chlorine and hydrogen chloride. Arch. Environ. Health. 32:68-76. (10-min)

Test Species/Strain/Number: F344 rats/ 8 males/concentration (30-min, 1-, 4-, and 8-hr); Male Swiss Webster mice (10-min)

Exposure Route/Concentrations/Durations: Inhalation: 0, or 1300 ppm/30 minutes (1300 ppm was determinant for 30-min, 1-, 4-, and 8-hr AEGL-2)

Effects (30-min, 1-, 4-, and 8-hr):
0 ppm: no effects
1300 ppm: Nose breathers: severe necrotizing rhinitis, turbinate necrosis, thrombosis of nasal submucosa vessels
1300 ppm: Mouth breathers: severe ulcerative tracheitis accompanied by necrosis and luminal ulceration (determinant for AEGL-2)
RD50 = 309 ppm (determinant for 10-min AEGL-2)

Endpoint/Concentration/Rationale: 1300 ppm for 30 min; severe lung effects (ulcerative tracheitis accompanied by necrosis and luminal ulceration) or nasal effects (necrotizing rhinitis, turbinate necrosis, thrombosis of nasal submucosa vessels histopathology) in pseudo-mouth breathing male F344 rats. (30-min, 1-, 4-, and 8-hr); RD50 of 309 ppm ÷ 3 to estimate irritation (10-min)

Uncertainty Factors/Rationale (30-min, 1-, 4-, and 8-hr):
Total uncertainty factor: 10
Intraspecies: 3- steep concentration-response curve implies limited individual variability
Interspecies: 3- The use of an intraspecies uncertainty factor of 10 would bring the total uncertainty/modifying factor to 100 instead of 30. This would generate AEGL-2 values which are not supported by data on exercising asthmatics; an especially sensitive subpopulation because exercise increases hydrogen chloride uptake and exacerbates irritation; no effects were noted in exercising young adult asthmatics exposed to 1.8 ppm HCl for 45 minutes (Stevens et al., 1992). Using a total UF of 30 would yield 4- and 8-hr values of 3.6 ppm (instead of 11 ppm). It is not supportable to predict that humans would be disabled by exposure for 4- or 8- hours to 3.6 ppm of hydrogen chloride when exercising asthmatics exposed to one-half this level for 45 minutes had no effects. The shorter time points would yield values 4- to 7-fold above 1.8 ppm; however, the confidence in the time scaling for hydrogen chloride is good for times up to 100-min because the value of 'n' was derived from a regression analysis of rat and mouse mortality data with exposure durations ranging from 1 to 100 minutes. The 30 minute value of 43 ppm derived with the total UF of 10 is reasonable in light of the fact that baboons exposed to 500 ppm for 15 minutes experienced only a slightly increased respiratory rate.

Modifying Factor (30-min, 1-, 4-, and 8-hr): 3- based on sparse database for AEGL-2 effects and the fact that the effects observed at the concentration used as the basis for AEGL-2 were somewhat severe
(10-min) : The 10-minute AEGL-2 value was derived by dividing the mouse RD_{50} of 309 ppm by a factor of 3 to obtain a concentration causing irritation (Barrow et al., 1977). One-third of the mouse RD_{50} for hydrogen chloride corresponds to an approximate decrease in respiratory rate of 30%, and decreases in the range of 20 to 50% correspond to moderate irritation (ASTM, 1991).

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^n \times t = k$ where $n = 1$: based on regression analysis of combined rat and mouse LC_{50} data (1 min. to 100 min.) reported by ten Berge et al., 1986. Data point used to derive AEGL-2 was 30 minutes. AEGL-2 values for 1-hr exposure period was based on extrapolation from the 30 minute value. The 4- and 8-hour AEGL-2 values were derived by applying a modifying factor of 2 to the 1-hr AEGL-2 value because time scaling would yield a 4-hour AEGL-2 value of 5.4 ppm and an 8-hour AEGL-2 of 2.7 ppm, close to the 1.8 ppm tolerated by exercising asthmatics without adverse health effects.

HYDROGEN CHLORIDE AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
620 ppm	210 ppm	100 ppm	26 ppm	26 ppm

Key Reference: Vernot, E.H., MacEwen, J.D., Haun, C.C., Kinkead, E.R. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42: 417-423.; Wohlslagel, J., DiPasquale, L..C., Vernot, E.H. 1976. Toxicity of solid rocket motor exhaust: effects of HCl, HF, and alumina on rodents. J. Combustion Toxicol. 3: 61-70.

Test Species/Strain/Sex/Number: Sprague-Dawley rats, 10 males per concentration

Exposure Route/Concentrations/Durations: Inhalation at 0, 1813, 2585, 3274, 3941, or 4455 ppm for 1 hr

Effects:

Concentration	Mortality
0 ppm	0/10
1813 ppm	0/10
2585 ppm	2/10
3274 ppm	6/10
3941 ppm	8/10
4455 ppm	10/10

LC_{50}: reported as 3124 ppm (determinant for AEGL-3)

Endpoint/Concentration/Rationale: 1/3 of the 1-hr LC_{50} (3124 x 1/3 = 1041 ppm) to estimate a concentration causing no deaths.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Intraspecies: 3- steep concentration-response curve implies limited individual variability
Interspecies: 3- **1)** The steep concentration-response curve for lethality observed in the Wohlslagel et al. (1976) study in which 1041 ppm (1/3 of the LC_{50} of 3124 ppm) was lower than the LC_0 of 1813 ppm. This is a conservative selection of the LC_0 and the steep concentration-response curve argues for little inter-individual variability; **2)** AEGL-3 values generated from a total uncertainty factor of 30 would be close to the AEGL-2 values (within a factor of 2) generated above which are reasonable when compared with data on exercising asthmatics; **3)** Sellakumar et al. (1985) exposed rats to 10 ppm of hydrogen chloride for 6 hours a day, 5 days a week for life and only observed increased trachael and laryngeal hyperplasia. The 360 minute AEGL-3 using an intraspecies uncertainty factor of 3 is 17 ppm, close to the level used in the lifetime study in which only mild effects were induced; **4)** Rats exposed to 50 ppm of hydrogen chloride for 6 hours per day, 5 days a week for 90 days (Toxigenics, 1984) exhibited mild rhinitis. This level is already 2-fold above the AEGL-3 value for death. Thus, the total uncertainty factor is 10. It was then time-scaled to the specified 10- and 30-minute and 4-hr AEGL exposure periods using the $c^n \times t = k$ relationship, where n=1 based on regression analysis of combined rat and mouse LC_{50} data (1 min. to 100 min.) as reported by ten Berge et al., 1986. The 4-hour AEGL-3 value was also adopted as the 8-hour AEGL-3 value because of the added uncertainty of time scaling to 8-hours utilizing a value of 'n' derived for exposure durations up to 100 minutes and because the value derived from extrapolation is inconsistent with the total database.

Modifying Factor: Not applicable

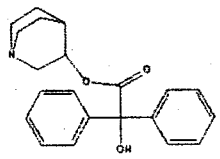
Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^n \times t = k$ where n = 1, based on regression analysis of rat and mouse mortality data (1 min. to 100 min.) reported by ten Berge et al., 1986. Reported 1-hour data point was used to derive AEGL-3 values. AEGL-3 values for 10-min, 30-min, and 4-hr were based on extrapolation from the 1-hour value. The 4-hr value was adopted as the 8-hr value.

Data quality and research needs: Study is considered appropriate for AEGL-3 derivation since exposures are over a wide range of HCl concentrations and utilize a sufficient number of animals. Data were insufficient to derive a no-effect-level for death. One-third of the LC_{50} has been utilized previously for chemicals with steep concentration-response curves. Also, in the key study, no deaths were observed in rats exposed to 1813 ppm.

ATTACHMENT 10

Agent BZ (3-quinuclidinyl benzilate)
(CAS Reg. No. 6581-06-2)



NAC/AEGL-43
Rotterdam, Netherlands
June 20-22, 2007

ORNL Staff Scientist: Robert A. Young
Chemical Manager: Glenn Leach
Chemical Reviewer: Richard Niemeier
Chemical Reviewer: George Woodall

Agent BZ

- Chewing on white lab coat thinking it is bread
- Shooting "enemy combatants" with a broom and dust pan
- Riding away on an imaginary horse
- Investigated for possible military use

Agent BZ

- **Quinuclidinyl benzilate (QNB); agent buzz**
- **"incapacitating agent"**
  - **actions are essentially opposite of OP nerve agents**
  - **muscarinic receptor blocker**
  - **all effects (except death) are reversible**
- **anticholinesterases are effective antidotes**
  - **physostigmine, scopolamine**
  - ☺ **VX, G agents** ☺

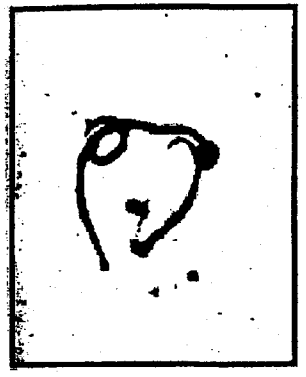
Agent BZ
Human Exposure

- **Data limited to military studies**
  - **informed male volunteers**
  - **most studies were parenteral administration**
  - **inhalation studies used aerosol exposure**

- **Effects based on performance & physiological criteria**
  - **Total Response Index**
    - **TRI = 4; mild**
    - **TRI = 5; moderate**
    - **TRI = 6; severe**
    - **TRI = 7; maximal**

Agent BZ
Human Effects Data

D.A.M. pre-test



D.A.M. at 5 hrs

D.A.M. (Draw-a-man) task for assessing effects of BZ on informed volunteers

(From Ketchum, 2006)

Agent BZ
Human Effects Data

- **Aerosol exposure studies (Ketchum, 1963)**

Probit analysis for response criteria for inhalation exposure to BZ			
Response criteria (TRI score)	Sample size	ED_{50} (mg-min/m^3)	95% conf. Limits (mg-min/m^3)
4.0	36	90.5	66.2-123.6
5.0	36	124.8	102.8-151.5
6.0	36	134.8	110.3-164.7
7.0	36	183.1	132.9-252.0

Ketchum, 1963

- **Project DORK – BZ aerosols (Ketchum et al, 1967)**
  - **ICt_{50} 60.1 mg-min/m^3 (41.3 – 87.5 mg-min/m^3; 95% c.i.)**

- **Based on overall assessments of all studies, Ketchum, (2006) stated that a dose of 0.5 mg BZ would incapacitate an normal size adult.**

Agent BZ
Animal Lethality Data

Lethality of BZ in Laboratory Animals Exposed by Inhalation			
Species	**LCt_{50} (mg-min/m^3)**	**Exposure Duration (min)**	**Reference**
Monkey	37,000	6 – 25	DoA, 1974
Dog	25,000	6 – 16	DoA, 1974
Rat	64,000	5 – 30	DoA, 1974
Mouse	12,000	5 – 19	DoA, 1974
Rabbit	32,000	15 – 40	DoA, 1974
Guinea pig	123,000	5 – 30	DoA, 1974

Agent BZ
Nonlethal Effects in Animals

Monkeys

Exposure ($mg\text{-}min/m^3$)	Exposure duration	Exposure distance (yds)	Effects
575	6 min, 10 sec	100	Mydriasis, cycloplegia, tranquility, erratic behavior, lethargy, hyperactivity, sedation, ataxia
ND		500	Mydriasis, cycloplegia
ND		1,000	Mydriasis, cycloplegia
164	8 min	100	Mydriasis, cycloplegia
70		300	Mydriasis, cycloplegia
40		500	No effects

Agent BZ
Nonlethal Effects in Animals

Dogs

Exposure ($mg\text{-}min/m^3$)	Exposure duration	Exposure distance (yds)	Effects
575	6 min, 10 sec	100	Mydriasis, cycloplegia, tranquility, erratic behavior, lethargy, hyperactivity, sedation, ataxia, incr. heart rate
ND		500	Mydriasis, cycloplegia, tranquility, erratic behavior, lethargy, hyperactivity, sedation, ataxia, incr. heart rate
ND		1,000	Mydriasis, cycloplegia, incr. heart rate
164	8 min	100	Mydriasis, cycloplegia, tranquility, erratic behavior, lethargy, hyperactivity, sedation, ataxia, incr. heart rate, apprehension
70		300	Mydriasis, cycloplegia, ataxia, lethargy, hyperactivity, incr. heart rate
40		500	No effects

Agent BZ
Nonlethal Effects in Animals

Rabbits

Exposure ($mg\text{-}min/m^3$)	Exposure duration	Exposure distance (yds)	Effects
575	6 min, 10 sec	100	Mydriasis, cycloplegia
ND		500	Mydriasis, cycloplegia, salivation
ND		1,000	Mydriasis, cycloplegia
164		100	Mydriasis, cycloplegia, respiratory distress, ataxia,
70	8 min	300	Mydriasis, cycloplegia, hyperpnea, ataxia
40		500	Mydriasis, cycloplegia

Agent BZ
Nonlethal Effects in Animals

- mydriasis and cycloplegia consistently observed in all species
- ataxia, lethargy, hyperactivity, also observed to varying extents
- effects most pronounced at 4-8 hrs post exposure; resolved within 24-48 hrs
- RCt_{50} of 10-50 mg-min/m^3 for mydriasis in rabbits (McNamara, 1963)
- rats exposed similarly to monkeys, dogs, and rabbits exhibited dyspnea (4/20) and ataxia (1/20)
- overt physiological responses not indicative of cognitive/behavioral effects

AEGL-1 Values for Agent BZ					
Classification	**10-min**	**30-min**	**1-h**	**4-hr**	**8-hr**
AEGL-1	**NR**	**NR**	**NR**	**NR**	**NR**

NR: not recommended due to insufficient data; absence of AEGL-1 values does not imply that exposure to concentrations less than the AEGL-2 values is without effect.

- **Although exposures resulting in no apparent effects in animals were reported, these experiments could not assess possible cognitive and behavioral effects characteristic of BZ which would be relevant to the human exposure situation**

AEGL-2 Values for Agent BZ (mg/m^3)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	0.67	0.22	0.11	0.028	0.014

Key Study: Ketchum et al., 1967.

Critical effect: **POD of 20 mg-min/m^3 (one-third of the ICt_{50} of 60.1 mg-min/m^3 (C.I.: 41.3-87.5 mg-min/m^3). One third of the ICt_{50} (a concentration-time product causing incapacitation of 50% of the test subjects) of 60.1 mg-min/m^3 (C.I.: 41.3-87.5 mg-min/m^3) estimated as threshold for incapacitation of humans. This is below the lower confidence limit of the ICt_{50}. Exposure to the AEGL-2 concentrations result in a total dose equivalent to the estimated no-effect range of 0.5-1.0 µg/kg for BZ (NRC, 1982).**

Time scaling: **a linear relationship; $C^n \times t = k$ where $n = 1$.**

Uncertainty factors: **Total uncertainty factor adjustment was 3**

Interspecies: 1; AEGL-2 values were derived using data from controlled exposures of informed, screened, human volunteers.

Intraspecies: 3; Although cognitive and behavioral responses varied qualitatively, the anticholinergic mechanism by which BZ operates is not likely to vary by an order of magnitude. The 3-fold adjustment is appropriate for dosimetric variability. Total dose received from AEGL-2 exposures is within the estimated no-effect range of 0.5-1.0µg/kg for BZ estimated by the NRC (1982).

AEGL-3 Values for Agent BZ (mg/m^3)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	12	4.1	2.1	0.51	0.26

Key Study: DoA, 1974.

Critical effect: **Lethality threshold estimated as one tenth of the LCt_{50} of 37,000 mg-min/m^3 for monkeys exposed to BZ for 6-25 minutes.**

Time scaling: **a linear relationship; $C^n \times t = k$ where $n = 1$.**

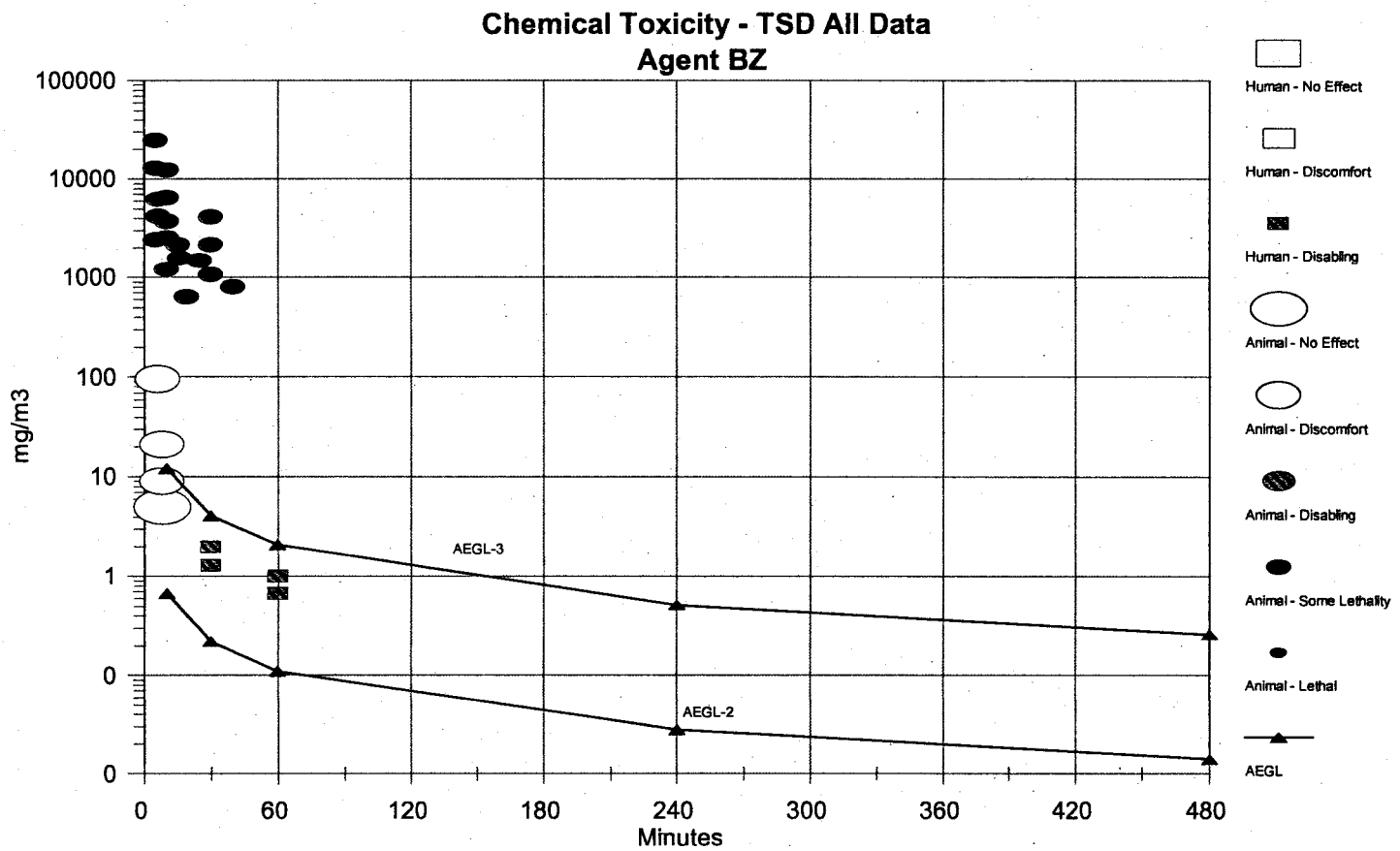
Uncertainty factors: **Total uncertainty factor adjustment was 30**

Interspecies: 10; **no lethality data are available for humans and LCt_{50} values for five animal species varied 10-fold.**

Intraspecies: 3; **Although cognitive and behavioral responses varied qualitatively, the anticholinergic mechanism by which BZ operates is not likely to vary by an order of magnitude. The 3-fold adjustment is appropriate for dosimetric variability. Further, the total dose received upon exposure to AEGL-3 values over AEGL-specific durations is equivalent to one-tenth of the human LD_{50} of 0.2 mg/kg (0.2 mg/kg ÷ 10 = 0.02 mg/kg) estimated by analogy to similarly acting atropine (Ketchum, 1964).**

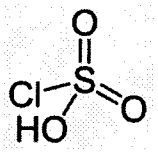
AEGL Values for Agent BZ (mg/m^3)					
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.67	0.22	0.11	0.028	0.014
AEGL-3 (Lethality)	12	4.1	2.1	0.51	0.26

NR: not recommended due to data deficiencies; absence of AEGL-1 values does not imply that exposure to concentrations less than the AEGL-2 values is without effect



Note: Response data for BZ were routinely expressed as a Ct product (concentration x time) of mg-min/m^3. Data points are derived for the lowest and highest exposure durations upon which the Ct values were determined as well as AEGL-specific durations (e.g., 10 minutes or 30 minutes) within or near the respective range of the experimental exposure duration.

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) for CHLOROSULFONIC ACID (CSA)



NAC/AEGL meeting on June 20-22, 2007

ORNL Staff Scientist: Sylvia Milanez
Chemical Manager: Susan Ripple
Chemical Reviewers: Henry Anderson Alan Becker

INTRODUCTION

- Chlorosulfonic acid (CSA), also commonly called chlorosulfuric acid, is highly reactive, corrosive, hygroscopic, and has a pungent odor (unknown threshold).
- It is a high-production volume liquid used in the synthesis of detergents, dyes, pharmaceuticals, and sulfate surfactants.
- CSA fumes upon contact with air and forms a mixture of gas and aerosol. CSA reacts with air vapor to form mists of HCl and H_2SO_4. Some studies saw condensate on the chamber walls and/or mists in the chamber air.
- CSA decomposes exothermically in water to form equimolar quantities of HCl and H_2SO_4, using a mole of water (dehydrating agent).

$$\mathbf{H_1SO_3Cl + H_2O \rightarrow H_2SO_4 + HCl} \text{ (+ heat)}$$

- Dose-response was inconsistent in animal studies. Possibly due to difficulty of achieving target CSA aerosol concentrations, which depended on the chamber humidity and temperature.
- CSA is severely irritating to the mucous membranes of the eyes, skin, and respiratory passages, and also causes CNS effects. Lethal doses caused lesions of the trachea, lungs, liver, kidneys, myocardium, spleen, brain, and thymus.

SPECIAL CONSIDERATIONS

Metabolism and Disposition: No studies. CSA hydrolyzes instantly in water (vapor or liquid) to form HCl and H_2SO_4 *in situ*, releasing heat and removing water. Presence of systemic effects indicates extensive absorption and distribution.

Mechanism of Toxicity: No studies. Unknown how much hydrolysis products contribute to CSA toxicity; each is acidic and corrosive to tissues. Mechanism by which CSA is toxic to non-respiratory organs is unknown (e.g. CNS effects).

Species Variability: Unclear. Mice may be more sensitive than rats: rat 4-hr LC_{50}=38.5 mg/m^3; mouse 2-hr LC_{50}=25 mg/m^3 (Mamleeva and Bakhtizina 76).

Susceptible Populations: None identified.

Structure-Activity Relationships: CSA is structurally similar to H_2SO_4, where a Cl replaces an H atom. Because H_2SO_4 is more toxic than HCl, only H_2SO_4 was considered for AEGL-1 and AEGL-2 derivation. CSA is more toxic than H_2SO_4.

Level	H_2SO_4 Interim Values (mg/m^3)					
	10 min	30 min	1 hr	4 hr	8 hr	UF (ter/tra), n
AEGL-1	0.2	0.2	0.2	0.2	0.2	1 x 1; no scaling
AEGL-2	8.7	8.7	8.7	8.7	8.7	1 x 3; no scaling
AEGL-3	260	200	160	110	93	1 x 3; n ~3.3

Level	HCl Final Values (mg/m^3)					
	10 min	30 min	1 hr	4 hr	8 hr	UF(ter/tra), n
AEGL-1	2.7	2.7	2.7	2.7	2.7	1 x 1; no scaling
AEGL-2	156	65	33	17	17	3 x 3, MF 3; n=1
AEGL-3	937	313	155	39	39	3 x 3, n=1

CSA TOXICITY DATA

- **No human studies.** Severe irritation of the eyes and respiratory tract, coughing, and choking have been attributed to CSA vapor.

CSA Animal Data

Species	time	Aerosol conc. (mg/m^3)	Effect	Reference
Rat (M, F)	4 hr	1765 2768 5864	Apnea, rales, gasping, red-stained muzzles and eyes, ataxia or prostration; 14-day mortality was 8/20, 13/20, and 9/20.	Hagan and Fisher 1987
Rat (sex ?)	4 hr	??	LC_{50} =38.5 mg/m^3; Eye irritation, shaky gait, convulsions, lesions of resp. tract, brain, myocardium, liver, bile duct, kidneys	Mamleeva and Bakhtizina 1976
Rat (M, F)	1 hr (M-F concs)	102-61 [70] 285-289 [282]	No effects noted No effects noted	Katz 1987
		379-735 [563]	Drooling, unkempt fur, wheezing 24-48 hr	
		1777-1539[1500] 2638-2091[2250] 3096-2743[3400]	**All died but one F at 1500**; as ↑, gasping, nasal discharge, lacrimation, abnormal gait, lesions of resp. tract, spleen, thymus, liver	
Rat (M)	1 hr	700*	3/4 died; drooling; pulmonary dysfunction	Gordon 1987
		1002*, 1266*	4/4 (each conc.) died; as ↑ and gasping	
Mouse (sex ?)	2 hr	??	LC_{50} =25 mg/m^3; Eye and respiratory tract irritation, shaky gait, convulsions	Mamleeva &Bak.1976

* Rats were **anesthetized and intubated** for pulmonary function analysis before and after exposure.

Derivation of AEGL-3

Key study: Katz (1987). POD was $BMCL_{05}$ of 598 mg/m^3 for M + F (BenchMark dose v. 1.3.2). Males: 265 mg/m^3 (too low); Females: 537 mg/m^3

Toxicity endpoint: Lethality threshold in rats

Scaling: $C^n \times t = k$ (ten Berge et al. 1986), using default values of n=3 to extrapolate to <1 hour, and n=1 to extrapolate to > 1 hour (no data to derive n).

Uncertainty Factors: Total uncertainty factor: 30
Interspecies: 10: Sufficient studies were not available to determine species variability, and there were inconsistencies among the animal studies.
Intraspecies: 3: Lethality dose-response was very steep, suggesting human variability is small.

Modifying Factor: None

TABLE 1. AEGL-3 Values for Chlorosulfonic Acid

10-min	30-min	1-hr	4-hr	8-hr
36 mg/m^3	25 mg/m^3	20 mg/m^3	5.0 mg/m^3	2.5 mg/m^3

Derivation of AEGL-2

Two approaches considered:
1. Base on human experimental H_2SO_4 study, by structure-activity analogy
2. Base on Katz (1987) rat CSA study with large UF/MF (contrasts TSD)

APPROACH 1

- Only H_2SO_4 study with near-AEGL-2 effects was **Linn et al. (1989)**. Healthy and asthmatic volunteers were exposed for **60 minutes to ~2 mg/m^3** H_2SO_4 aerosol (diameters 1, 10, or 20 μm). During exposure, had alternating 10-minute periods of exercise (ventilation rate of 40-45 mL/hour) and rest.
- The subjects gargled with grapefruit juice just prior to exposure to deplete oral ammonia. Asthmatics withheld their use of antihistamines and bronchodilators at least 12 hours before exposure. Exposure room was 10°C (50°F).
- Healthy subjects had irritation from only the 10 and 20 μm particles: coughing, burning in the nose, throat and chest for < one day. No effects on lung function.
- Asthmatics had wheezing, chest tightness, substernal discomfort, coughing, and throat irritation (all particles). Airway resistance was increased (251-255% of pre-exposure vs. 157-206% in controls) and FEV_1 decreased (21-24% vs. 14-19% in controls), prompting 4/19 to stop exercise or withdraw.
- Lung function deteriorated with exposure time in asthmatics (10 vs. 60 minutes), and subjects with more severe asthma had more severe responses.

Thus, although this appeared to be a "worst case scenario" and 4 subjects who withdrew had effects below the AEGL-2*** the data suggest CSA is more toxic than H_2SO_4 and thus 2 ppm may cause more severe, disabling effects (impeding escape) after 60 minutes

***Reason NAC rejected use of study as basis for AEGL-2 of H_2SO_4

Comparison of the 1 and 4-hour mortality of CSA and H_2SO_4

Chem	Exposure concentration [mg/m^3] (Mortality)								Reference
1-hour RAT									
H_2SO_4	240 (0/8)	470 (1/8)	730 (1/8)	800 (0/8)	1090 (0/8)				Runkle/Han 76
							3540 (5/10)	3940 (9/10)	Zwart 1984
CSA: M	285 (0/5)	379 (0/5)				1777 (5/5)	2638 (5/5)	3096 (5/5)	Katz 1987
CSA: F	289 (0/5)		735 (0/5)			1539 (4/5)	2091 (5/5)	2743 (5/5)	
1-hour MOUSE									
H_2SO_4	270 (0/10)	550 (0/10)	730 (3/10)		1040 (4/12)				Runkle/Han 76
4-hour RAT									
H_2SO_4	240 (0/8)	470 (5/8)	730 (5/8)	800 (6/8)	1080 (7/8)	1090 (5/8)			Runkle/Han 76
		549 (0/2)	718 (0/2)			1470 (2/2)			Treon et al. 50
CSA						1765 (8/20)	2768 (13/20)	5864 (9/20)	Hagan/Fish 87
4-hour MOUSE									
H_2SO_4	270 (1/10)	550 (2/10)	730 (3/10)		1040 (11/14)				Runkle/Han 76
		549 (2/5)	718 (3/5)			1470 (2/5)			Treon et al. 50

Comparison of CSA and H_2SO_4 mortality data

Chem	Exposure concentration [mg/m^3] (Mortality)								time
RAT – Katz (1987) data									
CSA: M	285 (0/5)	379 (0/5)				1777 (5/5)	2638 (5/5)	3096 (5/5)	1 hour
CSA: F	289 (0/5)		735 (0/5)			1539 (4/5)	2091 (5/5)	2743 (5/5)	
MOUSE – Runkle and Hahn (1976) data									
H_2SO_4	270 (0/10)	550 (0/10)	730 (3/10)		1040 (4-5/12)				1 hour
	240 (0/8)	470 (5/8)	730 (5/8)	800 (6/8)	1080/90 (5-7/8)				2 hour
	270 (0-1/10)	550 (2/10)	730 (3/10)		1040 (11/14)				4 hour
	270 (0/10)	550 (4/10)	730 (7/10)						8 hour

1-hr exp.	Rats (CSA)	Mice (H_2SO_4)	Rats (H_2SO_4)
BMC_{01}	1290 (M,F); 642 (M)	491 (319-613)	430 (252-595)
BMC_{50}	1469 (M,F); 808 (M)	1213 (1023-1546)	1789 (1304-2965)
BMC_{99}	**1671 (M,F); 1017 (M)**	**3457 (2392-7169)**	**7450 (4087-24370)**
	n = ?? (no data)	n = 3.2	n = 1.3 (poor dose-response)

Derivation of AEGL-2, (Approach 1, cont'd)

Key study: Linn et al. (1989). The POD was exposure to 2.03 mg/m^3 for 60 min.

Toxicity endpoint: Threshold for severe respiratory irritation and impaired pulmonary function sufficient to impede the ability to escape, by analogy to H_2SO_4 data

Scaling: $C^n \times t = k$ (ten Berge et al. 1986), using default n=3 and n=1. The 4-hr value was adopted for 8 hrs because the human H_2SO_4 data suggested that the scaled value of 0.25 ppm would cause only mild respiratory and eye irritation.

Uncertainty Factors: Total uncertainty factor: 1
Interspecies: Not applicable
Intraspecies: 1: A sensitive human population was tested (exercising asthmatics)

Modifying Factor: None; the AEGL-2 POD was very mild (below AEGL-2 severity).

AEGL-2 Values for Chlorosulfonic Acid : Human H_2SO_4 data				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
3.7 mg/m^3	2.6 mg/m^3	2.0 mg/m^3	0.51 mg/m^3	0.51 mg/m^3

Derivation of AEGL-2

APPROACH 2

Key study: Katz (1987). POD was exposure of rats for 60 minutes to 287 mg/m^3 CSA.

Toxicity endpoint: NOAEL for impaired pulmonary function and neurotoxicity.

Scaling: $C^n \times t = k$ (ten Berge et al. 1986), using default n=3 and n=1.

Uncertainty Factors: Total uncertainty factor: 30
Interspecies: 10: Sufficient studies were not available to determine species variability, and there were inconsistencies among the animal studies.
Intraspecies: 3: Lethality dose-response was very steep, suggesting human variability is small.

Modifying Factor: 3: Small database

AEGL-2 Values for Chlorosulfonic Acid : Rat CSA data (NEW NUMBERS)				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
5.2 mg/m^3	3.6 mg/m^3	2.9 mg/m^3	0.72 mg/m^3	0.36 mg/m^3

AEGL-2 Values for Chlorosulfonic Acid : Human H_2SO_4 data				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
3.7 mg/m^3	2.6 mg/m^3	2.0 mg/m^3	0.51 mg/m^3	0.51 mg/m^3

Derivation of AEGL-1

Two approaches considered:

1. Base on human experimental H_2SO_4 study, by structure-activity analogy

2. Do not derive AEGL-1 values due to lack of data

- No relevant human or animal CSA studies were located.
- Horvath et al. (1982) H_2SO_4 exposed healthy, intermittently exercising volunteers for 2 hrs to 0.233, 0.418, or 0.939 mg/m^3 H_2SO_4 aerosol (~1 μM).
- At 0.939 mg/m^3, had slightly ↓ FEV_1 and "throat irritation or dryness and cough were frequently noted." This is NOTABLE discomfort, >AEGL-1
- The point of departure (POD) for the AEGL-1 was 0.233 mg/m^3, which caused symptoms of respiratory irritation characterized as mild discomfort.

HUMAN EXPOSURE TO SULFURIC ACID AEROSOL 129

TABLE 5

NUMBER OF SUBJECTS REPORTING SYMPTOMS CONSEQUENT TO EXPOSURE

		Pollutant level (μg/m³ SO_4)		
	Filtered air	223	418	939
Unusual odor or taste	0	7	3	6
Sore throat, irritation, dryness	1	3	5	8
Cough	0	2	5	8
Shortness of breath, chest tightness	0	3	3	3
Dizziness, fatigue, or headache	6	4	2	6
Eye irritation	0	1	1	2
No symptoms	4	2	2	0

Derivation of AEGL-1 (cont'd)

- Toxicity endpoint: Mild eye and respiratory irritation, by analogy to H_2SO_4 data
- Scaling: None: The same AEGL-1 value was used for 10 min - 8 hrs because mild eye and respiratory irritation is not expected to vary significantly over time (key study exposure was 2 hrs).
- Uncertainty Factors: Total uncertainty factor: 1
  Interspecies: Not applicable
  Intraspecies: 1: Although a sensitive population was not tested, the POD was very mild, as the data indicated that higher concentrations may be tolerated without notable discomfort.
- Modifying Factor: 2: CSA is ~2-fold more toxic than H_2SO_4, based on animal acute toxicity data and chemistry (CSA hydrolysis).

TABLE 2. AEGL-1 Values for Chlorosulfonic Acid

10-min	30-min	1-hr	4-hr	8-hr
0.11 mg/m^3	0.11 mg/m^3	0.11 mg/m^3	0.11 mg/m^3	0.11 mg/m^3

Summary of AEGL Values for Chlorosulfonic Acid						
Classific	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1 (Non-disabling)	0.11 mg/m^3	0.11 mg/m^3	0.11 mg/m^3	0.11 mg/m^3	0.11 mg/m^3	Mild respiratory and eye irritation in humans, based on H_2SO_4 data (Horvath et al. 1982)
AEGL-2 (Disabling)	3.7 mg/m^3	2.6 mg/m^3	2.0 mg/m^3	0.51 mg/m^3	0.51 mg/m^3	Threshold for severe respir. irritation, impaired pulmonary function sufficient to impede the ability to escape, based on H_2SO_4 data (Linn et al. 1989)
AEGL-3 (Lethal)	36 mg/m^3	25 mg/m^3	20 mg/m^3	5.0 mg/m^3	2.5 mg/m^3	Lethality threshold in rats (Katz 1987)

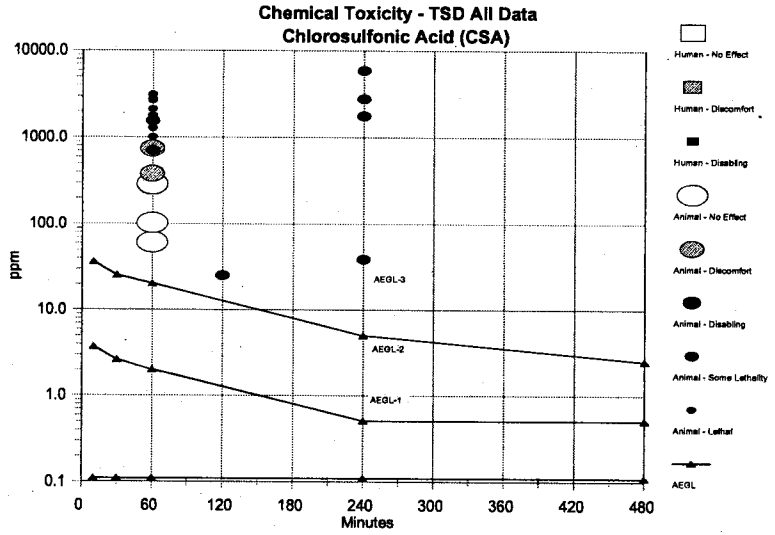
12 8.3 6.7 1.7 0.58 AEGL-3 ÷ 3

4.4 = H_2SO_4 AEGL-2 ÷ 2

AEGL-3 45 31 25 6.1 3.1

AEGL-3 ÷ 3 15 10 8.3 2.0 1.0

Category Plot for Chlorosulfonic Acid (CSA)



Note that the animal studies in which lethality occurred close to the AEGL-3 levels were considered outliers in the CSA data set and not used directly for AEGL derivation

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR METHANESULFONYL CHLORIDE

NAC/AEGL-43
June 20-22, 2007
Rotterdam, The Netherlands

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Roberta Grant

Chemical Reviewers: George Rusch and Richard Niemeier

Data Set: Very Sparse

Mortality and clinical signs in rats exposed to methanesulfonyl chloride (TerHaar, 1978)				
Concentration	**Duration**	**Mortality**	**Time to death**	**Clinical signs**
2145 ppm	45-min	3/3	1 dead in 30-min 1 dead in 40-min 1 dead in 45-min	Blinking & nose rubbing: 1-min Salivation: 4-min Dyspnea & piloerection: 5-min Lacrimation & clear nasal discharge: 10-min
29 ppm	6-hr	0/3	-	Blinking: 1-min Nose rubbing: 2-min Piloerection: 5-min Vasodilation: 15-min
132 ppm	6-hr	3/3	2 dead in 20-hr post-exposure 1 dead in 3-days post-exposure	Blinking & nose rubbing: 1-min Dyspnea & piloerection: 10-min Clear nasal discharge: 15-min Lacrimation & salivation: 25-min Wheezing: 265-min

Approximate 1-hr Rat LC_{50} value: 200 ppm (Shertzer, 2001)

Approximate 4-hr Rat LC_{50} value: 25 ppm (Shertzer, 2001)

Cannot derive values by analogy:

Methanesulfonyl chloride (CH_3ClO_2S) is structurally similar to:

Thionyl chloride (Cl_2OS)

Sulfuryl chloride (Cl_2O_2S)

Thionyl chloride and sulfuryl chloride readily hydrolyze to SO_2 and HCl

Methanesulfonyl chloride hydrolyses very slowly

Although the health effects of these three compounds are similar

Their mechanism of toxicity is likely different

With regard to animal lethality, methanesulfonyl chloride appears to be more toxic than thionyl chloride and sulfuryl chloride

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

NR: Not Recommended due to insufficient data.

AEGL-2 VALUES: METHANESULFONYL CHLORIDE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.22 ppm	0.22 ppm	0.18 ppm	0.11 ppm	0.073 ppm

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

<u>Approach justified by relatively steep concentration-response curve</u>

0% mortality in rats exposed to 29 ppm and 100% mortality at 132 ppm for 6-hr (TerHaar, 1978).

AEGL-3 VALUES: METHANESULFONYL CHLORIDE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.66 ppm	0.66 ppm	0.53 ppm	0.33 ppm	0.22 ppm

Species: Rat
Concentration: 29 ppm
Time: 6 hours
Endpoint: Concentration causing no mortality
Reference: TerHaar, 1978

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

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

Modifying Factor: 10
Sparse data base

Inconsistencies in available animal lethality data

*Unverified 4-hr rat LC_{50} value: ≈25 ppm (Shertzer, 2001)

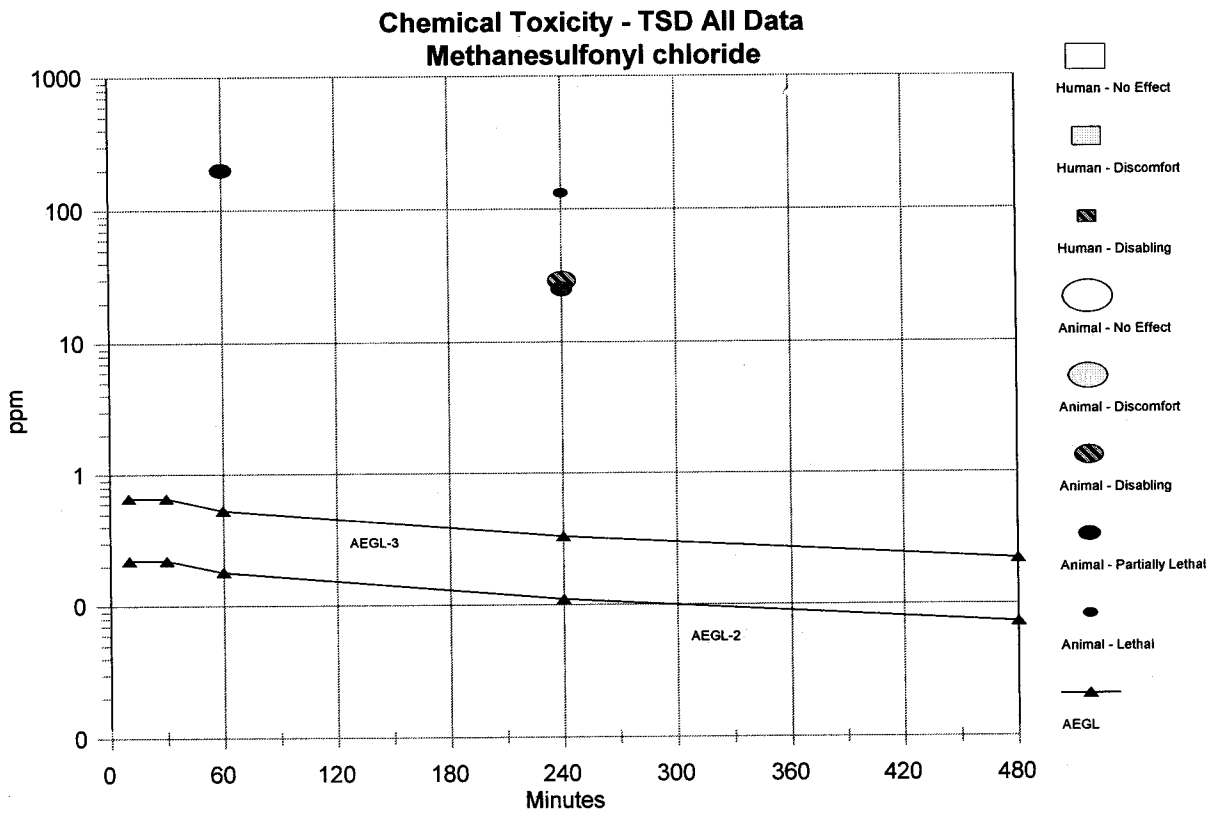
*LC_{50} value also listed in IUCLID Dataset as OECD Guideline 403/GLP study

Cited as: Pennwalt Corporation, Methanesulfonyl chloride, Acute inhalation toxicity study in rats, 4-hour exposure, Huntingdon Research Centre, Report No. PWT 45/861670, 23 Feb. 1987 as cited in ELF ATOCHEM Paris la defense

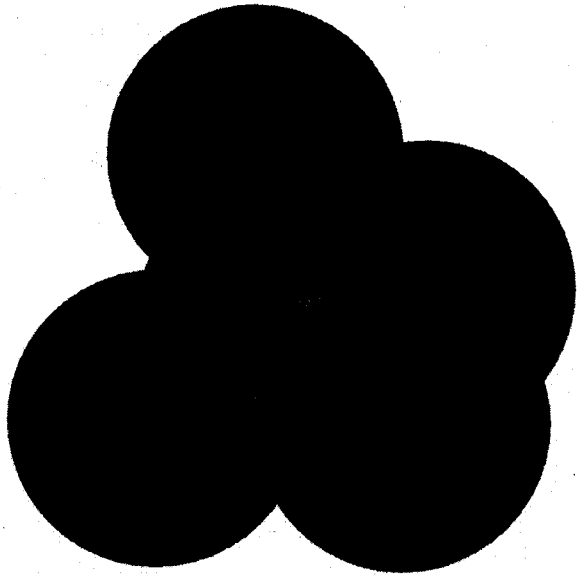
There are no other standards or guidelines for methanesulfonyl chloride

Summary of AEGL Values for Methanesulfonyl chloride						
Classification	10-mim	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1	NR	NR	NR	NR	NR	Insufficient data
AEGL-2	0.22 ppm (1.0 mg/m^3)	0.22 ppm (1.0 mg/m^3)	0.18 ppm (0.84 mg/m^3)	0.11 ppm (0.51 mg/m^3)	0.073 ppm (0.34 mg/m^3)	One third the AEGL-3 values (NRC, 2001)
AEGL-3	0.66 ppm (3.1 mg/m^3)	0.66 ppm (3.1 mg/m^3)	0.53 ppm (2.5 mg/m^3)	0.33 ppm (1.5 mg/m^3)	0.22 ppm (1.0 mg/m^3)	Concentration causing no lethality in rats (29 ppm for 6 hr) (TerHaar., 1978)

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.


Chemical Toxicity - TSD All Data
Methanesulfonyl chloride
1000
100
10
1
0
0
ppm
AEGL-3
AEGL-2
0
60
120
180
240
300
360
420
480
Minutes
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Partially Lethal
Animal - Lethal
AEGL

Osmium Tetroxide
(CAS Reg. No. 20816-12-0)



NAC/AEGL-43
Rotterdam, Netherlands
June 20-22, 2007

ORNL Staff Scientist: Robert A. Young
Chemical Manager: Dieter Heinz
Chemical Reviewer: Glenn Leach
Chemical Reviewer: Gail Chapman

Osmium tetroxide

- **Foul smelling, chlorine-like odor**
  - **0.0019 ppm odor threshold**

- **Oxidizing agent; converts olefins to glycols**

- **Commonly used fixative stain**

Osmium tetroxide
Human Toxicity

- No lethality data
- 6-hour no-effect level of 0.001 mg Os/m^3 (0.0001 ppm) (Flury and Zernick, 1931)
- Highly irritating to respiratory tract and eyes
- Effects for acute exposure may persist up to 12 hrs
- Occupational exposure (osmiridium refining)
  - 133-640 µg $osmium/m^3$ – ocular irritation, headache, visual disturbance (equivalent to 177-853 µg OsO_4/m^3 (0.02-0.08 ppm) (McLaughlin et al., 1946)

Osmium tetroxide
Animal Toxicity - Lethality

- **Rats (Shell Develop. Co., 1955)**
  - **8-hour LC_{50} estimated at 28.2 ppm**

Lethality of osmium tetroxide in male rats		
Concentration (ppm)	Exposure time (hrs)	Mortality ratio
2	8	0/5
20	8	0/5
40	8	5/5
40	4	3/5

- **Mice**
  - **4-hour LC_{50} was estimated as 28.2 ppm**

Lethality of osmium tetroxide in male mice		
Concentration (ppm)	Exposure time (hrs)	Mortality ratio
20	8	0/10
40	4	9/10

- **Rabbits**
  - **100% lethality following 30-minute exposure to an estimated concentration of 390 mg OsO_4/m^3 (37 ppm)**

Osmium tetroxide
Animal Toxicity - Nonlethal

- **Rats (Shell Development Co., 1955)**
  - **2 ppm for 8 hours**
    - **minor ocular and respiratory irritation; resolved by 10 days post exposure**
  - **20 ppm for 8 hours**
    - **moderate ocular and pulmonary irritation; persisted at 10 days post exposure (gross path)**

- **Mice (Shell Development Co., 1955)**
  - **20 ppm for 8 hours**
    - **ocular and respiratory irritation; resolved at 10 days post exposure (gross path. negative at 10 days)**

Osmium tetroxide AEGL-1

AEGL-1 Values for Osmium Tetroxide					
Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	NR	NR	NR	NR	NR

Insufficient data; occupational exposure data of McLaughlin et al. (1946) indicated effects (vision aberrations, headache, intense smarting of eyes with lacrimation) beyond AEGL-1 severity

Osmium tetroxide AEGL-2

AEGL-2 Values for Osmium Tetroxide					
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-2	**0.015 ppm** **0.16 mg/m^3**	**0.015 ppm** **0.16 mg/m^3**	**0.012 ppm** **0.12 mg/m^3**	**0.0078 ppm** **0.081 mg/m^3**	**0.0050 ppm** **0.052 mg/m^3**

Key study: McLaughlin et al. (1946)

Critical effect: intense smarting of eyes with lacrimation, headache, visual aberrations were considered a NOAEL for AEGL-2 effects

Point-of-Departure: 6-hr exposure to 0.02 ppm osmium tetroxide was lower limit of exposure for above effects.

Uncertainty factors: Interspecies: 1; human data
Intraspecies: 3; OsO_4 mode of action is via direct-contact irritation and subsequent damage to mucosal epithelial surfaces; UF of 3 applied to account for those with compromised respiratory function.

Time scaling: $C^n \times t = k$, where $n = 1$ for extrapolation to the 8-hr AEGL and $n = 3$ for extrapolation to durations < 6 hrs (default as per NRC, 2001); 10-min. AEGL-2 equivalent to 30-min. value due to uncertainties in extrapolating from the 6-hr POD

Osmium tetroxide AEGL-3

AEGL-3 Values for Osmium Tetroxide					
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-3	**4.0 ppm 42 mg/m^3**	**4.0 ppm 42 mg/m^3**	**3.2 ppm 33 mg/m^3**	**2.0 ppm 21 mg/m^3**	**1.6 ppm 17 mg/m^3**

Key study: Shell Development Co. 1955

Critical effect: lethality threshold in rats exposed for 8 hours; 10-day observation period

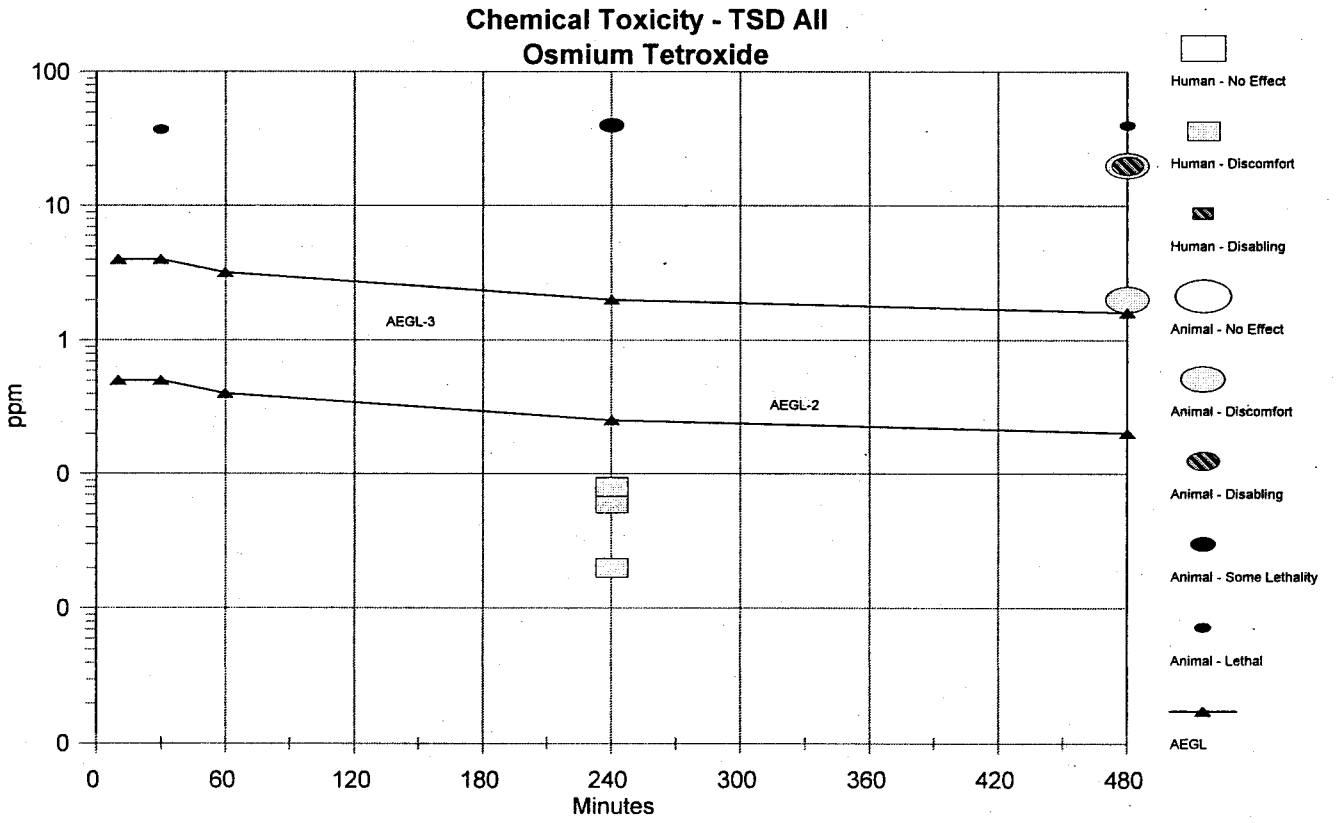
Point-of-Departure: $BMCL_{05}$ of 16 ppm for rat lethality data

Uncertainty factors: Interspecies: 3; LC_{50} values for rats and mice are the same; mode of action unlikely to vary considerably among species UF of 3 considered sufficient for dosimetric variability.
Intraspecies: 3; OsO_4 mode of action is via direct-contact irritation and subsequent damage to mucosal epithelial surfaces; UF of 3 applied to account for those with compromised respiratory function.

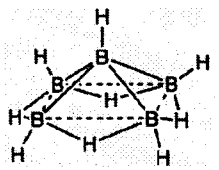
Time scaling: $C^n \times t = k$, where $n = 3$ for extrapolation to durations < 8 hrs (default as per NRC, 2001); 10-min. AEGL-3 equivalent to 30-minute value due to uncertainties in extrapolating from the 8-hr POD

AEGL Values for Osmium Tetroxide					
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1	**NR**	**NR**	**NR**	**NR**	**NR**
AEGL-2	**0.015 ppm** **0.16 mg/m^3**	**0.015 ppm** **0.16 mg/m^3**	**0.012 ppm** **0.12 mg/m^3**	**0.0078 ppm** **0.081 mg/m^3**	**0.0050 ppm** **0.052 mg/m^3**
AEGL-3 (Lethality)	**4.0 ppm** **42 mg/m^3**	**4.0 ppm** **42 mg/m^3**	**3.2 ppm** **33 mg/m^3**	**2.0 ppm** **21 mg/m^3**	**1.6 ppm** **17 mg/m^3**

NR: not recommended due to insufficient data; absence of AEGL-1 values does not imply that exposure to concentrations less than the AEGL-2 values is without effect.


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

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) for PENTABORANE (CAS# 19624-22-7)



NAC/AEGL meeting on June 20-22, 2007

ORNL Staff Scientist: Sylvia Milanez
Chemical Manager: George Woodall
Chemical Reviewers: Marc Baril Marcel van Raaij

INTRODUCTION

- Pentaborane is a flammable, colorless, liquid. Strong reducer; reacts with ammonia, organic amines, and unsaturated hydrocarbons.
- Insoluble in water, but hydrolyzes over a period of several hours to form the less toxic boric acid, hydrogen, and heat.
- Used as an experimental jet and rocket fuel, in catalysts, corrosion inhibitors, and fluxing agents. Not commercially available in significant quantities.
- Has pungent odor characterized as sweetish or smelling like sour milk. Median detectable concentration = 1 ppm (nominal; range: 0.2 ppm 5% detect; 2.0 ppm 100% detect). Olfactory fatigue noted.
- Human and animal studies have shown that the primary toxic effect of pentaborane is on the central nervous system (CNS), e.g. dizziness, drowsiness, incoordination, convulsions, etc.

SPECIAL CONSIDERATIONS

- **Metabolism and Disposition:** Not determined in humans or animals. Hydrolyzes after several hours in body-temperature water to produce the much less toxic boric acid (borane), hydrogen, and heat.

- Elimination of pentaborane/ boron appears to be slow:
  - Cumulative effects in dogs, etc. exposed repeatedly;
  - Serotonin levels decreased for week in rats;
  - Boron detected for a week in urine of workers exposed to high (undefined) levels of pentaborane.

- **Mechanism of Toxicity:** Not established. May involve decreased brain serotonin and norepinephrine levels. Appears to be similar among species; CNS is consistently the primary target organ.

- **Species Variability: Low.** CNS was target organ for all species tested: mice, rats, dogs, and monkeys. LC_{50} for 2-240 minutes varied <3-fold.

- **Susceptible Populations:** None identified

PENTABORANE - HUMAN DATA

- Occupational exposures with unknown concentrations and duration consistently showed that neurotoxicity is the primary, and most sensitive, effect, and can occur below the odor threshold.

- Symptoms included dizziness, drowsiness, headache, nervousness, restlessness, exhaustion, hiccups, cough, nausea, flushing, profuse perspiration, visual disturbances, conjunctivitis, inability to concentrate, memory loss, incoordination, muscle spasms, and convulsions.

- Less serious symptoms sometimes delayed 1-2 days.

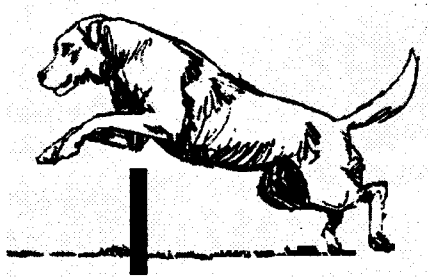
- EEG tracings revealed abnormalities, even when person experienced no symptoms. EEGs reverted to normal in most cases within weeks – months.

PENTABORANE - ANIMAL DATA

- Single and/or multiple-exposure studies were conducted using monkeys, dogs, rats, mice, hamsters, rabbits, and guinea pigs.
- Exposures were 0.5-60 minutes in 400 m^3 dynamic flow gassing chamber. **Animals inserted and removed using sliding carriage assembly**.
- CNS toxicity increased with exposure time and concentration. Signs included apprehensiveness, lethargy, aggressiveness, miosis, ataxia, drooling, tremors, and convulsions. Single-exposure deaths in 24 hr.
- Pathology examined in few animal studies:
  - Monkeys: 2 min to 37-143 ppm: no lesions (Weeks et al. 1964)
  - Rats: 4 hr to ~7 ppm had alveolar hemorrhage, edema (Feins.)
  - Mice: 4 hr to 3-6 ppm had alveolar hemorrhage, cong. (Feins.)
  - Multiple-exposure studies (Svirbely 1954b; Levinskas et al. 1958): lesions in adrenals, liver, spleen, lungs, testes, eyes.
- The most sensitive test of neurotoxicity was the CAR test for dogs. This found decreased performance (delays in jumping time) from exposures that produced no apparent signs of toxicity.

Conditioned Avoidance Response (CAR) Test for Dogs

- Method of Solomon and Wynne (1953)
- Dogs trained to jump over barrier by 5 seconds after stimulus (light + buzzer), OR get electric shock through floor – during training only.
- One session = 20 jump trials. Harmonic mean of response time was calculated for each session of 20 trials. Dogs considered trained if completed 5 sessions over 5-day period without error.
- Tested 1, 2, and 24 hrs after exposure, and up to week later.



Nonlethal Toxicity Animal Studies Considered for AEGL Development

Species (sex)	Concentra-tion (ppm)	Time (minutes)	Effects	Refere nce
Monkey (M)	37; 60 143	2.0	>No toxic signs or organ lesions >Convulsions 1st day; no organ lesions	Weeks et al. 64
Rat (M)	7.6	30	Dec. brain serotonin, norepinephrine (63%; 39%) in 3 hrs; OK after 7; 2 days	Weir et al. 1965
Mouse (?)	3.5-4.0 8.5-9.0	30 30	Increased pentobarbital (45; 30 mg/kg) sleeping time	Weir et al. 1965
Dog	14-55 18, 30 0.3-10.5	5 15 60	>Tremors, saliv., convulse at ≥38 ppm >Tremors-18 ppm; convulse @ 30 ppm >Convulsions, tremors at ≥ 4.5 ppm, 1/2 died at 5.0, 10.5 ppm	Weir et al. 1964
Dog	9.3 x5; 19.8 x2 5.0 x5; 10.2 x2 1.4 x5; 2.5 x2	5 min 15 min 60 min	After 2nd exposure: miosis, irritability, aggressiveness, scleral congestion, tremors, convulsions	(Weir etal.64)
Dog (M)	33; 73; 144 16; 33; 58 5.2; 9.1; 18	2.0 5.0 15.0	>No effects; >No toxic signs, CAR-d; >Convulsions, CAR-d >No effects; >Lethargy, CAR-d; >Convulsions, CAR-d >No toxic signs; equivocal CAR-d; >No effects; >Convulsions, tremors, CAR-d	Weeks et al. 1964
Dog (M)	14.0-28.0	30-60	At "lower" concs. appeared sedated; at "higher" concs. had convulsions, etc. Observation period not stated.	Weir et al. 1965

CAR-d = Conditioned-avoidance-response delay

CONCENTRATION – EXPOSURE DURATION RELATIONSHIP for PENTABORANE

- ten Berge et al. (1986) concentration-time relationship $C^n \times t = k$, was used, which = Haber's law ($C \times t = k$) when n=1.
- The value of n=1.0 was determined by linear regression analysis of the Weeks et al. (1964) dog LC_{50} data for 2-15 min. This yielded n=0.97.
- The value of n=1.0 was also obtained by multivariate linear regression analysis of dog 5-60 minute data (Weir et al. 1964; Weeks et al. 1964). The variables were exposure time, concentration, and the incidence of convulsions without lethality. This yielded n=0.99.
- Similar values for n were calculated by linear regression analysis of LC_{50} data for rats and mice:
  - Obtain n=1.30 for rats exposed 5-60 min (Weir)
  - Obtain n=1.47 for mice exposed 5-60 min (Weir)
  - Obtain n=1.11 for mice exposed 0.5-15 min (Weeks) (n=1.04 w/o 0.5')
  - Obtain n=1.17 for mice if combine Weir and Weeks (n=1.20 w/o 0.5')
- If include the 4-hr Feinsilver data obtain: n=1.55; 1.57; 1.28; 1.27. However, 4-hr different analytical method than 0.5-60 min values.
  - Both collected air in Cellosolve (ethylene glycol monoethyl ether)
  - 4-hr samples: boric acid was titrated with 1N NaOH.
  - 0.5-60 min samples: colorimetric rxn of boron with carmine in H_2SO_4.

Derivation of AEGL-1

Not recommended (NR): Neurotoxicity occurred at concentrations not detected by senses. This does not imply that exposures below the AEGL-2 are without adverse effect.

AEGL-1 Values for Pentaborane

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

Derivation of AEGL-2

Key study: Weir et al. (1964). The POD was exposure for 60 minutes to 1.4 ppm, which caused no neurological signs or CAR delays in dogs exposed once (Weir et al. 1964). Dogs exposed a second time the following day had CNS effects including decreased activity, decreased pupil size, and CAR delays.

Toxicity endpoint: NOEL for CNS toxicity

Scaling: $C^n \times t = k$ (ten Berge et al. 1986), using n=1.0. The 30-min value was adopted for 10 min as the scaled 10-minute value (0.80 ppm) was too close to the pentaborane odor detection threshold for of 1 ppm, which was associated with CNS toxicity in occupational studies.

Uncertainty Factors: Total uncertainty factor: 10
Interspecies: 3: Similar effects (CNS toxicity) occurred in four species of animals and humans, and LC_{50} s varied < 3-fold among species.
Intraspecies: 3: The homogenous response among species and the steep dose-response for lethality indicate little variability among humans.

Modifying Factor: none

AEGL-2 Values for Pentaborane

10-minute	30-minute	1-hour	4-hour	8-hour
0.28 ppm	0.28 ppm	0.14 ppm	0.035 ppm	0.018 ppm

Most Pertinent Animal Studies for AEGL-3 Development

Species (sex)	Concs. tested (ppm)	Exposure (min.)	Mortality	Reference(s)
Monkey	5 concs.	2.0	LC_{50} = 248 ppm	Weeks et al. 1964
Rat	62.2- 84.7 29.0-34.3 13.0-19.3 7.5-15.1	5 15 30 60	LC_{50} = 66.6 ppm LC_{50} = 31.2 ppm LC_{50} = 15.2 ppm LC_{50} = 10.4 ppm	Weir et al. 1961; 1964
Rat	4.3- 20.2	120	LC_{50} = 15.7 ppm	Svirbely 1954a
Rat	3.2-7.5	240	LC_{50} = 5.8 ppm	Feinsilver et al. '60
Mouse	5 concs. each	0.5 2.0 5.0 15.0	LC_{50} = 401 ppm LC_{50} = 133 ppm LC_{50} = 53 ppm LC_{50} = 19 ppm	Weeks et al. 1964
Mouse	28.7-43.5 15.4-21.9 9.6-15.8 6.9-11.6	5 15 30 60	LC_{50} = 40.5 ppm LC_{50} = 18.6 ppm LC_{50} = 10.6 ppm LC_{50} = 7.8 ppm	Weir et al. 1961; 1964
Mouse	4.3-20.2 4.6	120 240	LC_{50} =12.4 ppm 10/10	Svirbely 1954a
Mouse	19.8 10.2 3.7	5 x 4 15 x 4 60 x 4	2/20 15/20 16/20	Death after 2 or more exposures (Weir et al. 1964)
Mouse	3.0-5.6	240	LC_{50} = 3.4 ppm	Feinsilver et al. '60
Dog	5 concs. each	2 5 **15**	LC_{50} = 284 ppm LC_{50} = 126 ppm **LC_{50} = 36 ppm**	Weeks et al. 1964
Dog	5.0; 10.5 3.7x3	60 60	1/2 die at each conc. 1/3 die after 3rd exp.	Weir et al. 1964

Derivation of AEGL-3

Key study: Weeks et al. (1964). The key exposure scenario is dog 15-min LC_{50}. Animals had tremors, ataxia, and convulsions; died within 24 hrs. Because the mortality incidence data were not provided, the threshold for lethality was estimated as 1/2 of the 15-minute LC_{50} of 36 ppm, or 18 ppm.

- Dividing by 2 was conservative approach because the same or a higher exposure (15 minutes to 18 or 30 ppm) caused CNS effects but no death in two other dog trials (Weeks et al. 1964; Weir et al. 1964).

- Additionally, rat and mouse acute lethality data (Weir et al. 1961; 1964) showed that the dose-response for lethality was very steep.

Toxicity endpoint: Lethality threshold in dogs

Scaling: $C^n \times t = k$ (ten Berge et al. 1986), using n=1.0

Uncertainty Factors: Total uncertainty factor: 10
Interspecies: 3: Similar effects (CNS toxicity) occurred in four species and humans, and LC_{50} values varied < 3-fold among species.
Intraspecies: 3: The homogenous response among species and the steep lethality dose-response indicate that there would be little variability among humans.

Modifying Factor: None

AEGL-3 Values for Pentaborane

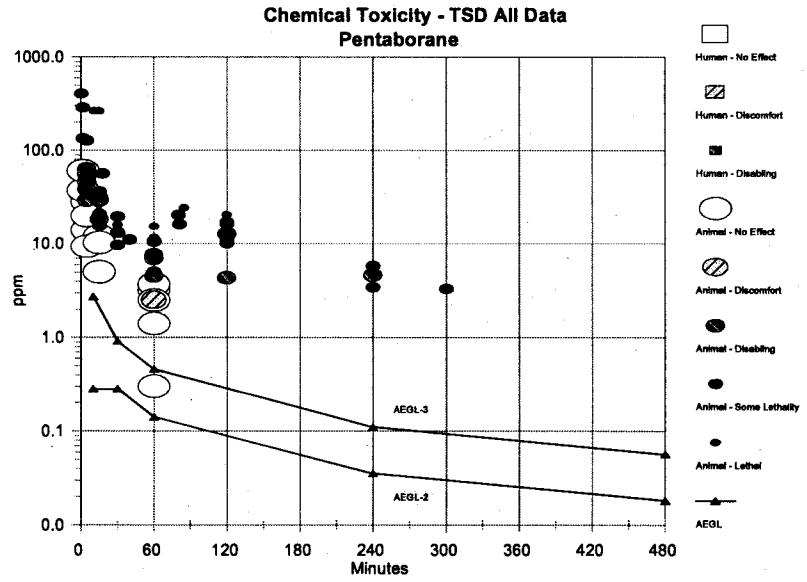
10-minute	30-minute	1-hour	4-hour	8-hour
2.7 ppm	0.90 ppm	0.45 ppm	0.11 ppm	0.056 ppm

Summary of AEGL Values for Pentaborane (ppm)

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Non-disabling)	NR	NR	NR	NR	NR	--
AEGL-2 (Disabling)	0.28	0.28	0.14	0.035	0.018	NOEL for CNS toxicity in dogs (Weir et al. 1964)
AEGL-3 (Lethal)	2.7	0.90	0.45	0.11	0.056	NOEL for dog lethality (Weeks et al. 1964)

NR = Not recommended because neurotoxicity occurred at concentrations not detected by the senses. This does not imply that exposures below the AEGL-2 are without adverse effect.

Category Plot for Pentaborane



The category plot included the single-exposure data for monkeys, dogs, rats, and mice. Results are included from multiple-exposure studies if data were available to indicate the effect of one exposure.