

**National Advisory Committee for
Acute Exposure Guideline Levels for Hazardous Substances**

ATTACHMENT 1

**NAC/AEGL-40
September 6-8, 2006**

**Hyatt Regency- Bethesda
One Bethesda Metro Center (7400 Wisconsin Ave)
Bethesda, MD 20814**

Metro: Bethesda (Red Line)

AGENDA

Wednesday, September 6, 2006

10:00 a.m. Introductory remarks and approval of NAC/AEGL-37 and NAC/AEGL-39 Highlights (George Rusch, Ernie Falke, and Paul Tobin)
10:15 Revised AEGL Chemical Priority List: Chemical Class Format (Paul Tobin)
10:45 Review of 1,2,3-Trimethyl benzene; 1,2,4-Trimethyl benzene, and Mesitylene (1,3,5-Trimethyl benzene) (John Hinz/Carol Wood)
12:30 p.m. Lunch
1:30 Revisit of Ethylene Oxide- AEGL-2 (Susan Ripple/Kowetha Davidson)
3:30 Break
3:45 Review of Trifluorochloroethylene (George Rusch/Sylvia Talmage)
5:30 Adjourn for the day

Thursday, September 7, 2006

8:30 a.m. Review of Hexafluoropropylene (George Rusch/Bob Young)
10:00 Break
10:15 Review of Tetrafluoroethylene (George Rusch/ Sylvia Talmage)
12:00 p.m. Lunch
1:00 Review of Ethyl benzene (John Hinz/Carol Wood)
2:30 Review of Selected Chloroformates- Benzyl Chloroformate, Phenyl Chloroformate, 2-Ethylhexyl Chloroformate (Ernie Falke/Cheryl Bast)
4:00 Break
4:15 Revisit of Dibromoethane (Bob Benson/Kowetha Davidson)
5:30 Adjourn for the day

Friday, September 8, 2006

8:30 a.m. Review of Propargyl Alcohol (George Cushmac/Bob Young)
10:00 Break
10:15 Review of Phenyl Mercaptan (Steve Barbee/Cheryl Bast)
11:45 Administrative matters
12:00 noon Adjourn meeting

NAC/AEGL Meeting 40: September 6-8, 2006

ATTENDANCE
SEPT 6, 2006

Chemical: _____

CAS Reg. No.: _____

ATTACHMENT 2

Action: Proposed _____ Interim _____ Other _____

Chemical Manager:

Staff Scientist:

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	<i>HA</i> ✓	✓			Warren Jederberg	ABSENT	X		
Steven Barbee	<i>SB</i> ✓	✓			Elaine Krueger	<i>EK</i> ✓	✓		
Marc Baril	<i>MB</i> ✓	✓			Glenn Leach	ABSENT	X		
Lynn Beasley	<i>LB</i> ✓	✓			Richard Niemeier	ABSENT	X		
Alan Becker	<i>AB</i> ✓	✓			Marinelle Payton	ABSENT	X		
Robert Benson	<i>RB</i> ✓	✓			Susan Ripple	<i>SR</i> ✓	✓		
George Cushmac	<i>JCC</i> ✓	✓			George Rodgers	<i>GR</i> ✓	✓		
Ernest Falke	<i>EF</i> ✓	✓			Marc Ruijten	<i>MR</i> ✓	✓		
Alfred Feldt	→ <i>Wad</i> ✓ <i>FRI</i> <i>mb</i>	✓			George Rusch, Chair	<i>GR</i> ✓	✓		
Roberta Grant	<i>RG</i> ✓	✓			Daniel Sudakin	<i>DS</i> ✓	✓		
Dieter Heinz	<i>DH</i> ✓	✓			Richard Thomas	<i>RT</i> ✓	✓		
John Hinz	<i>JH</i> ✓	✓			Calvin Willhite	<i>CW</i> ✓	✓		
Jim Holler	<i>JH</i> ✓	✓			George Woodall	<i>GW</i> ✓	✓		
					TALLY				
					PASS/ FAIL				

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

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
 ** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to _____

AEGL 1 Motion by: _____	Second by: _____
AEGL 2 Motion by: _____	Second by: _____
AEGL 3 Motion by: _____	Second by: _____
LOA Motion by: _____	Second by: _____

Approved by Chair: _____ DFO: *Paul S. Hill* Date: 9/6/2006

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JOE HADLEY, HADLEY & McKeune 202/365-1540

Jennifer Wagner, ORNL

Sylvia Talmage, ORNL

ROBERT YOUNG, ORNL

Cheryl Bast, ORNL

Carol Wood, ORNL

Kawetha Davidson, ORNL

Gail D. Chapman CDR 937-904-9433

USE OF INTENTIONAL DOSING HUMAN DATA FROM COMPLETED STUDIES IN THE DEVELOPMENT OF AEGL VALUES – ETHICAL CONSIDERATIONS

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**USE OF INTENTIONAL DOSING
HUMAN DATA FROM COMPLETED
STUDIES IN THE DEVELOPMENT OF
AEGL VALUES – ETHICAL
CONSIDERATIONS**

PRESENTATION

EPA FINAL RULE FEBRUARY 6, 2006

**CURRENT PROCEDURES FOR THE
AEGL PROGRAM**

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EPA FINAL RULE FEBRUARY 6, 2006

EPA FINAL RULE FEBRUARY 6, 2006

EPA FINAL RULE FEBRUARY 6, 2006

- Extended Common Rule to prospective 3rd party research which is intended for submission for a FIFRA or FFDCA action
- Banned EPA and 3rd party (covered by above) testing of children and pregnant women
- Established a Human Studies Review Board (HSRB) to consider the ethics of prospective and retrospective studies for actions under FIFRA and FFDCA

EPA FINAL RULE FEBRUARY 6, 2006

- EPA will not consider **retrospective studies** if there is “clear and convincing evidence that the conduct of the research was fundamentally unethical...” for actions under FIFRA and FFDCA.

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EPA FINAL RULE FEBRUARY 6, 2006

▪ HSRB REVIEWS OF RETROSPECTIVE STUDIES FOR ACTIONS UNDER FIFRA OR FFDCa

- HSRB reviews to date have found documentation about ethics of studies is usually missing but have okayed their use because there was no clear and convincing evidence that the conduct of the research was fundamentally unethical.

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DRAFT DOCUMENTS – Intended for submission to NAC/AEGL Committee

- EPA and ORNL staff perform an ethics review of intentional dosing human studies used as key or supporting studies to develop Draft AEGL values.
- The outcome and contents of the ethics reviews completed on Draft AEGL documents are consistent with the ethics assessments that were performed by the Office of Pesticides Programs (OPP) for submittal to the Human Studies Review Board (HSRB).
- For the current set of chemicals the ethics reviews concluded that there was no clear and convincing evidence that the research was fundamentally unethical or significantly deficient relative to the ethical standards prevailing when the studies were conducted.

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CURRENT PROCEDURES FOR THE AEGL PROGRAM

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PROPOSED, INTERIM AND NEW DOCUMENTS CONSIDERED BY NAC/AEGL COMMITTEE

- Ethics of any intentional dosing human studies added after Draft stage above will be considered by the NAC/AEGL Committee and documented in the minutes.
- Review will use SOP criteria (p53) and recommendation 5-7 of NAS Report

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Acute Exposure Guideline Levels & Emergency Chemical Database System

Paul S. Tobin, Ph D

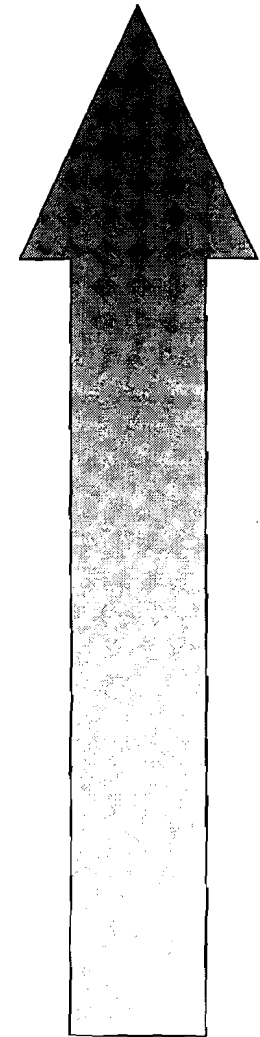
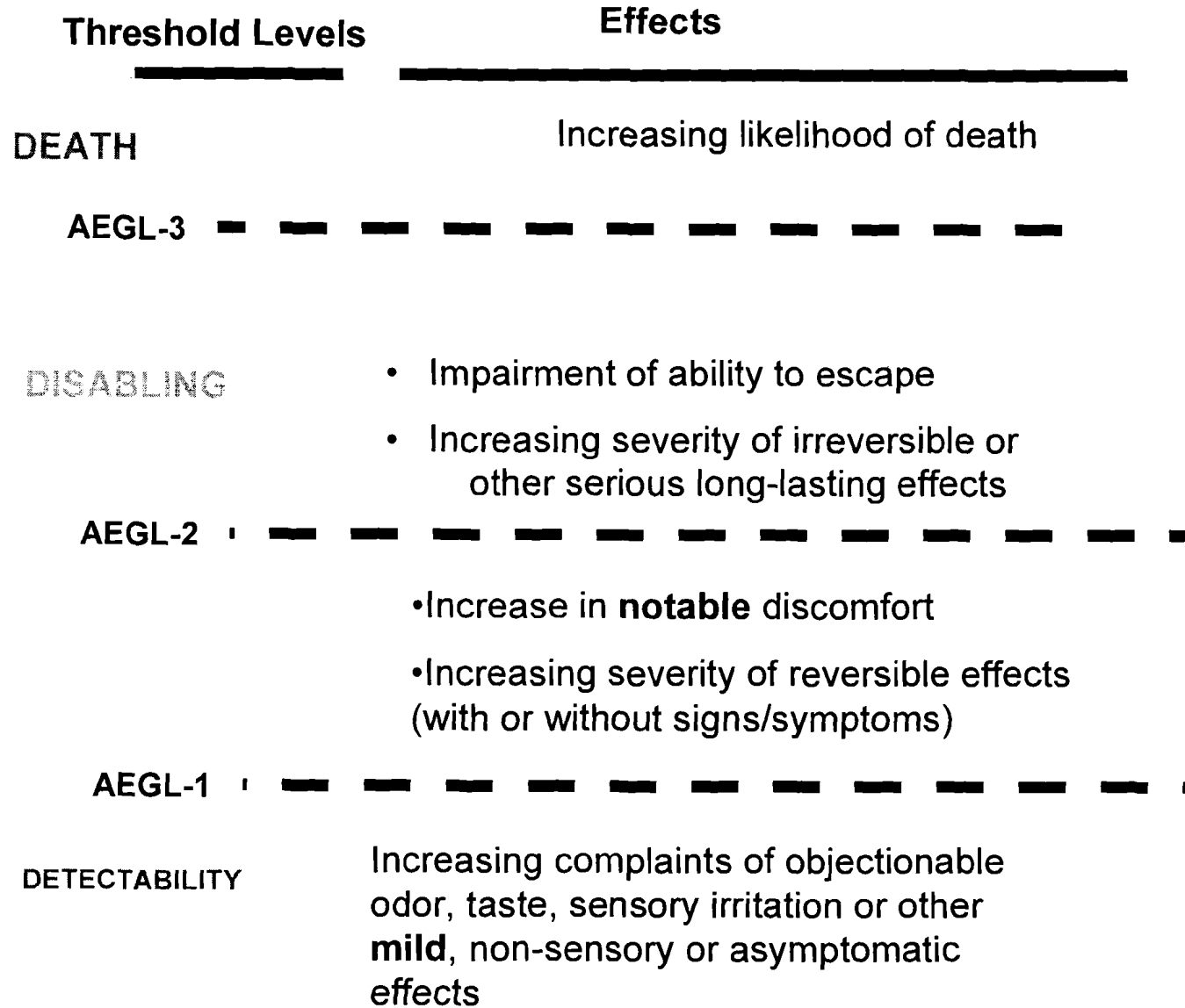
tobin.paul@epa.gov

U.S. Environmental Protection Agency



CHARACTERISTICS OF AEGLs

HAZARD ASSESSMENT



Results

Final, Interim and Proposed AEGL Chemicals

2006 TARGET

- 31 Final
- 110 Interim
- 54 Proposed
- 13 Holding

Total: 208

2007 TARGET

- 46 Final
- 143 Interim
- 36 Proposed
- 13 Holding

Total: 238

The AEGL Chemical Priority List

- 279 Chemicals
 - Almost all gases and volatile liquids
 - Mostly “toxic” but some high volume/less toxic
- 50 Chemical Classes
 - Arbitrary selection (e.g. Hydrogen Cyanide is assigned to nitriles chemical class rather than Inorganic Acids chemical class)

CHEMICAL CLASSES

279 AEGL CHEMICALS IN 50 CHEMICAL CATEGORIES

ACID HALIDES (18)	KETONES (5)
ALCOHOLS (2)	LEAD COMPOUNDS (1)
ALDEHYDES (7)	MERCAPTANS (4)
ALUMINUM COMPOUNDS (2)	MERCURY (1)
AMINES (15)	METAL CARBONYLS (2)
ANILINES (1)	METAL PHOSPHIDES (7)
ANTIMONY COMPOUNDS (2)	NITRILES (13)
ARSENIC COMPOUNDS (12)	NITRO COMPOUNDS (3)
BORON COMPOUNDS (5)	NITROGEN COMPOUNDS, INORG (7)
BROMINE COMPOUNDS (4)	ORGANIC ACIDS (3)
CHLORINE, INORGANIC (4)	ORGANOSULFATES (1)
CHLOROFORMATES (11)	OSMIUM COMPOUNDS (1)
CHLOROSILANES (21)	OXYGEN COMPOUNDS, INORG (1)
CHROMIUM (1)	PEROXIDES (1)
EPOXIDES (5)	PHENOLS (1)
ESTERS (6)	PHOSPHONATE ESTERS (5)
ETHERS (6)	PHOSPHORUS COMPDS, OTHER (12)
FLUORINES, INORGANIC (4)	PYRIDINES (1)
GERMANIUM COMPOUNDS (1)	SELENIUM COMPOUNDS (1)
HALOGENS, INORGANIC (22)	SILICON COMPOUNDS (5)
HYDROCARBONS, ALIPHATIC (5)	SULFUR COMPOUNDS (14)
HYDROCARBONS, AROMATIC (11)	TELLURIUM COMPOUNDS (1)
IMINES (2)	TITANIUM COMPOUNDS (1)
INORGANIC ACIDS (7)	TUNGSTEN COMPOUNDS (1)
ISOCYANATES (12)	ZINC COMPOUNDS (1)

AEGL EXPERT SYSTEM DATABASE: Nitriles

Microsoft Access - [Chemical Class Data : Form] Type a question for help

File Edit View Insert Format Records Tools Window Help Adobe PDF

Arial 12 **B** I U

Chemical Class: **Nitriles** View All Classes | View Database for Class

Overview: The category consists of the following members:

1. Propionitrile (EINECS Propionitrile), CAS No. 107-12-0, molecular structure: CH3CH2C#N
2. Butyronitrile, CAS No. 109-74-0, molecular structure: CH3CH2CH2C#N

Main Menu | Open Database | Close

Toxicity Data: The oral and inhalation LD50 values of propionitrile, n-butyronitrile and isobutyronitrile in rats are similar. The oral LD50 values in rats for all three nitriles are within the range of 40 – 270 mg/kg (Younger Laboratories Incorporated, 1979, 1980; Eastman/Kodak, 1957, 1960, 1961; Smyth et al., 1962). Inhalation LD50 values (for 1 or 4 hours of

Production and Usage: Butyronitrile and isobutyronitrile are manufactured by one producer at one site (Eastman Chemical Company). Propionitrile is manufactured solely by Solutia Inc. at one site. All three category members are used as industrial chemicals, primarily as intermediates that are chemically converted to other chemicals. Although they are sold and shipped

AEGL Chemicals within Chemical Class: Double-Click Chemical Name to View Chemical Data

- Acetone cyanohydrin
- acetonitrile
- acrylonitrile
- benzonitrile
- chloroacetonitrile
- cyanogen
- cyanogen chloride
- formaldehyde cyanohydrin
- hydrogen cyanide

Chemical Lists Double-Click Chemical Name to View Chemical Data

<p>DOT: Acetone cyanohydrin</p> <p><u>Criteria</u></p> <ul style="list-style-type: none"> acetonitrile acrylonitrile benzonitrile chloroacetonitrile cyanogen cyanogen chloride 	<p>OSHA: cyanogen</p> <p><u>Criteria</u></p> <ul style="list-style-type: none"> cyanogen chloride hydrogen cyanide methacrylonitrile 	<p>RMP: acrylonitrile</p> <p><u>Criteria</u></p> <ul style="list-style-type: none"> cyanogen chloride hydrogen cyanide isobutyronitrile methacrylonitrile propionitrile
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Close

Record: 14 | 4 | 28 | 11 | 11 of 46

AEGL EXPERT SYSTEM DATABASE: ACROLEIN

Microsoft Access - [AEGL Expert System] Type a question for help

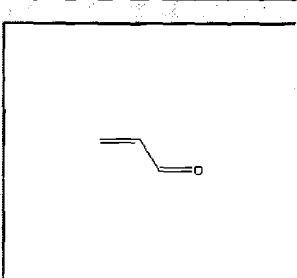
File Edit View Insert Format Records Tools Window Help Adobe PDF

Arial 12 **B** *I* U **ABCDEF**

Main Menu
Search
Display All Chemicals
AEGL Expert System
Values in ppm
Values in mg/m3

CAS# Chemical Name

Chemical Class Chemical Class Date _____ Functional Group _____



Physical Properties

Gas Liquid Solid

BP: VP:

Green Chemistry Expert System

Production Indicators

Prod:

Chemical Lists

DOT OSHA PSM

NHSRC RMP

NM SII

Acute Exposure Guideline Levels Status: **Derivation of AEGL Values**

	10 min	30 min	60 min	4 hr	8 hr
AEGL-1	<input type="text" value="0.030"/>	<input type="text" value="0.030"/>	<input type="text" value="0.030"/>	<input type="text" value="0.030"/>	<input type="text" value="0.030"/>
AEGL-2	<input type="text" value="0.44"/>	<input type="text" value="0.18"/>	<input type="text" value="0.10"/>	<input type="text" value="0.10"/>	<input type="text" value="0.10"/>
AEGL-3	<input type="text" value="6.2"/>	<input type="text" value="2.5"/>	<input type="text" value="1.4"/>	<input type="text" value="0.48"/>	<input type="text" value="0.27"/>

◆ AEGL-1 ◆ AEGL-2 ◆ AEGL-3

POD Test Species:

POD Exposure Route:

POD Concentration:

POD Duration:

POD Effect:

Emergency Response Planning Guidelines (AIHA)

ERPG-1 60min ERPG Basis: ◆ ERPG-1 ◆ ERPG-2 ◆ ERPG-3

ERPG-2 60min

ERPG-3 60min

Temporary Emergency Exposure Limits (DOE)

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)**FOR****1,3,5-TRIMETHYLBENZENE**
(CAS Reg. No. 108-67-8)**1,2,4-TRIMETHYLBENZENE**
(CAS Reg. No. 95-63-6)**1,2,3-TRIMETHYLBENZENE**
(CAS Reg. No. 526-73-8)**Draft 1: September/2006****TRIMETHYLBENZENE**

- Three isomers
 - 1,3,5,-TMB or mesitylene
 - 1,2,4-TMB or pseudocumene
 - 1,2,3-TMB or hemimellitene
- Components of fuels and hydrocarbon solvents
- Regulatory standards apply to individual isomer or any mixture

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Human data relevant to AGEL derivation

- No adverse effects in pharmacokinetic studies with all three isomers
 - 25 ppm for 2 hrs (Jarnberg et al. 1996)
 - 25 ppm for 4 hours (Jones et al. 2006)*
 - 30 ppm for 8 hours (Kostrzewski et al. 1997)

*not in TSD

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Summary of Rat Data Following Acute and Subchronic TMB exposure				
Species/sex	Conc. (ppm) [isomer]	Duration	Effects	Reference
Rat/m,f	2240 [1,3,5-TMB]	24 hours	4/16 died	Cameron et al. 1938
Rat/m,f	560 [1,3,5-TMB] 1800-2000 [1,2,4-TMB]	24 hours or 8 hrs/day for 14 days; 48 hours or 8 hrs/day for 14 days	none	Cameron et al. 1938
Rat/m	768-1212 [all three]	4 hours	calculated EC ₅₀ for mild neurotoxicity deficits	Korsak et al. 1995, Korsak and Rydzyński 1996
Rat/m,f	1000 [1,2,4-TMB] 2000 [1,2,4-TMB]	6 hours for 15 times	eye and nose irritation; severe irritation, lethargy	Gage 1970
Rats/m	25, 100, 250 [all three]	6 hr/day, 5 d/week, 28 days or 90 days	no clinical signs; mild neurotox. at 100 and 250 after 28 or 90 days	Gralewicz et al. 1997a, Wiaderna et al. 1998, Korsak and Rydzyński 1996, Korsak et al. 1997, Gralewicz and Wiaderna 2001
Rats/m,f	25, 100, 250 [1,2,3-TMB]	6 hr/day, 5 d/week, 90 days	hematology and clinical chemistry changes at 250 ppm, lesions in respiratory tract at 100 and 250 ppm	Korsak et al. 2000

Summary of Mouse Data Following TMB Exposure				
Species/sex	Conc. (ppm) [isomer]	Duration	Effects	Reference
Mice/m	519-578 [all three]	6 minutes	RD ₅₀	Korsak et al. 1995, 1997
Mice/m,f	560 [1,3,5-TMB] 1800-2000 [1,2,4-TMB]	24 hours or 8 hrs/day for 14 days; 12 hours	none	Cameron et al. 1938
Mice	5000-8100 7000-9000 [1,2,4- or 1,3,5-TMB]	2 hours	lateral position; loss of reflexes	Lazarew 1929

Summary of Developmental and Reproductive Toxicity Data Following TMB Exposure				
Species/sex	Conc. (ppm) [isomer]	Duration	Effects	Reference
Rat/f	100-1200 [1,3,5-TMB]	6 hr/d, GDs 6-20	Maternal: ≥300 ppm, dcr wt gain and food cons. Fetal: ≥600 ppm, dcr body wt	Saillenfait et al. 2005* *not in TSD
Rat/f	100-900 [1,2,4-TMB]	6 hr/d, GDs 6-20	Maternal: ≥600 ppm, dcr wt gain and food cons. Fetal: ≥600 ppm, dcr body wt	Saillenfait et al. 2005* *not in TSD
Mice/f	100-1500 [C-9 aromatics]	6 hr/d, GDs 6-15	Maternal: 1500 ppm, death, clinical signs; ≥500 ppm, dcr body wt gain Fetal: 1500 ppm, post-impl loss; ≥500 ppm, dcr body wt	IRDC 1988, 1989; McKee et al. 1990
Rat/m,f	100-1500 [C-9 aromatics]	6 hr/d, 5 d/wk, 10 wk pre mating, three generations	Systemic: 1500 ppm, death; ≥500 ppm, dcr body wt; ≥100 ppm dcr body wt F2 Repro: 1500 ppm, incr pre-coital interval Offspring: 1500 ppm, dcr live birth, dcr body wt; 500 ppm dcr body wt F3	McKee et al. 1990

Proposed AEGL-1 Values for Trimethylbenzene				
10-minute	30-minute	1-hour	4-hour	8-hour
100 ppm (492 mg/m ³)	100 ppm (492 mg/m ³)	100 ppm (492 mg/m ³)	100 ppm (492 mg/m ³)	100 ppm (492 mg/m ³)

Key Study: Gage 1970

Exposure: rats; 1000 ppm, 6h, 15 times

Effect: Threshold for AEGL 1 effects; slight eye and nose irritation in rats; multiple exposure

Scaling: None

UFs: 10 (3 for intraspecies variability and 3 for interspecies variability)

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Proposed AEGL-2 Values for Trimethylbenzene				
10-minute	30-minute	1-hour	4-hour	8-hour
460 ppm (2263 mg/m ³)	460 ppm (2263 mg/m ³)	360 ppm (1771 mg/m ³)	230 ppm (1132 mg/m ³)	150 ppm (738 mg/m ³)

Key Study: Gage 1970

Exposure: rats; 2000 ppm, 6h, 12 times

Effect: Threshold for AEGL 2 effects; eye and nose irritation, respiratory difficulty, lethargy, tremors, decreased wt gain in rats; multiple exposure

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

UFs: 10 (3 for intraspecies variability and 3 for interspecies variability)

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Proposed AEGL-3 Values for Trimethylbenzene				
10-minute	30-minute	1-hour	4-hour	8-hour
1100 ppm (5412 mg/m ³)	790 ppm (3887 mg/m ³)	630 ppm (3100 mg/m ³)	250 ppm (1230 mg/m ³)	250 ppm (1230 mg/m ³)

Key Study: Lazarew 1929

Exposure: mice; 5000 ppm, 2h

Effect: Threshold for AEGL 3 effects; no lethality; lateral position

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

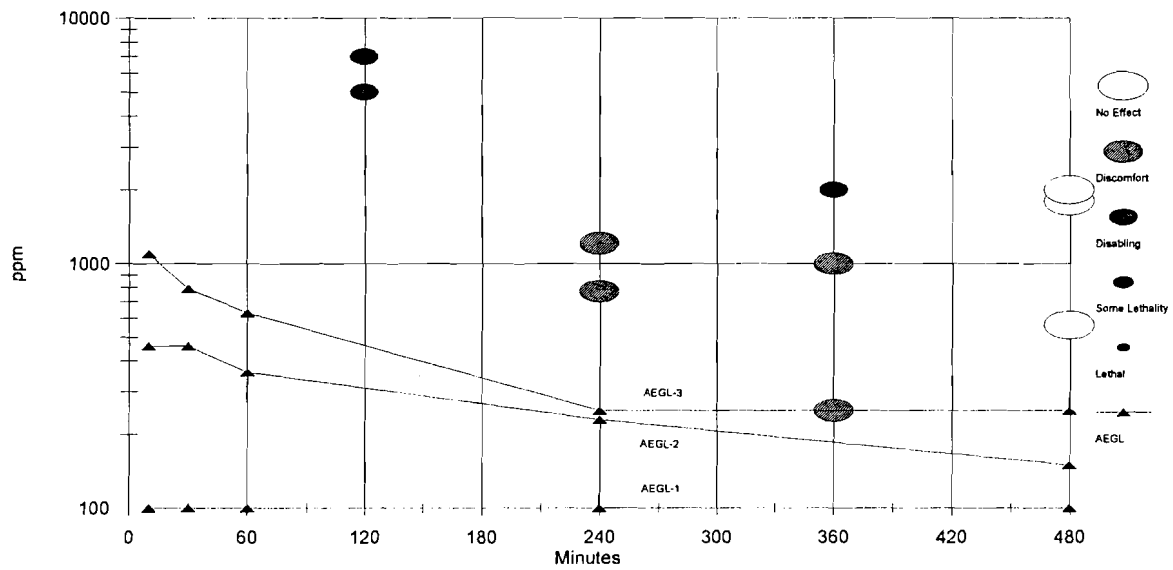
UFs: 10 (3 for intraspecies variability and 3 for interspecies variability)

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Summary of Proposed AEGL Values for TMB					
Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	100 ppm	100 ppm	100 ppm	100 ppm	100 ppm
AEGL-2 (Disabling)	460 ppm	460 ppm	360 ppm	230 ppm	150 ppm
AEGL-3 (Lethal)	1100 ppm	790 ppm	630 ppm	250 ppm	250 ppm

Chemical Toxicity - TSD Animal Data
Trimethylbenzene



ETHYLENE OXIDE

AEGL-2 DERIVATION

Kowetha Davidson, ORNL
Susan Ripple, Chemical Manager

NAC/AEGL Meeting
September 6-8, 2006
Bethesda, MD

INTRODUCTION

- **WHY ARE WE STILL DISCUSSING ETHYLENE OXIDE AFTER 10 YEARS?**
- **Issue**
 - Derivation of AEGL-2 values using a developmental toxicity endpoint
 - Almost always use multiple exposures by design
 - Repeated exposures are not necessarily required for induction of developmental toxicity
 - No developmental toxicity study in rats using a single exposure
 - A mouse study was available, but the mouse is not the best surrogate for humans
- **Solution**
 - Acute neurotoxicity toxicity study in rats
 - Thanks George Rusch

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Neurotoxicity VS Developmental Toxicity Study

- **Neurotoxicity**
 - Species: rat
 - Strain: Sprague-Dawley
 - Sex: Male & Female
 - Exposure duration: 6 hours, one time
 - Observation period: 14 days with evaluations on Days 1, 8, and 15
 - Endpoints evaluated: neurotoxicity (FOB & motor activity)
 - **NOAEL – 100 ppm**
- **Developmental Toxicity**
 - Species: rat
 - Strain:
 - Sex: Females
 - Exposure duration: 6 h/day, GD 6-15
 - Observation period: 5 or 6 days (study terminated on GD 20 or 21)
 - Endpoints evaluated: maternal and developmental toxicity
 - **NOAEL = 100 ppm**

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ACUTE NEUROTOXICITY STUDY

- Species/Strain/Sex: Rats/ Sprague-Dawley males and females
- Number/Group: 10 of each sex (20 /group)
- Exposure Protocol
 - Test Substance: ethylene oxide vapor
 - Exposure Concentrations: 0, 100, 300, 500 ppm
 - Exposure Duration: 6 hours
 - Observation period: 14 days
- Neurobehavioral assessment
 - Time of assessment: Day 1, 8, and 15 post-exposure
 - Standard functional observational battery (FOB) and motor activity
 - FOB: home cage, sensory, handling, physiological, open field, and neuromuscular observations
 - Neuropathologic examination: control and 500-ppm group

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Results of Neurotoxicity Test

- No exposure-related clinical signs
- No deaths during exposure or observation period
- Small decrease in weight gain at 500 ppm during observation period
- Motor activity decreased in both sexes at 500 ppm and males at 300 ppm when assessed on Day 1
- Several FOB parameters affected on Day 1 (drooping/half closed eyelids, slightly impaired locomotion, low arousal, & no reaction to approach)
- Except for droopy eyelids, these effects may be indicative of slowed mobility
- Parameters were not affected on Days 8 or 15

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Results of the acute neurotoxicity (FOB) study in rats				
Observation	0 ppm	100 ppm	300 ppm	500 ppm
Males (n = 10)				
Drooping/half closed eyelids	1 (10%)	1 (10%)	0	5 (50%)
Slightly impaired locomotion	0	0	2 (20%)	1 (10%)
Low arousal	0	2 (20%)	5* (50%)	9** (90%)
Approach response - no reaction	1 (10%)	2 (20%)	6* (60%)	6* (60%)

*p≤0.05

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**Results of the acute neurotoxicity test (FOB) in rats
(Cont.)**

Observation	0 ppm	100 ppm	300 ppm	500 ppm
Females (n = 10)				
Drooping/half closed eyelids	1 (10%)	1 (10%)	5 (25%)	3 (30%)
Slightly impaired locomotion	0	0	0	2 (20%)
Low arousal	0	1 (10%)	1 (10%)	6* (60%)
No reaction to approach	1 (10%)	1 (10%)	1 (10%)	4 (20%)

*p≤0.05

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**Results of the acute neurotoxicity (FOB) study in rats
(Cont.)**

Observation	0 ppm	100 ppm	300 ppm	500 ppm
Males + Females (n = 20)				
Drooping/half closed eyelids	2 (10%)	2 (10%)	5 (25%)	8** (40%)
Slightly impaired locomotion	0	0	2 (10%)	3 (15%)
Low arousal	0	3 (15%)	6** (30%)	15** (75%)
No reaction to approach	2 (10%)	3 (15%)	7* (35%)	10** (50%)

*p≤0.05, **p≤0.01

- All effects showed clear dose-related trends
- 300 ppm is a definite LOAEL (neurotoxicity)
- 100 ppm is the NOAEL

8

Supporting Data

- 4-week range-finding study in rats exposed to 0, 100, 300, 400, & 500 ppm, 6 h/d, 5 d/wk
 - Decreased hind limb grip strength at 300-500 ppm
 - **NOAEL = 100 ppm**

- 90-Day subchronic study in rats exposed to 25, 50, 100, or 200 ppm, 6 h/d, 5 d/wk
 - Decreased hind limb grip strength at 200 ppm
 - NOAEL = 100 ppm

- The 2-year monkey study (0, 50, or 100 ppm 7 h/day, 5 d/wk) was inconclusive

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AEGL-2 VALUES

	10 minutes	30 minutes	1 hour	4 hours	8 hours
	80 ppm	80 ppm	45 ppm	14 ppm	7.9 ppm
Key Reference:					
Mandella, R.C. 1997a. An Acute Inhalation Neurotoxicity Study of Ethylene Oxide (498-95-A) in the Rat Via Whole-Body Exposure. Final Report. Performed by Huntingdon Life Sciences, East Millstone, NJ for Allied Signal, Inc, Morristown, NJ and ARC Chemical Division, Balchem Corporation, Slate Hill, NY. Study No. 95-6097.					
Test Species/Strain/Number: Sprague-Dawley rats, 10/sex/group					
Exposure Route/Concentration/Durations: Inhalation; 0, 100, 300, or 500 ppm for 6 hours					
Effects:	0 ppm	100 ppm	300 ppm	500 ppm	
Droopy/half-closed eyelids	10%	10%	25%	40%	
Impaired locomotion	0%	0%	10%	15%	
Low arousal	0%	15%	30%	75%	
No reaction to approach	10%	15%	35%	50%	
Endpoint/Concentration/Rationale: NOAEL for neurotoxicity at 100 ppm; low arousal was observed at 100 ppm, but the incidence did not reach statistical significance ($p = 0.11$, Fisher's exact test); increased incidences of low arousal and no reaction to approach ($p \leq 0.05$) at 300 ppm (LOAEL); effects may indicate slowed mobility, which may affect ability to escape.					

10

Uncertainty Factors/Rationale:

Total uncertainty factor: 10

Interspecies: 3, one potential mechanism of toxicity, direct alkylation of DNA and proteins, is not expected to differ across species. Neurotoxicity similar in rats and humans (distal axonal degeneration/neuropathy); PBPK modeling indicate very little difference between the two species (AUC and dose/mg/kg bw); other measures of exposure show similarity or very little difference between humans and rats.

Intraspecies: 3, An uncertainty factor of 3 was selected for intraspecies variability because glutathione-S-transferase polymorphism can modulate systemic exposure as measured by hemoglobin adducts but appears to be within a factor of 3 within the population. Individuals with asthma are not expected to be affected differently to ethylene oxide concentrations below the odor and irritation threshold.

Modifying Factor: 1

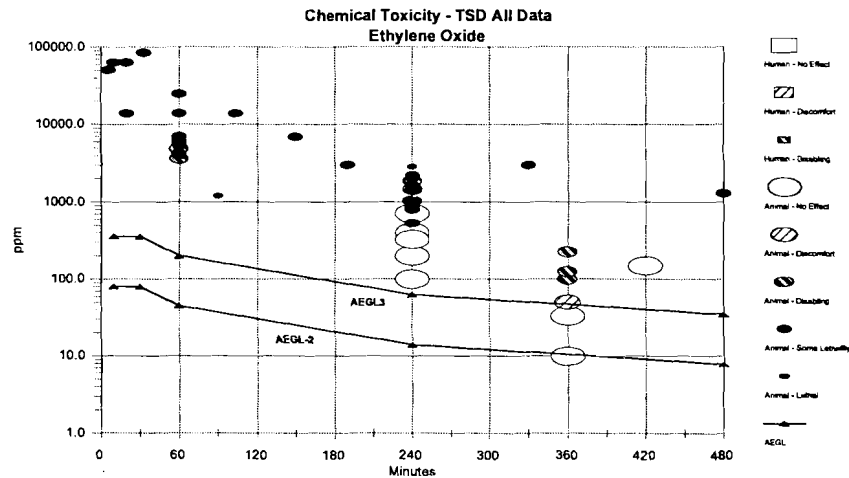
Animal to Human Dosimetric Adjustment: 1

Time Scaling: $C^n \times t = k$, where $n = 1.2$ as determined from empirical LC_{50} data for the rat for 1 and 4 hours.

Data Quality and Support for the AEGL Values: Humans and rats show similar manifestations of neurotoxicity; peripherally, the hind limbs are primary targets with distal axonal degeneration/neuropathy developing in both species. There is still residual uncertainty regarding developmental toxicity, but protection should be attained at the concentration derived for AEGL-2; nevertheless, pregnant women should take steps to minimize exposure. The AEGL-2 values are below the concentrations that cause respiratory tract irritation and are below the odor detection threshold.

11

Category Plot for Ethylene Oxide



12

Proposed AEGL Values for Ethylene Oxide [ppm (mg/m ³)						
Class.	10 min.	30 min.	1 h	4 h	8 h	Endpoint (Reference)
AEGL-1 (Nondisabling)	Not recommended ^a					
AEGL-2 ^b (Disabling)	80 (144)	80 (144)	45 (81)	14 (25)	7.9 (14)	Neurotoxicity (Mandella, 1997)
AEGL-3 (Lethal)	360 (648)	360 (648)	200 (360)	63 (113)	35 (63)	Lethality (Jacobson et al., 1956)

^aThe absence of AEGL-1 values does not imply that exposure below the AEGL-2 level is without adverse effects.

^bAEGL-2 values were derived from acute neurotoxicity data; ethylene oxide is a developmental toxicant; these values should be protective of the fetus.

*Considerations for Deriving
Value of n for Ethylene Oxide*

George Woodall
U.S. EPA / ORD / NCEA

Overview

- Concern that the value of $n = 1.2$ is not health protective enough
- Analysis performed using DoseResp software of ten Berge

<http://home.planet.nl/~wtberge/doseresp.html>

- Species Sensitivity
 - Rats < Dogs < Mice (Jacobson et al., 1956)
 - Relative sensitivity of humans is unknown

Filename = EtO-RatLethality.nrd
 12-05-2006 11:34:43 AM

EtO-ppm	Minutes	N	Dead
2298.00	240.00	10.	10.
1992.00	240.00	10.	10.
1843.00	240.00	10.	9.
1648.00	240.00	10.	4.
1343.00	240.00	10.	2.
882.00	240.00	10.	2.
2182.00	240.00	5.	4.
2026.00	240.00	5.	4.
1850.00	240.00	5.	0.
1443.00	240.00	5.	0.
1021.00	240.00	5.	0.
1850.00	240.00	5.	5.
1637.00	240.00	5.	4.
1443.00	240.00	5.	1.
1021.00	240.00	5.	0.
6161.00	60.00	5.	4.
5546.00	60.00	5.	1.
4827.00	60.00	5.	0.
4827.00	60.00	5.	5.
4202.00	60.00	5.	1.
4064.00	60.00	5.	5.
3966.00	60.00	5.	2.
3609.00	60.00	5.	0.

Jacobson et al., 1956 – Male white rats

Nachreiner, 1991 – Male Sprague Dawley rats

Nachreiner, 1991 – Female Sprague Dawley rats

Nachreiner, 1992 – Male Sprague Dawley rats

Nachreiner, 1992 – Female Sprague Dawley rats

Selection of trials from number 1 through 23

Transformation of variables

EtO-ppm is transformed logarithmically!
 Minutes is transformed logarithmically!

Probit model used without background response correction!

Variable 1 = EtO-ppm
 Variable 2 = Minutes

Chi-Square = 63.78
 Degrees of Freedom = 20

B 0 = -3.137E+01 Student t for B 0 = -5.05
 B 1 = 3.086E+00 Student t for B 1 = 5.77
 B 2 = 2.495E+00 Student t for B 2 = 5.72

n = B1/B2 = 1.2369

variance B 0 0 = 3.855E+01
 covariance B 0 1 = -3.287E+00
 covariance B 0 2 = -2.605E+00
 variance B 1 1 = 2.865E-01
 covariance B 1 2 = 2.126E-01
 variance B 2 2 = 1.905E-01

The prediction of the model is not sufficient. Use for estimation of the 95% confidence limits Student t with 20 degrees of freedom

Correction for variances Chi-Squares/Degrees of Freedom = 3.189

**Interim AEGL
 Value of n = 1.2**

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Filename = EtO-RatLethality.nrd
23-05-2006 3:34:09 PM

EtO-ppm	Minutes	N	Dead
2182.00	240.00	5.	4.
2026.00	240.00	5.	4.
1850.00	240.00	5.	0.
1443.00	240.00	5.	0.
1021.00	240.00	5.	0.
1850.00	240.00	5.	5.
1637.00	240.00	5.	4.
1443.00	240.00	5.	1.
1021.00	240.00	5.	0.
6161.00	60.00	5.	4.
5546.00	60.00	5.	1.
4827.00	60.00	5.	0.
4827.00	60.00	5.	5.
4202.00	60.00	5.	1.
4064.00	60.00	5.	5.
3966.00	60.00	5.	2.
3609.00	60.00	5.	0.

Selection of trials from number 7 through 23

Transformation of variables

EtO-ppm is transformed logarithmically!
Minutes is transformed logarithmically!
Study is transformed logarithmically!
Sex is transformed logarithmically!

Probit model used without background response correction!

Variable 1 = EtO-ppm
Variable 2 = Minutes

Chi-Square = 44.93
Degrees of Freedom = 14

B 0 = -3.067E+01 Student t for B 0 = -3.37
B 1 = 3.122E+00 Student t for B 1 = 3.94
B 2 = 2.249E+00 Student t for B 2 = 3.66

$n = B1/B2 = 1.3882$

variance B 0 0 = 8.288E+01
covariance B 0 1 = -7.169E+00
covariance B 0 2 = -5.437E+00
variance B 1 1 = 6.281E-01
covariance B 1 2 = 4.572E-01
variance B 2 2 = 3.785E-01

The prediction of the model is not sufficient. Use for estimation of the 95% confidence limits Student t with 14 degrees of freedom

Correction for variances Chi-Squares/Degrees of Freedom = 3.210

**Only studies of Nachreiner (1991, 1992)
Used in this analysis.**

- **Same strain rat**
- **Same laboratory**
- **Close Temporal spacing**
 - **Studies one year apart versus 35 years between 1956 and 1991**

Value of n = 1.4

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Filename = EtO-MiceLethality-c.nrd
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EtO-ppm	Minutes	N	Dead
1400.00	90.00	31.	3.
1800.00	90.00	70.	41.
1543.00	105.00	22.	15.
1350.00	120.00	69.	27.
700.00	180.00	19.	0.
900.00	180.00	39.	1.
350.00	360.00	14.	0.
450.00	360.00	21.	0.

Selection of trials from number 17 through 24

Transformation of variables

EtO-ppm is transformed logarithmically!
Minutes is transformed logarithmically!

Probit model used without background response correction!

Variable 1 = EtO-ppm
Variable 2 = Minutes

Chi-Square = 6.33
Degrees of Freedom = 5

B 0 = -6.370E+01 Student t for B 0 = -4.11
B 1 = 6.789E+00 Student t for B 1 = 5.1
B 2 = 4.047E+00 Student t for B 2 = 3.14

$n = B1/B2 = 1.6775$

variance B 0 0 = 2.406E+02
covariance B 0 1 = -2.045E+01
covariance B 0 2 = -1.955E+01
variance B 1 1 = 1.769E+00
covariance B 1 2 = 1.612E+00
variance B 2 2 = 1.664E+00

The prediction of the model is sufficient. Use for estimation of the 95% confidence limits the Standard Normal Deviate

No correction for variances required!

Weller et al. (1991) – Female C57BL/6J mice

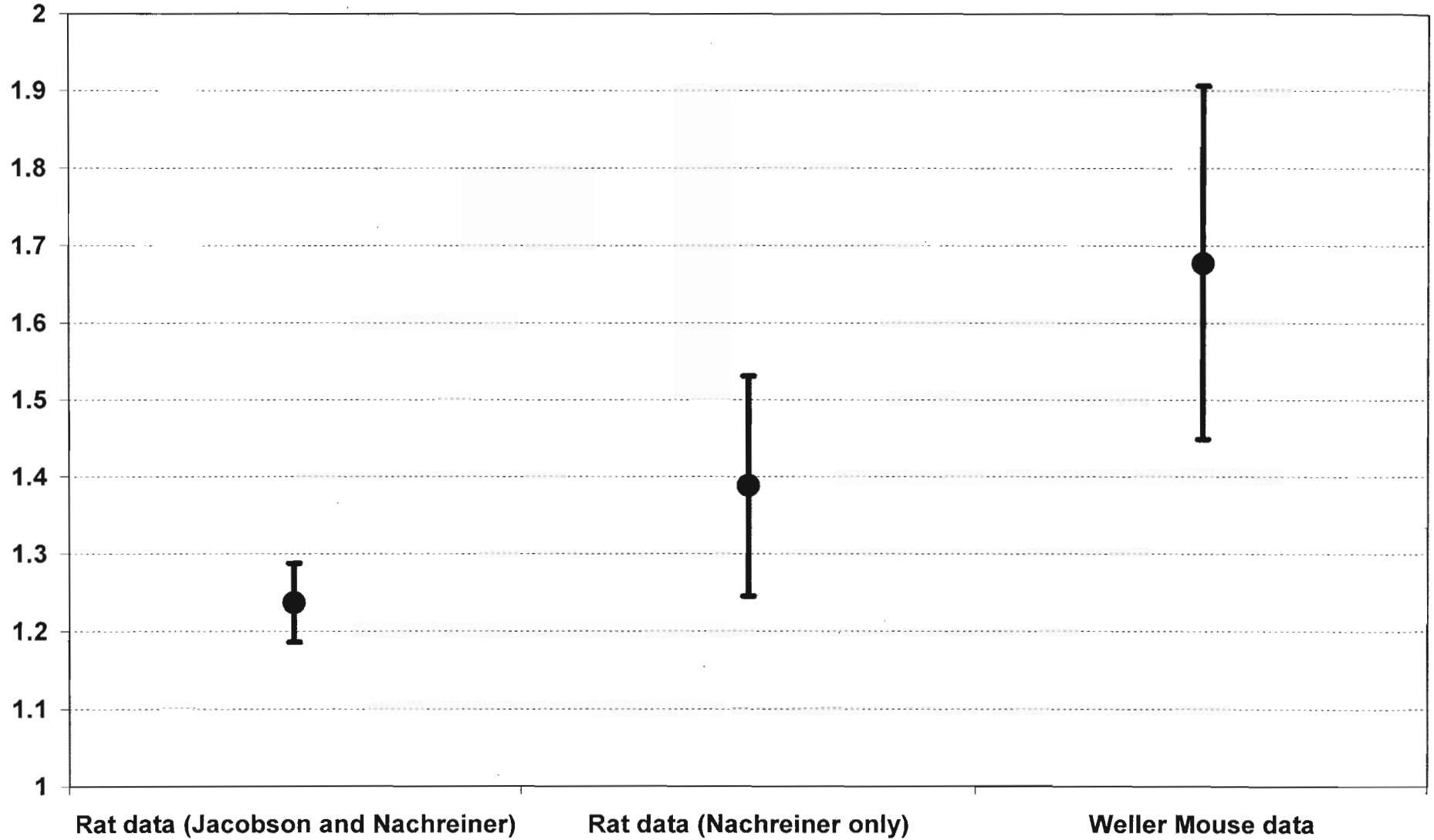
- More sensitive species
- Five durations instead of 2
- Contemporary analysis
 - Same lab
 - Same study
 - Same time
 - Same strain animals

Value of n = 1.7

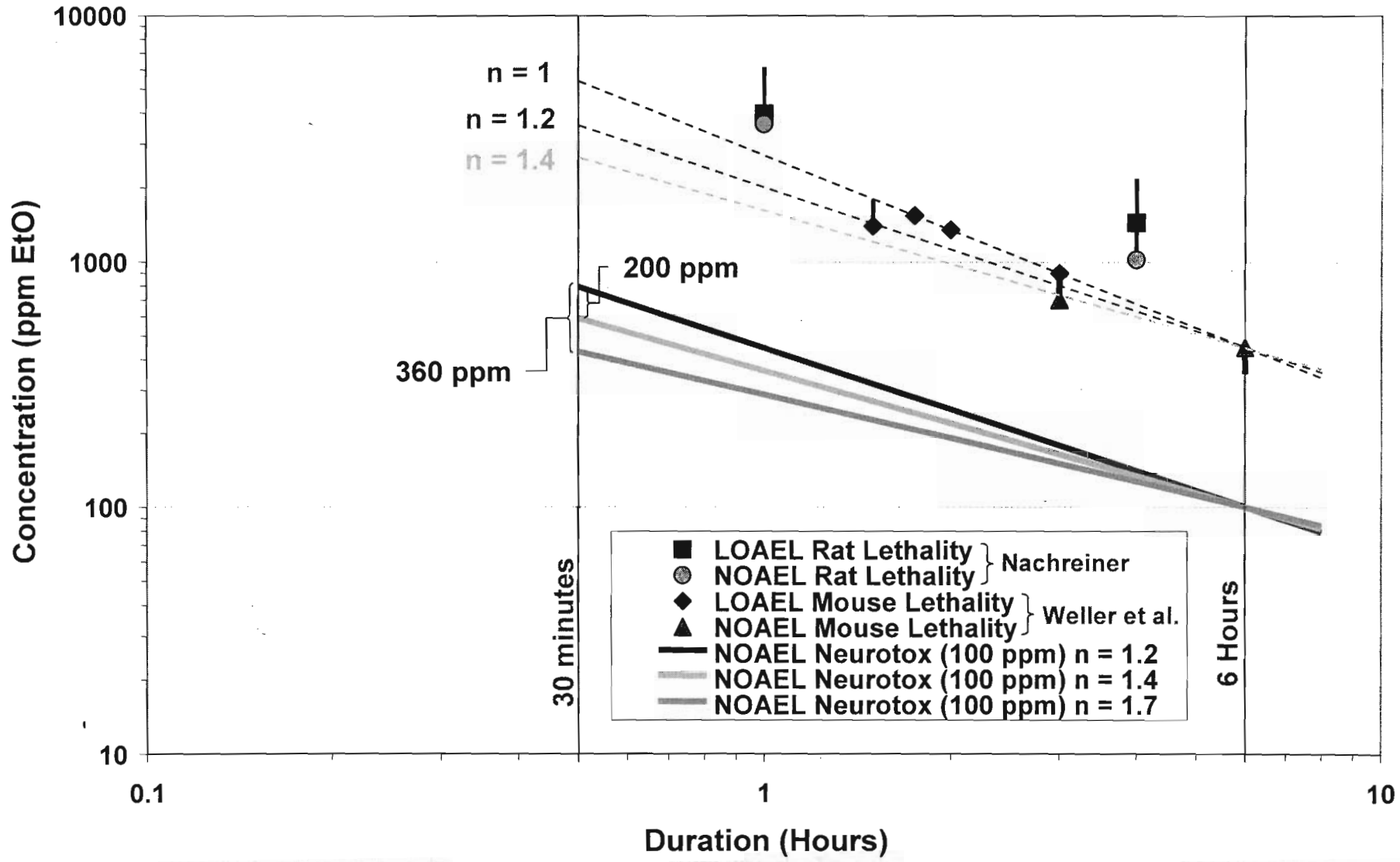
RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

**Value of n
(with 95% Confidence Intervals)**



Comparison of Value of n



Proposal

- ⊘ • Value of $n = 1.2$ may not be health protective enough
- ➔ • Value of $n = 1.4$ is more protective and based on more consistent data in rats
(20 ppm reduction in AEGL-2 at 30 minutes)
- ➔ • Value of $n = 1.7$ is based on more data on the most sensitive species
(36 ppm reduction in AEGL-2 at 30 minutes)

Nachreiner Rat Data

- **Pros**

- Same species as critical endpoint
- More concentrations tested at each duration

- **Cons**

- Only two durations tested
- Assays were not in the same study (1991 and 1992)

Weller et al. Mouse Data

- **Pros**

- Five durations tested
- Contemporary assays
- More sensitive species
- More health protective results

- **Cons**

- Not same species as critical endpoint
- Only two concentrations per duration

**ACUTE EXPOSURE GUIDELINE LEVELS
for
CHLOROTRIFLUOROETHYLENE**

National Advisory Committee for AEGLs Meeting 40
September 6-8, 2006

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
George Rusch

Chemical Reviewers:
Robert Benson
Richard Niemeier

CHLOROTRIFLUOROETHYLENE

Physical State: Colorless gas
High vapor pressure

No human studies (monitoring data: no-effect TWA of ≤ 20 ppm)
Sufficient animal studies, some very old

Mechanism of action:

Pulmonary congestion at lethal and near-lethal concentrations
Kidney lesions mediated via metabolism (conjugation) with glutathione
generally reversible

No information on time scaling

2

Chlorotrifluoroethylene Metabolism/Uncertainty Factors

Primary pathway of metabolism: conjugation with hepatic glutathione
Glutathione conjugate broken down to cysteine metabolite in kidney
Cysteine (thiol) metabolite considered the nephrotoxic species

Considerations for interspecies uncertainty factor

- Greater uptake in rodents than humans
 - Higher respiratory rate and cardiac output
 - Higher blood:air partition coefficient
- Higher tissue concentrations of glutathione transferases (GST)
 - Possible faster metabolism to the toxic metabolite

Considerations for intraspecies uncertainty factor:

- Humans differ in number of copies and classes of GST genes
 - Some individuals are non-conjugators (theoretically would be at lower risk)
 - Other individuals are "slow" or "fast" metabolizers
 - Difference not greater than three-fold;
 - Difference of questionable toxicological significance (Nolan et al. 1985)

3

Chlorotrifluoroethylene Data

Lethality Values:

4-hour LC_{50} values: Rat: 1550 ppm (Sakharova and Tolgskaya 1977)
Mouse: 1800 ppm (Sakharova and Tolgskaya 1977)

Non-Lethal Values and Effects:

Highest non-lethal value: Mouse: 1000 ppm for 8 hours (Walther and Fischer 1968)
Potter et al. 1981, 4-hour studies with the rat:
102 ppm: mild diuresis
222 ppm: reversible kidney lesions (necrosis, clinical chemistry changes)
330 ppm: reversible kidney lesions (necrosis, clinical chemistry changes)
540 ppm: reversible kidney lesions (necrosis, clinical chemistry changes)

Buckley et al. 1982, 4-hour study with the rat:
395 ppm: reversible kidney lesions (necrosis, clinical chemistry changes)

4

Chlorotrifluoroethylene AEGL-1

Basis for AEGL-1:

Rat, 102 ppm for 4 hours (Potter et al. 1981)

NOAEL for reversible kidney necrosis

Uncertainty factors:

Interspecies: 3, uptake greater in the rodent; higher tissue GST

Intraspecies: 3, difference among metabolizers not expected to vary greatly

Time-scaling: n = 3, 1 for shorter and longer exposure durations, respectively

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	29 ppm	20 ppm	16 ppm	10 ppm	10 ppm

Set 8-hour value equal to 4-hour value based on no-effect monitoring value of ≤ 20 ppm (Ryan 1991)

5

Chlorotrifluoroethylene AEGL-2

Basis for AEGL-2:

Rat, 540 ppm for 4 hours (Potter et al. 1981)

NOAEL for irreversible kidney necrosis

Uncertainty factors:

Interspecies: 3, uptake greater in the rodent; higher tissue GST

Intraspecies: 3, difference among metabolizers not expected to vary greatly

Time-scaling: n = 3, 1 for shorter and longer exposure durations, respectively

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	160 ppm	110 ppm	86 ppm	54 ppm	54 ppm

Set 8-hour value equal to 4 hour value based on no-effect monitoring value of ≤ 20 ppm (Ryan 1991)

6

Chlorotrifluoroethylene AEGL-3

Basis for AEGL-3:

Mouse: 1000 ppm for 4 hours (Walther and Fischer 1968)

NOAEL for lethality

Uncertainty factors:

Interspecies: 3, uptake greater in the rodent; higher tissue GST

Intraspecies: 3, difference among metabolizers not expected to vary greatly

Time-scaling: n = 3, 1 for shorter and longer exposure durations, respectively

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	360 ppm	250 ppm	200 ppm	130 ppm	100 ppm

The 8-hour value was time-scaled to the 10-minute value because there are short-term data, albeit old.

7

Chlorotrifluoroethylene AEGLs - Summary

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	29 ppm	20 ppm	16 ppm	10 ppm	10 ppm
AEGL-2	160 ppm	110 ppm	86 ppm	54 ppm	54 ppm
AEGL-3	360 ppm	250 ppm	200 ppm	130 ppm	100 ppm

8

Chloro trifluoroethylene Walther & Fischer 1968

Nominal concentrations, dynamic chamber conditions
animal groups ≥ 10 male mice

First test series, post-exposure observation period 6 days:

		immediately	6 day observation	
Conc ppm	Duration hr	% lethal	exposed	lethal
400	100	0	10?	0
1000	16	10	10	6
1000	24	50	10	10
3000	4	10	10	8
3000	7	50	10	10
8000	2	10	10	10
8000	3	50	10	10

Other exposure conditions NO post-exposure observation.
400 ppm: no behavioural changes

Second test series

**Same exposure concentrations, half the duration of LCT10 and LCT50
Post-exposure observation period 10 days.**

		immediately	6 day observation	
Conc ppm	Duration hr	% lethal	exposed	lethal
1000	8	0	10?	0
1000	12	40	10	4
3000	2	10	10	1
3000	3,5	80	10	8
8000	1	75	12	9
8000	1,5	100	10	10

Data used for calculations

conc ppm	minutes	exposed	responded
400.00	6000.00	10.	0.
1000.00	960.00	10.	6.
1000.00	1440.00	10.	10.
3000.00	240.00	10.	8.
3000.00	420.00	10.	10.
8000.00	120.00	10.	10.
8000.00	180.00	10.	10.
1000.00	480.00	10.	0.
1000.00	720.00	10.	4.
3000.00	120.00	10.	1.
3000.00	210.00	10.	8.
8000.00	60.00	12.	9.
8000.00	90.00	10.	10.

Chloro trifluoro ethylene

This was the first day presentation, where all data > 8 hours were included. Following this presentation, the NAC request a re-calculation excluding the 400 ppm data (too uncertain) and excluding data from exposures > 8 hours. These are presented on the next page.

All columns represent proposed AEGL values (i.e. after application of assessment / uncertainty factors). The column 'current' provides AEGL-3 values as proposed by ORNL.

Including 400 ppm			Excluding 400 ppm			Current
duration	AEGL-3		duration	AEGL-3		
10 min	690		10 min	1532		360
30 min	370		30 min	690		250
60 min	253		60 min	420		200
4 hrs	120		4 hrs	150		130
8 hrs	79		8 hrs	91		100
n-value	1.79		n-value	1.37		

Chloro trifluoro ethylene

This is the presentation on the second day. Data from exposure to 400 ppm are excluded.

A comparison is made between calculation INcluding and calculations EXcluding data from exposures > 8 hours.

Excluding 400 ppm, only ≤ 8 hours			Excluding 400 ppm includes > 8 hrs			Current
duration	AEGL-3		duration	AEGL-3		
10 min	1586		10 min	1532		360
30 min	707		30 min	690		250
60 min	424		60 min	420		200
4 hrs	153		4 hrs	150		130
8 hrs	92		8 hrs	91		100
n-value	1.36		n-value	1.37		

ACUTE EXPOSURE GUIDELINE LEVELS

HEXAFLUOROPROPYLENE (HFP)

NAC/AEGL-40

September, 2006
Bethesda, MD

- No human data
- Animal data
 - multiples species (rats, mice, rabbits, guinea pigs)
 - death generally occurs post exposure (hours to days later although in some instances concurrent with exposure)
 - pulmonary and renal involvement

ORNL Staff Scientist:
Robert Young

Chemical Manager:
George Rusch

Chemical Reviewers:
Robert Benson
Richard Niemeier

HFP - LETHAL TOXICITY

Lethal toxicity (LC ₅₀) of HFP in laboratory species	
Rat	Du Pont Co., 1960 Paulet and Debrousses, 1965
4-hr LC ₅₀	3060 ppm
30-min LC ₅₀	15,750 ppm
2-hr LC ₅₀	4000 ppm
4-hr LC ₅₀	2800 ppm
6-hr LC ₅₀	2350 ppm
8-hr LC ₅₀	2400 ppm
Mouse	Du Pont Co., 1960 Paulet and Debrousses, 1965
4-hr LC ₅₀	1766 ppm
30-min LC ₅₀	3000 ppm
2-hr LC ₅₀	1200 ppm
4-hr LC ₅₀	750 ppm
6-hr LC ₅₀	680 ppm
8-hr LC ₅₀	600 ppm
Guinea pig	Du Pont Co., 1960
4-hr LC ₅₀	2114 ppm

Acute inhalation toxicity of HFP in rats following a single 6-hour exposure		
Concentration (ppm)	Mortality (dead/exposed)	Pathology findings
1760	2/2	nephrosis, pulmonary congestion and edema
1250	2/2	nephrosis, pulmonary congestion and edema
880	0/2	nephrosis
735	1/2	nephrosis
600	0/2	nephrosis

Du Pont Co. (1960)

Lethal Toxicity of HFP in Laboratory Species			
Species	Exposure	Mortality ratio	Reference
Rabbit	4-hr 3440 ppm 2000 ppm	5/6 nephrosis, pulmonary edema 1/2 nephrosis, pulmonary congestion/edema	Du Pont Co., 1960
	1500 ppm	0/2 reversible nephrosis, tracheal congestion	
Guinea pig	4-hr 3440 ppm 1500 ppm 1000 ppm	8/10 nephrosis, pulmonary edema 2/4 nephrosis, pulmonary edema 0/4 reversible nephrosis	Du Pont Co., 1960

Lethal Toxicity of HFP in Laboratory Species			
Species	Exposure	Mortality ratio	Reference
Rat	6-hr 1760 ppm	2/2 renal toxicity in all exposure groups; pulmonary congestion and edema in 1760- and 1250-ppm groups	Du Pont, 1960
	735 ppm 600 ppm	1/2 nephrosis 0/2	
	4-hr 3440 ppm 2870 ppm 1980 ppm	6/10 nephrosis 8/10 nephrosis 0/10 reversible ("healing") nephrosis	
	0.5-8 hrs 15,750 ppm 4000 ppm 2800 ppm 2350 ppm 2400 ppm	30-min LC ₅₀ 2-hr LC ₅₀ 4-hr LC ₅₀ 6-hr LC ₅₀ 8-hr LC ₅₀	Paulet and Debrousses, 1965
	2.5 hrs 5000 ppm 500 ppm	4/4 2 or 5-hr exposure: 100% mortality 1/4 2-hr exposure 4/4 5-hr exposure	Salveneschi, 1971
	250 ppm	0/4 no signs of toxicity	

Lethal Toxicity of HFP in Laboratory Species			
Species	Exposure	Mortality ratio	Reference
Mouse	4-hr 3020 ppm 2600 ppm 1500 ppm 1000 ppm	8/10 nephrosis, bronchopneumonia 9/10 nephrosis 4/10 nephrosis 0/10 reversible ("healing") nephrosis	Du Pont Co., 1960
	6-hr 1900 ppm 1000 ppm	4/4 deaths occurred 1-6 days postexposure 0/4	Du Pont Co., 1986a
	0.5-8 hrs 3000 ppm 1200 ppm 750 ppm 680 ppm 600 ppm	30-min LC ₅₀ 2-hr LC ₅₀ 4-hr LC ₅₀ 6-hr LC ₅₀ 8-hr LC ₅₀	Paulet and Debrousses, 1965

HFP - NONLETHAL TOXICITY

• No human data

- Animal data
 - multiples species (rats, mice, rabbits, guinea pigs)
 - qualitatively similar response among species
 - characterized by pulmonary and renal effects
 - reversible upon cessation of exposure

HFP - NONLETHAL TOXICITY

Nonlethal toxicity of HFP in laboratory species following inhalation exposure			
Species	Exposure	Effect	Reference
Rat	140 ppm, 4 hrs	no signs of toxicity	Du Pont, Co., 1960
	320-1980 ppm, 4 hrs	reversible nephrosis	
	250 ppm, 5 hrs	no signs of toxicity	Salveneschi, 1971
	50 ppm, 8 hrs	no signs of toxicity	
Mouse	2600 ppm, 30 min	reversible nephrosis	Dilley et al., 1974
	380-1200 ppm, 4 hrs	reversible nephrosis	Potter et al., 1981
Mouse	1000 ppm, 4 hrs	labored respiration, reversible nephrosis	Du Pont Co., 1960
	1000 ppm, 6 hrs	lethargic/unresponsive	Du Pont Co., 1986a
Rabbit	1500 ppm, 4 hrs	reversible nephrosis, bronchitis, tracheal congestion	Du pont Co., 1960
Guinea pig	1000 ppm, 4 hrs	reversible nephrosis	Du Pont Co., 1960

HFP AEGL-1

Critical effect/POD: Absence of notable toxicity in rats exposed to 140 ppm for 4 hours (Du Pont Co., 1960)

Uncertainty factors: Total uncertainty adjustment of 30.

Interspecies: UF = 10; lack of corroborative data regarding absence of effects or minor effects in additional species

Intraspecies: UF=3; the continuum of HFP toxicity may vary slightly due to metabolism-mediated variability in production of reactive species resulting in nephrotoxicity. The variability in minor effects is not expected to vary greatly

Time scaling: $n = 1.3$ derived from rat lethality data; 10-min values equivalent to 30-min

AEGL-1 Values for HFP				
10-min	30-min	1-hr	4-hr	8-hr
22 ppm	22 ppm	13 ppm	4.7 ppm	2.8 ppm

HFP - NONLETHAL TOXICITY

- No human data
- Animal data
 - multiples species (rats, mice, rabbits, guinea pigs)
 - qualitatively similar response among species
 - characterized by pulmonary and renal effects
 - reversible upon cessation of exposure

HFP - NONLETHAL TOXICITY

Nonlethal toxicity of HFP in laboratory species following inhalation exposure			
Species	Exposure	Effect	Reference
Rat	140 ppm, 4 hrs	no signs of toxicity	Du Pont, Co., 1960
	320-1980 ppm, 4 hrs	reversible nephrosis	
	250 ppm, 5 hrs	no signs of toxicity	Salveneschi, 1971
	50 ppm, 8 hrs	no signs of toxicity	
Mouse	2600 ppm, 30 min	reversible nephrosis	Dilley et al., 1974
	380-1200 ppm, 4 hrs	reversible nephrosis	Potter et al., 1981
Mouse	1000 ppm, 4 hrs	labored respiration, reversible nephrosis	Du Pont Co., 1960
	1000 ppm, 6 hrs	lethargic/unresponsive	Du Pont Co., 1986a
Rabbit	1500 ppm, 4 hrs	reversible nephrosis, bronchitis, tracheal congestion	Du pont Co., 1960
Guinea pig	1000 ppm, 4 hrs	reversible nephrosis	Du Pont Co., 1960

HFP AEGL-2

Critical effect/POD: Reversible nephrosis and resulting alterations in renal function in rats exposed to 320 ppm HFP for 4 hours (Du Pont Co., 1960)

Uncertainty factors: Total uncertainty adjustment of 10.

Interspecies: UF = 3; HFP toxicity was qualitatively similar among all the species tested, exposures causing nephrosis did not vary greatly across the species tested

Intraspecies: UF of 3 was considered sufficient to account for variability in metabolism and subsequent formation of reactive species involved in nephrotoxicity

Time scaling: $n = 1.3$ 10-min values equivalent to 30-min

AEGL-2 Values for HFP				
10-min	30-min	1-hr	4-hr	8-hr
150 ppm	150 ppm	91 ppm	32 ppm	19 ppm

HFP AEGL-3

Critical effect/POD: Estimated lethality threshold in rats; 4-hr BMCL₀₅ (log probit model) of 1677 ppm (Du Pont Co., 1960)

Uncertainty factors: Total uncertainty adjustment of 10.

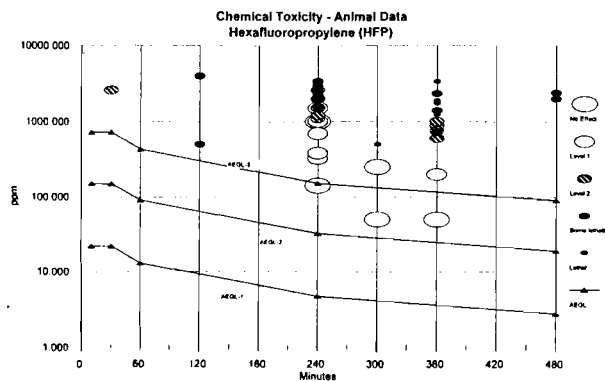
Interspecies: UF = 3; HFP toxicity was qualitatively similar among all the species tested, lethality estimates varied by ~ 2 to 4-fold

Intraspecies: UF of 3 was considered sufficient to account for variability in metabolism and subsequent formation of reactive species involved in nephrotoxicity

Time scaling: $n = 1.3$ 10-min values equivalent to 30-min

AEGL-3 Values for HFP				
10-min	30-min	1-hr	4-hr	8-hr
800 ppm	800 ppm	480 ppm	170 ppm	100 ppm

AEGL Values for Hexafluoropropylene					
Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	22 ppm	22 ppm	13 ppm	4.7 ppm	2.8 ppm
AEGL-2 (Disabling)	150 ppm	150 ppm	91 ppm	32 ppm	19 ppm
AEGL-3 (Lethality)	800 ppm	800 ppm	480 ppm	170 ppm	100 ppm

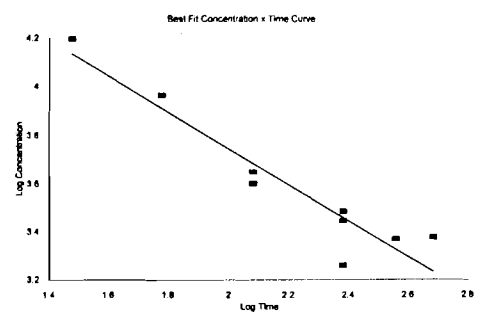


Rat lethality (Du Pont & Co., 1960; Paulet and Debrousses, 1965)

Time	Conc.	Log Time	Log Conc.
30	15760	1.4771	4.1973
80	9226	1.7782	3.9650
120	4000	2.0792	3.8021
120	4466	2.0792	3.8499
240	2800	2.3802	3.4472
240	3080	2.3802	3.4857
240	1628	2.3802	3.2615
380	2350	2.5683	3.3711
480	2400	2.6812	3.3802

Regression Output:
 Intercept 5.2435
 Slope -0.7494
 R Squared 0.8950
 Correlation -0.9460
 Degrees of Freedom 7
 Observations 9

n = 1.33
 k = 9831315.06



**ACUTE EXPOSURE GUIDELINE LEVELS
for
TETRAFLUOROETHYLENE**

National Advisory Committee for AEGLs Meeting 40
September 6-8, 2006

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
George Rusch

Chemical Reviewers:
Robert Benson
Richard Niemeier

TETRAFLUOROETHYLENE

Physical State: Colorless gas
High vapor pressure

No human studies (monitoring data: no-effect TWA of ≤ 6.5 ppm)
Sufficient animal studies

Mechanism of action:

Pulmonary congestion at lethal and near-lethal concentrations
Kidney lesions mediated via metabolism (conjugation) with glutathione
generally reversible

No information on time scaling

2

Tetrafluoroethylene Metabolism/Uncertainty Factors

Primary pathway of metabolism: conjugation with hepatic glutathione
Glutathione conjugate broken down to cysteine metabolite in kidney
Cysteine (thiol) metabolite considered the nephrotoxic species

Considerations for interspecies uncertainty factor

Greater uptake in rodents than humans
Higher respiratory rate and cardiac output
Higher blood:air partition coefficient

Higher tissue concentrations of glutathione transferases (GST)
Possible faster metabolism to the toxic metabolite

Considerations for intraspecies uncertainty factor:

Humans differ in number of copies and classes of GST genes
Some individuals are non-conjugators (theoretically would be at lower risk)
Other individuals are "slow" or "fast" metabolizers
Difference of questionable toxicological significance (Nolan et al. 1985)

3

Tetrafluoroethylene Data

Lethality Values:

4-hour LC₅₀ values:

All species (rat, mouse, guinea pig, hamster): 28,000-40,000 ppm

Non-Lethal Values and Effects:

Highest non-lethal value:

Rat: 20,000 ppm for 4 hours (DuPont 1959)
Hamster: 20,700 ppm for 4 hours (DuPont 1980)

Sublethal effects (rats):

3500 ppm for 30 minutes - reversible kidney lesions (Dilley et al. 1974)
3700 ppm for 4 hours - renal tubule fibrosis (DuPont 1977)
1200 ppm for 6 hours - no kidney cell proliferation (Keller et al. 2000)
1000 ppm for 6 hours - no effect (Odum and Green 1984)
2000 ppm for 6 hours - NOAEL for kidney lesions
3000 ppm for 6 hours - possible threshold for clinical chemistry changes
4000 ppm for 6 hours - clinical chemistry changes... due to kidney effects
6000 ppm for 6 hours - kidney necrosis (no recovery period)

4

Tetrafluoroethylene AEGL-1

Basis for AEGL-1 (Keller et al. 2000):

Rat, 1200 ppm for 6 hours
NOAEL for reversible kidney effects

Uncertainty factors:

Interspecies: 3, uptake greater in the rodent; higher tissue GST

Intraspecies: 3, difference among metabolizers not expected to vary greatly

Time-scaling: n = 3, 1 for shorter and longer exposure durations, respectively

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	400 ppm	270 ppm	220 ppm	140 ppm	90 ppm

The 4-hour study was time-scaled to 10 minutes because a 30-minute study was available.

5

Tetrafluoroethylene AEGL-2

Basis for AEGL-2 (Odum and Green 1984):

Rat, 3000 ppm for 6 hours
NOAEL for irreversible kidney effects

Uncertainty factors:

Interspecies: 3, uptake greater in the rodent; higher tissue GST

Intraspecies: 3, difference among metabolizers not expected to vary greatly

Time-scaling: n = 3, 1 for shorter and longer exposure durations, respectively

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	990 ppm	690 ppm	550 ppm	340 ppm	230 ppm

6

Tetrafluoroethylene AEGL-3

Basis for AEGL-3:

Rat: 20,000 ppm for 4 hours (DuPont 1959)
NOAEL for lethality

Uncertainty factors:

Interspecies: 3, uptake greater in the rodent; higher tissue GST

Intraspecies: 3, difference among metabolizers not expected to vary greatly

Time-scaling: n = 3, 1 for shorter and longer exposure durations, respectively

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	5800 ppm	4000 ppm	3200 ppm	2000 ppm	1000 ppm

7

Tetrafluoroethylene AEGLs - Summary

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	400 ppm	270 ppm	220 ppm	140 ppm	90 ppm
AEGL-2	990 ppm	690 ppm	550 ppm	340 ppm	230 ppm
AEGL-3	5800 ppm	4000 ppm	3200 ppm	2000 ppm	1000 ppm

AEGL-1: 1200 ppm for 6 hours (Keller et al. 2000)

AEGL-2: 3000 ppm for 6 hours (Odum and Green 1984)

AEGL-3: 20,000 ppm for 4 hours (DuPont 1959)

8

**ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR**

**ETHYLBENZENE
(CAS Reg. No. 100-41-4)**

Draft 1: September/2006

ATTACHMENT 11

ETHYLBENZENE

Almost exclusively used for production of styrene

~20% of mixed xylenes

1

2

• Human data relevant to AGEL derivation

- Six male volunteers (Yant et al. 1930)
 - 1000 ppm: eye irritation with lacrimation which decreased to hardly noticeable after 1-2 min
 - 2000 ppm: severe eye and throat irritation which decreased with continued exposure; vertigo at 5 min
 - 5000 ppm: intolerable
- No adverse effects in pharmacokinetic studies
 - 46 ppm for 8 hrs (Gromiec and Piotrowski 1984)
 - 85 ppm for 8 hours (Bardodej and Bardodejova 1970)
 - 150 ppm for 4 hours (Engström et al. 1984)

3

4

Summary of Animal Lethality Data Following Ethylbenzene exposure

Species/sex	Conc. (ppm)	Duration	Effects	Reference
Guinea pig/f	2500	8 hours 6 hours	1/8 died no effects	Cappaert et al. 2002
Guinea pig/not stated	10,000	2 hours	2/6	Yant et al. 1930
Rat/m	2400 1200	6 hours/day; 4 days	5/5; one on day 1 lacrimation	Bio/dynamics 1986
Rat/not stated	4000	4 hours	LC ₅₀	Smyth et al. 1962; Mellon Institute 1949
Mouse/m	2400 1200	6 hours/day; 4 days	5/5; all on day 2 4/5; on day 3	Bio/dynamics 1986

Summary of Nonlethal Animal Data Following Ethylbenzene Exposure

Species/sex	Conc. (ppm)	Duration	Effects	Reference
Guinea pig/not stated	1000-10,000	up to 480 min	1000: irritation after 3-8 min disappeared after 30 min 2000: immediate irritation, unsteadiness after 390 min, ataxia after 480 min 5000: immediate irritation, unsteadiness and ataxia after 26-30 min, tremors, abnormal respiration	Yant et al. 1930
Rabbit/m	400-2400	6 hours/day for 4 days	lacrimation	Bio/dynamics 1986
Rabbit/m,f	382-1610	6 hours/day, 5 days/week, 4 weeks	no clinical signs, decr wt gain at 1610 ppm	Cragg et al. 1989
Rat/f	550 ppm	8 hours/day, 5 days	no effects	Cappaert et al. 2002
Rat/m	400, 1200	6 hours/day for 4 days	400: lacrimation after 3 days 1200: lacrimation on 2/5 after 1 day	Bio/dynamics 1986
Rat/m	400-2180	4 hours	400-1500: increased activity >1500: decreased activity 2180: minimum narcotic	Molnár et al. 1986
Rat/m	2000 ppm	6 hours/day for 3 days	no death or clinical signs	Andersson et al. 1981
Rat/m,f Mice/m,f	99-782	6 hours/day, 5 days/week, 4 weeks	no clinical signs, incr liver wt at 782 ppm	Cragg et al. 1989
Mice/m	400	6 hours/day for 4 days	lacrimation after 3 days	Bio/dynamics 1986

Proposed AEGL-1 Values for Ethylbenzene				
10-minute	30-minute	1-hour	4-hour	8-hour
330 ppm (1440 mg/m ³)	330 ppm (1440 mg/m ³)	330 ppm (1440 mg/m ³)	330 ppm (1440 mg/m ³)	330 ppm (1440 mg/m ³)

Key Study: Yant et al. 1930

Exposure: humans and guinea pigs; 1000 ppm

Effect: Threshold for AEGL 1 effects; immediate irritation which diminished

Scaling: None

UFs: 3 (3 for intraspecies variability and 1 for interspecies variability)

7

Proposed AEGL-2 Values for Ethylbenzene				
10-minute	30-minute	1-hour	4-hour	8-hour
1600 ppm (6960 mg/m ³)	1600 ppm (6960 mg/m ³)	1200 ppm (5220 mg/m ³)	780 ppm (3393 mg/m ³)	540 ppm (2349 mg/m ³)

Key Study: Yant et al. 1930

Exposure: humans and guinea pigs; 2000 ppm

Effect: Threshold for AEGL 2 effects; unsteadiness in guinea pig after 6.5 hours; vertigo in human

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

UFs: 3 (3 for intraspecies variability and 3 for interspecies variability)

8

Proposed AEGL-3 Values for Ethylbenzene				
10-minute	30-minute	1-hour	4-hour	8-hour
1800 ppm (7830 mg/m ³)	1800 ppm (7830 mg/m ³)	1500 ppm (6525 mg/m ³)	920 ppm (4002 mg/m ³)	600 ppm (2610 mg/m ³)

Key Study: Bio/dynamics 1986

Exposure: rats; 2400 ppm, 6 hours

Effect: Threshold for AEGL 3 effects; approximate threshold for lethality

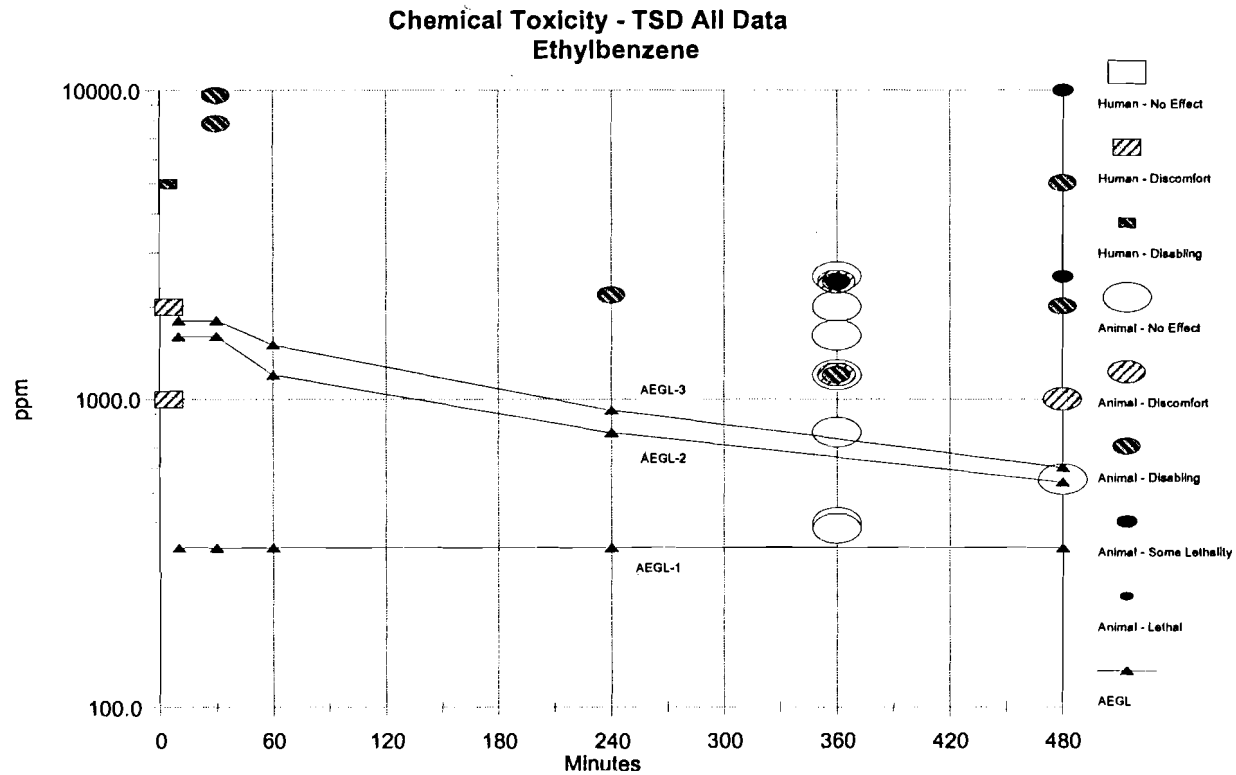
Scaling: $C^n \times t = k$, where $n = 1$ or 3

UFs: 3 (3 for intraspecies variability and 1 for interspecies variability)

9

10

Summary of Proposed AEGL Values for Ethylbenzene					
Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	330 ppm	330 ppm	330 ppm	330 ppm	330 ppm
AEGL-2 (Disabling)	1600 ppm	1600 ppm	1200 ppm	780 ppm	540 ppm
AEGL-3 (Lethal)	1800 ppm	1800 ppm	1500 ppm	920 ppm	600 ppm



**ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
SELECTED CHLOROFORMATES**

**NAC/AEGL-40
September 6-8, 2006**

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Ernest Falke

Chemical Reviewers: Lynn Beasley and Paul Tobin

- **Hydrolyze in water or moist air to produce the parent hydroxy compound, hydrogen chloride, carbon dioxide, and a carbonate.**
- **All title chloroformates are direct-acting contact irritants, and are corrosive to the eyes, skin, gastrointestinal and respiratory tracts.**
- **NAC-39: Values derived for nine chloroformates**
- **NAC-40: benzyl chloroformate
phenyl chloroformate
2-ethylhexyl chloroformate**
- **In all cases the inter- and intra- species uncertainty factors were 3 and 3, respectively.**
- **Where an AEGL-2 was calculated it was determined by dividing the AEGL-3 by 3.**

**Justified by steep concentration-response curve
(SOP Section 2.2.2.3)**

- **AEGL-1 values are Not Recommended for any chloroformates due to insufficient data**

Chloroformate	1-hour Rat LC ₅₀ Data	4-hour Rat LC ₅₀ Data	Mouse RD ₅₀	1-hr AEGL-3
<i>Phenyl</i>		<i>30 ppm (BASF, 1990; Hoechst, 1989)</i>	<i>19.5 ppm (Carpenter, 1982)</i>	<i>0.57 ppm</i>
Allyl	65.1 ppm (Stillmeadow, 1987)	-	-	2.1 ppm
<i>2-Ethylhexyl</i>	-	<i>33.9 ppm (BASF, 1985)</i>	-	<i>2.9 ppm</i>
<i>Benzyl</i>	-	<i>Approx. 85 ppm (BASF, 1990)</i>	-	<i>2.9 ppm</i>
Ethyl	145-170 ppm (Vernot et al., 1977) 189-200 ppm (Fisher et al., 1981)	-	77.5 ppm (Carpenter, 1982)	4.8 ppm
Methyl	88-103 ppm (Vernot et al., 1977) 92-123 ppm (Fisher et al., 1981)	52 ppm (Hoechst, 1986)	52.4 ppm (Carpenter, 1982)	6.7 ppm
n-Butyl	Approx. 200 ppm: 4/10 rats dead (BASF, 1970)	-	-	6.7 ppm
Isobutyl				n-butyl values adopted as surrogate
sec-Butyl				
Isopropyl	1-hr- 300 ppm (Bio-Test, 1970)	-	104 ppm (Carpenter, 1982)	10 ppm
Propyl	1-hr- 410 ppm (Bio-Test, 1970)	-	83.5 ppm (Carpenter, 1982)	11 ppm
Ethyl chlorothio	-	45 ppm (Stauffer,1983)	-	0.79 ppm

AEGL-1 VALUES: BENZYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR

Not Recommended due to insufficient data.

AEGL-2 VALUES: BENZYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
1.2 ppm	1.2 ppm	0.97 ppm	0.63 ppm	0.31 ppm

Endpoint: $\frac{1}{3}$ The AEGL-3 values

Endpoint is justified based on the steep concentration-response curve:

Rat 4-hr exposure (BASF, 1990):

0% Mortality at 18.6 ppm

50% mortality at 85 ppm

Clinical signs noted at 18.6 ppm resolved within 2 days post-exposure

AEGL-3 VALUES: BENZYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
3.7 ppm	3.7 ppm	2.9 ppm	1.9 ppm	0.93 ppm

Species: Rat (5 sex/group)
Concentration: 18.6 ppm
Time: 4-hours
Endpoint: No mortality (experimental concentration)
Reference: BASF, 1990

Time Scaling: $C^n \times t = k$, where $n= 3$ for the 30-minute and 1-hour time periods, and $n= 1$ for the 8-hour time period, to provide AEGL values that would be protective of human health (NRC, 2001). The 30-minute AEGL-3 value is adopted as the 10-minute AEGL-3 value.

Uncertainty Factors:

Interspecies = 3 Intraspecies = 3

Highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

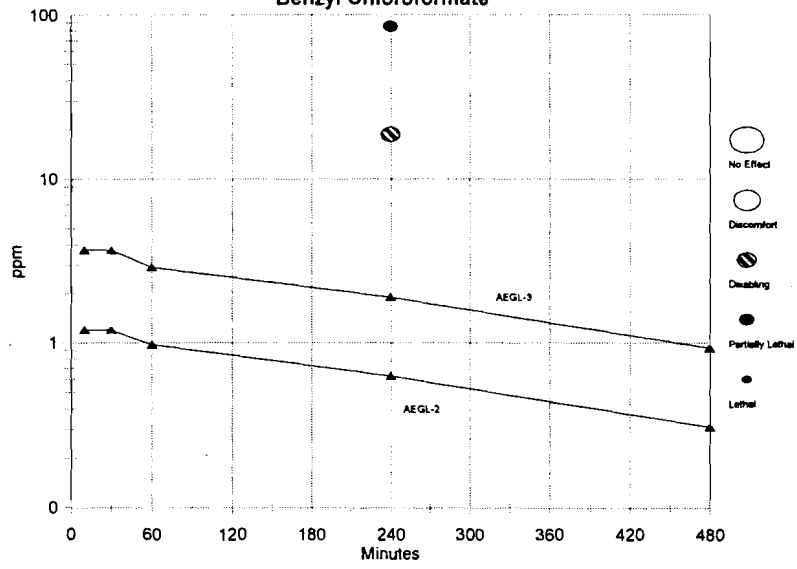
Inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate, isopropyl chloroformate, and n-butyl chloroformate.

These resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs.

THERE ARE NO OTHER EXTANT STANDARDS AND GUIDELINES FOR BENZYL CHLOROFORMATE!

Summary of Proposed AEGL Values for Benzyl Chloroformate					
Guideline	Exposure Duration				
	10-minutes	30-minutes	1-hour	4-hours	8-hours
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	1.2 ppm	1.2 ppm	0.97 ppm	0.63 ppm	0.31 ppm
AEGL-3	3.7 ppm	3.7 ppm	2.9 ppm	1.9 ppm	0.93 ppm

Chemical Toxicity - TSD Animal Data
Benzyl Chloroformate



AEGL-1 VALUES: PHENYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR

Not Recommended due to insufficient data.

AEGL-2 VALUES: PHENYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.24 ppm	0.24 ppm	0.19 ppm	0.12 ppm	0.06 ppm

Endpoint: $\frac{1}{3}$ The AEGL-3 values

Endpoint is justified based on the steep concentration-response curve:

Rat 4-hr exposure (BASF, 1990; Hoechst, 1989):

20% Mortality at 15.6 ppm

70% Mortality at 44.5 ppm

90% Mortality at 74.9 ppm

Clinical signs noted at 15.6 ppm resolved within 3 days post-exposure

AEGL-3 VALUES: PHENYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.72 ppm	0.72 ppm	0.57 ppm	0.36 ppm	0.18 ppm

Species: Rat (5 sex/group)
Concentration: 3.6 ppm
Time: 4-hour
Endpoint: Estimated lethality threshold: BMCL₀₅
References: BASF, 1990; Hoechst, 1989

Time Scaling: $C^n \times t = k$, where $n=3$ for the 30-minute and 1-hour time periods, and $n=1$ for the 8-hour time period, to provide AEGL values that would be protective of human health (NRC, 2001). The 30-minute AEGL-3 value is adopted as the 10-minute AEGL-3 value.

Uncertainty Factors:

Interspecies = 3 Intraspecies = 3

Highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

Inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate, isopropyl chloroformate, and n-butyl chloroformate.

These resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs.

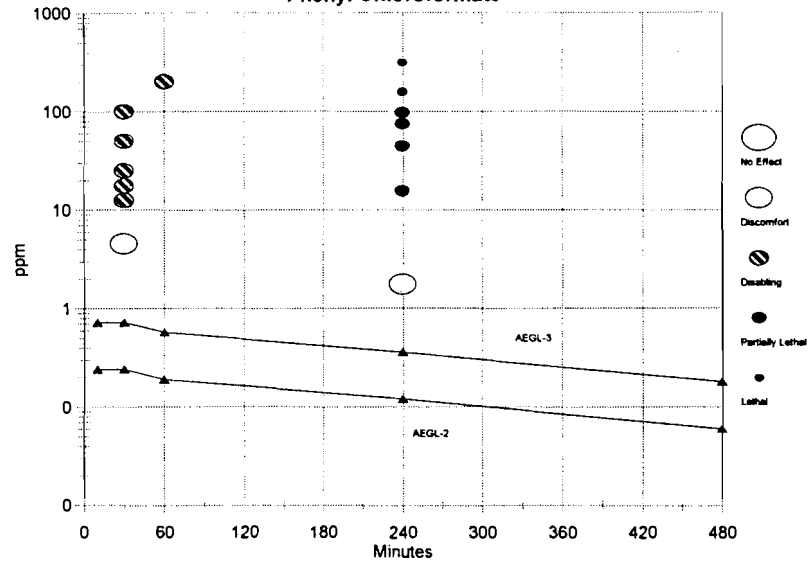
Table IX-3. Mortality in Rats Exposed to Phenyl Chloroformate for 4 hours*				
	Males	Females	Combined Males and Females	Reference
1.76 ppm	0/5	0/5	0/10	Hoechst, 1989
15.6 ppm	0/5	2/5	2/10	BASF, 1990
44.5 ppm	4/5	3/5	7/10	Hoechst, 1989
74.9 ppm	4/5	5/5	9/10	BASF, 1990
97 ppm	5/5	4/5	9/10	Hoechst, 1989
156 ppm	5/5	5/5	10/10	Hoechst, 1989
159.3 ppm	5/5	5/5	10/10	BASF, 1990
311 ppm	5/5	5/5	10/10	Hoechst, 1989
LC₅₀	37.6 ppm	24.2 ppm	30.0 ppm	
BMCL₀₅	6.3 ppm	0.82 ppm	3.6 ppm	
BMC₀₁	12.4 ppm	2.6 ppm	5.4 ppm	

Because mortality results are similar in both studies, the data sets were combined to provide a more complete concentration-response curve, especially at the lower-concentration portion of the curve. Combination of the data sets is justified because both studies are nose-only exposures of Wistar rats and mortality data are similar for both studies.

THERE ARE NO OTHER EXTANT STANDARDS AND GUIDELINES FOR PHENYL CHLOROFORMATE!

Summary of Proposed AEGL Values for Phenyl Chloroformate					
Guideline	Exposure Duration				
	10-minutes	30-minutes	1-hour	4-hours	8-hours
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.24 ppm	0.24 ppm	0.19 ppm	0.12 ppm	0.06 ppm
AEGL-3	0.72 ppm	0.72 ppm	0.57 ppm	0.36 ppm	0.18 ppm

Chemical Toxicity - TSD Animal Data
Phenyl Chloroformate



AEGL-1 VALUES: 2-ETHYL HEXYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR

Not Recommended due to insufficient data.

AEGL-2 VALUES: 2-ETHYL HEXYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
1.2 ppm	1.2 ppm	0.97 ppm	0.60 ppm	0.30 ppm

Endpoint: $\frac{1}{3}$ The AEGL-3 values

Endpoint is justified based on the steep concentration-response curve:

Rat 4-hr exposure (BASF, 1985):

Mortality	Concentration
0%	22.8 ppm
25%	26.6 ppm
45%	34.3 ppm
100%	46.9 ppm

AEGL-3 VALUES: 2-ETHYL HEXYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
3.6 ppm	3.6 ppm	2.9 ppm	1.8 ppm	0.91 ppm

Species: Rat (10/sex/group)
Concentration: 18.1 ppm
Time: 4-hours
Endpoint: Estimated lethality threshold: BMCL₀₅
Reference: BASF, 1985

Time Scaling: $C^n \times t = k$, where $n=3$ for the 30-minute and 1-hour time periods, and $n=1$ for the 8-hour time period, to provide AEGL values that would be protective of human health (NRC, 2001). The 30-minute AEGL-3 value is adopted as the 10-minute AEGL-3 value.

Uncertainty Factors:

Interspecies = 3 Intraspecies = 3

Highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

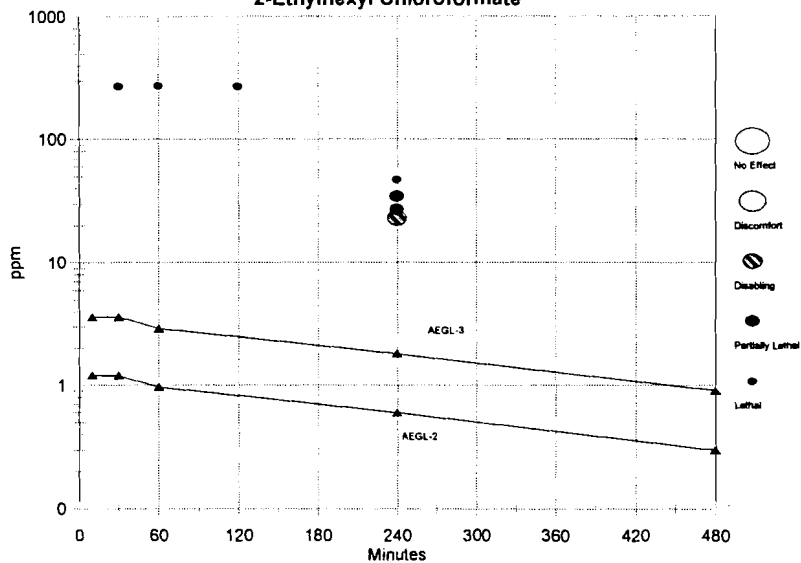
Inter- and intraspecies uncertainty factors of 3 each were also applied when AEGL-3 values were calculated for the structural analogs, methyl chloroformate, isopropyl chloroformate, and n-butyl chloroformate.

These resulting AEGL values were considered protective when compared with chemical-specific, repeated-exposure data for these analogs.

THERE ARE NO OTHER EXTANT STANDARDS AND GUIDELINES FOR 2-ETHYL HEXYL CHLOROFORMATE!

Summary of Proposed AEGL Values for 2-Ethyl Hexyl Chloroformate					
Guideline	Exposure Duration				
	10-minutes	30-minutes	1-hour	4-hours	8-hours
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	1.2 ppm	1.2 ppm	0.97 ppm	0.60 ppm	0.30 ppm
AEGL-3	3.6 ppm	3.6 ppm	2.9 ppm	1.8 ppm	0.91 ppm

Chemical Toxicity - TSD Animal Data
2-Ethylhexyl Chloroformate



**ACUTE EXPOSURE GUIDELINE LEVELS FOR
DIBROMOETHANE
(CAS NO. 106-93-4)**

**PRESENTED BY
KOWETHA DAVIDSON**

**CHEMICAL MANAGER
BOB BENSON**

**NAC/AEGL MEETING, BETHESDA, MD
SEPTEMBER 6-8, 2006**

DIBROMOETHANE

CAS NO. 106-93-4

COMMON SYNONYMS: Ethylene dibromide; EDB

PHYSICAL CHARACTERISTICS:

- heavy colorless liquid
- Vapor pressure: 11 mm Hg at 25°C; 17.4 mm HG at 30°C
- Vapor density: 6.5 (air = 1)
- Soluble in ethanol and ethyl ether
- Conversion: 1 ppm = 0.13 mg/m³

OTHER INFORMATION

- **Past use:** scavenger in leaded gasoline and as an agricultural fumigant
- **Current use:** chemical intermediate for pharmaceuticals, dyes, polymers, and other chemicals
- **ODOR:** chloroform-like, foul, pungent, or sweetish
- **ODOR DETECTION THRESHOLD:** 10 ppm

HUMAN DATA

- Effects at lethal concentrations
 - Irritating to eyes, throat and respiratory tract
 - Diarrhea
 - CNS effects: restlessness, nervousness, combativeness, lethargy
 - Pulmonary edema
 - Hepatomegaly, degenerative changes in the liver
 - Liver and renal failure
 - Congestion of the viscera and brain
 - Elevated blood and tissue bromine levels

HUMAN DATA

- **Effects at Non-lethal Concentrations**
 - Irritation to the eyes (conjunctiva, eyelids)
 - Respiratory tract irritation (75 ppm?)
 - Fatigue, loss of appetite, headache, and depression
 - Gastrointestinal discomfort and vomiting (100-200 ppm?)
 - No clear exposure-response data
 - Occupational exposure:
 - TWA, 2.9 ppm (range = 0.4-38 ppm)
 - TWA, 5.0 ppm (range = 1.9-96 ppm)
 - TWA, 3.5 to 4.0 ppm (range = 0-110 ppm)
 - Other occupational exposures: 13.4 ppm when filling drums, up to 71 ppm after a spill

ANIMAL DATA

Lethality Data (Single Inhalation Exposure)

Clinical signs and gross and microscopic findings

- **Dog:** 1 hour exposure to 1, 2, or 5 mL DBE vaporized in a 100-L Chamber
- **Effects:** evidence of eye (conjunctivitis, corneal opacity) and respiratory tract irritation (rales, rattling, labored breathing, pulmonary hemorrhage, bronchopneumonic foci ; CNS effects (restlessness, clonic twitching, strong salivation); brain and intestinal hemorrhage, liver damage; death within 12-18 hours after 2 or 5 mL or 3 weeks after 1 mL
- **Rat:** 200-10,000 ppm for 1.2 minutes to 16 hours
- **Effect:** weight loss, irritability, unkempt appearance, respiratory tract irritation (bloody discharge from the nose, pulmonary congestion, edema, hemorrhage, and inflammation, liver damage (cloudy swelling, fatty degeneration and necrosis), kidney damage (interstitial congestion, edema, cloudy swelling of tubular epithelium)

ANIMAL DATA (Cont.)

Lethality Data (Single Inhalation Exposure)

Clinical signs and gross and microscopic findings

- **Guinea Pig:** 2000-8000 ppm for 30-150 minutes
- **Effects:** upper respiratory tract irritation, generalized weakness, damage to the kidney, pancreas, spleen, heart, liver, and adrenals; swelling and interstitial edematous degeneration of the abdominal vascular system; death within 18 hours
- **Rabbit:** Unknown conc. That induced light anesthesia for 10 minutes
- **Effects:** evidence of respiratory tract irritation (rapid breathing and snuffing, enlarged lungs filled with frothy exudate), evidence of vascular congestion and cyanosis, liver damage (enlarged and mottled, fatty change, marked congestion); death within 18 hours

Similar effects were observed in animals exposed repeatedly to DBE

Acute exposure of rats to 1,2-dibromoethane				
Concentration (ppm)	Duration of exposure	Mortality	% lethality	Lethal times* (LCt)
10,000	6.0 min	20/20	100	$LCt_{99.99} = 9 \text{ min}$ $LCt_{50} = 2.4 \text{ min}$ $LCt_{01} = 0.6 \text{ min}$
	4.2 min	7/10	70	
	3.0 min	2/4	50	
	1.8 min	1/20	5	
	1.2 min	0/20	0	
5000	8.4 min	20/20	100	$LCt_{99.99} = 21 \text{ min}$ $LCt_{50} = 5.4 \text{ min}$ $LCt_{01} = 1.8 \text{ min}$
	6.0 min	9/10	90	
	4.2 min	5/15	33	
	3.0 min	3/30	10	
	2.4 min	0/20	0	
3000	12 min	5/10	50	$LCt_{99.99} = 36 \text{ min}$ $LCt_{50} = 10.8 \text{ min}$ $LCt_{01} = 3.6 \text{ min}$
	6 min	0/20	0	
1600	30 min	20/20	100	$LCt_{99.99} = 66 \text{ min}$ $LCt_{50} = 18 \text{ min}$ $LCt_{01} = 6 \text{ min}$
	24 min	12/15	80	
	18 min	4/15	27	
	12 min	0/30	0	
800	48 min	13/20	65	$LCt_{99.99} = 132 \text{ min}$ $LCt_{50} = 45 \text{ min}$ $LCt_{01} = 16.8 \text{ min}$
	32.8 min	10/20	50	
	30 min	4/20	20	
	24 min	4/20	20	

Source: Rowe et al., 1952

*Calculated by NIOSH 1977a.

Acute inhalation exposure to rats to 1,2-dibromoethane (Continued)				
Concentration (ppm)	Duration of Exposure	Mortality	% Lethality	Lethal times* (LCt)
400	5.0 h	20/20	200	LCt _{99.99} = 7.50 h LCt ₅₀ = 2.00 h LCt ₀₁ = 0.62 h
	3.0 h	17/20	85	
	2.5 h	19/20	95	
	2.0 h	16/25	64	
	1.4 h	5/25	25	
	1.0 h	2/20	10	
	48 min	1/20	5	
	36 min	0/20	0	
200	16.0 h	19/20	95	LCt _{99.99} = 42 h LCt ₅₀ = 12 h LCt ₀₁ = 2 h
	12.0 h	10/20	50	
	8.5 h	9/20	45	
	7.0 h	4/11	36	
	5.0 h	3/10	33	
	4.0 h	0/5	0	
	3.0 h	1/11	9	
	2.0 h	0/5	0	
	1.4 h	0/20	0	
100	8.5 h	0/20	0	NA
	12.0 h	0/20	0	
	16.0 h	0/20	0	

Source: Rowe et al., 1952
*Calculated by NIOSH 1977a

Acute inhalation exposure to guinea pigs to 1,2-dibromoethane				
Concentration (ppm)	Duration of exposure	Mortality	% lethality	Lethal times* (LCt)
400	7.0 h	20/20	100	Not calculated by NIOSH
	5.0 h	18/20	90	
	3.0 h	5/10	50	
	2.0 h	0/20	0	
200	7.0	0/15	0	

Source: Rowe et al., 1952
*Calculated by NIOSH 1977a

ANIMAL DATA

Non-Lethal Toxicity (Single Inhalation Exposure)

Concentrations & times associated with adverse effects (↑ liver wt. & slight histopathological changes in the liver (Rowe et al., 1952)

Concentration (ppm)	Time (min)
800	9
200	60
100	240

ANIMAL DATA

Non-Lethal Toxicity (Single Inhalation Exposure)

Concentrations & times associated with no adverse effects (Rowe et al., 1952)

Concentration (ppm)	Time (min)
800	6
200	42
100	150
50	420

ANIMAL DATA: DEVELOPMENTAL TOXICITY

- **Rats: Developmental neurotoxicity test:** 0, 0.43, 6.67, or 66.67 ppm, 4 h/d, 3 d/wk, GD 3-20
 - **Maternal:** ↓ weight gain at
 - **Developmental:** no neurotoxicity at 30, 63, 78, 83, 95, and 100 days

- **Rats:** 65 ppm for 6 h/d or 130 ppm for 3 h/day, GD 10, 11, & 12
 - **Maternal:** transient toxicity (not described) at 130 ppm
 - **Developmental: 130 ppm:** fetal death and spontaneous activity; **65 ppm:** ↓ exploratory activity, peak night activity, & index of neurobehavioral development up to week 8 of age

- **Mouse:** 20, 38, 80 ppm, 23 h/d, GD 6-15
 - **Maternal: 80 ppm,** 100% mortality; **38 ppm.** 22% mortality; **20 ppm,** ↓ fd consumption & ↓ wt. gain
 - **Developmental: 38 ppm,** ↓ no. viable fetuses, live litters; and ↓ fetal wt. & ↑ incidence of soft tissue & skeletal abnormalities; **20 ppm,** ↓ fetal wt. & ↑ incidence of skeletal abnormalities

Effects to Repeated Exposure to Inhaled 1,2-dibromoethane Vapor in Experimental Animals

Species/ Strain/Sex	Expt. Protocol	Effects/Comments	Reference
Monkeys (M&F)	50 ppm, 7 h/d, 49 times in 70 days (10 weeks; 25 ppm, 7 h/d, 156 times in 220 days (~31 weeks)	50 ppm: 5% weight loss, ill, nervous, & unkempt appearance throughout study, ↑ liver and kidney wt, slight central fatty degen in liver 25 ppm: no effects	Rowe et al., 1952
Rat/F344/ M&F	0, 3, 15, 75 ppm, 6 h/d, 5 d/wk, 13 wks	Systemic: 15 (M) & 75 ppm: ↓ wt. gain (M/F), adrenal cortical and thyroid follicular lesions (F) Nasal cavity: 3 ppm: no effect; 15 & 75 ppm: cytomegaly, hyperplasia, metaplasia, cilia loss	NTP 1982; Reznik et al. 1980,
Rat/F344/ M&F	0, 3, 10, 40 ppm, 6 h/d, 5 d/wk, 13 wks	Systemic: 40 ppm: mild liver lesions Nasal cavity: 3 ppm: no effect; 10 ppm: hyperplasia & single cell necrosis; 40 ppm: same as 10 ppm plus squamous metaplasia	Nitschke et al. 1980, 1981

Summary of Nonlethal Effects of Inhaled 1,2-dibromoethane Vapor in Experimental Animals

Mice/B6C3F ₁ /M&F	0, 3, 15, 75 ppm, 6 h/d, 5 d/wk, 13 wks	Systemic: 3 (F), 15 & 75 ppm (M&F): ↓ wt. gain Nasal cavity: 3 & 15 ppm: no effect 75 ppm: cytomegaly, hyperplasia, squamous metaplasia, cilia loss other effects: 75 ppm: eye irritation and megalocytes in bronchioles	NTP 1982; Reznik, 1980
Guinea pigs/M&F	200 ppm for 7 h	no effects observed	Rowe et al., 1952
Guinea pigs/M&F	50 ppm, 7 h/d. 57 times in 80 d	growth depression, inc. liver, lung, kidney wt., microscopic lesions in liver & kidney	Rowe et al 1952
Guinea pigs/M&F	25 ppm, 7 h/d, 13 times in 17 d & 145 times in 205 d	no effects observed	Rowe et al. 1952

Genetic Toxicity & Carcinogenicity

- **Genetic Toxicity**
 - Negative by inhalation route
 - Positive in liver and testicular germ cells of mice and rats, in vivo
 - Positive, in vitro systems: bacteria (not in glutathione deficient Salmonella strains), fungi, Drosophila, and cultured mammalian cells; exogenous metabolic activation is not required
- **Carcinogenicity**
 - **Rats:**
 - ≥10 ppm (6 h/day for 88 to 104 wks): nasal cavity, tunica vaginalis, mammary gland
 - ≥20 ppm (6 h/d, 18 months): blood vessels, adrenal gland, subcutaneous tissue
 - 40 ppm (6 h/d, 91-104 wks): lungs
 - **Mouse:**
 - ≥ 10 ppm (6 h/d, 90-104 wks): bronchus, bronchiole, lungs, blood vessels, mammary gland
 - 20 ppm (6 h/d, 6 months): lungs
 - 40 ppm (6 h/d, 78-104 wks) nasal cavity, lungs

Metabolism & Disposition

- **DBE is metabolized by two pathways**
 - **Microsomal oxidation via cytochrome P450 pathway metabolites**
 - CYP2E1 most reactive isoenzyme
 - Produces protein reactive
 - Responsible for tissue toxicity
 - Accounts for 15-27% of the metabolic activity in the rat
 - **Glutathione conjugation via glutathione-S-transferase pathway**
 - Produces DNA reactive metabolites
 - Isoenzymes activity range from fast and slow activity
 - Responsible for genotoxicity and carcinogenicity
 - Accounts for about 85% of the metabolic activity in the rat

Metabolism & Disposition (Cont.)

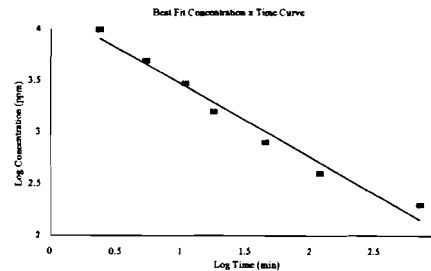
- **PBPK Model**
 - Rats have much higher (about three times) predicted blood concentrations of DBE than humans after an 8-hour exposure to 40 ppm
 - Production of P450 & GSH metabolites approximately equal in humans
 - Rat produces about four times more P459 metabolites than most sensitive human and about 80 times more GSH metabolites
 - About twofold difference in production of P450 metabolites in humans with high & low P450 activity
 - About a 10-fold difference in production of GSH metabolites in humans with high & low GSH activity

Susceptible Populations

- Individuals undergoing disulfiram (antabuse) treatment for alcohol abuse may be more sensitive to effects of DBE.
- Genetic polymorphism of the P450 and GSH enzyme systems contribute to variability in the population.

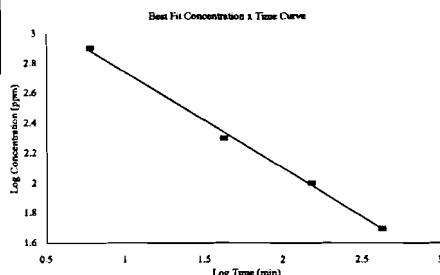
Concentration-Exposure Duration Relationship

LC ₅₀ (LD _{t50}) Data			
Time (min)	Conc.	Log Time	Log Conc.
2.4	10,000	0.38	4.00
504	5,000	0.73	3.70
10.8	3,000	1.03	3.48
18.0	1,600	1.26	3.20
45.0	800	1.65	2.90
120.0	400	2.08	2.60
720.0	200	2.86	2.30
Correlation = 0.97			
n = 1.4			



Concentration-Exposure Duration Relationship

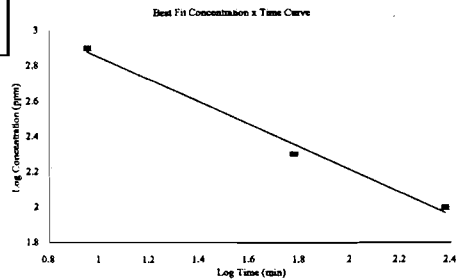
Conc. & Time – No Adverse Effects			
Time (min)	Conc.	Log Time	Log Conc.
6	800	0.78	2.90
42	200	1.62	2.30
150	100	2.18	2.00
420	50	2.62	1.70
Correlation = 0.999			
n = 1.6			



AEGL-1 VALUES for 1,2-Dibromoethane				
10-minute	30-minute	1-hour	4-hour	8-hour
52 ppm (400 mg/m ³)	26 ppm (200 mg/m ³)	17 ppm (131 mg/m ³)	7.1 ppm (55 mg/m ³)	4.6 ppm (55 mg/m ³)
Key Reference: Rowe et al., 1952				
Test Species/Strain/Number: rats/strain not specified/10 females				
Exposure Route/Concentrations/Durations: inhalation/50, 100, 200, and 800 ppm for 420, 150, 42, and 6 minutes, respectively				
Effects: No adverse effects				
Endpoint/Concentration/Rationale: No adverse effects in rats at 50 ppm for a 420-minute (7-hour) exposure				
Uncertainty Factors/Rationale: Total uncertainty factor: 10				
Interspecies = 1: The effects of exposure to 1,2-dibromoethane appear to be similar across species including canine, rodents, non-human primates, and humans, and non-human primates and humans are not expected to vary significantly regarding pharmacokinetics. PBPK modeling indicate that rats may be 4-80 times more sensitive than humans; effects are similar between animals and humans indicating similar pharmacodynamics				
Intraspecies = 10: PBPK modeling indicate that humans vary by a factor of about 10 in the production of reactive metabolites., and human taking therapeutic doses of disulfiram could have an increased sensitivity to 1,2-dibromoethane.				
Time Scaling: C ⁿ × t = k, where n = 1.6 based on regression of exposure concentrations and durations not associated with adverse effects				
Data Adequacy: The data for deriving AEGL-1 values were very limited; the report did not include some important details regarding the methods and results.				

Concentration-Exposure Duration Relationship

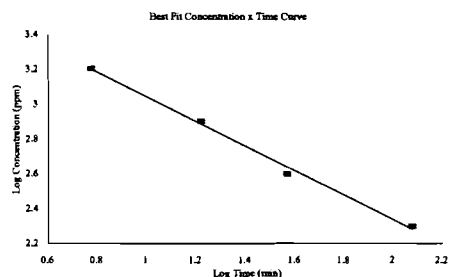
Conc. & Time – Adverse Effects			
Time (min)	Conc.	Log Time	Log Conc.
9	800	0.95	2.90
60	200	1.78	2.30
240	100	2.38	2.00
Correlation = 0.99			
n = 1.6			



AEGL-2 VALUES for 1,2-Dibromoethane				
10-minute	30-minute	1-hour	4-hour	8-hour
73 ppm (561 mg/m ³)	37 ppm (282 mg/m ³)	24 ppm (183 mg/m ³)	10 ppm (77 mg/m ³)	6.5 ppm (50 mg/m ³)
Key Reference: Rowe et al., 1952				
Test Species/Strain/Number: Rat/unknown strain/10 females/group				
Exposure Route/Concentrations/Durations: inhalation, 100, 200, and 800 ppm for 240, 60, and 9 min.				
Effects: Effects in rats (increased weight and slight histopathological changes in the liver) at each concentration and associated exposure duration				
Endpoint/Concentration/Rationale: slight histopathological changes in the liver//100 ppm for 240 min.				
Uncertainty Factors/Rationale: Total uncertainty factor: 10				
Interspecies = 1: The effects of exposure to 1,2-dibromoethane appear to be similar across species including canine, rodents, non-human primates, and humans, and non-human primates and humans are not expected to vary significantly regarding pharmacokinetics. PBPK modeling indicate that rats may be 4-80 times more sensitive than humans; effects are similar between animals and humans indicating similar pharmacodynamics				
Intraspecies = 10: PBPK modeling indicate that humans vary by a factor of about 10 in the production of reactive metabolites, and human taking therapeutic doses of disulfiram could have an increased sensitivity to 1,2-dibromoethane.				
Time Scaling: $C^n \times t = k$, where $n = 1.6$ based on regression of exposure concentrations and durations associated with adverse effects in rats increased liver weight and slight histopathological changes.				
Data Adequacy: The data for deriving AEGL-2 values were very limited; the report did not include some important details regarding the methods and results.				

Concentration-Exposure Duration Relationship

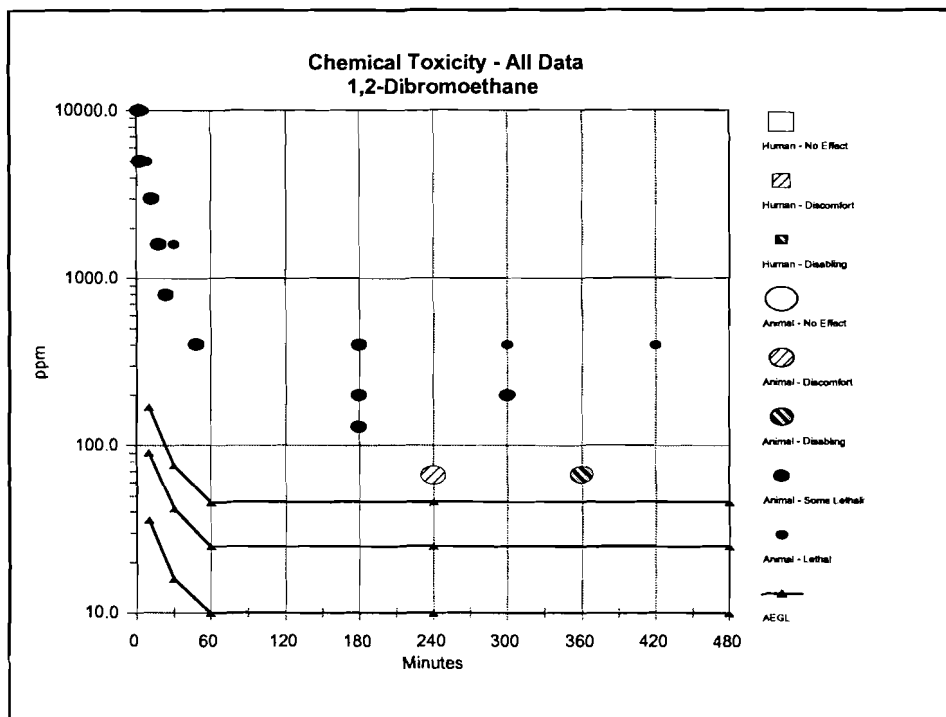
LC ₀₁ (LD _{t01}) Data			
Time (min)	Conc.	Log Time	Log Conc.
6	1600	0.78	3.20
16.8	800	1.23	2.90
37.2	400	1.57	2.60
120	200	2.08	2.30
Correlation = 0.998			
n = 1.4			



AEGL-3 VALUES for 1,2-Dibromoethane				
10-minute	30-minute	1-hour	4-hour	8-hour
170 ppm (1277 mg/m ³)	76 ppm (585 mg/m ³)	46 ppm (354 mg/m ³)	17 ppm (131 mg/m ³)	10 ppm (77 mg/m ³)
Key Reference: Rowe et al. 1952				
Test Species/Strain/Number: rat/strain was not reported/4-20 animals/group				
Exposure Route/Concentrations/Durations: inhalation/100-10,000 ppm for 1.2 minutes to 16 hours				
Effects: death occurred at all exposure concentrations except 100 ppm, but not all exposure durations. Deaths within the first 24 hours was attributed to cardiac and respiratory failure, later deaths were attributed to secondary pneumonia. Rats that died lost weight, showed evidence of upper and lower respiratory tract irritation. Microscopic findings included severe pulmonary damage, degeneration and necrosis in the liver, and congestion and edema in the kidney tubules 16-24 hours after exposure.				
Endpoint/Concentration/Rationale: 100 ppm for 8.5 hours; no effect level for lethality. Although the no-effect levels extended to 12 and 16 hours at 100 ppm, the 8.5 hour duration was selected for the POD because it approximates the exposure duration for the AEGL values.				
Uncertainty Factors/Rationale: Total uncertainty factor: 10				
Interspecies = 1: The effects of exposure to 1,2-dibromoethane appear to be similar across species including canine, rodents, non-human primates, and humans, and non-human primates and humans are not expected to vary significantly regarding pharmacokinetics. PBPK modeling indicate that rats may be 4-80 times more sensitive than humans; effects are similar between animals and humans indicating similar pharmacodynamics				
Intraspecies = 10: PBPK modeling indicate that humans vary by a factor of about 10 in the production of reactive metabolites, and human taking therapeutic doses of disulfiram could have an increased sensitivity to 1,2-dibromoethane.				
Time Scaling: C ⁿ × t = k, where n = 1.4 based on regression of LC ₀₁ values for exposure duration ranging from 6-120 minutes at concentrations ranging from 1600 down to 200 ppm.				
Data Adequacy: A very detailed acute inhalation exposure study was available with exposure concentrations ranging from 200 to 10,000 ppm and exposure duration ranging from 0.6 minutes to 16 hours. LC ₁ values were calculated for each exposure concentration.				

SUMMARY OF AEGL VALUES (ppm [mg/m³])

Class.	Exposure Duration					Endpoint/Reference
	10-min	30-min.	1-hour	4-hour	8-hour	
AEGL-1 (non-disabling)	52 [400]	26 [200]	17 [131]	7.1 [55]	4.6 [35]	No adverse effect (Rowe et al., 1952)
AEGL-2 (Disabling)	73 [562]	37 [285]	24 [185]	10 [77]	6.5 [50]	Slight histopathological changes in the liver; no-effect- level for irreversible toxicity or impaired ability to escape (Rowe et al., 1952)
AEGL-3 (Lethal)	170 [1308]	76 [585]	46 [354]	17 (131)	10 [77]	no effect level for lethality [Rowe et al. 1952]



**ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
PHENYL MERCAPTAN**

**NAC/AEGL-40
September 6-8, 2006**

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Steve Barbee

Chemical Reviewers: Jim Holler and Paul Tobin

Mechanism of Toxicity

Acts similarly to hydrogen sulfide, methyl mercaptan, ethyl mercaptan and cyanide

Interrupts electron transport through inhibition of cytochrome oxidase

Relative Toxicity (Rat Lethality Data)

Acute toxicity of phenyl mercaptan is much greater than that of

Ethyl mercaptan

Methyl mercaptan

Hydrogen sulfide

4-Hour Rat LC₅₀ Values (Tansy et al., 1981; Fairchild and Stokinger, 1958)	
Phenyl Mercaptan	33 ppm
Ethyl Mercaptan	4740 ppm (140-fold)
Methyl Mercaptan	675 ppm (20-fold)
Hydrogen Sulfide	444 ppm (13-fold)

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

Not Recommended due to insufficient data.

AEGL-2 VALUES: PHENYL MERCAPTAN				
10 minute	30 minute	1 hour	4 hour	8 hour
1.0 ppm	0.70 ppm	0.53 ppm	0.33 ppm	0.17 ppm

Endpoint: **Three-fold reduction of AEGL-3 values. Estimated threshold for the inability to escape.**

Endpoint is justified because of the steep concentration-response curve.

Rat 4-hour exposure

0% lethality at 20 ppm

100% lethality at 52 ppm

Mouse 4-hour exposure

0% lethality at 20 ppm

70% lethality at 41 ppm

AEGL-3 VALUES: PHENYL MERCAPTAN				
10 minute	30 minute	1 hour	4 hour	8 hour
3.0 ppm	2.1 ppm	1.6 ppm	1.0 ppm	0.52 ppm

Species: Rat
Concentration: 10.3 ppm
Time: 4 hours
Endpoint: LC₀₁ (Estimated threshold for death. Used instead of BMCL₀₅ for consistency with H₂S and methyl and ethyl mercaptans)
Reference: Fairchild and Stokinger, 1958

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

Time scaling from the 4-hour point-of-departure to the 10-minute AEGL-3 value is supported by 1-hour rat lethality data (Stauffer Chemical Company, 1969). The estimated 1-hour rat lethality threshold is 141 ppm ($\frac{1}{3}$ of the LC₅₀ value; $\frac{1}{3} \times 422$ ppm = 141 ppm). Time scaling, to the 10-minute time period using an exponent of n=3 and applying a total UF of 10, yields a 10-minute AEGL-3 value of 26 ppm, suggesting that the derived 10-minute value of 3.0 ppm is protective.

Uncertainty Factors:

Intraspecies = 3 Considered sufficient due to the steepness of the lethal response curve which implies limited individual variability.

Rat 4-hour exposure

0% lethality at 20 ppm
 100% lethality at 52 ppm

Mouse 4-hour exposure

0% lethality at 20 ppm
 70% lethality at 41 ppm

Interspecies = 3 Use of the full factor of 10 yields AEGL values inconsistent with structural and mechanistic analogs with more robust data sets.

	Ratios of 4-hr Rat LC ₅₀ Values	Total UF	Ratios of AEGL-3 values				
			10-min	30-min	1-hr	4-hr	8-hr
Phenyl mercaptan: H ₂ S	13	10	25	28	31	37	58
		30	77	86	91	109	182
Phenyl mercaptan: Methyl mercaptan	20	10	40	40	29	43	42
		30	121	125	123	126	129
Phenyl mercaptan: Ethyl mercaptan	140	10	150	200	225	230	211
		30	450	652	654	676	647

Extant Standards and Guidelines for Phenyl Mercaptan

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	1.0 ppm	0.70 ppm	0.53 ppm	0.33 ppm	0.17 ppm
AEGL-3	3.0 ppm	2.1 ppm	1.6 ppm	1.0 ppm	0.52 ppm
NIOSH REL	0.1 ppm				
ACGIH-TLV TWA					0.1 ppm
MAC (Dutch)					0.5 ppm

Chemical Toxicity - TSD Animal Data Phenyl Mercaptan

