National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-45
March 3-5, 2008

Hilton- Old Town Alexandria
1867 King Street
Alexandria, VA

ATTACHMENT 1

AGENDA

Monday, March 3, 2008

10:00 a.m.	*Development team meetings: Isocyanates; PBPK issue chemicals (1,1,1-trichloroethane; Ethyl benzene; Tetrachloroethylene); Cyanogen
11:00	Introductory remarks and approval of NAC/AEGL-44 Highlights (George Rusch, Ernie Falke, and Paul Tobin)
11:15	Status Update:Ethylphosphonothioic dichloride; methoxymethyl isocyanate (Cheryl Bast)
11:20	Review of Nitrogen trioxide and Nitrogen tetroxide (George Woodall/Carol Wood)
12:00 p.m.	Lunch
1:00	Review of Ethyl benzene (John Hinz/Carol Wood/Jim Dennison)
3:00	Break
3:15	Progress Report: 1,1,1-Trichloroethane: PBPK Issues (Bob Benson/Sylvia Talmage/Jim Dennison)
4:15	Progress Report: Tetrachloroethylene: PBPK Issues (Bob Benson/Claudia Troxel/Jim Dennison)
4:30	Review of Cyanogen (Glenn Leach /Cheryl Bast)
5:30	Adjourn for the day

Tuesday, March 4, 2008

8:30 a.m.	*Development team meetings: 1,2-Butylene oxide; Ethyl Phosphorodichloridate; Isocyanates (if needed)
9:30	Review of Ethyl isocyanate (Susan Ripple/Bob Young)
10:30	Break
10:45	Review of Phenyl Isocyanate (Susan Ripple/Bob Young)
12:00 p.m.	Lunch
1:00	Review of n-Butyl isocyanate; Isobutyl isocyanate; n-Propyl isocyanate; Isopropyl isocyanate; and t-Butyl isocyanate (Susan Ripple/Bob Young)
2:30	Benchmark Concentration Analysis (Jay Zhao)
3:30	Break
3:45	Review of Methyl isothiocyanate (Susan Ripple/ Sylvia Talmage)
5:30	Adjourn for the day

Wednesday, March 5, 2008

8:30 a.m.	Review of Ethyl phosphorodichloridate (Gail Chapman/Cheryl Bast)
9:30	Break
9:45	Review of 1,2-Butylene oxide (Jim Holler/Sylvia Talmage)
11:45	Administrative matters
12:00 noon	Adjourn meeting

*See page 2.

NAC/AEGL Meeting 45: March 3-5, 2008

Chemical: ATTENDANCE 3/3/08 **CAS Reg. No.:**

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

Chemical Manager: **Staff Scientist:**

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

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

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

NR= Not Recommended due to_____

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

Approved by Chair: _____ **DFO:** _____ **Date:** _____

1,1,1-Trichloroethane
NAC-45, March 3-5, 2008

NRC/NAS Committee on Toxicology, AEGL Subcommittee
Comments on 1,1,1-Trichloroethane, July 2000

These comments affect the choice of key studies

AEGL-1 (4-hour exposure to 450 ppm – slight eye irritation [Salvini et al. 1971])
Why choose Salvini et al. (1971) as the key study for AEGL-1?
- Give rationale why this is the ***best*** human study
- Value is inconsistent with several other well-conducted studies
- Consider using the 500 ppm for eye irritation in the study of Stewart et al. (1961).
- A two-fold intraspecies uncertainty factor is not warranted for slight eye irritation, "a slight, reversible, subjective effect" (i.e., a UF of 1 is sufficient)

Agree with using the same value across time for AEGL-1
- But consider raising the 10-minute value

AEGL-2 (3780 ppm for 4 hours - EC_{50} for ataxia in rats [Mullin and Krivanek 1982])
There are ***substantial problems*** with the use of rodent CNS depression
- Behavior performance studies are notoriously insensitive and difficult to interpret
- Rats receive a much higher internal dose of inhaled 1,1,1-trichloroethane than humans

The calculated AEGL-2 values range from 930 ppm to 300 ppm
- 350 ppm is the TLV
- 900 ppm was the threshold for lightheadedness in humans (Stewart et al. 1961; 1969; Torkelson et al. 1958)
- 1900 ppm for 5 minutes – disturbance in equilibrium of human subjects (Torkelson et al. 1958) appears to be a better basis.
- Need 10,000-26,000 for light plane anesthesia in humans (Dornette and Jones 1960)

Suggest using 2000 ppm as a reasonable basis for AEGL-2 and using UF of 2.
- Make 10-minute value higher

Approaches steady-state in the brain at 30-45 minutes
Use validated PBPK modeling to time-scale

AEGL-3 (6-hour, 7000 ppm estimate of lethality threshold in rats [Bonnet et al. 1980])
- Estimated from a graph not much detail… study is in French

The most sensitive subjects inhaling 6000 ppm during surgery **did not die**
Light plane anesthesia is not lethality
Questioned keeping the values below the threshold for cardiac sensitization because the injected dose of epinephrine in dogs was 10X physiological levels

Summary of Interim Values for 1,1,1-Trichloroethane						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	230 ppm	230 ppm	230 ppm	230 ppm	230 ppm	Eye irritation and slight dizziness in humans (Salvini et al., 1971)
AEGL-2 (Disabling)	930 ppm	670 ppm	600 ppm	380 ppm	310 ppm	EC_{50} for ataxia in rats (Mullin and Krivanek, 1982)
AEGL-3[a] (Lethal)	4200 ppm	4200 ppm	4200 ppm	2700 ppm	2100 ppm	Estimated concentration causing no deaths in rats (Bonnet et al., 1980)

[a] The 1-hour value was used as the 10-minute and 30-minute values so as not to exceed the threshold for cardiac sensitization of 5000 ppm observed in dogs (Reinhardt et al., 1973).

Effects of Exposure to 1,1,1-Trichloroethane			
Concentration (ppm)	**Duration**	**Effect**	**Reference**
Clinical Studies			
35-400	0.5-6 hours (avg 4 hours)	Effects included no symptoms; no effect on body sway; initial noticeable odor; slight eye irritation; both slower and enhanced neurobehavioral performance (subclinical deficits)	Eight clinical studies
500 (450-561) 500 (498-509)	6.5-7 hours, 5 days	No consistent symptoms No consistent symptoms	Stewart et al. 1969 Stewart et al. 1975
500 (6 male subjects) 500 (6 male subjects) 900 (2 male subjects) 910 (2 male subjects) 955 (3 male subjects) 0-2650 (7 subjects)	1.3 hours 3.1 hours 20 minutes 35 minutes 1.2 hours 15 minutes	Slight eye irritation, 3 of 6 subjects No effects reported Lightheadedness, positive Romberg test in 1 of 2 subjects Lightheadedness, in 1 of 2 subjects, Romberg test difficult Positive Romberg test in 1 of 3 subjects Loss of equilibrium in 2 of 7 subjects at peak of 2650 ppm	Stewart et al. 1961
546 (450-710) 506 (415-590) 920 (900-1000) 1000 (890-1190) 1900 (1740-2180)	1.5 hours 7.5 hours 70-75 minutes 30 minutes 5 minutes	NOAEL for subjective symptoms; normal Romberg test Transient odor detection; normal Romberg test Very slight equilibrium disturbance in 3 of 4 subjects, rapid recovery Strong odor; equilibrium not disturbed Noticeable odor; equilibrium disturbance	Torkelson et al. 1958
10,000-16,000 6000-22,500 (with N_2O)	2 minutes No data	Induction of light plane anesthesia Maintenance of light anesthesia during surgical procedures	Dornette and Jones 1960
Laboratory Animal Studies			
1000 (rat) 2000	100 minutes 100 minutes	No deficits in neurobehavioral tests Small decrease in response after 1 hour	Warren et al. 1998
1750 (rat) 3780	4 hours 4 hours	No neurobehavioral deficits EC_{50} for ataxia	Mullin and Krivanek 1982
700, 1400 (baboon) 1800, 2100	4 hours 4 hours	No change in response in neurobehavioral test No effect on correct responses, decreased responses, 29 and 33%	Geller et al. 1982
5000 (monkey)	7 hours	Ataxia after 1 hour; trembling of hands after 5 hours	Adams et al. 1950
12,500 (rat)	4 hours	Highest non-lethal value (average of 4 studies)	Hazleton Labs 1989
15,525 (rat)	4 hours	Highest non-lethal value	Calhoun et al. 1988

Romberg test: standing on one foot with arms extended, both with eyes open and with eyes closed.
Equilibrium test: walking heel-to-toe in a straight line for 5 feet.

AEGL-2 Values from the PBPK Modeling (no Uncertainty Factors applied)

Study	Exposure	CV	10 min	30 min	1 hour	4 hour	8 hour
Stewart	900 ppm/20 min	3.91 mg/L	1440	710	530	390	380
Stewart	910 ppm/35 min	5.38 mg/L	2000	980	730	530	520
Stewart	955 ppm/73 min	7.61 mg/L	2830	1390	1020	750	740
Torkelson	920 ppm/72.5 min	7.33 mg/L	2730	1340	990	730	710
Torkelson	1000 ppm/30 min	5.48 mg/L	2040	1000	740	540	530
Torkelson	1900 ppm/5 min	3.00 mg/L	1120	550	410	300	300

Note: values based on preliminary revised model and may be different after additional work

ATTACHMENT 4

AEGL for NITROGEN OXIDES

NAC-AEGL #45
[3-5 Mar 08]

Chemical manager	George Woodall
Chemical reviewers	Daniel Sudakin
	Marc Baril
Principal author	Carol Wood

STATUS

- Nitrogen dioxide: Interim
  - accepted by the NAC
  - currently in review by COT
- Nitrogen tetroxide and Nitrogen trioxide: Draft
  - chemical specific information added to NO_2 document
  - literature search for data

Atmospheric Reactions

$2NO + O_2 \rightarrow 2NO_2$
(minor at ambient temp)
$NO + O_3 \rightarrow NO_2 + O_2$
$NO + HO_2\bullet \rightarrow NO_2 + HO\bullet$
$NO + RO_2\bullet \rightarrow NO_2 + RO\bullet$
$NO_2 + HO\bullet \rightarrow HNO_3$
$2NO_2 \leftrightarrow N_2O_4$

- temperature dependent
- favors NO_2 production

Data Summary for N_2O_4 and N_2O_3

- N_2O_4
  - Physicochemical properties
  - Case reports of respiratory complaints after accident
  - LC_{50} values for four species; no experimental details
  - Pulmonary lesions in rats; questionable protocol
- N_2O_3
  - Physicochemical properties
  - No exposure data

Other relevant information

- No standards or guidelines for N_2O_4 or N_2O_3
- Oxides of nitrogen = NO_2 toxicity
  - NIOSH, EPA, etc.
- N_2O_4 in rocket emissions but NRC considered NO_2, nitric acid, and HCl

NAC/AEGL Action

- Adopt the NO_2 values for these three oxides of nitrogen
- Include data for N_2O_4 and N_2O_3 in TSD as written

#2

ATTACHMENT 5

AEGL for ETHYLBENZENE

NAC-AEGL #45
[3-5 March 08]

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

History

- First addressed by the NAC in September, 2006; industry presented unpublished data (Stump 2003)
- Second draft was brought to the NAC in December, 2006; it was decided to look at PBPK modeling for AEGL 2 and 3
  - the NAC discussed and decided upon the key studies and points of departure to use in the model
  - these were communicated to industry and the model was run

AEGL 1: Key Study and POD

- Bardodej and Bardodejova 1961
  - Humans
  - 100 ppm for 8 hours: no complaints or any problems in nine subjects
  - 180 ppm for 8 hours: irritation of respiratory tract and conjunctiva, headaches, sleepiness in eleven subjects

AEGL 2: Key Study and POD

- Cappaert et al. 2002
  - Ototoxicity in female rats
  - 550 ppm, 8 hr/d, 5 days
    - Pronounced outer hair cell loss
    - Threshold shift measured in mid-frequency hearing range

AEGL 3: Key Study and POD

- Andersson et al. 1981
  - Male rats: highest non-lethal
  - 2000 ppm, 6 hrs: no clinical signs or deaths

PBPK model for Ethylbenzene

- Lisa Sweeney, *The Sapphire Group, Inc.*
- Supported by ACC EB Panel
- Peer review by Jim Dennison

- AEGL 2 and 3 run based on POD chosen by NAC

Summary of Proposed AEGL values for Ethylbenzene (PBPK model used for derivation of AEGL 2 and 3)					
	10-min	30-min	1-hr	4-hr	8-hr
AEGL 1	10 ppm	10 ppm	10 ppm	10 ppm	10 ppm
AEGL 2	***4000 ppm***	***1400 ppm***	***710 ppm***	200 ppm	120 ppm
AEGL 3	***1400 ppm***	***810 ppm***	***580 ppm***	360 ppm	320 ppm

UF = 10 for all

Why is AEGL 2 > AEGL 3?

- AEGL 3 (POD = 2000 ppm for 6 hr, highest non-lethal)
  - Based on peak blood concentrations (peak CR)
  - Endpoint (death) measured after single exposure
- AEGL 2 (POD = 550 ppm, 8 hr, 5 days, ototoxicity)
  - Based on cumulative exposure (AUC)
  - Endpoint (ototoxicity) measured after 5 exposures

Options

1. Use AEGL 2 values from model, but not AEGL 3 values (but data are available)
2. Use AEGL 3 values from model, but not AEGL 2 values (but data are available)
3. Use model with different UFs (see upcoming slide)
4. Use POD and calculate the old fashioned way (as presented in TSD; may need different UFs)

Summary of Proposed AEGL values for Ethylbenzene (calculated from data)					
	10-min	30-min	1-hr	4-hr	8-hr
AEGL 1 (UF = 10)	10 ppm	10 ppm	10 ppm	10 ppm	10 ppm
AEGL 2 (UF = 30)	46 ppm	46 ppm	37 ppm	23 ppm	18 ppm
AEGL 3 (UF = 30)	150 ppm	150 ppm	120 ppm	76 ppm	50 ppm

UF: 10 for intra- for systemic toxicity

3 for inter- because effects consistent between species

Application of UFs

- UF_H = 10 because the mechanism of systemic toxicity is unknown
  - *Reduce to 3 for AEGL 3 and AEGL 1
    - Mechanism for lethality is probably CNS depression
    - Mechanism for ototoxicity is unknown so leave as 10 for AEGL 2
    - Irritation threshold is basis for AEGL 1
  - Reduce to 3 for all AEGL levels:
    - mechanism is probably CNS depression or contact irritation
    - limited data suggest steady-state reached quickly in both rat and human
    - rapid metabolism with little tissue retention
    - toluene, xylenes, 1,2-dichloroethene use 3 [Among humans the minimum alveolar concentration (MAC) for volatile anesthetics (CNS) typically varies by about 2-3 fold.]

Application of UFs

- UF_A = 3 because clinical signs and systemic effects were consistent between experimental animal systems
  - *Reduce to 1 for AEGL 3:
    - CNS effects do not differ
    - May not be same endpoint for AEGL 2
  - Reduce to 1 for AEGL-2 and -3:
    - toluene and xylenes use 1

ATTACHMENT 6

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

CYANOGEN

NAC/AEGL-45
March 3-5, 2008
Alexandria, VA

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Glenn Leach

Chemical Reviewers: Henry Anderson and Gail Chapman

Cyanogen is structurally similar to cyanide and other nitriles.

$$N \equiv C\text{-}C \equiv N$$

Reportedly converted in the body partly to hydrogen cyanide and partly to cyanic acid (HOCN)

Reportedly hydrolyzes to yield one mole of hydrogen cyanide and one mole of cyanate

The mechanism of toxicity of cyanogen is reportedly similar to that of hydrogen cyanide (HCN)

Qualitatively, many clinical signs noted in cyanogen-exposed animals are similar to those noted in cyanide-exposed animals.

However, at relatively low concentrations, cyanogen appears to be much more irritating than hydrogen cyanide.

Reported that rat data suggest that cyanogen is less acutely toxic than cyanide by a factor of 10

HOWEVER:

Analysis of available rat data suggests that this assumption may be true for very short exposure durations (up to approx 15 minutes), but not for longer durations (30 minutes to 1 hour).

TABLE 1. Comparative rat toxicity of HCN and cyanogen

Concentration (ppm)	Exposure duration (min)	HCN Endpoint	Cyanogen Endpoint
400-500	5	LC_{50}	-
4000	7.5	-	Mortality: 3/6
196	15	LC_{50}	-
1000	15	-	Mortality: 0/6
2000	15	-	Mortality: 6/6
150-200	30	LC_{50}	-
500	30	-	Mortality: 0/6
1000	30	-	Mortality: 6/6
120-140	60	LC_{50}	-
250	60	-	Mortality: 0/6
400	60	-	Mortality: 6/6

STEEP CONCENTRATION-RESPONSE CURVE

McNerney and Schrenk (1960) : Rats

0% mortality:	1000 ppm for 15-min
100% mortality:	1000 ppm for 30-min
0% mortality:	500 ppm for 30-min
100% mortality:	1000 ppm for 30-min
0% mortality:	400 ppm for 45-min
100% mortality:	500 ppm for 45-min
0% mortality:	250 ppm for 60-min
100% mortality:	400 ppm for 60-min

AEGL-1 Values for Cyanogen				
10-min	30-min	1-h	4-h	8-h
2.7 ppm	2.7 ppm	0.90 ppm	0.90 ppm	0.90 ppm

Species: Human
Concentration: 8 ppm
Time: 6 minutes
Endpoint: NOEL for ocular and nasal irritation (irritation was noted at next highest concentration of 16 ppm for 6 or 8 minutes)
Reference: McNerney and Schrenk, 1960

Time Scaling: None Applied. Minor contact irritation.

Uncertainty Factors:

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

Interspecies: 1 Human data

Modifying Factor:3

Applied to the 1-, 4-, and 8-hour time points because of the lack of human data beyond 8-minutes and because of the potential for a systemic effect from the cyanide metabolite.
(Similar to Methacrylonitrile)

AEGL-2 Values for Cyanogen				
10-min	30-min	1-h	4-h	8-h
50 ppm	15 ppm	7.0 ppm	3.7 ppm	3.7 ppm

Endpoint: Three-fold reduction of AEGL-3 values

Approach justified by steep concentration-response relationship

McNerney and Schrenk (1960) : Rats

0% mortality: 1000 ppm for 15-min
100% mortality: 1000 ppm for 30-min

0% mortality: 500 ppm for 30-min
100% mortality: 1000 ppm for 30-min

0% mortality: 400 ppm for 45-min
100% mortality: 500 ppm for 45-min

0% mortality: 250 ppm for 60-min
100% mortality: 400 ppm for 60-min

AEGL-3 Values for Cyanogen				
10-min	30-min	1-h	4-h	8-h
150 ppm	45 ppm	21 ppm	11 ppm	11 ppm

Species: Rat
Concentration: Range of 250 to 400 ppm
Time: Range of 7.5 to 120 minutes
Endpoint: Lethality threshold (LC_{01}) calculated using probit-analysis dose-response ten Berge program
Reference: McNerney and Schrenk, 1960

Time Scaling:
10-min, 30-min, and 1-hr values:

$c^n \times t = k$, where the exponent, n, is 0.90, as determined by analysis of rat lethality data using ten Berge (2006) software.

4- and 8-hour values:

Modifying factor of 2 applied to the 1-hour AEGL-3 value to derive the 4- and 8-hour AEGL-3 values. (Similar to HCl and HF)

Using the calculated probit values (and UFs described below), yields 4- and 8-hour AEGL-3 values of 4.5 and 2.1 ppm, respectively.

These values are inconsistent with the repeated-exposure data in both monkeys and rats (Lewis et al., 1984).

Rats repeatedly exposed to 25 ppm cyanogen 6 hours/day, 5 days/week for up to 6 months, experienced only decreased body weight

Monkeys similarly exposed showed only marginal behavioral effects.

No effects were noted in either species similarly exposed at 11 ppm.

Uncertainty Factors:
Intraspecies: 3: Considered sufficient due to the steep concentration-response curve

Interspecies: 3
Use of the full default interspecies UF of 10 would yield AEGL-3 values that are less consistent with the overall database.

AEGL-3 values derived with a total UF of 30:

10-min	30-min	1-hr	4-hr	8-hr
51 ppm	15 ppm	7.0 ppm	3.7 ppm	3.7 ppm

Humans exposed to 8 ppm cyanogen for 6 min experienced no irritation; Humans exposed to 16 ppm for 6 min experienced transient ocular and nasal irritation (McNerney and Schrenk, 1960).

Rats and monkeys repeatedly exposed to 11 ppm cyanogen 6 hours/day, 5 days/week for up to 6 months experienced no treatment-related adverse effects.

Rats repeatedly exposed to 25 ppm cyanogen 6 hours/day, 5 days/week for up to 6 months experienced only decreased body weight, and monkeys similarly exposed showed only marginal behavioral effects (Lewis et al., 1984).

SUPPORT FOR AEGL-3 VALUES:

If the actual experimental concentrations causing no death in rats (McNerney and Schrenk, 1960) are divided by a total UF of 10, the resulting values support the proposed AEGL-3 values.

No death was noted in rats exposed to 2000 ppm for 7.5 minutes or 1000 ppm for 15 minutes.

Applying the UF of 10, would yield a 7.5 minute value of 200 ppm and a 15 minute value of 100 ppm, values which encompass the derived 10-minute AEGL-3 value of 150 ppm.

No deaths were noted in rats exposed to 500 ppm for 30 minutes; applying the UF of 10, yields a value of 50 ppm, which is in agreement with the derived 30-minute AEGL-3 value of 45 ppm.

No deaths were noted in rats exposed to 250 ppm for 60 minutes; applying the UF of 10 yields a value of 25 ppm, which is in agreement with the derived 60-minute AEGL-3 value of 21 ppm.

Extant Standards and Guidelines for Cyanogen					
	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	2.7 ppm	2.7 ppm	0.90 ppm	0.90 ppm	0.90 ppm
AEGL-2	50 ppm	15 ppm	7.0 ppm	3.7 ppm	3.7 ppm
AEGL-3	150 ppm	45 ppm	21 ppm	11 ppm	11 ppm
TLV-TWA (ACGIH)					10 ppm
MAC (The Netherlands)					10 ppm
MAK (Germany)					5 ppm
NIOSH REL					10 ppm

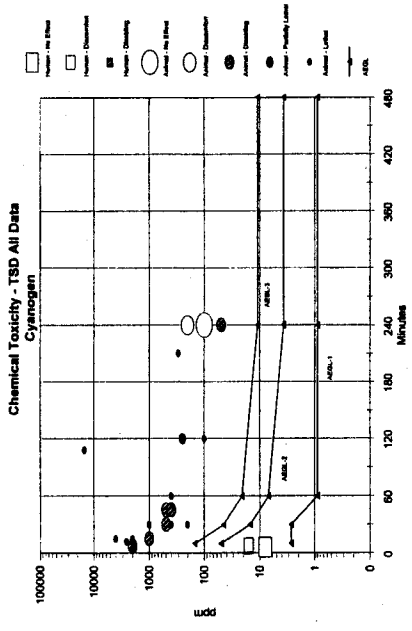


TABLE 2. Effects of Acute Cyanogen Exposure in Humans*

Exposure Concentration	Exposure Duration	Incidence of subjects experiencing effects		
		Odor	Ocular Irritation	Nasal Irritation
8 ppm	6 min.	0/7	0/7	0/7
16 ppm	6 min.	0/5	5/5	4/5**
16 ppm	8 min.	0/7	7/7	7/7

*McNerney and Schrenk, 1960.
**The subject without irritation had mild cold symptoms.

TABLE 3. Acute inhalation of cyanogen in male albino rats*		
Concentration (ppm)	**Exposure duration (min)**	**Mortality incidence**
4000	7.5	3/6
4000	15	6/6
2000	7.5	0/6
2000	15	6/6
1000	15	0/6
1000	30	6/6
500	30	0/6
500	45	6/6
400	45	0/6
400	60	6/6
250	60	0/6
250	120	4/6

ATTACHMENT 7

n-BUTYL ISOCYANATE
(CAS Reg. No. 111-36-4)

CH_3-CH_2-CH_2-CH_2-N=C=O

NAC/AEGL-45
Alexandria, VA
March 3-5, 2008

ORNL Staff Scientist: Robert A. Young
Chemical Manager: Susan Ripple
Chemical Reviewer: David Freshwater
Chemical Reviewer: Ralph Gingell

n-BUTYL ISOCYANATE

- Pungent smelling liquid with a high vapor pressure
- Intermediate in the manufacture of chemicals, dyes, and pesticides
- Respiratory tract and ocular irritation

n-BUTYL ISOCYANATE
Human Data

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

n-BUTYL ISOCYANATE
Animal Lethality Data

- IRDC (1965): acute inhalation toxicity
  - 6 ♂ Sprague-Dawley rats/group) exposed to 5.5, 7.9, 10.9., 12.0, 18.9, 21.7, 27.9, 28.2, or 34.6 mg/m^3 (1.4, 1.9, 2.7, 3.0, 4.7, 5.4, 7.0, 7.1, 8.7 ppm) for 1 hr
  - 14-day observation
  - 1-hr LC_{50} of 15.2 mg/m^3 (12.1-19.0 95% c.i.)

n-BUTYL ISOCYANATE
Animal Lethality Data

Lethality in rats exposed to n-butyl isocyanate for 4 hours.			
Exposure Concentration (ppm)	Mortality		
	During exposure	14 days post exp.	30 days post exp.
12.5	0/6	0/6	2/6
17.5	0/6	2/6	3/6
22	0/6	2/6	5/6
31.5	2/6	6/6	6/6
53.5	2/6	6/6	6/6

Du Pont, 1968.

Lethality of rats exposed to n-butyl isocyanate vapor for one hour(IRDC, 1965)		
Concentration (mg/m^3) [ppm]	Lethality at 14 days	Comments
5.5 [1.4]	0/6	No deaths; 4/6 no gross lesions; 2/6 had 8 mm area of congestion in lungs
7.9 [1.9]	1/6	Death at 1 day post exposure; in the 5 survivors, lungs remained inflated after sacrifice; 4/5 exhibited mucus in trachea and bronchi; 2/5 had lungs with dark areas or areas of consolidation; 1/5 with gastric edema and hemorrhage in 4 survivors, lungs remained inflated after sacrifice; ¾ survivors exhibited fluid in small intestine
10.9 [2.7]	2/6	Deaths at post exposure day 9, and day 13 post exposure (lungs inflated after sacrifice); consolidation/congestion and dark areas in lungs
12.[3.0]	0/6	No deaths; no details regarding nonlethal effects
18.9 [4.7]	6/6	5 Deaths at day 2, 1 at day 13 post exposure; lungs with dark foci/consolidation, fluid in g.i. tract
21.7 [5.4]	4/6	2 Deaths at day 2, 1 each at days 9 and 11 post exp.
27.9 [7.0]	6/6	2 Deaths on 1st day, 4 deaths at day 1 post exp.
28.2 [7.1]	6/6	1 Death on day of exposure, 5 at day 1 post exp.
34.6 [8.7]	6/6	6 Deaths on day of exposure

n-BUTYL ISOCYANATE
Animal Lethality Data

- Pauluhn and Eben (1991): repeat-exposure lung function study
  - 20 ♂Wistar rats exposed (head-nose only) to 0, 1.09, 6.22, 14.67, and 25.97 mg/m^3 (analytical; equivalent to 0, 0.27, 1.55, 3.67, and 6.49 ppm) for 5 hrs/day for 5 days
  - 5-wk observation
  - no clinical signs in rats of the 1 or 6 mg/m^3 (0.25 or 1.5 ppm) groups
  - 12 of 20 rats of the highest exposure group died during post exposure week 2
  - delayed lethality was the result of obstructive and progressive lung damage with associated severe disturbance of ventilatory perfusion

n-BUTYL ISOCYANATE
Animal Lethality Data

- Bayer AG (1978)
  - ♂& ♀ Wistar rats; no experimental details
  - 1-hr LC_{50} : 425 mg/m^3 (280-646 mg/m^3 95% c.i.; equivalent to 106 ppm, 70-162 ppm, 95% c.i.)
  - 4-hr LC_{50}: <90 mg/m^3 (<22.5 ppm) males
  - 4-hr LC_{50}: ~ 80 mg/m^3 (20 ppm) females
- Du Pont & Co. (1968): lethality assay
  - 6 ♂ ChR-CD rats exposed to 12.5, 17.5, 22, 31.5, 33.5 ppm (analytical; purity not specified) for 4 hours
  - irregular breathing, hyperemia, gasping, pale ears and lacrimation during exposure
  - 4-hr LC_{50}: 15.6 ppm (13.3-18.2 ppm, 95% c.i.)
  - post-exposure observations:
    - 10-20% loss of body weight during the first day, respiratory distress characterized by gasping, labored breathing, congestion and rales, red discharge from the eyes
    - all exposures resulted in some deaths during the 30-day observation period
    - pathology findings: dark red-colored, edematous lungs, necrosis and desquamation of respiratory epithelium, and signs of increased capillary permeability
    - surviving rats exhibited signs of regeneration of bronchial epithelium and proliferation of connective tissue resulting in fibrotic changes and atelectasis
    - bronchopneumonia was evident in many rats by 14 days post exposure

n-BUTYL ISOCYANATE
Animal Nonlethal

- Pauluhn et al. (1990): pulmonary function, arterial blood gases, acid-base status, and bronchioalveolar lavage fluid (BALF) composition
  - groups of 20 ♂ Wistar rats exposed (head-only) for 4 hours to n-butyl isocyanate (technical grade; 99.5%) at concentrations of 7.6, 23.5, and 55.2 mg/m^3 (analytical; equivalent to 1.9, 5.9, and 14 ppm)
  - 1.9 ppm: transient clinical signs (hypothermia, bradypnea, and irritation of mucous membranes) during the first day
  - 5.9 and 14 ppm: signs of severe respiratory distress were observed
    - 5.9 ppm group: resolved within one week
    - 14 ppm group: persisted through the 4-week observation period
  - high-dose rats
    - gross findings of consolidation, distention, hemorrhagic areas, edema, and pleural effusions
    - microscopic changes included increased numbers of alveolar macrophages, perivascular round-cell infiltration, focal fibroproliferative reactions, emphysema, thickening of the septa, and pneumonia.
  - Summary
    - 4-hour exposure to 1.9 ppm: minor transient clinical effects that fully resolved with 24 hours
    - 4-hr exposure to 5.9 ppm: notable effects which resolved within one week
    - 4-hr exposure to 14 ppm: persistent clinical effects and notable histopathological findings consistent with significant pulmonary injury.

n-BUTYL ISOCYANATE
Animal Lethality Data

Lethality in rats following single acute exposure to n-butyl isocyanate		
Study	**Lethality benchmark**	**Comments**
IRDC, 1965	1-hr LC_{50}: 3.8 ppm	Deaths delayed 1 to 13 days
Du Pont & Co., 1968	4-hr LC_{50}: 15.6 ppm	Post exposure deaths; time to death was a function to exposure concentration
Bayer AG, 1978	1-hr LC_{50}: 106 ppm 4-hr LC_{50}: <22.5 ppm (♂) 4-hr LC_{50}: ≈18 ppm (♀)	

n-BUTYL ISOCYANATE
AEGL-1

AEGL-1 values for n-butyl isocyanate (ppm)					
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	0.0017	0.0017	0.0017	0.0017	0.0017

Key study: Du Pont (Du Pont de Nemours & Co.) 1986. n-Butyl isocyanate industrial hygiene survey. Personal Communication, Central Research and Development Department, Haskell Laboratory for Toxicology and Industrial Medicine.

Critical effect/POD: occupational exposure; noticeable eye irritation at exposures of 0.005 to 0.01 ppm; the lower range of 0.005 ppm was selected as the point-of-departure for AEGL-1 development.

Uncertainty factors: Total uncertainty factor adjustment is 3
Interspecies: 1; occupational exposure data; the critical effect and point-or-departure (POD) pertain to humans, no interspecies uncertainty factor is necessary.

Intraspecies: 3; because the critical effect was "noticeable" irritation and involved workers who were likely familiar with the effects of n-butyl isocyanate, a 3-fold uncertainty adjustment was applied in the development of the AEGL-1 values.

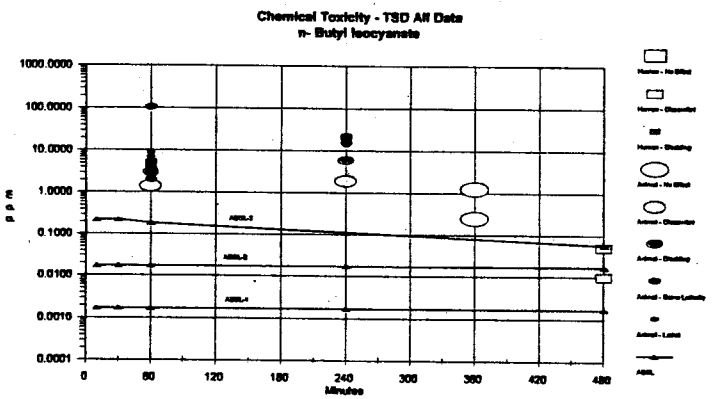
Modifying Factor: none

Time scaling: not applicable; direct-contact irritant (NRC, 2001)

n-BUTYL ISOCYANATE
Animal Nonlethal

- IRDC (1965): 1-hour exposure of rats
  - no deaths occurred in a groups of 6 rats exposed to n-butyl isocyanate 5.5 mg/m^3 for 1 hour
  - no deaths among 6 rats exposed to 12.0 mg/m^3 for 1 hour
    - lethality occurred at 7.9 and 10.9 mg/m^3 (absence of lethality at 12.0 mg/m^3 is likely a function of small group size)
    - clinical signs: hypoactivity, increased grooming, and escape behavior during exposure only, salivation, lacrimation, and dyspnea.

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



n-BUTYL ISOCYANATE
AEGL-2

AEGL-2 values for n-butyl isocyanate (ppm)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	0.017	0.017	0.017	0.017	0.017

Key study: Du Pont (Du Pont de Nemours & Co.) 1986. n-Butyl isocyanate industrial hygiene survey. Personal Communication, Central Research and Development Department, Haskell Laboratory for Toxicology and Industrial Medicine.

Critical effect/POD: the occupational exposure analysis stated that exposure to 50 ppb (0.05 ppm) for a nonspecified duration was considered incompatible with normal work operations but not considered escape impairing

Uncertainty factors: Total uncertainty factor adjustment is 3

Interspecies: 1; occupational exposure data; the critical effect and point-or-departure (POD) pertain to humans, no interspecies uncertainty factor is necessary.

Intraspecies: 3; the 50 ppb (0.05 ppm) exposure from the Du Pont (1986) report is considered a protective POD for AEGL-2 derivation because the ocular irritation was neither escape impairing nor irreversible in humans. Although the 0.05 ppm exposure concentration is a protective POD for AEGL-2 derivation, it is assumed that the worker population upon which this is based was accustomed to the irritant effects of n-butyl isocyanate and that sensitive responders may experience similar effects at lower exposures. Therefore, an intraspecies uncertainty factor of 3 was applied for deriving the AEGL-2 values.

Modifying Factor: none

Time scaling: not applicable; direct-contact irritant (NRC, 2001)

n-BUTYL ISOCYANATE
AEGL-3

AEGL-3 values for n-butyl isocyanate (ppm)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	0.22	0.22	0.18	0.11	0.057

Key study: Du Pont (Du Pont de Nemours & Co.) 1968. Acute inhalation toxicity; isocyanic acid n-butyl ester. Haskell Laboratory for Toxicology and Industrial Medicine. Report No. 289-68, MR No. 581-243.

Critical effect/POD: 4-hr $BMCL_{05}$ of 3.35 ppm as estimated of lethality threshold

Uncertainty factors: Total uncertainty factor adjustment is 30

Interspecies: 10; lethality data for n-butyl isocyanate are available for only one species and there is no information regarding lethality in humans.

Intraspecies: 3; although the lethal response in rats exposed to n-butyl isocyanate exhibits latency, the initial insult appears to be the result of pulmonary damage. This mode of action is not likely to vary considerably across individuals although dosimetric factors may be instrumental. To account for possible dosimetric variability, the intraspecies uncertainty factor is 3.

Modifying Factor: none

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

ATTACHMENT 8

ETHYL ISOCYANATE

ETHYL ISOCYANATE
(CAS Reg. No. 109-90-0)

CH_3-CH_2-N=C=O

- **Pungent smelling liquid with a high vapor pressure**
- **Intermediate in the manufacture of pharmaceuticals and pesticides**
- **Respiratory tract and ocular irritation**
- **Very limited data**

NAC/AEGL-45
Alexandria, VA
March 3-5 , 2008

ORNL Staff Scientist: Robert A. Young
Chemical Manager: Susan Ripple
Chemical Reviewer: David Freshwater
Chemical Reviewer: Ralph Gingell

ETHYL ISOCYANATE

- **Human data – none**
- **Animal data**
  - **rats only (Eastman Kodak, 1964)**
    - **3 rats/group**
    - **exposure concentration by wt./volume**

Exposure of rats to ethyl isocyanate (Eastman Kodak, 1964)

Conc. (ppm)	Duration	Mortality incidence	Time of death	Clinical signs: time noted
27	6-hr	0/3	-	Blepharism: 1-min Pilo-erection: 1-min Lacrimation: 15-min Eyes are dark: 1-hr Nasal discharge: 1-hr, 20-min
82	6-hr	3/3	0/3 dead during exposure 3/3 dead in 24-hrs.	Blepharism: 1-min Pilo-erection: 1-min Lacrimation: 1-min Eyes are dark: 20-min Gasping and dyspnea: 20-min Ptyalism: 55-min
506	2.8 hrs	3/3	1 dead in 2.25 hrs 1 dead in 2.3-hrs 1 dead in 2.8 hrs	Blepharism: immediately upon exposure Pilo-erection: immediately upon exposure Lacrimation: immediately upon exposure Ptyalism: 1-min Eyes are dark: 5-min Gasping and dyspnea: 5-min Nasal discharge: 15-min Prostration: 1-hr, 35-min Convulsions: 2-hr, 15-min

ETHYL ISOCYANATE
AEGL-3

AEGL-3 values for ethyl isocyanate (ppm)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	0.69	0.69	0.54	0.34	0.23

Key study: Eastman Kodak. 1964. Toxicity and Health Hazard Summary. Ethyl Isocyanate. Laboratory of Industrial Medicine, Eastman Kodak, Co., Rochester, NY. OTS0528345.

Critical effect/POD: NOAEL for lethality -27 ppm for 6-hr; lethality occurred at next highest concentration (82 ppm for 6-hr).

Uncertainty factors: Total uncertainty factor adjustment is 30
Interspecies: 10; lethality data for ethyl isocyanate are available for only one species; no human data.

Intraspecies: 3; clinical signs consistent with contact irritation which is not likely to vary considerably across individuals, although dosimetric factors may be instrumental. To account for possible dosimetric variability, the intraspecies uncertainty factor is 3 is considered sufficient. The intraspecies uncertainty factor of 3 is also supported by the steep concentration-response with regard to lethality (0% mortality in rats exposed to 27 ppm and 100% mortality at 82 ppm for 6-hr; Eastman Kodak, 1964).

Modifying Factor: 3: sparse data base

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

AEGL values for ethyl isocyanate (ppm)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.23	0.23	0.18	0.11	0.077
AEGL-3 (Lethality)	0.69	0.69	0.54	0.34	0.23

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

ETHYL ISOCYANATE
AEGL-1

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

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

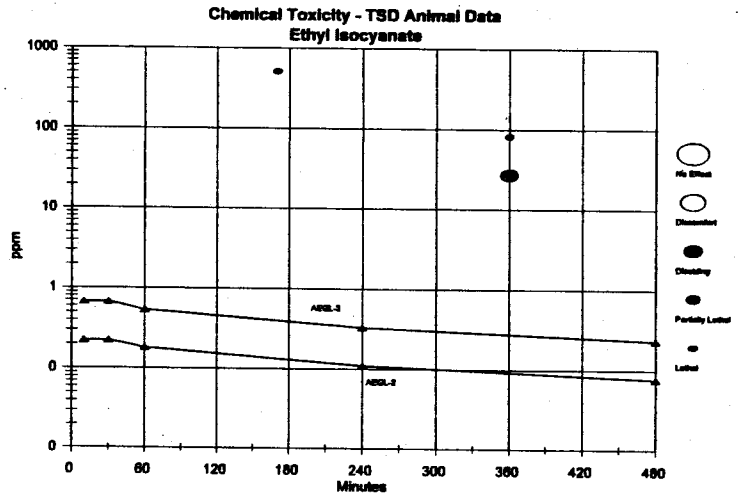
- Not recommended - insufficient data

ETHYL ISOCYANATE
AEGL-2

AEGL-2 values for ethyl isocyanate (ppm)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	0.23	0.23	0.18	0.11	0.077

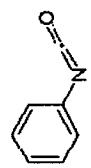
- Insufficient data

- AEGL-2 values estimated as three-fold reduction of AEGL-3 values (NRC, 2001)


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

ATTACHMENT 9

PHENYL ISOCYANATE
(CAS Reg. No. 103-71-9)



NAC/AEGL-45
Alexandria, VA
March 3-5, 2008

ORNL Staff Scientist: Robert A. Young
Chemical Manager: Susan Ripple
Chemical Reviewer: David Freshwater
Chemical Reviewer: Ralph Gingell

PHENYL ISOCYANATE

- **Pungent smelling liquid with a high vapor pressure**
- **Intermediate in the manufacture of pharmaceuticals and pesticides**
- **Respiratory tract and ocular irritation**

PHENYL ISOCYANATE
Human Data

- **no quantitative human data; irritant/lacrimator**

PHENYL ISOCYANATE
Animal Lethality Data

Summary of Animal Lethality Benchmarks		
Study	Lethality benchmark	Comments
Monsanto, 1954	~67 ppm; 1x2.5 hrs	Rats; 100% lethality; 40 rats died at 80 ppm for 4 hrs
Mobay, 1978	1-hr LC_{50} 12.6 ppm	Rats; 8-12 days post exposure
Imp. Chem. Ind. Ltd., 1980a	1-hr LC_{50} 3.92 ppm	Rats; delayed lethality
Bayer AG, 1981a	1600 ppm 5 minutes	Rats; 100% lethality
	800 ppm 30 minutes	Rats; 10% lethality at 2-4 hours
	1600 ppm 30 minutes	Rats; 90% lethality at 32-5% hours
Bayer AG, 1981b	4-hr LC_{50} 0.09 mg/L	Rats; most deaths at 7-14 days post exposure

- **Monsanto (1954)**
  - **rats exposed to 0.33 mg/L (~67 ppm) died at 1 hour, 2 hours and 2.5 hours of exposure**
  - **second experiment rats were exposed for 4 hours to 0.14 mg/L (~29 ppm): all rats survived.**

- **Mobay (1978)**
  - **1-hr LC_{50} of 12.6 ppm (8.4-19.0; 95% c.i.)**
  - **4 ♂ 4 ♀/group (up to 80 ppm)**
  - **8-12 days latency**

#8

PHENYL ISOCYANATE
Animal Nonlethal

- Pauluhn et al. (1995) (pilot study for 2-week study)
  - ♂ Wistar rats (4/group) exposed (nose-only) to 0, 1.9, 5.14, or 12.92 mg/m^3 (equivalent to 0, 0.4, 1.1, and 2.7 ppm; analytically determined)) for 45 minutes
  - 1.1 mg/m^3 (0.2 ppm) estimated threshold exposure for upper respiratory tract sensory irritation.

- Pauluhn et al., (1995)
  - 20 ♂ Wistar rats exposed (nose-only) for 6 hrs/day, 5 days/wk to 0, 1.04, 4.1, 7.18, or 10.39 mg/m^3 (0, 0.2, 0.8, 1.5, or 2.1 ppm)
  - no clinical signs in 0.2 or 0.8 ppm groups
  - incidences of histopathologic lesions in rats of 1 or 4 mg/m^3 (0.2 or 0.8 ppm) groups was not significantly different than controls (exception of Goblet cell hyperplasia in the nasal and paranasal regions and main bronchi of rats in the 4 mg/m^3 group)
  - 7 and 10 mg/m^3 groups exhibited significant airway injury and decrement in pulmonary function consistent with the clinical signs of respiratory tract irritation
    - most of the signs regressed during the first post exposure week
    - sporadic recurrence of irregular breathing patterns and wheezing was observed
    - necropsy findings in rats of these groups included macroscopic lung lesions and pleural adhesions.

PHENYL ISOCYANATE
Animal Lethality Data

- Imperial Chemical Industries Limited (1980a)
  - 4 ♂ 4 ♀ rats/group exposed for 1 hour to 0.358, 1.325, 1.45, 2.167, 4.368, 6.08, 7.942, or 9.187 ppm; 14-day observation
  - 1-hour LC_{50}: 3.9 ppm (2.9-5.3 ppm; 95% c.i.)
  - delayed lethality

- Bayer AG (1981a)
  - 5 ♂ 5 ♀ Wistar rats exposed to a saturated atmosphere of phenyl isocyanate (~1600 ppm at 20 °C) for 3, 10, or 30 minutes; observation period 14 days
  - all rats died
  - time-to-death was inversely related to exposure duration (see table)

- Bayer AG (1991a)
  - 4 ♂ 4 ♀ Wistar rats were exposed for 4 hrs to 0, 2.1, 10.4, 20.8, 31.3, 64.6, 82.9, or 150.2 mg/m^3 (equivalent to 0, 0.4, 2.2, 4.4, 6.6, 7.7, 17.4, and 31.3 ppm)
  - clinical signs and gross path. findings indicated respiratory tract as primary target
  - most rats died within 9 days
    - 4-hr LC_{50}: 22 mg/m^3 (19-27 mg/m^3; 95% c.i.) (4.6 ppm)
    - NOAEL: 0.7 mg/m^3 (0.15 ppm)

PHENYL ISOCYANATE
AEGL-1

AEGL-1 values for phenyl isocyanate (ppm)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	0.0067	0.0067	0.0067	0.0067	0.0067

Key study: Pauluhn, J., Rüngeler, W., Mohr, U. 1995. Phenyl isocyanate-induced asthma in rats following a 2-week exposure period. Fundam. Appl. Toxicol. 24: 217-228.

Critical effect/POD: threshold for respiratory tract irritation; 1.1 mg/m^3 (0.2 ppm); 6-hr repeated exposure

Uncertainty factors: Total uncertainty factor adjustment is 30
Interspecies: 10; absence of human data and animal data in only one species justify retention of the default interspecies uncertainty factor of 10.

Intraspecies: 3; phenyl isocyanate is a direct-contact irritant; toxicodyaamics would not be expected to vary; the POD appears to be a protective estimate (multiple exposures to higher concentrations produced no clinical signs or histopathologic evidence of pulmonary damage); isocyanates react with nucleophiles at the point of contact which, in respiratory tract tissue, includes proteins with sulfhydryl, hydroxyl, amine, and carboxyl groups (OECD, 2005). Pauluhn et al. (1995) noted that experimental evidence suggests that tissue damage is consistent with a persistent inflammatory response involving direct contact with the tissue.

Modifying Factor: none

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

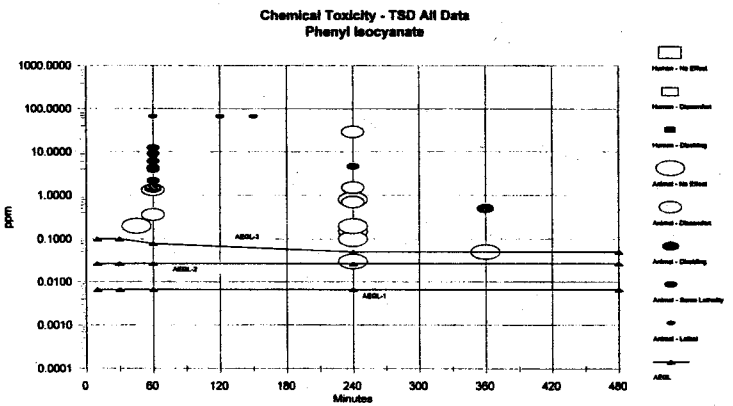
PHENYL ISOCYANATE
Animal Nonlethal

- Monsanto (1954)
  - no deaths in rats exposed for 4 hrs to ~29 ppm

- Imperial Chemical Industries Limited (1980b)
  - 8 ♂ 8 ♀ Wistar-derived rats exposed to 0.05 ppm or 0.5 ppm, 6 hrs/day for 11 days
  - 0.05 ppm concentration was close to a no-effect level

- Bayer AG (1991b)
  - 10 ♂ 10 ♀Wistar rats/group exposed to 0, 0.12, 0.57, or 3.14 mg/m^3 (analytically determined b y HPLC analysis; equivalent to 0, 0.03, 0.1, or 0.7 ppm), 6 hrs/day for 5 days; 3-wk observation
  - no rats died ; no significant clinical signs in 0.03 or 0.1 ppm groups
  - serous nasal discharge but no cumulative effects in the 0.7 ppm group
  - multiple 6-hr exposures to 0.1 ppm were without serious effect
  - multiple exposures at 0.7 ppm resulted in no significant toxicological consequences

AEGL values for phenyl isocyanate (ppm)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	0.0067	0.0067	0.0067	0.0067	0.0067
AEGL-2 (Disabling)	0.027	0.027	0.027	0.027	0.027
AEGL-3 (Lethality)	0.10	0.10	0.079	0.050	0.050



PHENYL ISOCYANATE
AEGL-2

AEGL-2 values for phenyl isocyanate (ppm)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	0.027	0.027	0.027	0.027	0.027

Key study: Pauluhn, J., Rüngeler, W., Mohr, U. 1995. Phenyl isocyanate-induced asthma in rats following a 2-week exposure period. Fundam. Appl. Toxicol. 24: 217-228.

Critical effect/POD: 0.8 ppm, 6–hr repeated exposure; NOAEL for AEGL-2 severity effects based upon clinical signs, clinical chemistry evaluations and gross/histopathology findings.

Uncertainty factors: Total uncertainty factor adjustment is 30
Interspecies: 10; absence of human data and animal data in only one species justify retention of the default interspecies uncertainty factor of 10.
Intraspecies: 3; phenyl isocyanate is a direct-contact irritant; toxicodynamics would not be expected to vary; the POD appears to be a protective estimate (multiple exposures to higher concentrations produced no clinical signs or histopathologic evidence of pulmonary damage); isocyanates react with nucleophiles at the point of contact which, in respiratory tract tissue, includes proteins with sulfhydryl, hydroxyl, amine, and carboxyl groups (OECD, 2005). Pauluhn et al. (1995) noted that experimental evidence suggests that tissue damage is consistent with a persistent inflammatory response involving direct contact with the tissue.

Modifying Factor: none

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

PHENYL ISOCYANATE
AEGL-3

AEGL-3 values for phenyl isocyanate (ppm)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	0.10	0.10	0.079	0.050	0.050

Key study: Bayer, AG. 1991a. Phenyl isocyanate; Untersuchungen zur akuten inahlationstoxizität an der Ratte. Bercht- Nr. 20354. Studien-Nr. T7037386, Bayer AG Institut für Toxikologie

Critical effect/POD: 3-fold reduction of rat 4-hr LC_{50} (4.6 ppm/3 = 1.5 ppm) considered an estimate of the lethality threshold.

Uncertainty factors: Total uncertainty factor adjustment is 30
Interspecies: 10; absence of human data and animal data in only one species justify retention of the default interspecies uncertainty factor of 10.
Intraspecies: 3; phenyl isocyanate is a direct-contact irritant for which the dynamic aspect of toxicity would not be expected to vary. It has been reported that isocyanates react with nucleophiles at the point of contact which, in respiratory tract tissue, includes proteins with sulfhydryl, hydroxyl, amine, and carboxyl groups (OECD, 2005). Pauluhn et al. (1995) noted that experimental evidence suggests that tissue damage is consistent with a persistent inflammatory response involving direct contact with the tissue.

Modifying Factor: none
Time scaling: $C^n \times t = k$, where n = 1 or 3; the 10-minute value is held constant with the 30-min. value. The 8-hour AEGL-3 value was set equivalent to the 4-hour value to maintain consistency with the AEGL-2 values.

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHYL ISOTHIOCYANATE ($CH_3N=C=S$)

National Advisory Committee for AEGLs Meeting-45
March 3-5, 2008

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Susan Ripple

Chemical Reviewers:
David Freshwater
Ralph Gingell

METHYL ISOTHIOCYANATE

Studies reported from secondary sources

Solid, rapidly vaporizes
Pungent, horse-radish-like odor
Use – pesticide, injected into soil

Toxicity: isothiocyanates (R-N=C=S) less toxic than the isocyanates (R-N=C=O)

Clinical Study:
Odor and eye irritation threshold (Russell and Rush 1996)

Animal Studies:
Acute toxicity, rat – Clark and Jackson 1977; Clark et al. 1981
Repeat-exposure studies – Klimish 1987; Rosskamp et al. 1978
Metabolism study, rat – Lam et al. 1993
Developmental/Reproductive studies, rat and rabbit (oral): not a teratogen
Carcinogenicity studies, rat and mouse (oral): not carcinogenic

METHYL ISOTHIOCYANATE

Clinical Study

Eye Irritation in Human Subjects			
Exposure time	**NOEL (ppm)**	**LOEL (ppm)**	**Effect**
1 minute	3.3	—	—
4 minutes	0.60	1.9	Subjective eye irritation
14 minutes	0.60	1.9	Subjective eye irritation
1 hour	0.23	0.80	Subjective eye irritation
1.5 hours	0.22	—	—
2 hours	0.23	0.80	Subjective eye irritation and increased blink rate
3 hours	0.23	0.80	Subjective eye irritation and increased blink rate
3.5 hours	0.22	—	—
4 hours	0.23	0.80	Subjective eye irritation
6 hours	0.22	—	—
8 hours	0.22	—	—

The 0.22 and 0.23 ppm concentrations were used on different days.
— = not tested
Source: Russell and Rush 1996; reported in Rubin et al. 2003.

LOELs were determined by statistical significance; variability was great among control and tested subjects. Irritation at the LOEL of 0.80 ppm was judged 25-26% on a scale of 1-100.

METHYL ISOTHIOCYANATE

Acute Toxicity Data - Rat

Summary of Acute Lethal Inhalation Data in Laboratory Animals				
Species	**Concentration (ppm)**	**Exposure Time**	**Effect**	**Reference**
Rat	210 635	1 hour 1 hour	No mortality LC_{50}	Clark and Jackson 1977
Rat	80 180	4 hours 4 hours	No mortality LC_{50}	Jackson et al. 1981

METHYL ISOTHIOCYANATE

Repeat-Exposure Studies - Rat

TABLE 1. Summary of Repeat-Exposure Studies

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	1.7 6.8 34	6 hours/day, 5 days/week 28 days	No clinical signs Eyelid closure, somnolence, ruffled fur Eyelid closure, somnolence, ruffled fur, nasal discharge, salivation, eye discharge, difficulty in breathing; nasal and lung lesions	Klimisch 1987
Rat	1 10 45	4 hours/day, 5 days/week, 12-13 weeks	No clinical signs No clinical signs Apathetic appearance, salivation, nasal discharge, reduced body weight	Rosskamp et al. 1978

METHYL ISOTHIOCYANATE

AEGL-1

Point of departure:
Clinical study: NOELs for eye irritation
14-minute exposure to 0.60 ppm
1-8 hour exposure to 0.22/0.23 ppm

Uncertainty factor (NOEL):
Intraspecies: 1, A NOEL for eye irritation is below the definition of an AEGL-1.

Alternate point of departure:
LOELs (slight) for eye irritation meet the definition of an AEGL-1.
Uncertainty factor (LOEL):
Intraspecies: 3, slight irritation should not vary greatly among individuals.

No time-scaling: there is adaptation to the slight irritation that defines the AEGL-1

METHYL ISOTHIOCYANATE

AEGL-2

No acute studies that meet the definition of an AEGL-2.
In lethality studies, the dose-response curve is steep.
The AEGL-2 values can be derived by dividing the AEGL-3 values by 3 (NRC 2001).

METHYL ISOTHIOCYANATE

AEGL-3

Point of departure:
Highest non-lethal value – 4-hour exposure of rats to 80 ppm (Jackson et al. 1981)

Uncertainty factors:
Interspecies: 1, direct-acting irritant
Intraspecies; 3, direct-acting irritant

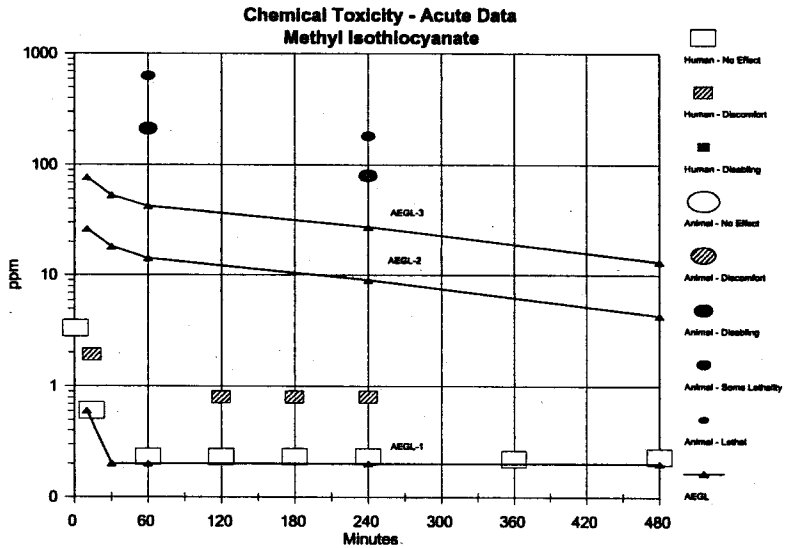
Application of greater uncertainty factors, 3 and 3 for a total of 10, would bring the 4-hour value to 8 ppm, a concentration inconsistent with the repeat-exposure studies. No rats died during exposures to 35 ppm, 6 hours/day, 5 days/week, for 28 days (Klimisch 1978) or to 45 ppm, 4 hour/day, 5 days/week for 12-13 weeks (Rosskamp et al. 1978.)

Time-scaling ($C^n \times t = k$):
Default values of $n = 3$ and $n = 1$ for shorter and longer exposure durations, respectively. The 10-minute value was set equal to the 30-minute value.

METHYL ISOTHIOCYANATE

Proposed Methyl Isothiocyanate AEGL Values					
Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1					
(NOEL)	0.60 ppm	0.22 ppm	0.22 ppm	0.22 ppm	0.22 ppm
(LOEL)	0.63 ppm	0.27 ppm	0.27 ppm	0.27 ppm	0.27 ppm
AEGL-2	26 ppm	18 ppm	14 ppm	9.0 ppm	4.3 ppm
AEGL-3	77 ppm	53 ppm	42 ppm	27 ppm	13 ppm

AEGL-1: NOEL, LOEL for eye irritation – clinical study of 1 minute to 8 hours
AEGL-2: AEGL-3 divided by 3
AEGL-3: Highest non-lethal concentration – 4-hour exposure of rats to 80 ppm



METHYL ISOTHIOCYANATE

Proposed Methyl Isothiocyanate AEGL Values					
Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1					
(NOEL)	0.60 ppm	0.22 ppm	0.22 ppm	0.22 ppm	0.22 ppm
(LOEL)	0.63 ppm	0.27 ppm	0.27 ppm	0.27 ppm	0.27 ppm
AEGL-2	26 ppm	18 ppm	14 ppm	9.0 ppm	4.3 ppm
AEGL-3					
(4 hours)	77 ppm	53 ppm	42 ppm	27 ppm	13 ppm
(1 hour)	127 ppm	88 ppm	70 ppm	18 ppm	8.8 ppm

AEGL-1: NOEL, LOEL for eye irritation – clinical study of 1 minute to 8 hours
AEGL-2: AEGL-3 divided by 3
AEGL-3: Highest non-lethal concentration – 4-hour exposure of rats to 80 ppm;
" 1 hour exposure of rats to 210 ppm.

ATTACHMENT 11

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR ETHYL PHOSPHORODICHLORIDATE

NAC/AEGL-45
March 3-5, 2008
Alexandria, VA

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Gail Chapman

Chemical Reviewers: Dieter Heinz and Martha Steele

AEGL-1 VALUES: ETHYL PHOSPHORODICHLORIDATE				
10 minute	30 minute	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR

NR: Not Recommended due to insufficient data.

Limited Database:

No human Data

Acute Inhalation data limited to rats:

1-hr range-finding study (Rhone-Poulenc, Inc., 1990)

4-hr acute toxicity study (Bayer, 1983)

Mechanism:

Primary Irritation

Rat studies suggest that vapors are irritating to the eyes and nose, and that pulmonary edema increases as concentration increases (Rhone Poulenc, Inc., 1990; Bayer, 1983).

The liquid was corrosive to the skin and eyes of rabbits (Rhone Poulenc, Inc., 1990).

May react with water to produce hydrogen chloride fumes

AEGL-2 Values for ETHYL PHOSPHORODICHLORIDATE				
10-min	30-min	1-h	4-h	8-h
0.76 ppm	0.76 ppm	0.60 ppm	0.38 ppm	0.19 ppm

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

SOP (NRC, 2001):

In the absence of appropriate chemical-specific data, a fractional reduction of the AEGL-3 values may be used to derive AEGL-2 values.

In cases of a steep-concentration-response curve, AEGL-3 values may be divided by 3 to estimate AEGL-2 values.

DERIVATION RATIONALE:

4-Hour rat lethality data suggest that the concentration-response curve is not steep (Bayer, 1983):

Concentration	Mortality
37 ppm	0%
61 ppm	20%
75 ppm	20%
90 ppm	60%
143 ppm	85%
355 ppm	100%

Therefore, the factor of 3 is not considered sufficient, and AEGL-2 values are estimated by dividing AEGL-3 values by 10.

AEGL-3 VALUES: ETHYL PHOSPHORODICHLORIDATE				
10 minute	30 minute	1 hour	4 hour	8 hour
7.6 ppm	7.6 ppm	6.0 ppm	3.8 ppm	1.9 ppm

Species: Rat
Concentration: 38.0 ppm
Time: 4 hours
Endpoint: $BMCL_{05}$ (male and female combined)
Reference: Bayer, 1983

The 4-hour study was chosen over the 1-hour study because it includes more animals per exposure group and yields a better concentration-response relationship. Furthermore, the goodness of fit for the benchmark calculations is better for the 4-hour data.

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

<u>Uncertainty Factors:</u>
Interspecies = 3: Irritant
Intraspecies = 3: Irritant

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

AEGL Values for Ethyl phosphorodichloridate					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.76 ppm	0.76 ppm	0.60 ppm	0.38 ppm	0.19 ppm
AEGL-3 (Lethality)	7.6 ppm	7.6 ppm	6.0 ppm	3.8 ppm	1.9 ppm

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.

There are no other standards or guidelines for ethyl phosphorodichloridate!

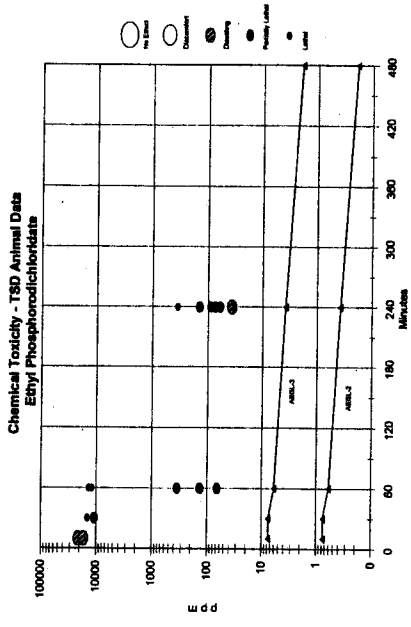


TABLE 1. Inhalation of ethyl phosphorodichloridate in Sprague-Dawley rats for 1-hour*

Concentration (ppm)	Body weight (grams; mean ± SD) (N)		Terminal lung weight (grams; mean ± SD)		Mortality incidence		
	Male	Female	Male	Female	Male	Female	Total
6.16	Day 1: 248±15 (5) Day 8: 287±17 (5) Day 15: 334±30 (5)	Day 1: 198±7 (5) Day 8: 222±6 (5) Day 15: 236±5 (5)	1.360±0.111	1.099±0.065	0/5	0/5	0/10
66	Day 1: 331±18 (5) Day 8: - (0) Day 15: - (0)	Day 1: 238±11 (5) Day 8: 203±33 (3) Day 15: 252±51 (2)	-	1.933±0.215	5/5	3/5	8/10
134	Day 1: 286±16 (5) Day 8: 206±35 (4) Day 15: 246±105 (2)	Day 1: 200±14 (5) Day 8: 181±0 (1) Day 15: 237±0 (1)	1.929± 0.402	2.408±0.0	3/5	4/5	7/10
LC_{50} (ppm)					64.6	48.1	43.4
$BMCL_{05}$ (ppm)**					0.10	0.71	1.28
BMC_{01} (ppm)**					2.39	7.50	3.85

Rhone-Poulenc, Inc., 1990; ** Values calculated for this TSD.

TABLE 2. Inhalation of ethyl phosphorodichloridate in rats for 4-hours*			
Concentration (ppm)	Mortality incidence		
	Male	Female	Total
37	0/10	0/10	0/20
61	2/10	**	2/10
75	1/10	3/10	4/20
90	7/10	5/10	12/20
143	10/10	7/10	17/20
355	10/10	10/10	20/20
LC_{50} (ppm)	85	99.8	91.6
$BMCL_{05}$ (ppm)***	43.7	25.8	38.0
BMC_{01} (ppm)***	48.1	32.1	38.2

*Bayer, 1983 ; **Data not reported. No explanation provided ; *** Values calculated for this TSD.

ACUTE EXPOSURE GUIDELINE LEVELS FOR 1,2-BUTYLENE OXIDE (C_4H_8O)

National Advisory Committee for AEGLs Meeting-45
March 3-5, 2008

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Jim Holler

Chemical Reviewers:
Alan Woolf
Lynn Beasley

1,2-BUTYLENE OXIDE

Highly flammable, reactive liquid at ambient temperature
Pungent odor
Use – stabilizer in hydrocarbon solvents

Clinical Studies:
No data

Animal Studies:
Acute toxicity, rats and mice – NTP 1988
Repeat-exposure toxicity studies, rat and mouse - (Miller et al. 1981; NTP 1988)
Metabolism study, rat – Reitz et al. 1983
Conjugated with glutathione
Developmental/Reproductive studies (Sikov et al. 1981)
Effects on the fetus only at maternally toxic concentrations
Genotoxicity studies (NTP 1988)
Positive in several tests
Chronic Toxicity/Carcinogenicity study
Male rats – nasal neoplasms (NTP 1988)

1,2-BUTYLENE OXIDE

Effects:

Acute: Direct acting irritant
Target – eye, respiratory tract
Chronic: Carcinogenic in rats, not in mice
Target – nasal mucosa

ATTACHMENT 12

1,2-BUTYLENE OXIDE

Acute Toxicity Data - Rat

NTP (1988) – 4 hour study

Concentration	Effect
398 ppm	No signs reported
721 ppm	No signs reported
1420 ppm	Signs of eye irritation
2050 ppm	Ocular discharge, dyspnea
6550 ppm	Dyspnea, death of 10 of 10 rats

Reitz et al. 1983 – 6 hour study

Concentration	Effect
50 ppm	No effect reported
1000 ppm	Moderate respiratory rate decrease

Support Studies – Repeat-exposure, Rat, mouse
Miller et al. 1981; NTP 1988

Concentration	Effect
400 ppm, 6 hours/day, 2 weeks	No lesions

1,2-BUTYLENE OXIDE

AEGL-1

Point of departure:
NOAEL for eye irritation – 4-hour exposure of rats to 721 ppm (NTP 1988)

Uncertainty factors:
Interspecies: 3: slight irritation from a direct-acting irritant should not vary greatly between species

Intraspecies: 3: slight irritation from a direct-acting irritant should not vary greatly among individuals

Application of greater uncertainty factors, 3 and 10 for a total of 30, would bring the 4-hour value to 24 ppm, 16-fold less than the no effect concentration of 400 ppm in repeat-exposure studies (Miller et al. 1981; NTP 1988)

Time-scaling:
No time scaling – there is adaptation to the slight irritation that defines the AEGL-1. The 8-hour value was adjusted by a MF of 2.

1,2-BUTYLENE OXIDE

AEGL-2

Point of departure:
Moderate eye irritation – 4-hour exposure of rats to 1420 ppm (NTP 1988)
Support: Moderate decrease in respiratory rate – 6-hour exposure to 1000 ppm (Reitz et al. 1983)

Uncertainty factors:
Interspecies: 3, direct-acting irritant
Intraspecies: 3, direct-acting irritant

Application of greater uncertainty factors, 3 and 10 for a total of 30, would bring the 4-hour value to 47 ppm, 10-fold less than the no effect concentration of 400 ppm in repeat-exposure studies (Miller et al. 1981; NTP 1988)

Time-scaling ($C^n \times t = k$):
Default values of n = 3 and n = 1 for shorter and longer exposure durations, respectively. The 10-minute value was set equal to the 30-minute value.

1,2-BUTYLENE OXIDE

AEGL-3

Point of departure:
Highest non-lethal value – 4-hour exposure of rats to 2050 ppm (NTP 1988)

Uncertainty factors:
Interspecies: 3, direct-acting irritant
Intraspecies: 3, direct-acting irritant

Application of greater uncertainty factors, 3 and 10 for a total of 30, would bring the 4-hour values to 68 ppm, approximately 6-fold less than the no effect concentration of 400 ppm in repeat-exposure studies (Miller et al. 1981; NTP 1988)

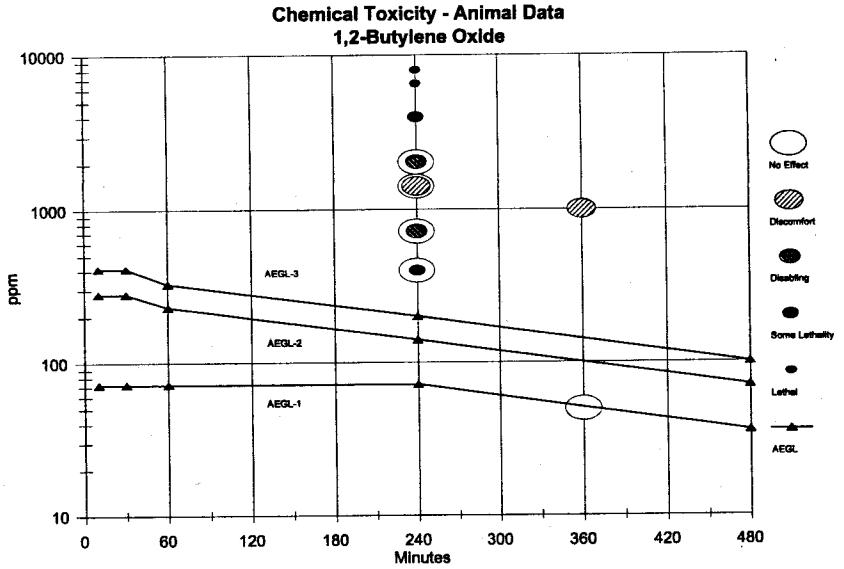
Time-scaling ($C^n \times t = k$):
Default values of n = 3 and n = 1 for shorter and longer exposure durations, respectively. The 10-minute value was set equal to the 30-minute value.

1,2-BUTYLENE OXIDE

Proposed 1,2-Butylene Oxide AEGL Values

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	72 ppm	72 ppm	72 ppm	72 ppm	36 ppm
AEGL-2	280 ppm	280 ppm	230 ppm	140 ppm	71 ppm
AEGL-3	410 ppm	410 ppm	325 ppm	200 ppm	100 ppm

AEGL-1: NOAEL for eye irritation – 4-hour exposure of rats to 721 ppm
AEGL-2: Moderate eye irritation – 4-hour exposure of rats to 1421 ppm
AEGL-3: Highest non-lethal concentration – 4-hour exposure of rats to 2050 ppm


Chemical Toxicity - Animal Data
1,2-Butylene Oxide
10000
1000
100
10
ppm
AEGL-3
AEGL-2
AEGL-1
0
60
120
180
240
300
360
420
480
Minutes
No Effect
Discomfort
Disabling
Some Lethality
Lethal
AEGL

EPA

Dose-Response Modeling Techniques for Analyzing Animal Data

EPA United States Environmental Protection Agency

Objective

- Introduce Benchmark Dose Modeling and its application in dose-response analysis for the data obtained from animal studies.

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Outline

- Introduction to benchmark dose method
  - –Traditional method (NOAEL)
  - –Concept of BMD method
  - –Pros and cons for BMD method
- EPA's BMD software (BMDS) and its available models
- BMD modeling procedure
- Evaluation of BMD modeling results

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Glossary

- BMD: An estimate of the dose or concentration that produces a predetermined change in response rate
- BMDL: 95% lower-bound confidence limit on the BMD
- BMR: A predetermined response level based on which a BMD or BMDL is calculated
- POD: a point of departure used in estimate risk values when divided by an uncertainty factor
- UF: Factors used in risk assessment to account for uncertainty in the data or extrapolations to human no-effect levels
- Confidence interval: an interval estimate of a population parameter at a certain confidence level
- AIC: Akaike's Information Criterion used to assist in model evaluation based on overall data fitting and number of parameters used in the model

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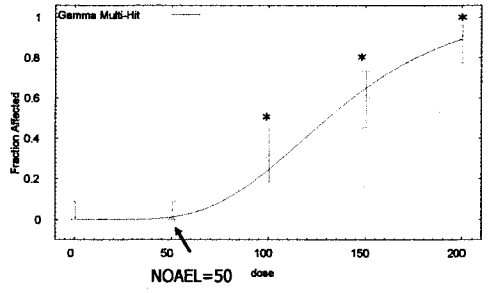
Reference Dose/Reference Concentration

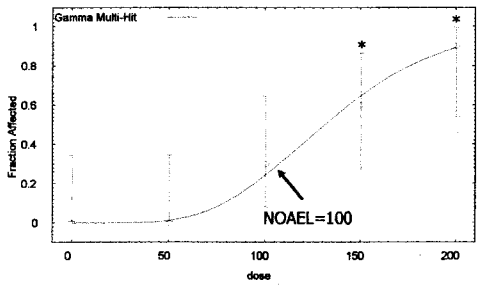
$$\text{RfD or RfC} = \frac{\text{NOAEL or LOAEL}}{\text{UF}}$$

NOAEL or LOAEL: No or Low Observed Adverse Effect Level
UF: Uncertainty Factor

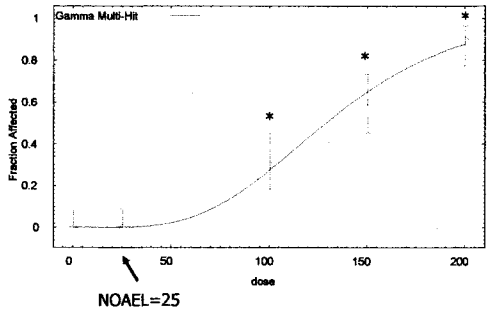
Study Conducted with 50 Animals per Dose



Study Conducted with 10 Animals per Dose



Study Conducted with 50 Animals per Dose

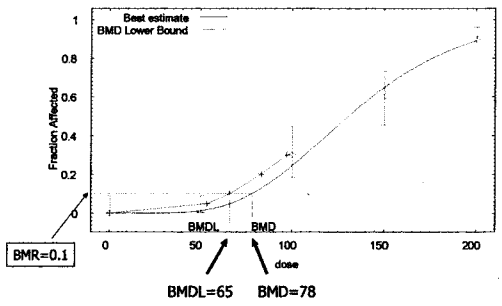


Limitations of Using a NOAEL or LOAEL

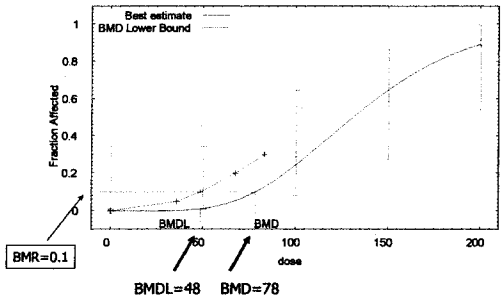
- Limited to the doses tested
- Response levels not comparable
- Does not represent 0% response
- Not always available
- Does not consider dose-response slope ("Wastes" data)
- Highly dependent on sample size

5

Study Conducted with 50 Animals per Dose



Study Conducted with 10 Animals per Dose



Benchmark Dose Definitions

BMD: An estimate of the dose or concentration that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background.

- *For example, an estimate of the dose that causes a 10% increase in the number of animals developing fatty liver compared with untreated animals.*

12

Benchmark Dose Definitions

BMDL: 95% Lower-Bound Confidence Limit on the BMD.

Benchmark Dose

- Goal is to estimate a point of departure (POD) that is relatively independent of study design.

Deriving an RfD using a BMD

Equation for an RfD or RfC becomes:

$$\text{RfD or RfC} = \frac{\text{BMDL or BMCL}}{\text{UF}}$$

No UF for LOAEL to NOAEL extrapolation

Advantages of BMD Approach

- Not limited to doses tested experimentally
- Less dependent on dose spacing
- Takes into account the shape of the dose-response curve
- Flexibility in determining biologically significant rates
- Comparable results across chemicals and endpoints
- Incentive to conduct better (larger) studies (less uncertainty)

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Challenges in the Use of BMD

- Ability to estimate a BMD may be limited by the format of the data presented
- Generally more complicated and time consuming

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Are the Data Worth Modeling?

- Evaluate database as for NOAEL approach
  - –good quality studies
  - –appropriate duration and route of exposure
  - –measured endpoints of concern

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Are the Data Worth Modeling?

- Significant dose-related trend
- Two doses with responses in excess of the control
- Responses that define the low end of the dose-response region are preferred

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Are the Data Worth Modeling?

- Model all biologically, statistically significant responses, if feasible
- Model all the endpoints with LOAEL < 10-fold above the lowest LOAEL of the database
- Consider dropping high dose group(s) that negatively impact low dose fit

Benchmark Dose Software

- Benchmark Dose Software is also called BMDS software.
- It is developed by US EPA and it is free available from website: www.epa.gov/ncea/bmds.

Types of Models

- Dichotomous Model: for dichotomous or quantal data
- Continuous Model: for continuous data
- Nested Model: for nested dichotomous data

Model Selection - Dichotomous Data

- Dichotomous models are used to evaluate quantal data, where an effect for an individual may be classified by one of two possible outcomes.
- For example: dead or alive, tissue pathology (present/absent), and cancer incidence (yes/no)

BMDS Models for Dichotomous Data

- Gamma
- Logistic
  - Dose
  - Log dose
- Probit
  - Dose
  - Log dose
- Multi-stage
- Weibull
  - Quantal-Linear (power = 1)

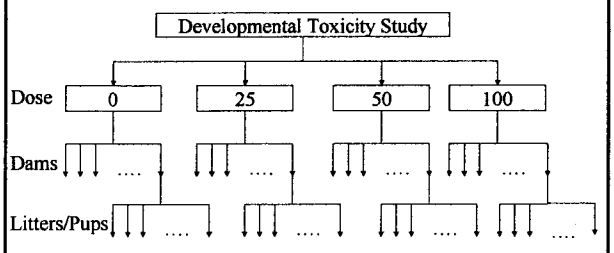
Model Selection - Continuous Data

- Effects measured on a continuum
- For example: body weight, organ weight, enzyme levels

BMDS Models for Continuous Data

- Polynomial (all-purpose model)
  - –Linear (simplest model)
  - –Non linear
- Power (L-shaped dose-responses)
  - –Linear
  - –Non linear
- Hill (dose-responses that plateau)

Model Selection - Nested Dichotomous Data



Endpoints – Fetal weight, malformations, etc.

Nested Dichotomous Data

- Malformation in neonates
  - –Sternebral defect
  - –Vertebral arch defect
- Ossification changes in neonates

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BMDS Models for Nested Dichotomous Data

- Logistic Nested Model (NLogistic)
- NCTR
- Rai & Van Ryzin Model

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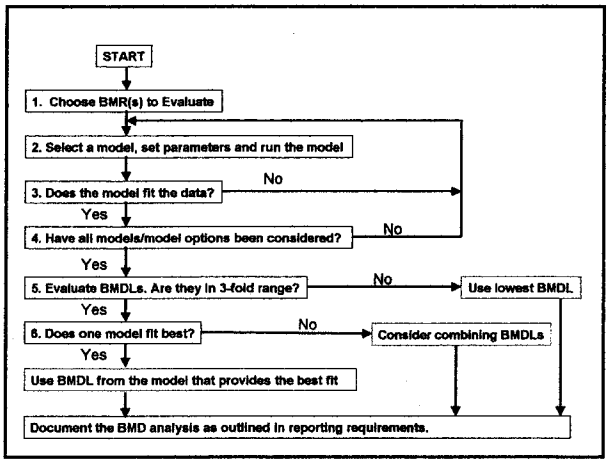
Model Selection – Other Considerations?

- Most BMD models are not biologically based, but all model fits must be biologically tenable
- To be biologically tenable, model parameters may need to be restricted
- Consider using model with asymptote term for saturable responses



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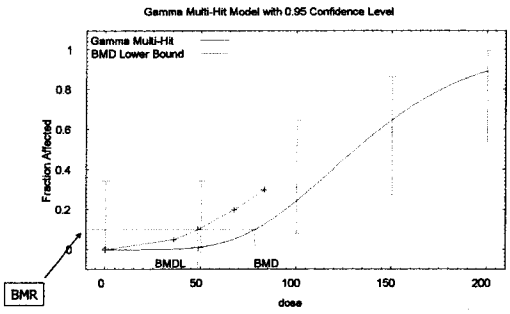
Select A Benchmark Response

- BMR should be near the low end of the range of increased risks that can be detected by a bioassay.
- Low BMRs can impart high model dependence, i.e., different models will provide different BMDL estimates.

Benchmark Dose



BMR Selection: Choose BMR(s) (Dichotomous Data)

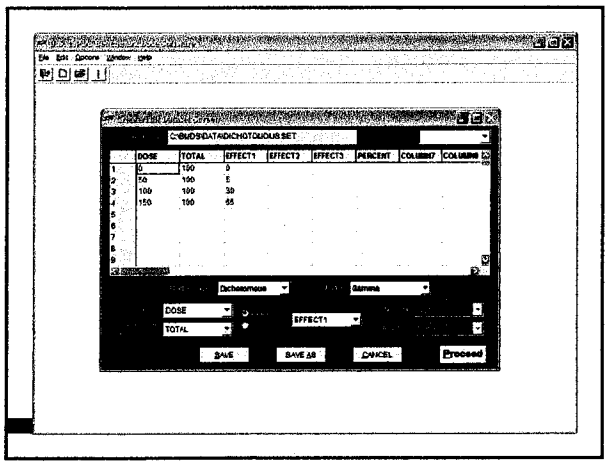
- Extra risk of 10% is the default BMR, since the 10% response is at or near the limit of sensitivity in most cancer bioassays and in some non-cancer bioassays.
- If a study has greater than usual sensitivity, a lower BMR can be used.
- BMD10 and BMDL10 should always be presented for comparison purpose.

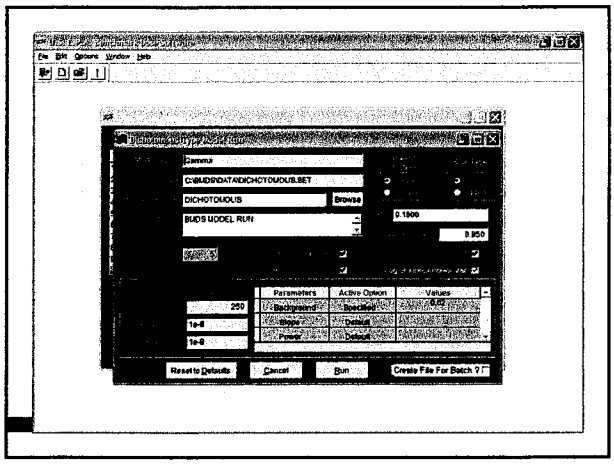
BMR Selection: Choose BMR(s) (Continuous Data)

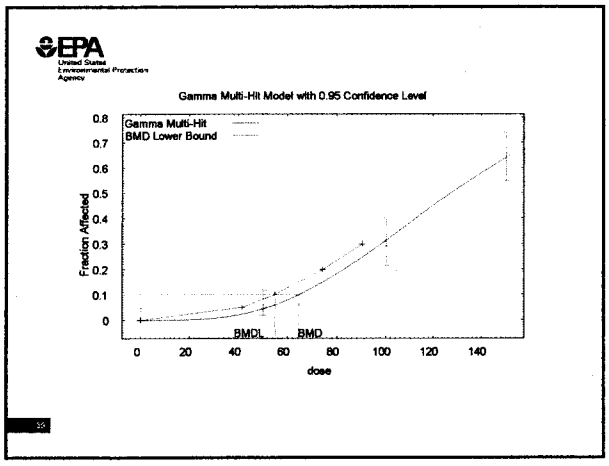
- If there is an accepted level of change in the endpoint that is considered to be biologically significant, then that amount of change is the BMR.
- In the absence of any other idea of what level of response to consider adverse, a change in the mean equal to one control standard deviation (1.0 SD) from the control mean can be used.

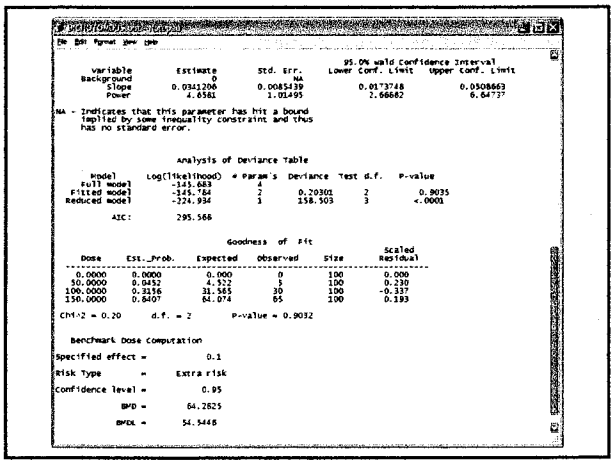
Restricting Parameters

- BMD Guidance suggests restricting models initially.
- Unrestricted, some models take on unrealistic forms.
- Number of parameters in a model cannot exceed the number of dose groups.









```
                                                    95.0% Wald Confidence Interval
Variable          Estimate          Std. Err.     Lower Conf. Limit   Upper Conf. Limit
Background               0                NA
Slope           0.0341206         0.0085439           0.0173748           0.0508663
Power             4.8581            1.01495             2.86682             6.84937

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


                    Analysis of Deviance Table

Model            Log(likelihood)    # Param's   Deviance   Test d.f.   P-value
Full model           -145.683           4
Fitted model         -145.784           2         0.20301       2          0.9035
Reduced model        -224.934           1         158.503       3          <.0001

         AIC:          295.568


                           Goodness of Fit

  Dose       Est._Prob.     Expected     Observed      Size      Scaled Residual
------------------------------------------------------------------------------
  0.0000       0.0000        0.000           0         100          0.000
 50.0000       0.0452        4.522           5         100          0.230
100.0000       0.3156       31.565          30         100         -0.337
150.0000       0.8407       84.074          85         100          0.193

Chi^2 = 0.20     d.f. = 2     P-value = 0.9032


  Benchmark Dose Computation

Specified effect =         0.1

Risk Type        =     Extra risk

Confidence level =        0.95

             BMD =     64.2825

            BMDL =     54.5448
```

Does the Model Fit the Data?

- Global measurement: goodness-of-fit p value ($p > 0.1$)
- Local measurement: Scaled residuals (absolute value < 2.0)
- Visual inspection of model fitting

Note: Consider how well the model predicts both responses and response variance (in the case of continuous data).

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Have All Options Been Considered?

- Goal of BMD modeling - fit a model to dose-response data that describes the data, especially at the lower end of the dose-response range.
- This may require the application of several models and model options, or just a few.

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Summary of BMD Results

Model	P value	AIC	Residual at 0	Residual at 5%	BMD	BMDL
Gamma	0.9032	295.6	0	0.230	64.3	54.5
Logistic						
Log-Logistic						
Multistage						
Probit						
Log-Probit						
Quantal-Linear						
Weibull						

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BMDL Estimates Within 3-fold Range?

- Often, more than one model will result in an acceptable fit to the data.
- Consider using the lowest BMDL if BMDL estimates from acceptable models are widely divergent (e.g., outside of a 3-fold range).
- Consider relative model fit of BMDL if model results in similar BMDL estimates (e.g., within a 3-fold range).

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Is There One Model That Fits the Data Best?

- Global measurement: goodness-of-fit p value ($p > 0.1$)
- Local measurement: Scaled residuals near the BMR
- Visual comparison of model fits (e.g., to detect systemic or high dose bias)
- Comparison of Akaike's Information Criterion (AIC) (smaller is better)

Akaike's Information Criterion (AIC)

$$AIC = -2 \times LL + 2 \times P$$

LL = log-likelihood at the maximum likelihood estimates for parameters

p = number of model parameters estimated

- Within a family of models, fit will improve as parameters are added.
- For a similar degree of fit, AIC rewards the less complex model (with less parameters).

Summary of BMD Results

Model	P value	AIC	Residual at 0	Residual at 5%	BMD	BMDL
Gamma	0.9032	295.6	0	0.230	64.3	54.5
Logistic	0.3317	298.5	-0.996	-0.246	70.5	61.8
Log-Logistic	0.8851	295.6	0	0.287	65.1	55.3
Multistage	0.2520	297.9	0	-1.545	51.3	45.7
Probit	0.6543	296.6	-0.628	-0.077	67.8	58.9
Log-Probit	0.6513	296.2	0	0.443	63.7	54.9
Quantal-Linear	0	324.4	0	-3.69	24.1	20.5
Weibull	0.9912	295.4	0	-0.083	64.3	53.7

Deriving an RfD/RFC from a BMDL

$$\text{RfD or RfC} = \frac{\text{BMDL or BMCL}}{\text{UF}}$$

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Conclusion

- BMD method uses more dose-response information.
- It provides a better way for comparing different endpoints.
- This method gives incentive to conduct better studies (with less uncertainty).
- BMD modeling requires more information on the data and it is more time consuming.

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