COT/AEGL SUGGESTED REVISION OF AEGLS FOR IRON PENTACARBONYL

- Iron pentacarbonyl AEGL-3 originally developed using n =1 based upon similarity of Ct products for two LC_{50} values
    - Ct products for 30-minute LC_{50} of 118 ppm (Sunderman et al., 1959) and the 4-hour LC_{50} of 10 ppm (Biodynamics, 1988) are 59 and 40 ppm hrs, respectively.

- Due to paucity of data, COT (12th Interim Report, January 2005) suggested that AEGLs be derived using default of $n = 1$ or $n = 3$ as specified in SOPs (NRC, 2001)

- Currently, two data points would not be considered sufficient or appropriate for empirical derivation of n by regression analysis

- Revised AEGL-3 values are more protective but justified by SOPs

- AEGL-2 values (1/3 of AEGL-3) are adjusted accordingly

Summary of Proposed AEGL Values For Iron Pentacarbonyl						
Classification	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended; insufficient data
AEGL-2 (Disabling)	1.2 ppm 9.6 mg/m^3 **0.11 ppm** **0.88 mg/m^3**	0.40 ppm 3.2 mg/m^3 **0.077 ppm** **0.61 mg/m^3**	0.20 ppm 1.6 mg/m^3 **0.060 ppm** **0.48 mg/m^3**	0.050 ppm 0.40 mg/m^3 **0.037 ppm** **0.29 mg/m^3**	0.025 ppm 2.0 mg/m^3	Based upon a three-fold reduction in the AEGL-3 values
AEGL-3 (Lethal)	3.6 ppm 29 mg/m^3 **0.33 ppm** **2.6 mg/m^3**	1.2 ppm 9.6 mg/m^3 **0.23 ppm** **1.8 mg/m^3**	0.60 ppm 4.8 mg/m^3 **0.18 ppm** **1.4 mg/m^3**	0.15 ppm 1.2 mg/m^3 **0.11 ppm** **0.88mg/m^3**	0.075 ppm 0.60 mg/m^3	Estimated lethality threshold in rats (1.0 ppm determined by BMD analysis (BASF, 1995). n = 1or 3; UF = 10 (3 for interspecies variability, 3 for individual variability)

NR: Not recommended. Numeric values for AEGL-1 are not recommended because (1) the lack of available data, and (2) an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

RESPONSE TO COT COMMENTS ON THE AMMONIA TSD

KOWETHA DAVIDSON, ORNL STAFF SCIENTIST

SUSAN RIPPLE, CHEMICAL MANAGER

NAC/AEGL MEETING, Research Triangle Park, NC
April 12-14, 2005

1. Subject: Selection of Intraspecies Uncertainty Factors for AEGL-1, -2, and -3

- ***Response:*** *The intraspecies uncertainty factor and rationale for the three AEGL levels as presented in the TSD are summarized below for discussion by the NAC. This information should aid the NAC in determining whether the intraspecies uncertainty factors and/or rationale should be changed for the three AEGL levels.*

AEGL-1, UF = 1: Rationale from the TSD

- Ammonia is efficiently scrubbed in the upper respiratory tract, and if irritation is detected, it would be confined to the nasal cavity (and possibly the eyes).
- Nonatopic and atopic subjects, including asthmatics, responded similarly in a nasal airway resistance test when 100 ppm of ammonia was introduced into each nostril for up to 30 seconds (McLean et al.,(1979).
- Exercising subjects showed only a small equivocal decrease in pulmonary function after exposure to higher concentrations of ammonia (Cole et al., 1977).

AEGL-2, Intraspecies UF = 1: Rationale from the TSD

- Ammonia is a contact irritant, it is efficiently scrubbed in the upper respiratory tract, and any perceived irritation is not expected to be greater than that of most sensitive non-expert subjects.
- The effects at the AEGL-2 levels would primarily involved the eyes and upper respiratory tract and asthmatics would be unlikely to respond differently from the most sensitive nonexpert subjects.
- Atopic and non-atopic subjects responded similarly to a brief nasal exposure to ammonia (McLean et al., 1979).
- Exercising subjects showed only small equivocal changes in pulmonary function during exposure to ammonia at concentrations up to 336 ppm (Cole et al., 1979).
- A child experienced less severe effects than an adult exposed to much higher concentrations (Kass et al., 1972).
- The effects reported by the non-expert subjects were less serious than those described in the AEGL-2 definition, and no residual effects were reported for any subject after termination of exposure.

AEGL-3, Intraspecies UF = 3: Rationale from the TSD

- High concentrations of ammonia elicit severe irritation immediately upon contact with the eyes or mucous membranes of the respiratory tract and the severity of effects, such as pulmonary edema and tracheobronchial injury, would be similar in asthmatics and non-asthmatics. Severe long-lasting or irreversible damage to the respiratory tract may be a greater concern than that of asthma.
- Asthmatics and non-asthmatics responded similarly to a brief nasal exposure to a lower concentration of ammonia (McLean, 1979).
- One study showed that a child suffered reversible damage to the respiratory tract, whereas the mother carrying the child suffered permanent severe damage to the respiratory tract after exposure to a high concentration of ammonia (Kass et al., 1972).
- The protective mechanism of reflex glottis closure is threefold less sensitive in the elderly than young subjects exposed to high concentrations of ammonia (Erskine, 1993). ***Reflex glottis closure is a protective mechanism stimulated by inhaling irritants or noxious vapors. The reflex mechanism occurred at 571 ppm in young subjects and at 1791 ppm on the elderly, which is approximately a threefold difference.***
- Exercising adults showed only equivocal effects on pulmonary function at concentrations up to 336 ppm (Cole et al., 1979).
- A larger interspecies or intraspecies uncertainty factors would lower the 30-minute AEGL-3 value to a level comparable to the 500 ppm shown to be tolerated by humans without lethal or long-term consequences (Silverman et al., 1949).

2. Subject: Interspecies uncertainty factor for AEGL-3 derivation

- ***Response:*** *the interspecies UF = 1 for AEGL-3 derivation was based on ten Berge et al., 1986.*
- **AEGL-3, Interspecies UF = 1: Rationale as presented in the TSD**

The mouse is unusually sensitive to exposure to respiratory irritants, including ammonia (ten Berge et al., 1986); therefore, an interspecies uncertainty factor of 1 was applied

3. Subject: Derivation of 5-minute AEGL values

- ***Response:*** *NAC's decision to maintain the 5-minute AEGL values that were requested by industry. The 5-minute values were requested because in most catastrophic accidents, the highest ammonia concentrations occur within the first 5 minutes after the accidents, after which the concentrations decrease rapidly.*

- ***Technical staff recommendation*****:** *Industry requested the 5-minute value. The AEGL values should provide relevant guidance to those who will use it. The SOPs do not require a 5-minute value, however, in this case, adherence to the SOPs should not supercede industry's need.*

4. Subject: Revision of the summary of the Verberk (1977) study

Average (Range) Scores of Subjective Responses of Expert and Nonexpert Subjects Exposed to Ammonia[a]								
Response	50 ppm		80 ppm		110 ppm		140 ppm	
	Expert	Non-expert	Expert	Non-expert	Expert	Non-expert	Expert	Non-expert
Smell								
½ h	2.0 (1-3)	2.5 (2-3)	2.0 (1-3)	3.0 (2-4.5)	2.0 (2-3)	3.0 (2-4)	2.0 (1-3)	4.0 (2-4.5)
1 h	2.0 (1-3)	2.5 (1-4)	2.0 (1-3)	3.0 (2-4)	2.0 (2-3)	3.0 (2-4)	2.0 (1-3)	4.0 (3.5-4.5)
2 h	2.0 (0.5-3)	3.0 (2-4)	1.5 (0.5-3)	3.0 (2-4)	2.0 (1.5-3)	3.0 (2-4)	2.(1-3)	WD
Eye irrit.								
½ h	1.5 (0-3)	0.8 (0-3)	1.5 (1-2)	1.5 (0-4)	2.5 (1-3)	2.5 (0-4)	3.0 (1.5-3.5)	3.0 (1-4.8)
1 h	1.5 (0-3))	0.8 (0-3)	2.0 (0-3)	1.5 (0-3)	2.5 (2-3.5)	2.5 (0-4)	2.0 (2-3)	3.5 (1-5)
2 h	1.0 (0-2)	1.2 (0-3)	1.5(0-2)	2.0 (0-4)	2.0 (0.3-3)	2.5 (0-4)	2.5 (1-3)	WD
Throat irrit.								
½ h	0.4 (0-2)	0.4 (0-1)	0.8 (0-2)	1.0 (0-3	1.5 (0-3.5)	2.0 (0-4)	1.0 (0-2)	3.7 (3.5-5)
1 h	0.4 (0-3)	0.5 (0-3)	1.0 (0-3)	1.4 (1-3)	1.4 (0-3)	2.5 (1-4)	1.5 (0-2)	4.5 (2-4)
2 h	0.7 (0-3)	1.5 (0.3)	0.8 (0-2)	2.0 (0-4)	1.0 (0-2)	3.0 (2-4)	1.0 (0-3.7)	WD
cough								
½ h	0.2 (0-1.2)	0.2 (0-1)	0.3 (0-1)	0.5 (0-2)	0.8 (0-2)	1.5 (0-2)	0.5 (0-2)	2.0 (0-5)
1 h	0.3 (0-2)	0.2 (0-2)	0.5 (0-2)	1.0 (0-2)	0.5 (0-3.5)	1.7 (0-3)	0.6 (0-2.5)	1.7 (0-3)
2 h	0.3 (0-2)	0.4 (0-2)	0.4 (0-2)	0.3 (0-4)	0.3 (0-2.5)	1.7 (0-4)	0.4 (0-2.3)	WD
Discomf.								
½ h	0	0.1 (0-1)	0	1.0 (0-3)	0.2 (0-2)	1.0 (0-3)	0	2.2 (0-4)
1 h	0	0.2 (0-1)	0	1.2 (0-3)	0.2 (0-1)	1.2 (0-3)	0	3.3 (0-4.7)
2 h	0	1.0 (0-2)	0	1.3 (0-3)	0.3 (0-1)	1.5 (0-4)	0	WD
Chest Irrit.	Similar to throat irritation, hut scores tended to be slightly lower							

5. Subject: Selection of point-of-departure for AEGL-2 derivation

- ***Response:*** *Based on the Verberk (1977) data presented in the table, AEGL-2 values are derived from the exposure to 140 ppm for 30 minutes; none of the non-experts exposed to this concentration exited the room in less than 30 minutes. The responses did not exceed offensive for any effect except odor.*

- *AEGL-2 values based on a point-of-departure of 140 minutes for 30 minutes are presented below. The uncertainty factor (intraspecies UF = 1) and time scaling are the same as described previously.*

AEGL-2 DERIVATION

AEGL-2 Values for Ammonia (ppm [mg/m^3]) - Revised					
5 min	10 min	30 min	1h	4 h	8 h
340 [238]	240 [168]	140 [98]	99 [69]	99 [69]	99 [69]

AEGL-2 Values for Ammonia (ppm [mg/m^3]) – as in TSD					
5 min	10 min	30 min	1 h	4 h	8 h
380 [266]	270 [266]	160 [112]	110 [77]	110 [77]	110 [77]

COT Comments on Ammonia AEGL TSD from August 2004 Meeting

Subject: Selection of Uncertainty Factors for AEGL-1, -1, and -3

General Comment Section

Page 35, Section 5.3. Proposed value of 30 ppm to derive the AEGL-1 is justified, although the rationale for not applying an intraspecies UF is flawed. Please provide a better rationale.

Page 38, Section 6.3. Similar comment regarding asthmatics as above. Basis concentration justified.

Page 40, Section 7.3. While there is good rationale presented for using the mouse studies to derive AEGL-3, there is one problem relating to the interspecies UF of 1 used for this AEGL. While the mouse is relatively sensitive to ammonia compared to the rat, we do not know the relationship between mouse and human. Furthermore, the nasal passages of the mouse are more efficient in scrubbing inhaled ammonia that would be the nasal passages of humans. Thus, in an exposure atmosphere, the relative percentage between the URT and LRT would likely differ, with a greater percentage reaching the LRT in humans than in mice. Thus, some reconsideration of the interspecies UF should be given.

The rationale for using an intraspecies UF of 3 for AEGL-3, where there would likely be little difference in response between sensitive and nonsensitive people due to highly irritating properties of ammonia at AEGL-3 levels, while the UF is only 1 for AEGLs 1 and 2 is not sound. From the discussion presented, it appears that the UF for AEGL-3 should be less than that for 1 and 2.

On page 41, one of the reasons for using the stated inter- and intraspecies UFs is that larger UF values would lower one of the AEGL-3 values to a concentration inconsistent with the definition of AEGL-3. Cite the specific section of the SOP that describes this situation.

Specific Comment Section

Page 35, line 42. AEGL1 intraspecies UF is 1- why? Why is 3 not appropriate? The data suggest variability between the elderly subpopulation and the general population. Is it because in Erskine et al. (1993) a response was elicited only at a high concentration (~600 ppm), or because the response was considered protective (pg. 19 TSD)? The rationale for this UF needs to be better explained.

Page 38, line 9. Are there sufficient data to support an intraspecies UF of 1?

Response: *The intraspecies uncertainty factor and rationale for the three AEGL levels as presented in the TSD are summarized below for discussion by the NAC. This information should aid the NAC in determining whether change the intraspecies uncertainty factors are the same for the three AEGL levels.*

AEGL-2, UF = 1: Rationale as presented in the TSD

- Ammonia is efficiently scrubbed in the upper respiratory tract, and if irritation is detected, it would be confined to the nasal cavity (and possibly the eyes).

- Nonatopic and atopic subjects, including asthmatics, responded similarly in a nasal airway resistance test when 100 ppm of ammonia was introduced into each nostril for up to 30 seconds (McLean et al.,(1979).

- Exercising subjects showed only a small equivocal decrease in pulmonary function after exposure to higher concentrations of ammonia (Cole et al., 1977).

AEGL-2, UF = 1: Rationale

- Ammonia is a contact irritant, it is efficiently scrubbed in the upper respiratory tract, and any perceived irritation is not expected to be greater than the most sensitive non-expert subjects.

- The effects at the AEGL-2 levels would primarily involved the eyes and upper respiratory tract and asthmatics would be unlikely to respond differently from the most sensitive nonexpert subjects.

- Atopic and non-atopic subjects responded similarly to a brief nasal exposure to ammonia (McLean et al., 1979).

- Exercising subjects showed only small equivocal changes in pulmonary function during exposure to ammonia at concentrations up to 336 ppm (Cole et al., 1979).

- A child experienced less severe effects than an adult exposed to higher concentrations (Kass et al., 1972).

- The effects reported by the non-expert subjects were less serious than those described in the AEGL-2 definition, and no residual effects were reported for any subject after termination of exposure.

AEGL-3, UF = 1: Rationale

- High concentrations of ammonia elicit severe irritation immediately upon contact with the eyes or mucous membranes of the respiratory tract and the severity of effects, such as pulmonary edema and tracheobronchial injury, would be similar in asthmatics and non-asthmatics. Severe long-lasting or irreversible damage to the respiratory tract may be a greater concern than that of asthma.

- Asthmatics and non-asthmatics responded similarly to a brief nasal exposure to a lower concentration of ammonia (McLean, 1979).

- One study showed that a child suffered reversible damage to the respiratory tract, whereas the mother carrying the child suffered permanent severe damage to the respiratory tract after exposure to a high concentration of ammonia (Kass et al., 1972).

- The protective mechanism of reflex glottis closure is threefold less sensitive in the elderly than young subjects exposed to high concentrations of ammonia (Erskine, 1993). *Reflex glottis closure is a*

protective mechanism stimulated by inhaling irritants or noxious vapors. The reflex mechanism occurred at 571 ppm in young subjects and at 1791 ppm on the elderly, which is approximately a threefold difference.

- Exercising adults showed only equivocal effects on pulmonary function at concentrations up to 336 ppm (Cole et al., 1979).

- A larger interspecies or intraspecies uncertainty factors would lower the 30-minute AEGL-3 value to a level comparable to the 500 ppm shown to be tolerated by humans without lethal or long-term consequences (Silverman et al., 1949).

Subject: **Derivation of 5-minute AEGL values**

Page 7, line 12. Is it standard practice to derive a 5-min AEGL? The SOP (page 95) points out that it is inappropriate to extrapolate to the time periods shorter than 10 min. Should a 5-min AEGL be derived, using the very short duration studies would be a better basis.

Page 41, lst line before Table 12. 5-min AEGL values are not routinely derived (see SOP page 95); these should be deleted.

Page 42, Table 13. Delete 5 min values.

Response: *NAC's decision to maintain the 5-minute AEGL values that were requested by industry. The 5-minute values were requested because in most catastrophic accidents, the highest ammonia concentrations occur within the first 5 minutes after the accidents, after which the concentrations decrease rapidly.*

Technical staff recommendation: *Industry requested the 5-minute value. The AEGL values should provide relevant guidance to those who will use it. The SOPs do not require a 5-minute value, however, in this case, adherence to the SOPs should not supercede industry's need.*

Subject: **Revision of the summary of the Verberk (1977) study**:

Page 18, Table 3. Combining the results for the two groups of subjects (i.e., experts and student/non-experts) is not appropriate as one of the key findings is that the expert group generally scored lower than the student non-experts. Further, this is the key study for AEGL-2, based upon increased concentration and duration-response in the non-experts. The table needs to be revised to better support the effects for the AEGL derivation.

Response: *The revised table is presented below:*

Average (Range) Scores of Subjective Responses of Expert and Nonexpert Subjects Exposed to Ammonia[a]								
Response	**50 ppm**		**80 ppm**		**110 ppm**		**140 ppm[c]**	
	Expert[a]	Non-expert[a]	Expert	Non-expert	Expert	Non-expert	Expert	Non-expert
Smell								
½ h	2.0 (1-3)[b]	2.5 (2-3)	2.0 (1-3)	3.0 (2-4.5)	2.0 (2-3)	3.0 (2-4)	2.0 (1-3)	4.0 (2-4.5)
1 h	2.0 (1-3)	2.5 (1-4)	2.0 (1-3)	3.0 (2-4)	2.0 (2-3)	3.0 (2-4)	2.0 (1-3)	4.0 (3.5-4.5)
2 h	2.0 (0.5-3)	3.0 (2-4)	1.5 (0.5-3)	3.0 (2-4)	2.0 (1.5-3)	3.0 (2-4)	2.(1-3)	WD[c]
Eye irritation								
½ h	1.5 (0-3)	0.8 (0-3)	1.5 (1-2)	1.5 (0-4)	2.5 (1-3)	2.5 (0-4)	3.0 (1.5-3.5)	3.0 (1-4.8)
1 h	1.5 (0-3))	0.8 (0-3)	2.0 (0-3)	1.5 (0-3)	2.5 (2-3.5)	2.5 (0-4)	2.0 (2-3)	3.5 (1-5)
2 h	1.0 (0-2)	1.2 (0-3)	1.5(0-2)	2.0 (0-4)	2.0 (0.3-3)	2.5 (0-4)	2.5 (1-3)	WD
Throat irritation								
½ h	0.4 (0-2)	0.4 (0-1)	0.8 (0-2)	1.0 (0-3	1.5 (0-3.5)	2.0 (0-4)	1.0 (0-2)	3.7 (3.5-5)
1 h	0.4 (0-3)	0.5 (0-3)	1.0 (0-3)	1.4 (1-3)	1.4 (0-3)	2.5 (1-4)	1.5 (0-2)	4.5 (2-4)
2 h	0.7 (0-3)	1.5 (0.3)	0.8 (0-2)	2.0 (0-4)	1.0 (0-2)	3.0 (2-4)	1.0 (0-3.7)	WD
Urge to cough								
½ h	0.2 (0-1.2)	0.2 (0-1)	0.3 (0-1)	0.5 (0-2)	0.8 (0-2)	1.5 (0-2)	0.5 (0-2)	2.0 (0-5)
1 h	0.3 (0-2)	0.2 (0-2)	0.5 (0-2)	1.0 (0-2)	0.5 (0-3.5)	1.7 (0-3)	0.6 (0-2.5)	1.7 (0-3)
2 h	0.3 (0-2)	0.4 (0-2)	0.4 (0-2)	0.3 (0-4)	0.3 (0-2.5)	1.7 (0-4)	0.4 (0-2.3)	WD
General discomfort								
½ h	0	0.1 (0-1)	0	1.0 (0-3)	0.2 (0-2)	1.0 (0-3)	0	2.2 (0-4)
1 h	0	0.2 (0-1)	0	1.2 (0-3)	0.2 (0-1)	1.2 (0-3)	0	3.3 (0-4.7)
2 h	0	1.0 (0-2)	0	1.3 (0-3)	0.3 (0-1)	1.5 (0-4)	0	WD
Irritation to Chest	Similar to urge to cough, but scores tended to be a little lower							

Source: Verberk, 1977

[a]Expert subjects were familiar with the effects of ammonia, the non-expert subjects were not.

[b]Based on a scale of 1-5: 0 = no sensation; 1 = just perceptible; 2 = distinctly perceptible; 3 = nuisance; 4 = offensive; 5 = unbearable.

[c]Only four of the non-expert subjects tolerated the ammonia for 1 h; none of the non-expert subjects tolerated the ammonia for 2 hours, the upper range of the score in the table is the same as recorded at 1 hour or 110 ppm after 2 hours (urge to cough).

Subject: **Selection of point-of-departure for AEGL-2 derivation**

Page 37, last line. Additional explanation is needed as to why 100 ppm (110 ppm) at 1 hr (Verbeck, 1977) was chosen as the point of departure for AEGL-2. Why not 140 ppm or why not at 30 min or 2 hr? The effect appears to be the same at 100 (110 ppm) and 140 ppm for 30 min to 2 hr (see Table 9).

Response: *Based on data presented in the above table, AEGL-2 values could be derived from the exposure to 140 ppm for 30 minutes; none of the non-experts exposed to this concentration exited the room in less than 30 minutes. The responses did not exceed offensive for any effect except odor.*

AEGL-2 values based on a point-of-departure of 140 minutes for 30 minutes are presented below. The uncertainty factor and time scaling are the same as described previously.

Alternative for deriving AEGL-2 values:

Derivation of AEGL-2

The point of departure for deriving AEGL-1 values is 140 ppm for a 30-minute exposure of non-expert subjects (Verberk, 1977). The average score for eye, throat, and chest irritation, urge to cough, and general discomfort ranged from distinctly perceptible to nuisance/offensive among non-expert subjects after exposure of the non-expert subjects to 140 ppm for 30 minutes (Verberk, 1977). None of the non-expert subjects left the chamber during the first 30 minute of exposure. No residual or irreversible effects or decreases in respiratory function were described for subjects exposed to any concentration. Some irritation to the eyes, nose, throat, and chest along with a disagreeable odor are expected at the AEGL-2 level. An intraspecies uncertainty factor of 1 was selected because ammonia is a contact irritant, it is efficiently scrubbed in the upper respiratory tract, and any perceived irritation is not expected to be greater than the most sensitive non-expert subjects. In addition, the effects at the AEGL-2 levels would primarily involved the eyes and upper respiratory tract and asthmatics would be unlikely to respond differently from the most sensitive non-expert subjects. Atopic and non-atopic subjects responded similarly to a brief nasal exposure to ammonia (McLean et al., 1979); exercising subjects showed only small equivocal changes in pulmonary function during exposure to ammonia at concentrations up to 336 ppm (Cole et al., 1979); and a child experienced less severe effects than an adult exposed to significantly higher concentrations.

Time-scaling across the pertinent time frames was based on the ten Berge et al. (1986) equation ($C^n \times t = k$, where C = concentration, $n = 2$, and k is a constant). The value of n was derived from mouse and rat lethality data and was reported by Appelman et al. (1982) and ten Berge et al. (1986). The proposed AEGL-2 values for 4- and 8-hour exposures are also 99 ppm, because the maximum severity rating for irritation changed very little between 1 and 2 hours and is not expected to change for up to 8 hours.

TABLE 10. AEGL-2 Values for Ammonia (ppm [mg/m^3])					
5 minutes	**10 minutes**	**30 minutes**	**60 minutes**	**240 minutes**	**480 minutes**
340 [238]	240 [168]	140 [98]	99 [69]	99 [69]	99 [69]

Acrylic Acid

(CAS Reg. No. 79-10-7)

Discussion of NAS-COT Comments

NAC/AEGL Meeting 36, April 19-21, 2005

The AEGL document on acrylic acid was reviewed by the Subcommittee on Acute Exposure Guideline Levels of the National Academy of Sciences Committee on Toxicology on January 28-30, 2004.

Major concerns were

(1) that NAS questioned the Renshaw data as a suitable AEGL-1 basis and required more information on the data;

(2) that a time scaling exponent n derived on lethality data following aerosol exposure was used for AEGL-2 time scaling;

(3) that AEGL-3 values should be based on vapor data and not on aerosol data.

The NAS subcommittee will reevaluate a revised acrylic acid AEGL document after the NAC/AEGL committee responds to the concerns.

The changes proposed in the following have already been discussed at the NAC April 2004 meeting, however, without a formal vote on the new values.

Comments on AEGL-1

- The subcommittee is uncomfortable with NAC citing the Renshaw personal communication. Describe here whether the people were male or female adults, smokers or nonsmokers, what the age range was, and whether the subjects were naïve or were workers accustomed to elevated concentrations of acrylic acid in workplace air. Were these complaints of irritation (what kind?) from people subjected to a single (preferably once-in-a-lifetime) exposure or from people who had a history of repeated occupational acrylic acid exposures (describe duration and range of concentrations routinely encountered) in workplace air?
- It should be emphasized that the present AEGL-1 value of 1.5 ppm is based on an evaluation of a wide range of occupational concentrations and provide a stronger rationale for the choice of 4.5 ppm as the starting point for the derivation of the AEGL-1. More details on the 11 human subjects should be given, including their inurement status. The RD50 should be included in the document, and its implications for the AEGL-1 should be considered. The AEGL-1 should also be discussed in relation to the TLV.

Reply

- The Renshaw data will be provided again to the NAS. Unfortunately, no further information on the subjects or there pattern and history of exposure are available.
- However, the AEGL-1 derivation starting point is supported by the study by Lomax et al. (1994) reporting 5 ppm for 6 hours/day, 2 weeks as a NOEL for histopathological effects on the nasal olfactory mucosa in mice.
- The reported RD50 values of 513 ppm for rats and 685 ppm in mice (Buckley et al., 1984) support the derived AEGL-1 values because the latter are about 2 orders of magnitude below the RD50 values. They are however not considered a suitable basis for AEGL-1 derivation.

Comments on AEGL-2

- The monkey study, which represents the most suitable animal model for human risk assessment, seems most appropriate for the derivation of AEGL-2 values. Clearer explanations of the use of an interspecies UF of 1 and an intraspecies UF of 3 also need to be provided. The rodent data provide useful supporting information, leading to similar AEGL-2 values. Time-scaling should be based on default levels of n = 1 and n = 3, because n = 1.8 is based on whole-body aerosol exposures.
- [Regarding intraspecies UF of 3 justification:] What data are available to justify the NAC generalization that "For local effects [what kind? Anesthesia?], the toxicokinetic differences [what kind? Rate of absorption?] between individuals are usually much smaller [by what factor?] when compared to systemic effects [like what?]." Delete the generalization unless specifics for acrylic acid can be included.

Reply

- There are no experimental data for acrylic acid on which a reduction of the intraspecies factor could be based on. Thus, a somewhat general statement must be made here. However, the wording was changed to give a more acrylic acid-specific rationale.
- Default time scaling was applied because the aerosol study from which n was derived is no longer used for AEGL-3 derivation.

Comments on AEGL-3

- The vapor data appears to be more relevant than the aerosol data. If the AEGL-3 is based on the vapor data (using the highest NOAEL from all of the available studies), the default time-scaling values of n = 1 and 3 should be used.
- What is the likely form of an exposure to the general public? It would seem that even if an aerosol was formed, it would quickly convert to vapor because of the relatively high vapor pressure of acrylic acid. Basing the AEGL on the aerosol requires further information. Is acrylic acid generally heated in the plant? It definitely is not when transported. The subcommittee postulates aerosols will rapidly evaporate to the vapor state. If that is the case, an AEGL derived on the basis of the vapor is more applicable.

Reply

- No reports on chemical accidents were located that definitely reported whether exposure to a vapor or an aerosol would be more likely in case of an emergency.
- The basis of the AEGL3 derivation has been changed to a vapor study in rats. The resulting values do not differ much from the original values based on the aerosol exposure study.

AEGL-1

Keystudy: Renshaw (1988); [Lomax et al., 1994]

Endpoint: Eye irritation was noted after exposure to concentrations of 4.5 - 23 ppm for 16 - 30 minutes. As a point-of-depature, 4.5 ppm was used;

[5 ppm for 6 h/d (2 weeks) in mice was the NOEL for histological changes of the olfactory epithelium (hypertrophy, necrosis, desquamation)]

Time scaling: the same exposure concentration for all exposure durations between 10 minutes and 8 hours

because very slight irritative effects depend primarily on the actual exposure concentration and not much on exposure time

Total uncertainty factor: 3

Intraspecies: 3

The intraspecies uncertainty factor is used to compensate for both, toxicokinetic and toxicodynamic differences between individuals. For local effects, the toxicokinetic differences between individuals are usually much smaller when compared to systemic effects. Therefore, a reduced uncertainty factor was retained to account for toxicodynamic differences between individuals.

AEGL-1 Values for Acrylic Acid				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
1.5 ppm 4.5 mg/m^3	1.5 ppm 4.5 mg/m^3	1.5 ppm 4.5 mg/m^3	1.5 ppm 4.5 mg/m^3	1.5 ppm 4.5 mg/m^3

AEGL-2

Keystudy: Rohm and Haas Co. (1995); Harkema (2001); Harkema et al. (1997)

Endpoint: Single exposure of monkeys to 75 ppm acrylic acid for 3 hours resulted in histopathological changes of the nasal epithelium (olfactory epithelial cell degeneration, sustentacular cell necrosis; severity of effects increased with exposure time). Effects after 6 hours were considered irreversible.

The AEGL-2 starting point is supported by the observation that 77 ppm was the NOEL for blepharospasm in rabbits (Neeper-Bradley et al., 1997).

Time scaling: $C^n \times t = k$ with n = 3 for shorter and n = 1 for longer periods; extended to 10 min because resulting value was still below blepharospasm threshold

Total uncertainty factor: 3

Interspecies: 1

for the toxicokinetic component a factor of 1 was used because a monkey inhalation study was used and because acrylic acid is a locally acting irritant not requiring metabolic activation. The toxicodynamic component of the uncertainty factor was reduced to 1 because single inhalation exposure of monkeys resulted in similar olfactory lesions than in rats

Intraspecies: 3

because tissue damage of the nasal mucosa by local cytotoxicity was considered not to vary considerably between individuals.

AEGL-2 Values for Acrylic Acid				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
66 ppm (140 mg/m³)	45 ppm (140 mg/m³)	36 ppm (110 mg/m³)	19 ppm (56 mg/m³)	9.4 ppm (28 mg/m³)

AEGL-2 - old version

Keystudy: Rohm and Haas Co. (1995); Harkema (2001); Harkema et al. (1997); Frederick et al. (1998)

Endpoint: Single exposure of monkeys and rats to 75 ppm acrylic acid for 3 hours resulted in histopathological changes of the nasal epithelium (olfactory epithelial cell degeneration, sustentacular cell necrosis; severity of effects increased with exposure time). Effects after 6 hours were considered irreversible.

The AEGL-2 starting point is supported by the observation that 77 ppm was the NOEL for blepharospasm in rabbits (Neeper-Bradley et al., 1997).

Time scaling: $C^n \times t = k$ with n = 1.8 (derived from lethality data) for shorter and longer exposure periods; 30-min = 10-min

Total uncertainty factor: 3

Interspecies: 1

because the deposited concentration of acrylic acid on the olfactory epithelium is about two- to threefold higher in rats than in humans (Frederick et al., 1998). The toxicodynamic component of the uncertainty factor was reduced to 1 because single inhalation exposure of monkeys resulted in similar olfactory lesions than in rats (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997).

Intraspecies: 3

For local effects, the toxicokinetic differences between individuals are usually much smaller when compared to systemic effects. Therefore the toxicokinetic component of the uncertainty factor was reduced to 1 while the factor of 3 for the toxicodynamic component, reflecting a possible variability of the target-tissue response in the human population was retained.

AEGL-2 Values for Acrylic Acid				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
68 ppm 200 mg/m^3	68 ppm 200 mg/m^3	46 ppm 140 mg/m^3	21 ppm 63 mg/m^3	14 ppm 42 mg/m^3

AEGL-3

Keystudy: BASF (1980)

Endpoint: no lethality in 10 rats exposed at 1705 ppm for 4 hours.

Time scaling: $C^n \times t = k$ with n = 3 for shorter and n = 1 for longer periods; 10-min value set at 30-min value

Total uncertainty factor: 10

Interspecies: 3

Intraspecies: 3

Rationale: acrylic acid causes lethal effects by local tissue destruction in the lung with limited influence of systemic distribution, metabolism and elimination. Therefore, the toxicokinetic differences do not vary considerably within and between species. Also the toxicodynamic variability within and between species is considered to be limited because acrylic acid causes cell necrosis by reducing the pH and destroying mitochondria, which are unlikely to be influenced by species-specific differences. Overall these arguments support reduced interspecies and intraspecies uncertainty factors of 3 each.

AEGL-3 Values for Acrylic Acid				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
340 ppm (1000 mg/m³)	340 ppm (1000 mg/m³)	270 ppm (810 mg/m³)	170 ppm (510 mg/m³)	85 ppm (260 mg/m³)

AEGL-3 - old version

Keystudy: Hagan and Emmons (1988)

Endpoint: Lethality in rats after single inhalation exposure to acrylic acid aerosol. BMD_{01} values were calculated using Probit analysis.

Time scaling: $C^n \times t = k$ (n = 1.8) for shorter and longer exposure periods; n was derived by Probit analysis from key study

Total uncertainty factor: 10

Interspecies: 3

Published interspecies comparisons are focused on the upper respiratory tract at lower doses. No definitive data for the involvement of the lung at higher doses are available. Acrylic acid causes lethal effects by local tissue destruction in the lung with limited influence of systemic distribution, metabolism and elimination. Therefore, the toxicokinetic differences are considered smaller than for other chemicals that require systemic distribution and metabolism. Also the toxicodynamic variability is considered to be limited because acrylic acid causes cell necrosis by reducing the pH and destroying mitochondria, which are unlikely to be influenced by species-specific differences. Overall these arguments support a reduced interspecies uncertainty factor of 3

Intraspecies: 3

the toxicokinetic differences are considered smaller than for other chemicals that require systemic distribution and metabolism because acrylic acid causes lethal effects by local tissue destruction in the lung with limited influence of systemic distribution, metabolism and elimination although there might be some difference between babies and adults based upon projections from breathing rates, lung capacity, etc. The toxicodynamic variability is considered to be limited because acrylic acid causes cell necrosis by reducing the pH and destroying mitochondria, which are unlikely to be influenced by interindividual differences. Taken together, these arguments support a reduced intraspecies uncertainty factor of 3

AEGL-3 Values for Acrylic Acid				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
480 ppm 1400 mg/m^3	260 ppm 780 mg/m^3	180 ppm 540 mg/m^3	85 ppm 260 mg/m^3	58 ppm 170 mg/m^3

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR METHYL-tertiary-BUTYL ETHER (MTBE)

NAC/AEGL-36
April 12-14
Research Triangle Park, North Carolina

ORNL Staff Scientist- Dana F. Glass
Chemical Manager- Steve Barbee
Chemical Reviewers- George Woodall and Bob Benson

MTBE- Background

- Currently used as gasoline additive for its octane-enhancing and air pollution-reducing properties

- United States is the largest consumer

- Colorless liquid at room temperature

- Distinct, terpene-like odor with low odor threshold

Exposure Symptoms

- Exposures from inhalation

  — Transient CNS signs in animals

  — Vague sensory signs in humans exposed: headaches, eye irritation, nasal irritation.

AEGL-1 Values

AEGL-1 Values				
10 minute	30 minute	1 hour	4 hour	8 hour
50 ppm	50 ppm	50 ppm	50 ppm	50 ppm

- Key Reference:
  - Nihlén, A. et al., 1998.

- Test Species/Strain/Number/Sex: 10 male humans

- Exposure: Inhalation: ~~0 (controls),~~ 5 25 or 50 ppm, 2 hours

- Effect: No effects noted at any concentration. Increase in awareness of odor in entering chamber that increased with concentration but diminished with time.

- Endpoint/Concentration/Rationale: 50 ppm- highest concentration used in human study with no effects.

AEGL-1 Values (contd.)

- **Uncertainty Factors/Rationale: None applied because human study with no effects noted at either 25 or 50 ppm. Decreasing 50 ppm by factor of 3 would produce concentrations <25 ppm.**

- **Time Scaling: Extrapolation to time points was not performed because of no effect.**

AEGL-2 Values

AEGL-2 Values				
10 minute	30 minute	1 hour	4 hour	8 hour
1400 ppm	1400 ppm	980 ppm	400 ppm	400 ppm

- Key Reference:
  - Daughtrey et al., 1997.

- Test species: 22 M/F Fischer 344 rats

- Exposure: Inhalation: 0, 800, 4000 or 8000 ppm for 6 hours.

- Effect: (1 hr post-exposure)
  - 0 and 800 ppm: No effects
  - 4000 ppm:
    - ataxia, ↑ piloerection, ↓ body temp., ↓ hind-limb grip strength (f)
  - 8000 ppm:
    - ataxia, labored respiration, ↑ leg splay (m), ↓ muscle tone (m), ↓ body temp. (m), ↓ mean motor activity

AEGL-2 Values (contd.)

- Endpoint/Concentration/Rationale: Transient/reversible CNS signs at 4000 ppm

- Uncertainty Factors/Rationale: 10
  - Interspecies: 3, PBPK modeling data indicates humans have a 1.5 to 2.5-fold increase of MTBE concentration in blood compared to rats after exposure.
  - Intraspecies: 3, Variability of effect seen with CNS depression being no greater than 3-fold in the human population

AEGL-2 Values (contd.)

- Time Scaling: Extrapolation to time points was performed only for the 30-min. and 1 hr time-points. Extrapolation utilized was $C^n \times t = k$, with n=2 based on ten Berge, 1986. The 30 min AEGL-2 value adopted for 10 min value because exposure time ≥ 4 hrs. Values flat-lined at 4 and 8 hrs due to the steady-state achieved by 2 hrs in the rat and 4 hrs in humans.

COMPARISON OF RAT-HUMAN (MTBE)

At rest, rats achieved steady state in about two hours and humans achieved it in about four hours. At 50W of workload, humans reached steady state in about 1.5 hours. At both exposure levels, rats had the lowest blood MTBE concentrations at all times. By the end of an eight hour exposure, the human resting model nearly reaches the same blood concentrations as the human exercise model. In other words, the human at rest will have a lower blood level than during exercise, particularly during early time periods. The significance of these differences is shown in the following figure.

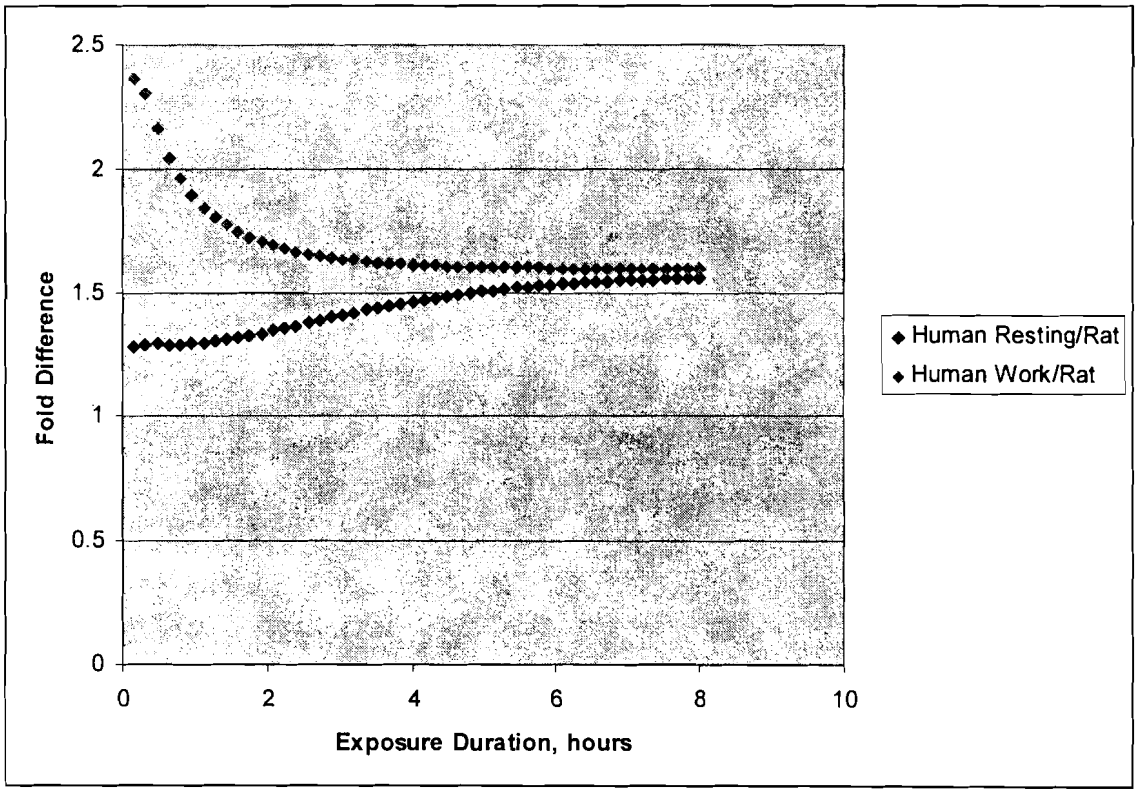


Fig. D-14. The fold difference between blood concentrations in the human at rest or work and the rat at 500 ppm. The upper curve indicates that a human exercising at 50W will have between 1.5 and 2.5 more MTBE in blood than the rat. Results were very similar at 5000 ppm (data not shown).

AEGL-3 Values

AEGL-3 Values				
10 minute	30 minute	1 hour	4 hour	8 hour
7500 ppm	7500 ppm	5300 ppm	2700 ppm	1900 ppm

- **Key Reference:**
  - **ARCO Chemical Co., 1978**

- **Test species: 10 M Sprague-Dawley rats**

- **Exposure: Inhalation: 18800, 34800, 38600, 41800 or 63800 ppm, 4 hours**

- **Effect:**
  - **4-hour LC_{50} = 33,427 ppm**

Acute Inhalation Data	
Concentration	No. dead/No. tested
18,800 ppm	0/10
34,800 ppm	2/10
38,600 ppm	9/10
41,800 ppm	9/10
63,800 ppm	10/10

AEGL-3 Values (contd.)

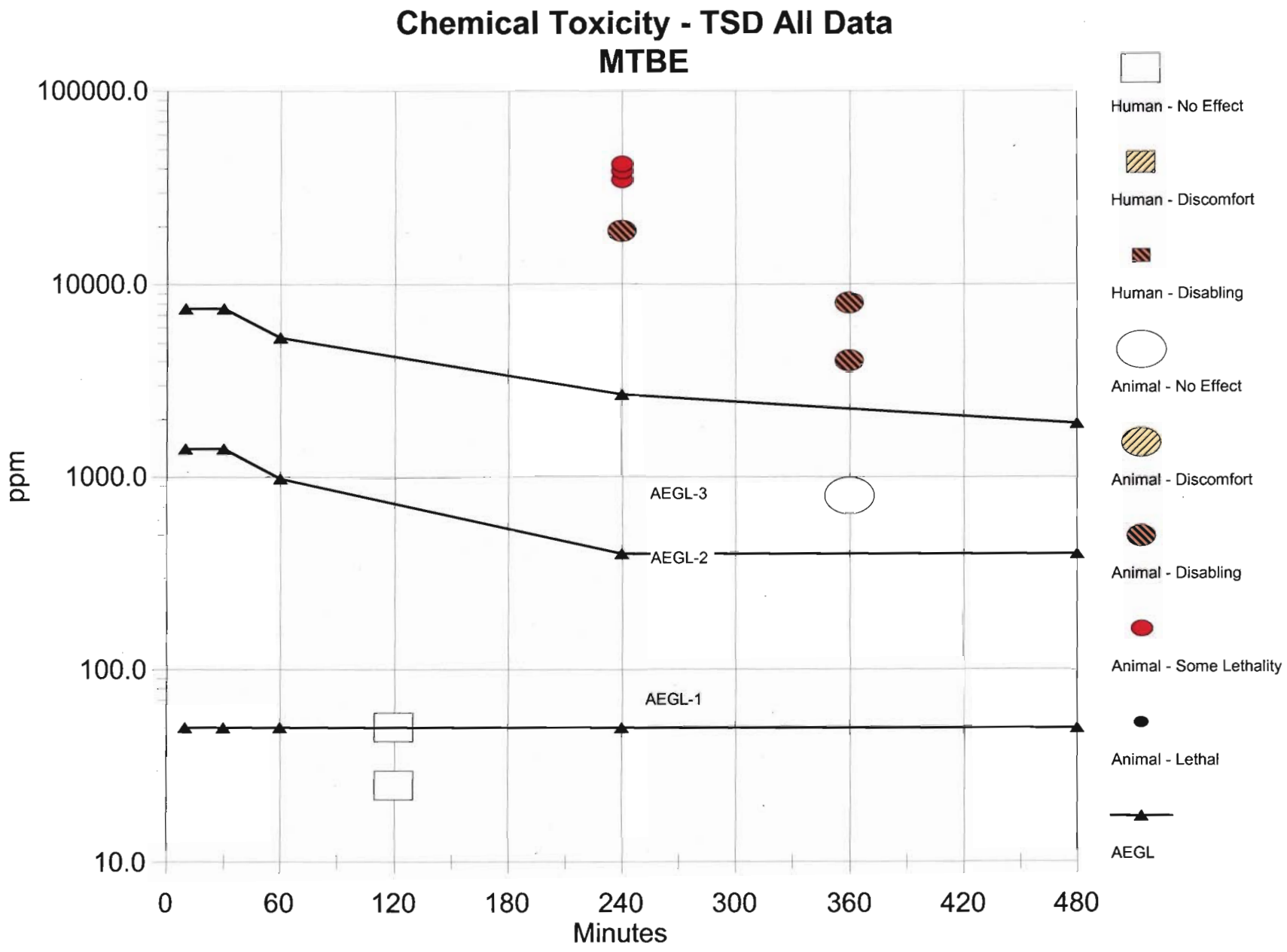
- Endpoint/Concentration/Rationale: A 4 hr $BMCL_{05}$ value was calculated by a log-probit analysis. The resulting $BMCL_{05}$ of 26,690 was used to derive the AEGL-3 values.

- Uncertainty Factors/Rationale: 10
  - Interspecies: 3, PBPK modeling data indicates humans have a 1.5 to 2.5-fold increase of MTBE concentration in blood compared to rats after exposure.
  - Intraspecies: 3, Variability of effect seen with CNS depression being no greater than 3-fold in the human population

- Time Scaling: Extrapolation to time points was performed for all time-points. Extrapolation utilized $C^n \times t = k$, with n=2 based on ten Berge, 1986. The 30 min AEGL-2 value adopted for 10 min value because exposure time ≥ 4 hrs.

Exposure Guidelines

Extant Standards and Guidelines for MTBE (ppm)					
Guideline	**Exposure Duration**				
	10 min	**30 min**	**1 hr**	**4 hr**	**8 hr**
AEGL-1	50	50	50	50	50
AEGL-2	1400	1400	980	400	400
AEGL-3	7500	7500	5300	2700	1900
ERPG	MTBE is currently under consideration/review for ERPG				
TLV-TWA (ACGIH)					40
MAK (Germany)					50
LLV (Dutch)					50
LLV (Sweden)					30


Chemical Toxicity - TSD All Data
MTBE
100000.0
10000.0
1000.0
100.0
10.0
ppm
AEGL-3
AEGL-2
AEGL-1
0
60
120
180
240
300
360
420
480
Minutes
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

Hexafluoroacetone (HFA)

- **highly reactive with water forming a series of hydrates**
- **odor threshold values not available**
- **human experience data limited**
  - **4 ppm irritating to upper respiratory tract; no exposure duration (abstract only)**

Hexafluoroacetone - Animal Data

Acute Lethality

- **Rats (E. I. du Pont de Nemours & Co., 1962a)**
  - **4-hr exposure to 200, 400, or 800 ppm HFA dihydrate**
  - **clinical signs: prostration, hind leg paralysis, labored breathing, unconsciousness (400 and 800 ppm groups)**
  - **mortality ratio**

    200 ppm: 0/4
    400 ppm: 3/4 (all deaths on 4th day)
    800 ppm: 4/4 (two deaths within 2.5 hrs; one each on 3rd and 5th day)
  - **necropsy: multi-organ involvement; severe effects on stem cells and developing sprem**
  - **histopathology: g.i. tract, spleen, pituitary hyperplasia (all groups but minimal severity in 200-ppm group)**

Hexafluoroacetone - Animal Data

Acute Lethality

- **Rats (E. I. du Pont de Nemours & Co., 1962b)**
  - **4-hr exposure to 100, 200, 400, or 800 ppm HFA or 300, 400, 500, and 1000 ppm HFA nonahydrate**
  - **histopathology: concentration-dependent aspermatogenesis and interstitial damage**

Table 2. Lethal toxicity of HFA and HFA nonahydrate in male rats following single 4-hr inhalation exposure			
Chemical	**Conc. (ppm)**	**Mortality ratio**	**Comments**
HFA	100	0/4	all killed at 14 days post exposure
	200	0/4	all killed at 14 days post exposure
	300	2/4	one death each on post-exposure day 3 and 6; 2 killed on post-exposure day 14
	400	2/4	one death each on post-exposure day 5 and 7; 2 killed on post-exposure day 14
HFA nonahydrate	300	0/4	all killed at 14 days post exposure
	400	1/4	one death on post-exposure day 5; remainder killed on day 14
	500	3/4	one death each on post-exposure day 4, 7 and 10; 1 killed on post-exposure day 14
	1000	4/4	all died 17 hrs to 5 days post exposure

E. I. du Pont de Nemours & Co., 1962b

Hexafluoroacetone - Animal Data

Acute Lethality

- **Rats (E. I. du Pont de Nemours & Co., 1965)**
  - **4-hr exposure to 200 ppm HFA: testicular effects study**
  - **30-min exposure to 1200, 3600, 4800, or 6000 ppm: lethality study**
  - **15-min exposure to 9600 ppm: lethality study**
  - **clinical signs in all groups as previously described**
  - **all lost weight during 14-day post exposure period**

Table 3. Lethal toxicity of HFA in male rats following acute inhalation exposure.

Concentration	Duration	Mortality ratio	Comments
2400 ppm	30 min	0/4	all survived to 14-day post exposure
3600 ppm	30 min	0/4	all survived to 14-day post exposure
4800 ppm	30 min	3/4	3 dead at 4-6 days post exposure
6000 ppm	30 min	4/4	all dead at 1-4 days post exposure
9600 ppm	15 min	3/4	3 dead at 1-2 days post exposure

Hexafluoroacetone - Animal Data

Acute Lethality

- **Rats (E. I. du Pont de Nemours & Co., 1988)**
  - **30 ppm 6 hrs/day: 4/6 mortality at 2 days**
  - **60 ppm 6 hrs/day: 4 of 6 sacrificed *in extremis* after 2 days**
  - **15-day observation**

- **Rats (Borzelleca and Lester, 1965)**
  - **30-min LC_{50}: 900 ppm**
  - **3-hr LC_{50}:**

- **Dogs [anesthetized] (Borzelleca and Lester, 1965)**
  - **5000 ppm, 30 min: no deaths**
  - **5000 ppm, 45 min: 1 of 2 died**
  - **10,000 ppm, 30 min: 1 of 3 died**
  - **10,000 ppm, 45 min: 1 of 3 died**
  - **deaths at 2-3 days post exposure; necropsy indicated pulmonary hemmorrhage and edema; no evidence of systemic involvement**

Hexafluoroacetone - Animal Data

Nonlethal

- **Rats (E. I. du Pont de Nemours, 1962b)**
  - **4-hr exposure of male rats to 100 or 200 ppm HFA not lethal**
  - **4-hr exposure of male rats to 300 ppm HFA nonahydrate not lethal**
  - **ten 4-hr exposures to 60 ppm HFA not lethal**

- **Rats (E. I. du Pont de Nemours, 1965)**
  - **30-min exposure of male rats to 2400 or 3600 ppm not lethal**
  - **4-hr exposure to 200 ppm HFA: lacrimation, salivation, redness of ears, deep respiration, body weight loss; non-specified effects on g. i. tract, spleen, pituitary, spermatazoa**

Hexafluoroacetone - Animal Data

Nonlethal

- **Rat (E. I. du Pont de Nemours, 1971)**
  - **13-week exposure (6 hrs/day, 5 days/wk)**
    - **0.1 ppm: no observable effects**
    - **1.0 ppm: reversible kidney dysfunction**
    - **12 ppm: reversible testicular atrophy, interstitial edema; cessation of spermiogenesis**

- **Rat (Lee and Kennedy, 1991)**
  - **testicular atrophy in rats following exposure to 12 ppm HFA, 6 hrs/day, 5 days/wk for 30 days - some regeneration at 28 days post exposure**
  - **0.1 or 1.0 ppm: no effects**

Hexafluoroacetone - Animal Data

- **Rat (E. I. du Pont de Nemours, 1989)**
  - **0, 0.11, 1.0, or 6.9 ppm 6 hrs/day, gestation days 7-16 (nose-only)**

Table 4. Effects of HFA Exposure in Rats Exposed for 6 hrs/day on Gestation Days 7-16.

Effect	Control	0.1 ppm	1.0 ppm	6.9 ppm
Maternal effects				
Liver wt. (abs)	14.3	14.7	15.7*	16.2*
Liver wt. (rel)	4.9	4.8	5.2*	5.4*
Reproductive effects				
No. live fetuses	300	270	339	277
Live fetuses/litter	14.3	13.5	14.1	11.5*
Total resorptions/litter	1.0	1.8	1.0	3.5*
Fetal effects				
Mean fetal wt.	5.30	5.21	4.94*	4.11*
Malformations[a]	0	0	3	68*
Variations[a]				
Developmental	60	36	86	204
Retarded development	27	26	64	194

[a] Total no. fetuses affected; includes external, visceral, head, and skeletal malformations.

* $p \leq 0.05$ relative to untreated controls

Hexafluoroacetone - Animal Data

Nonlethal

- **Dog (E. I. du Pont de Nemours, 1971)**
  - **0, 0.1, 1.0, or 12 ppm HFA 6 hrs/day. 5 days/week**
  - **severe but reversible testicular damage**

Hexafluoroacetone - AEGL-1

- **Insufficient data; AEGL-1 values not recommended**

Hexafluoroacetone AEGL-2

AEGL-2 Values For HFA					
Classification	**10-min***	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-2	0.076 ppm	0.076 ppm	0.061 ppm	0.038 ppm	0.025 ppm

*** Due to uncertainties in extrapolating from the 6-hour POD to 10 minutes, the 30-minute AEGL-2 was set equivalent to the 30-minute value.**

- **Key study: E. I. du Pont de Nemours and Co. 1989.**

- **Critical effect/POD: Decrease in live fetuses/litter, total resorptions/litter, and mean fetal weight observed following exposure of dams to 6.9 ppm HFA, 6 hrs/day on gestation days 7-16. Therefore, 1.0 ppm exposure was selected as the POD with the assumption that developmental effects could be induced by a single 6-hr exposure.**

- **Uncertainty Factors:**
  - **Interspecies: 10; data for one laboratory species and no human data.**
  - **Intraspecies: 3; HFA does not appear to undergo significant metabolism; fetus considered a uniquely sensitive target.**
  -
- **Time scaling:**
  - **default *n* of 1 or 3**

Hexafluoroacetone - AEGL-3

AEGL-3 Values for HFA					
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-3	19 ppm	13 ppm	11 ppm	6.7 ppm	3.3 ppm

- **Key studies:** **E. I. du Pont de Nemours & Co., 1962a; E. I. du Pont de Nemours & Co., 1962b**

- **Critical effect/POD: NOAEL for lethality in rats**

- **Uncertainty Factors:**
  - **Interspecies: 10; data limited in laboratory species and no human data.**
  - **Intraspecies: 3; HFA does not appear to undergo significant metabolism; further downward reduction would result in AEGL-3 values less than AEGL-2 values and below those shown to be non lethal following multiple exposures of dogs and rats.**

- **Time scaling:**
  - **default *n* of 1 or 3**

AEGL Values for HFA					
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (Nondisabling)	**NR**	**NR**	**NR**	**NR**	**NR**
AEGL-2 (Disabling)	**0.076 ppm**	**0.076 ppm**	**0.061 ppm**	**0.038 ppm**	**0.025 ppm**
AEGL-3 (Lethality)	**19 ppm**	**13 ppm**	**11 ppm**	**6.7 ppm**	**3.3 ppm**

NR: not recommended. Absence of AEGL-1 does not imply that exposures below AEGL-2 are without effect.

ATTACHMENT 14

ACUTE EXPOSURE GUIDELINE LEVELS FOR ALUMINUM PHOSPHIDE

NAC/AEGL-36
April 12-14, 2005

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Ernest Falke

Chemical Reviewers: Lynn Beasley and George Cushmac

- **Aluminum phosphide is a solid.**

- **One mole of aluminum phosphide reacts rapidly with water or moisture to produce a maximum of one mole of phosphine gas as follows:**

$$AlP + 3H_2O \rightarrow Al(OH)_3 + PH_3.$$

- **The phosphine gas is responsible for acute toxicity from aluminum phosphide:**

  Qualitative: similar clinical signs

  Quantitative : phosphine blood levels correlate with severity of clinical signs

  Some inhalation toxicity studies generate phosphine via hydrolysis of solid aluminum phosphide

- **Appropriate chemical-specific data are not available for derivation of AEGL values for aluminum phosphide.**

- **Phosphine AEGL values have been approved as "final" by COT Subcommittee.**

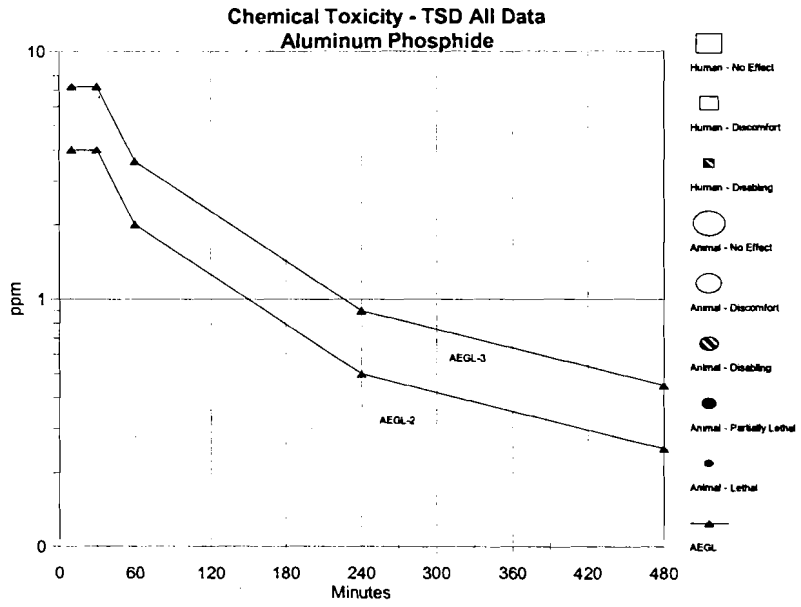
- **AEGL-1, AEGL-2 and AEGL-3 values for aluminum phosphide will be set equivalent to the phosphine AEGL-1, AEGL-2, and AEGL-3 values, respectively.**

RELATIONAL COMPARISON OF AEGL VALUES FOR ALUMINUM PHOSPHIDE (EXPRESSED AS PPM OR MG/M^3 PHOSPHINE)					
Classification	10-min	30-min	1-hour	4-hour	8-hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	4.0 ppm 5.6 mg/m^3	4.0 ppm 5.6 mg/m^3	2.0 ppm 2.8 mg/m^3	0.50 ppm 0.71 mg/m^3	0.25 ppm 0.35 mg/m^3
AEGL-3	7.2 ppm 10 mg/m^3	7.2 ppm 10 mg/m^3	3.6 ppm 5.1 mg/m^3	0.90 ppm 1.3 mg/m^3	0.45 ppm 0.63 mg/m^3

- **Approach considered valid because:**

  One mole of phosphine is produced for each mole of aluminum phosphide hydrolyzed

  Acute effects are due to phosphine hydrolysis product


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

ATTACHMENT 15

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

NITROGEN MUSTARDS
(HN1 CAS Reg. No. 538-07-8)
(HN2 CAS Reg. No. 51-75-2)
(HN3 CAS Reg. No. 555-77-1)

April 12-14, 2005

Nitrogen Mustards - Nonlethal Toxicity in Humans

- eyes are sensitive target [similar to agent HD (sulfur mustard)]

- respiratory tract effects possible but not reported at exposures inducing ocular effects

Estimated effect thresholds in humans exposed to nitrogen mustard vapors.			
HN1	HN2	HN3	Effect
-	0.012 mg-min/m^3	-	No observable effect level during therapeutic use of HN2 (Van Vloten et al., 1993)
90 mg-min/m^3	70 mg-min/m^3	42 mg-min/m^3	Moderate but reversible ocular effects (Porton report, 1942a, 1943d; U.S. Army Med. Div., 1945c,d; NDRC, 1946)
>21,170 mg-min/m^3	5800 mg-min/m^3	1800 mg-min/m^3 1300 mg-min/m^3	Median blistering Ct (10-min or 20-min exposure) for normal skin Median blistering Ct (20-min exposure) for sweating skin (NDRC, 1944)

Nitrogen Mustards - Lethal Toxicity in Humans

- **No quantitative data regarding lethal toxicity of HN**

Nitrogen Mustards - Nonlethal Toxicity in Animals

- **Studies in animals focused on lethality; no information available regarding nonlethal effects**

Nitrogen Mustards - Lethal Toxicity in Animals

- **LCt_{50} values for multiple species; various concentrations and durations**

  - **HN1**

Monkey:	**1500 mg-min/m^3**
Dog:	**800 mg-min/m^3**
Rat:	**750-1200 mg-min/m^3**
Mouse:	**900-1300 mg-min/m^3**
Rabbit:	**900->4000 mg-min/m^3**
Cat:	**400 mg-min/m^3**
Guinea pig:	**1500-3000 mg-min/m^3**

  - **HN2**

Dog:	**2000 mg-min/m^3**
Rat:	**600-4000 mg-min/m^3**
Mouse:	**1500-7000 mg-min/m^3**
Rabbit:	**1000-8000 mg-min/m^3**
Guinea pig:	**>1200-8000 mg-min/m^3**

Nitrogen Mustards - Lethal Toxicity in Animals

- **HN3**

Dog:	**400-1500 mg-min/m^3**
Rat:	**670-1700 mg-min/m^3**
Mouse:	**165-600 mg-min/m^3**
Rabbit:	**500-3000 mg-min/m^3**
Cat:	**400 mg-min/m^3**
Guinea pig:	**>1000->23000 mg-min/m^3**

Nitrogen Mustards - Data Evaluation/Study Selection Criteria

- analytical vs nominal exposure concentrations
- exposure duration data
- number of animals
- post-exposure observation period
- environmental conditions (temp., humidity)
- species sensitivity

Nitrogen Mustards - Special Considerations

- **Metabolism/Disposition**
  - **dermal penetration of HN vapor**
    - **linear with time**
    - **enhanced with increasing temperature & humidity**

- **Mechanism of action**
  - **formation of immonium ion which is reactive with nucelophiles**
  - **all HN alkylators**
  - **precise mechanism unclear**

Summary of AEGL Values (mg/m^3) for Nitrogen Mustards						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1						
HN1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Not recommended
HN2	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Not recommended
HN3	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Not recommended
AEGL-2						
HN1	0.90	0.30	0.15	0.038	0.019	Threshold for ocular irritation in humans sufficient to compromise operational effectiveness (Porton Report 1942a, 1943d; U.S. Army Med. Div. 1945c, d.)
HN2	0.55	0.18	0.092	0.023	0.011	
HN3	0.42	0.14	0.070	0.018	0.0088	
AEGL-3						
HN1	1.8 **(2.9)**	0.96	0.48	0.12	0.060	Lethality threshold in rats estimated as 3-fold reduction of LCt_{50} values (Porton Report. 1943b,c; U.S. Army Med. Div., 1945a)
HN2	1.3 **(6.7)**	0.88 **(2.2)**	0.70 **(1.1)**	0.28	0.14	
HN3	2.2	0.74	0.37	0.093	0.047	

[a] NR: not recommended due to insufficient data and because adverse effects are know to occur in the absence of detection

Bolded red values indicate values derived using empirically-derive *n* from lethality data in multiple species as opposed to default *n*=3.

AEGL-2 VALUES FOR HN1				
10 minutes	30 minutes	1 hour	4 hours	8 hours
0.90 mg/m^3	0.30 mg/m^3	0.15 mg/m^3	0.038 mg/m^3	0.019 mg/m^3

Reference: Porton Report. 1943d. The effects of HN1 vapour on human and rabbit eyes. No. 2563. November 18, 1943. Cited in NDRC, 1946.

Test Species/Strain/Sex/Number: Human volunteers/males/21

Exposure Route/Concentrations/Durations: ocular exposure to vapors; CT determined based upon exposure durations of 5 to 67 minutes.

Effects: Ocular irritation in human volunteer subjects; lacrimation, feeling of grittiness in eyes, belpharospasm, photophobia, conjunctival injection.

Endpoint/Concentration/Rationale: 90 mg-min/m^3 based upon exposure durations of 5-67 minutes.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: none; human subjects
Intraspecies: 3; intraspecies adjustment was limited to 3 because the ocular response is considered the result of direct-contact with the nitrogen mustard vapors rather than a systemically-mediated process.

Modifying Factor: 3; some of the tests were apparently performed using volunteers with oronasal masks which would have precluded development of respiratory tract effects. Therefore, a modifying factor of 3 was applied to account for possible effects on the respiratory tract.

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: For the 10-min., 30-min, and 1-hr AEGL-2, concentrations determined directly from cumulative exposure threshold value of 90 mg-min/m^3. The exposure concentration-time relationship for longer durations (e.g., the 4-hr and 8-hr AEGL time points) is uncertain and an empirically-derived value for the exponent, n, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an n of 1 was used in extrapolating from the 60-minute experimental exposure of 1.5 mg/m^3 period to the 4-hour and 8-hour AEGL-2 time periods resulting in exposures of 0.38 mg/m^3 and 1.88 mg/m^3.

Data Adequacy: The available data provide exposure-response data characterizing a sensitive critical effect in human volunteer subjects. The effect is consistent with the continuum of effects observed for this class of compounds. The data are considered appropriate for setting AEGL-2 values for HN1.

AEGL-3 VALUES FOR HN1				
10 minutes	30 minutes	1 hour	4 hours	8 hours
1.8 mg/m^3	0.96 mg/m^3	0.48 mg/m^3	0.12 mg/m^3	0.060 mg/m^3

Reference: U.S. Army Medical Division. 1945a. Medical Division monthly progress report. September, 1945. Cited in NRDC, 1946.

Test Species/Strain/Sex/Number: 84 male rats

Exposure Route/Concentrations/Durations: inhalation/experimental exposure durations of 20-100 minutes/ analytically determined concentrations.; 90°F chamber temp., 10-15 day observation period

Effects: Lethality response data only

Endpoint/Concentration/Rationale: Lethality threshold of 287 mg-min/m^3 in rats estimated by 3-fold reduction of inhalation LCt_{50} of 860 mg-min/m^3

Uncertainty Factors/Rationale:
Total uncertainty factor: 10

Interspecies: Limited to 3 because LCt_{50} values among seven species (including nonhuman primates) did not appear to vary by more than three-fold; the rat being somewhat more sensitive.

Intraspecies: Limited to 3 because of the direct action of nitrogen mustards on tissue and because additional downward adjustment would result in AEGL-3 values inconsistent with AEGL-2 values and available human data (ocular and dermal response data and monitoring data for therapeutic use of nitrogen mustard

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling:	$C^n \times t = k$; data were unavailable for empirical derivation of a scaling factor. The exposure concentration-time relationship for many irritant and systemically acting vapors and gases may described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical-specific data, temporal scaling was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001). For 10-min. AEGL-3: point-of-departure based upon estimated lethality threshold of 287 mg-min/m^3 resulting from 20-minute exposure (14.4 mg/m^3) (14.4 mg/m^3)^3 x 20 min. = 59,719 mg-min/m^3
Data Adequacy: The AEGL-3 values were based upon lethality assessment (analytically determined concentrations) using the most sensitive species exposed to high temperature conditions optimal for enhancing HN1 activity (i.e., worst-case scenario). A 10 to15-day post exposure observation period accounted for kown latency in toxic responses to HN1	

AEGL-2 VALUES FOR HN2				
10 minutes	30 minutes	1 hour	4 hours	8 hours
0.55 mg/m^3	0.18 mg/m^3	0.092 mg/m^3	0.023 mg/m^3	0.011 mg/m^3

Reference: Porton Report. 1942a. On the action of S on the eye; its comparison with allied compounds and with H. No. 2402. August 7, 1942. Cited in NDRC, 1946

Test Species/Strain/Sex/Number: Human male volunteers/number not specified

Exposure Route/Concentrations/Durations: 10-55 mg/m^3; exposure durations of 0.5 min to 10 min.; Ct values of 40-55 mgpmin/m^3; subjects wore oronasal masks

Effects: ocular irritation following exposure (grittiness in eyes; photophobia, belpharospasm; ocular pain).

Endpoint/Concentration/Rationale: 55 mg-min/m^3 considered threshold for inducing military fine-skill operational ineffectiveness

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: none; human subjects
Intraspecies: 3; intraspecies adjustment was limited to 3 because the ocular response is considered the result of direct-contact with the nitrogen mustard vapors rather than a systemically-mediated process.

Modifying Factor: 3. Some of the tests were apparently performed using volunteers with oronasal masks which would have precluded development of respiratory tract effects. Therefore, a modifying factor of 3 was applied to account for possible effects on the respiratory tract.

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: For the 10-min. AEGL-2, concentrations were determined directly from cumulative exposure threshold value of 55 mg-min/m^3. The exposure concentration-time relationship for remaining AEGL-specific time points durations is uncertain and an empirically-derived value for the exponent, n, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an n of 1 was used in extrapolating to these time points.

Data Adequacy: The available data provide exposure-response data characterizing a sensitive critical effect in human volunteer subjects. The effect is consistent with the continuum of effects observed for this class of compounds. The data are considered appropriate for setting AEGL-2 values for HN2.

AEGL-3 VALUES FOR HN2				
10 minutes	30 minutes	1 hour	4 hours	8 hours
1.3 mg/m^3	0.88 mg/m^3	0.70 mg/m^3	0.28 mg/m^3	0.14 mg/m^3

Reference: Porton Report. 1943b. Toxicity of S vapour. Further experiments on the exposure of animals to S vapour. No. 2464. February 9, 1943. Cited in NDRC, 1946.

Test Species/Strain/Sex/Number: rat/gender not specified/56

Exposure Route/Concentrations/Durations: inhalation/experimental exposure durations of 120-360 minutes resulting in cumulative exposures of 2000 mg-min/m^3

Effects: Lethality only

Endpoint/Concentration/Rationale: Lethality threshold of 667 mg-min/m^3 in rats estimated by 3-fold reduction of LCt_{50} of 2000 mg-min/m^3.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10

- Interspecies: Limited to 3 because LCt_{50} values among seven species (including nonhuman primates) did not appear to vary by more than three-fold; the rat being somewhat more sensitive.
- Intraspecies: Limited to 3 because of the direct action of nitrogen mustards on tissue and because additional downward adjustment would result in AEGL-3 values inconsistent with AEGL-2 values and available human data (ocular and dermal response data and monitoring data for therapeutic use of nitrogen mustard

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling:	$C^n x\ t = k$; data were unavailable for empirical derivation of a scaling factor. The concentration-time relationship for many irritant and systemically acting vapors and gases may described by $C^n x\ t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical-specific data, temporal scaling was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $Cn\ x\ t = k$ equation (NRC, 2001). For 10-min., 30-min, and 1-hr AEGL-3: point-of-departure based upon estimated lethality threshold of 667 mg-min/m^3 resulting from 120-minute exposure (5.56 mg/m^3) (5.56 mg/m^3)^3 x 120 min. = 20,625.6 mg-min/m^3
Data Adequacy: The AEGL-3 values were based upon lethality assessment (analytically determined concentrations) using the most sensitive species. A 14-day post exposure observation period accounted for known latency in toxic responses to HN2.	

AEGL-2 VALUES FOR HN3				
10 minutes	30 minutes	1 hour	4 hours	8 hours
0.42 mg/m^3	0.14 mg/m^3	0.070 mg/m^3	0.018 mg/m^3	0.0088 mg/m^3

Reference: U.S. Army Medical Division. 1945c. Medical Division monthly progress report. March, 1945. Cited in NRDC, 1946.
U.S. Army Medical Division. 1945d. Medical Division monthly progress report. February, 1945. Cited in NRDC, 1946.

Test Species/Strain/Sex/Number: Human volunteer subjects/male/7

Exposure Route/Concentrations/Durations: inhalation/20-40 mg-min/m^3; 7 min.

Effects: exposure to 20 mg-min/m^3 (duration not specified) resulted in conjunctival injection and corneal edema with no symptoms being reported by subjects
exposure to 40-mg-min/m^3 produced lacrimation, feeling of grittiness, photophobia, marked conjunctival injection

Endpoint/Concentration/Rationale:40-mg-min/m^3 considered threshold for compromised task efficiency.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: human subjects, none applied
Intraspecies: adjustment was limited to 3 because the ocular response is considered the result of direct-contact with the nitrogen mustard vapors rather than a systemically-mediated process.
Intraspecies:

Modifying Factor: 3; some of the tests may have been performed using volunteers with oronasal masks which would have precluded development of respiratory tract effects. Therefore, a modifying factor of 3 was applied to account for possible effects on the respiratory tract.

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: The exposure-time response relationship for AEGL-specific time points durations is uncertain and an empirically-derived value for the exponent, n, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an n of 1 was used in extrapolating from the 7-minute experimental period to the AEGL-specific time points.

Data Adequacy: The available data provide exposure-response data characterizing a sensitive critical effect in human volunteer subjects. The effect is consistent with the continuum of effects observed for this class of compounds. Although the short exposure duration results in extensive extrapolation, an *n* of 1 was applied to provide more conservative exposure concentration estimates. Furthermore, the critical effect is a conservative point-of-departure for AEGL-2 severity effects. The data are considered appropriate for setting AEGL-2 values for HN3.

AEGL-3 VALUES FOR HN3				
10 minutes	30 minutes	1 hour	4 hours	8 hours
2.2 mg/m^3	0.74 mg/m^3	0.37 mg/m^3	0.093 mg/m^3	0.047 mg/m^3

Reference: Porton Report, 1943c. Toxicity and pathology of HN3. No. 2548. November 18, 1944. Cited in NDRC, 1946

Test Species/Strain/Sex/Number: 69 rats/gender not specified/exposure group

Exposure Route/Concentrations/Durations: inhalation LCt_{50} of 670 mg-min/m^3; exposure durations of 10-100 min.

Effects: Lethality response data only

Endpoint/Concentration/Rationale: Lethality threshold of 223.3 mg-min/m3 in rats estimated by 3-fold reduction of LCt_{50} of 670 mg-min/m3; experimental exposure durations of 10-100 minutes.

Uncertainty Factors/Rationale:

Total uncertainty factor: 10

- Interspecies: Limited to 3 because LCt_{50} values among seven species (including nonhuman primates) did not appear to vary by more than three-fold; the rat being somewhat more sensitive.
- Intraspecies: Limited to 3 because of the direct action of nitrogen mustards on tissue and because additional downward adjustment would result in AEGL-3 values inconsistent with AEGL-2 values and available human data (ocular and dermal response data and monitoring data for therapeutic use of nitrogen mustard

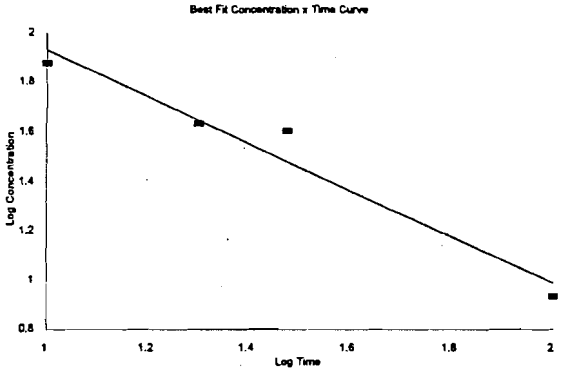
Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

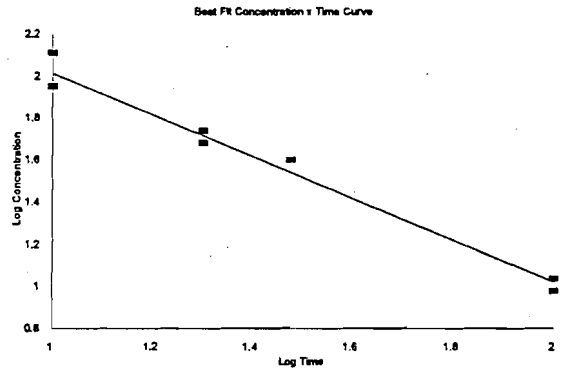
Time Scaling: Point-of-departure concentrations for each AEGL time point were determined directly from cumulative exposure threshold value of 223.3 mg-min/m^3. This is effectively the use of $n = 1$ for $C^n \times t = k$.

Data Adequacy: The AEGL-3 values were based upon lethality assessment (analytically determined concentrations) using the most sensitive species and a chamber temperature (85°F) which would represent a worst-case scenario. A 15-day post exposure observation period accounted for kown latency in toxic responses to HN3.

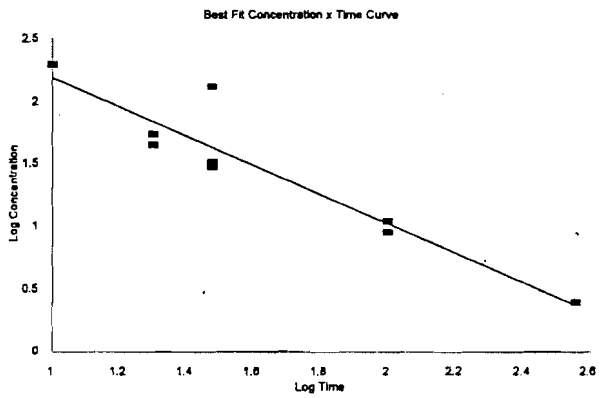
Time Scaling HN1



Rat: n=1.06, k=1123.4 r^2=0.96

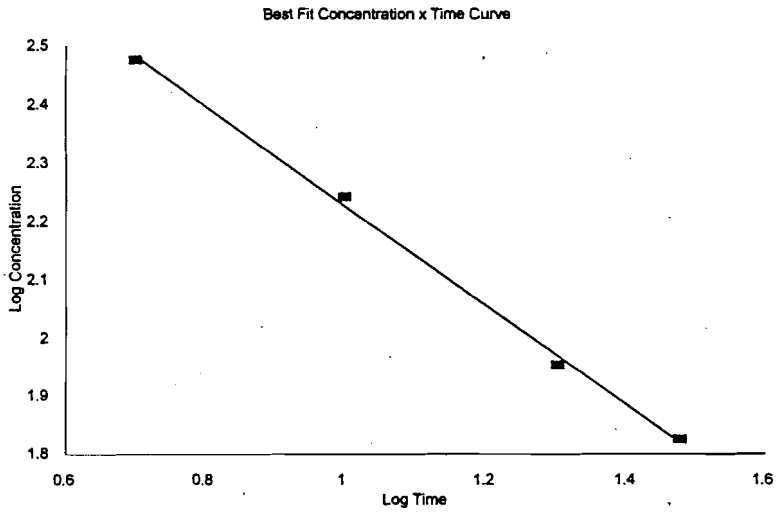


Mouse: n=1.01, k=1080.84, r^2=0.98

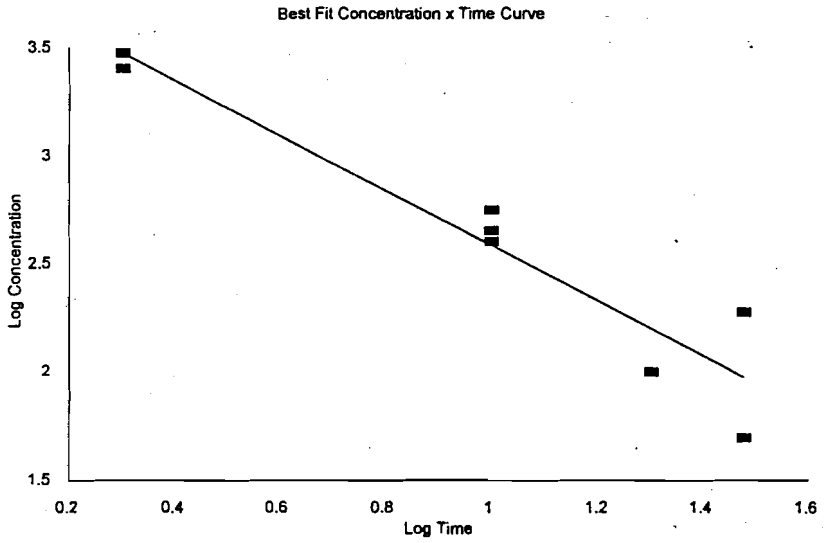


Rabbit: n=0.85, k=749.68, r^2=0.88

Time Scaling HN2

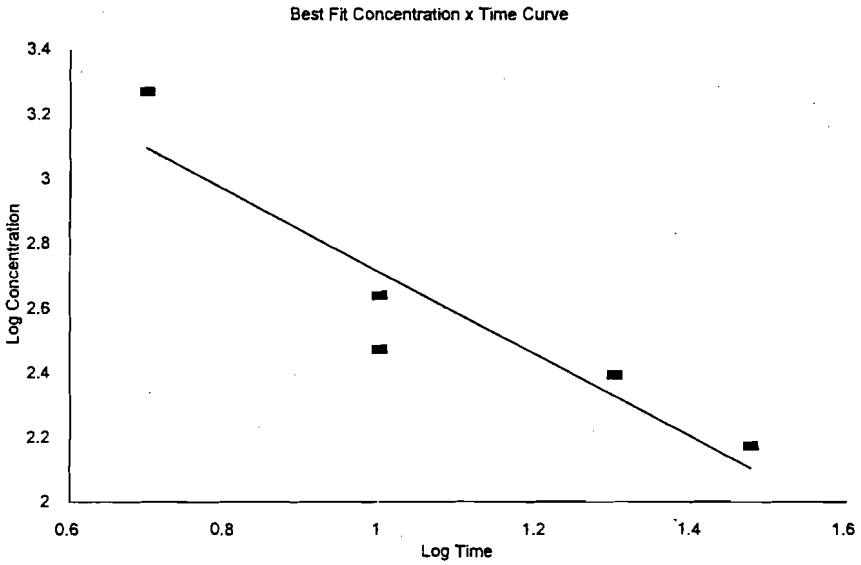


Rat: n=1.17, k=4091.35 r^2=0.99

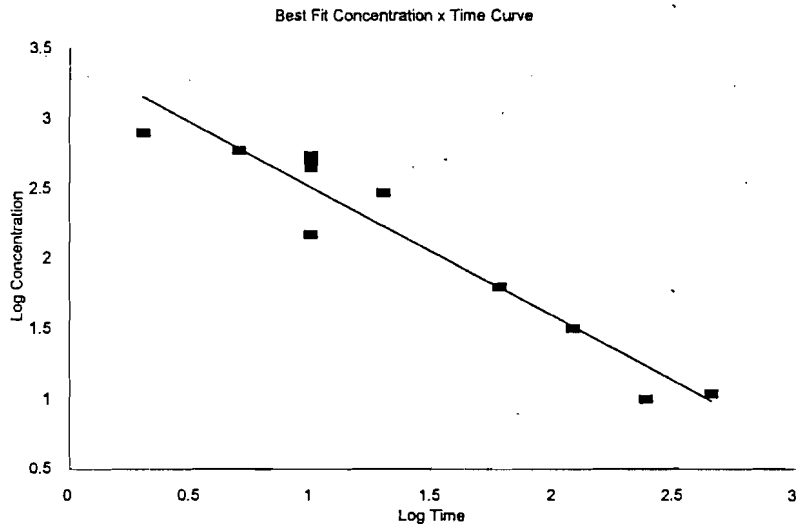


Mouse: n=0.78, k=1063.76, r^2=0.91

Time Scaling HN2

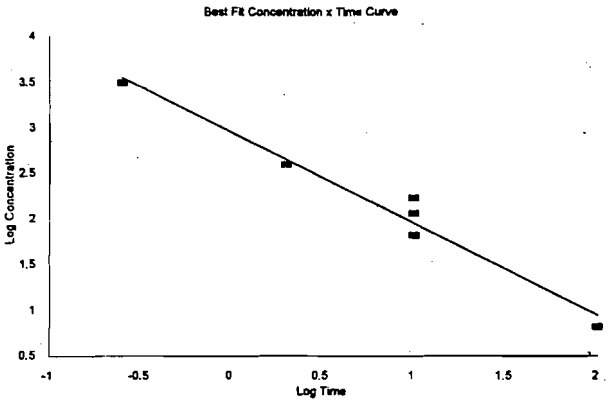


Rabbit: n=0.79, k=1357.06, r^2=0.85

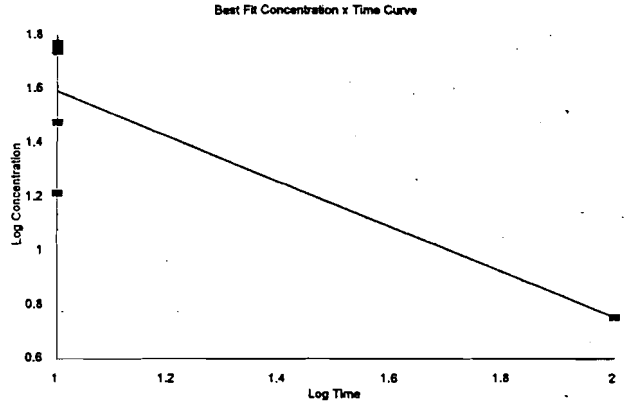


Guinea Pig: n=1.08, k=5292.77, r^2=0.98

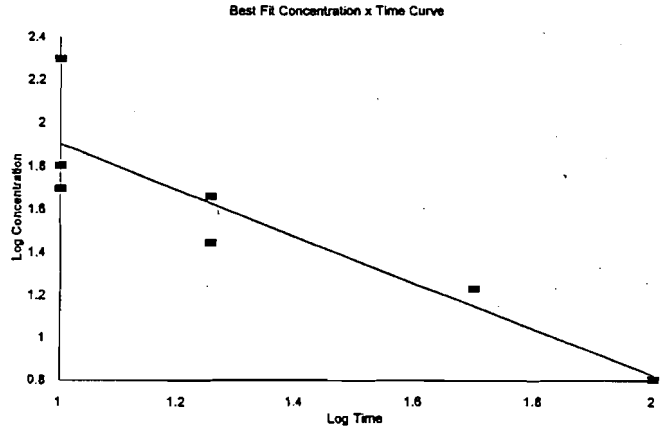
Time Scaling HN3



Rat: n=1.0, k=902.03 r^2=0.97



Mouse: n=1.2, k=801.04, r^2=0.7

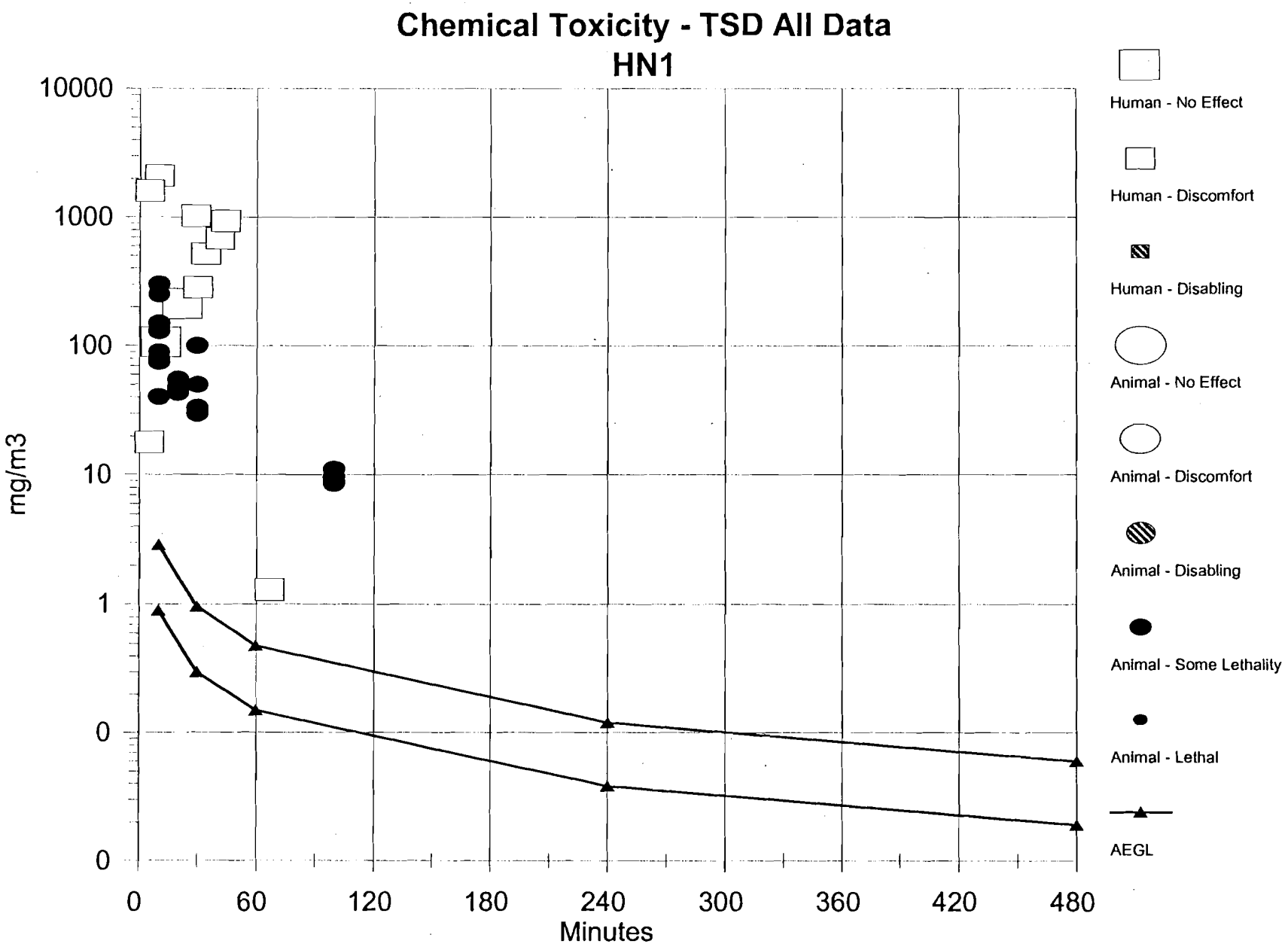


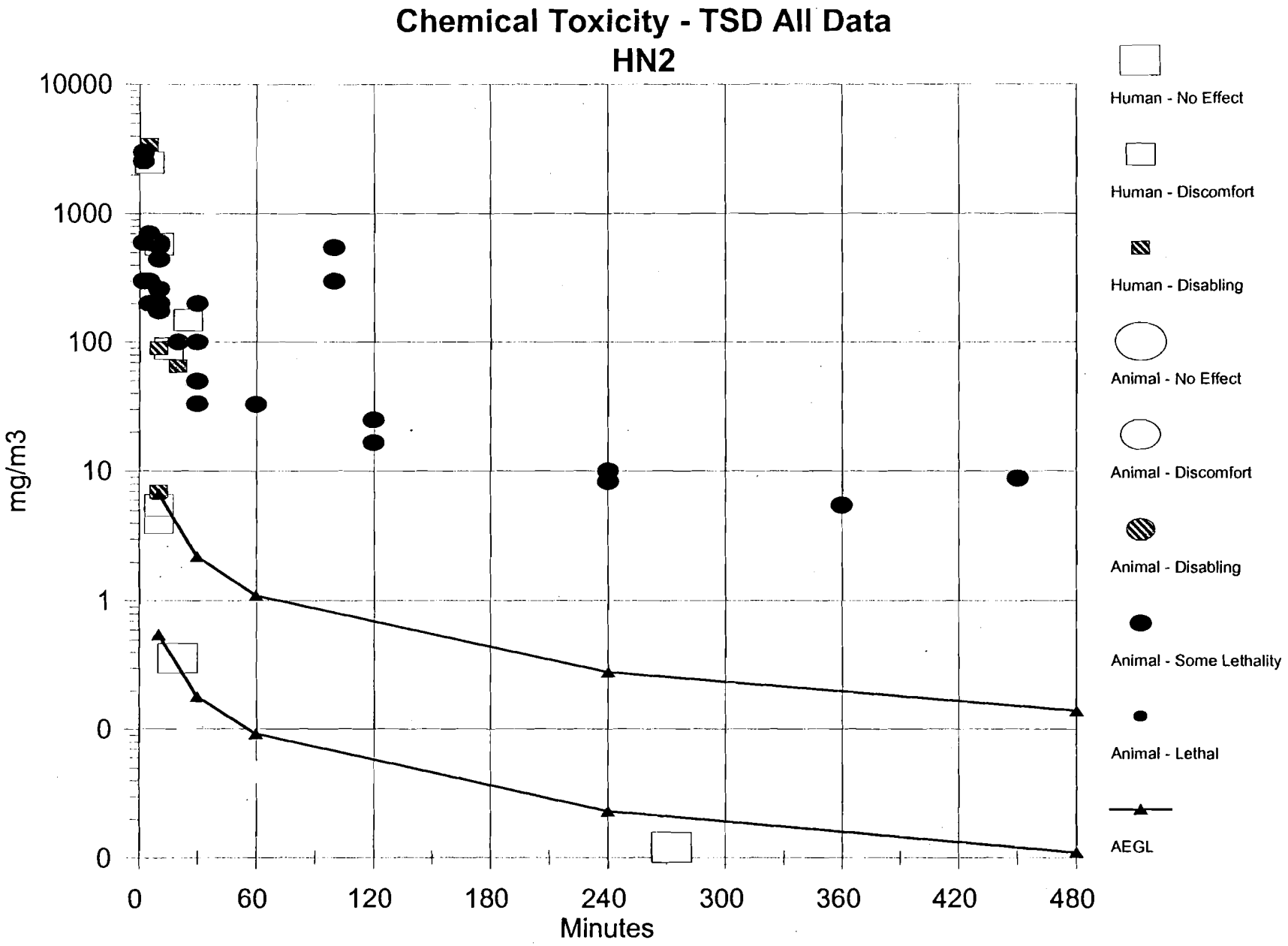
Rabbit: n=0.92, k=577.66, r^2=0.81

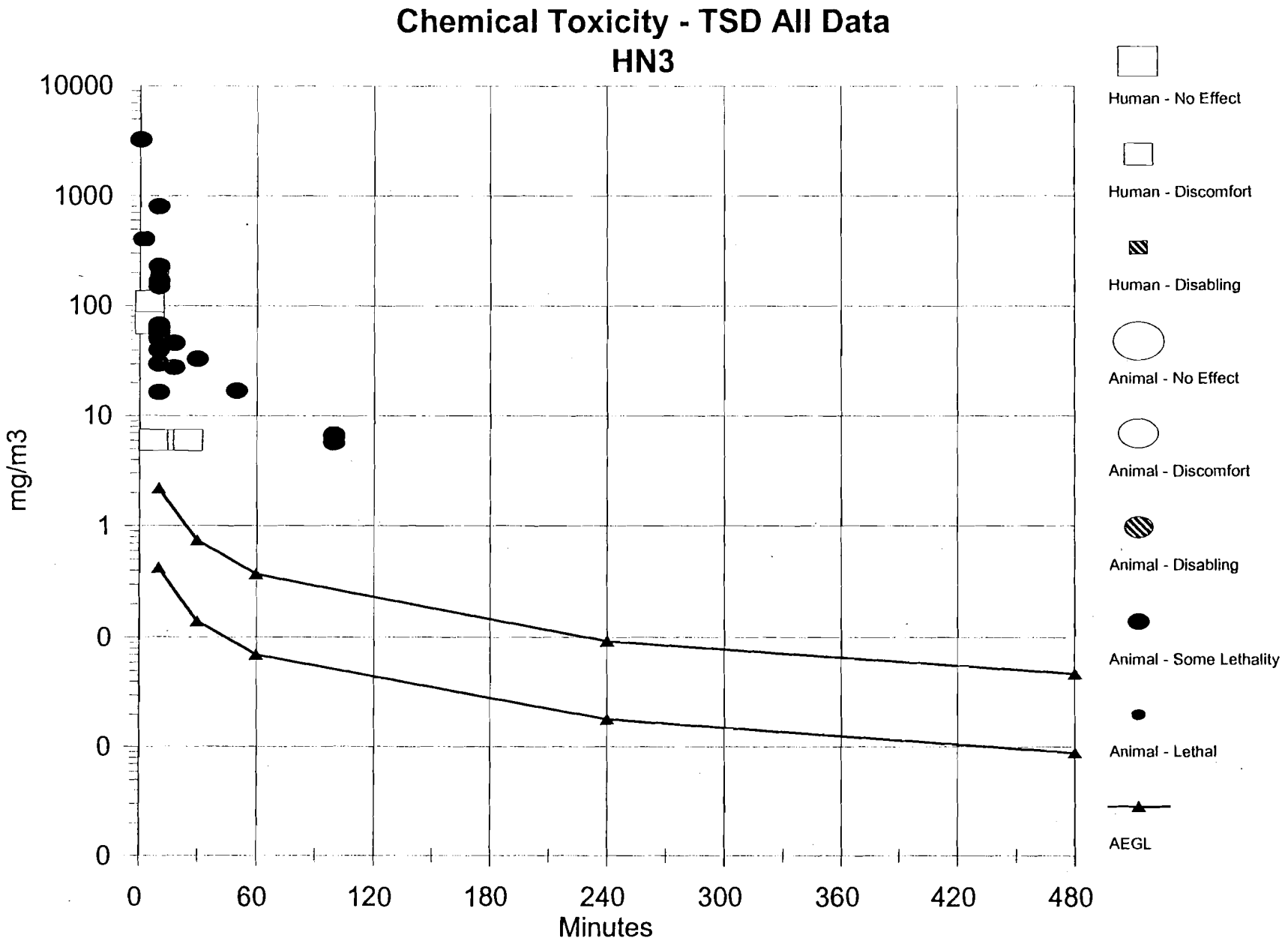
Summary of AEGL Values (mg/m^3) for Nitrogen Mustards						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1						
HN1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Not recommended
HN2	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Not recommended
HN3	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Not recommended
AEGL-2						
HN1	0.90	0.30	0.15	0.038	0.019	Threshold for ocular irritation in humans sufficient to compromise operational effectiveness (Porton Report 1942a, 1943d; U.S. Army Med. Div. 1945c, d.)
HN2	0.55	0.18	0.092	0.023	0.011	
HN3	0.42	0.14	0.070	0.018	0.0088	
AEGL-3						
HN1	1.8 **(2.9)**	0.96	0.48	0.12	0.060	Lethality threshold in rats estimated as 3-fold reduction of LCt_{50} values (Porton Report. 1943b,c; U.S. Army Med. Div., 1945a)
HN2	1.3 **(6.7)**	0.88 **(2.2)**	0.70 **(1.1)**	0.28	0.14	
HN3	2.2	0.74	0.37	0.093	0.047	

[a] NR: not recommended due to insufficient data and because adverse effects are know to occur in the absence of detection

Bolded red values indicate values derived using empirically-derive *n* from lethality data in multiple species as opposed to default *n*=3.


Chemical Toxicity - TSD All Data
HN1
10000
1000
100
10
1
0
0
mg/m3
0
60
120
180
240
300
360
420
480
Minutes
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL


Chemical Toxicity - TSD All Data
HN2
10000
1000
100
10
1
0
0
mg/m3
0
60
120
180
240
300
360
420
480
Minutes
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL


Chemical Toxicity - TSD All Data
HN3
10000
1000
100
10
1
0
0
0
mg/m3
0
60
120
180
240
300
360
420
480
Minutes
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHYLCHLOROSILANE

NAC/AEGL-35
December 13-15, 2004

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Ernest Falke

Chemical Reviewers: Steve Barbee and Bill Bress

No human or animal data on methylchlorosilane are available.

The acute toxicity of other chlorosilanes is both qualitatively and quantitatively similar to HCl.

Measured and predicted (based on molar HCl equivalents) LC_{50} values for chlorosilanes

	Measured 1-hr LC_{50}	**Predicted LC_{50} value**	**Predicted Ratio of LC_{50} values**	**Measured Ratio of LC_{50} values**
Hydrogen Chloride	3627 ppm	-	-	-
Dimethyldichlorosilane	2092 ppm	3627 ÷ 2 = 1814 ppm	2 : 1	1.7 : 1
Methyltrichlorosilane	1365 ppm	3627 ÷ 3 = 1209 ppm	3 : 1	2.7 : 1
Trimethylchlorosilane	4257 ppm	3627 ÷ 1 = 3627 ppm	1 : 1	0.9 : 1
Methyldichlorosilane	1785 ppm	3627 ÷ 2 = 1814 ppm	2 : 1	2 : 1

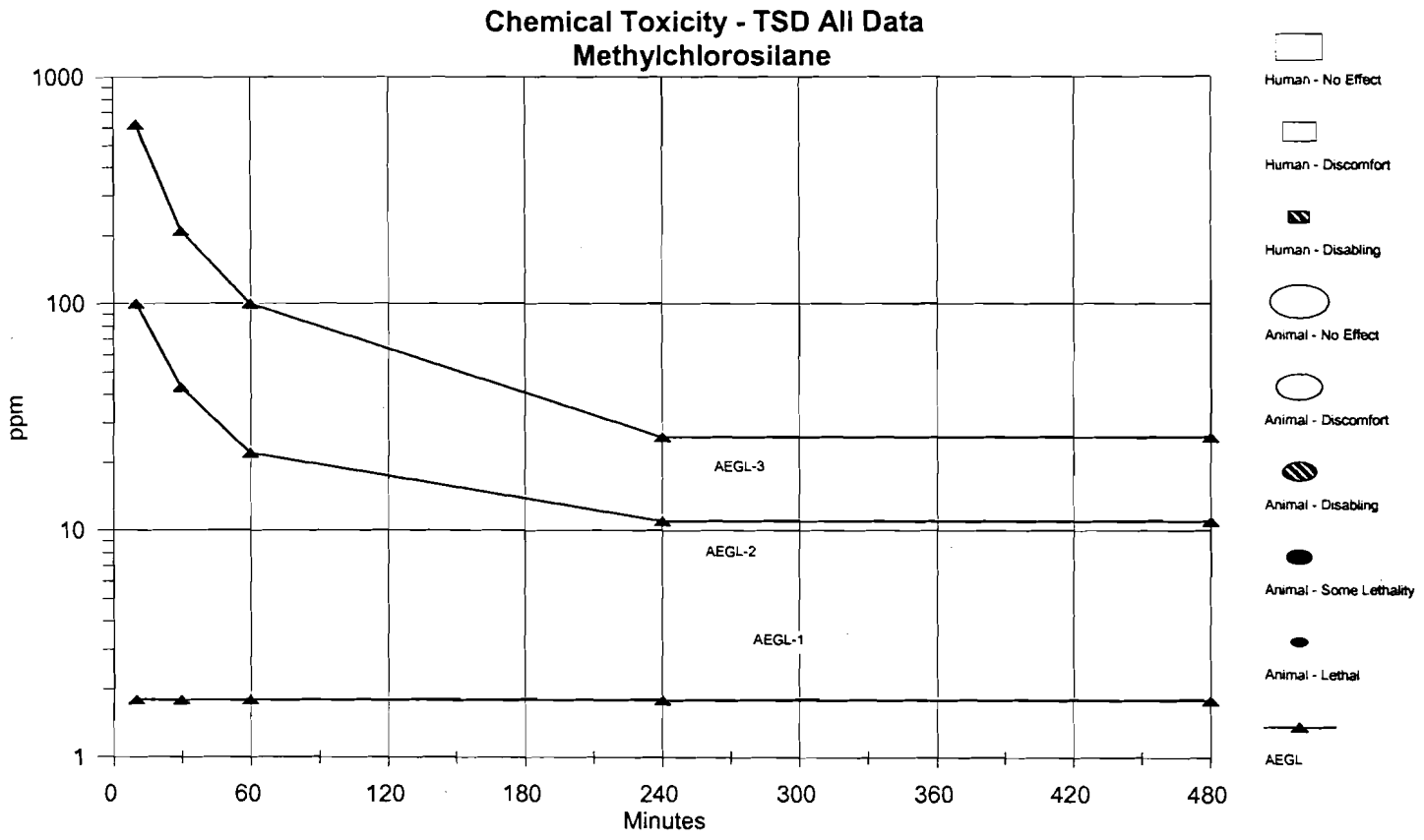
The predicted 1-hr LC_{50} values for chlorosilanes, based on hydrogen chloride equivalents, are comparable to the experimentally-derived 1-hr LC_{50} values.

The hydrogen chloride hydrolysis product is responsible for the acute toxicity of chlorosilanes.

Complete hydrolysis of one mole of methylchlorosilane yields a maximum of one mole of hydrogen chloride.

AEGL-1, AEGL-2 and AEGL-3 values for methylchlorosilane will be set equivalent to the hydrogen chloride AEGL-1, AEGL-2, and AEGL-3 values, respectively.

AEGL Values for Methylchlorosilane					
Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm
AEGL-2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm
AEGL-3	620 ppm	210 ppm	100 ppm	26 ppm	26 ppm


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

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHYLDICHLOROSILANE

NAC/AEGL-35
December 13-15, 2004

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Ernest Falke

Chemical Reviewers: Steve Barbee and Bill Bress

The acute toxicity of methyldichlorosilane is both qualitatively and quantitatively similar to HCl.

The hydrogen chloride hydrolysis product is responsible for the acute toxicity of chlorosilanes.

Two moles of hydrogen chloride are released from complete hydrolysis of one mole of methyldichlorosilane.

1-hr rat LC_{50} for HCl = 3627 ppm (Dow Corning, 1997)

1-hr rat LC_{50} for methyldichlorosilane = 1785 ppm (Dow Corning, 2001)

The predicted 1-hr LC_{50} for methyldichlorosilane, based on hydrogen chloride equivalents, is 1814 ppm (3627 ppm ÷ 2), which is comparable to the experimentally-derived 1-hr LC_{50} of 1785 ppm.

AEGL-1 VALUES				
10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
0.9 ppm	**0.9 ppm**	**0.9 ppm**	**0.9 ppm**	**0.9 ppm**

Endpoint: Based on molar equivalence of HCl AEGL-1 values (HCl AEGL-1 values ÷2)

Reference: NRC (National Research Council). 2004. Acute Exposure Guideline Levels for Selected Airborne Chemicals. Volume 4. Hydrogen Chloride. pp. 77-122.

Molar Adjustment Factor = 2

Two moles of hydrogen chloride are released from complete hydrolysis of one mole of methyldichlorosilane.

AEGL-2 VALUES				
10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
50 ppm	**22 ppm**	**11 ppm**	**5.5 ppm**	**5.5 ppm**

Endpoint: Based on molar equivalence of HCl AEGL-2 values (HCl AEGL-2 values ÷2)

Reference: NRC (National Research Council). 2004. Acute Exposure Guideline Levels for Selected Airborne Chemicals. Volume 4. Hydrogen Chloride. pp. 77-122.

Molar Adjustment Factor = 2

Two moles of hydrogen chloride are released from complete hydrolysis of one mole of methyldichlorosilane.

AEGL-3 VALUES				
10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
280 ppm	**93 ppm**	**47 ppm**	**12 ppm**	**12 ppm**

Species: Rat
Concentration: 1400 ppm
Time: 1 hour
Endpoint: Calculated 1-hr LC_{01}
Reference: Dow Corning, 2001

Time Scaling: n = 1; value is for hydrogen chloride based on regression analysis of combined rat and mouse LC_{50} data (1 min. to 100 min.)

Utilized for time scaling for methyldichlorosilane for time points up to 4-hours

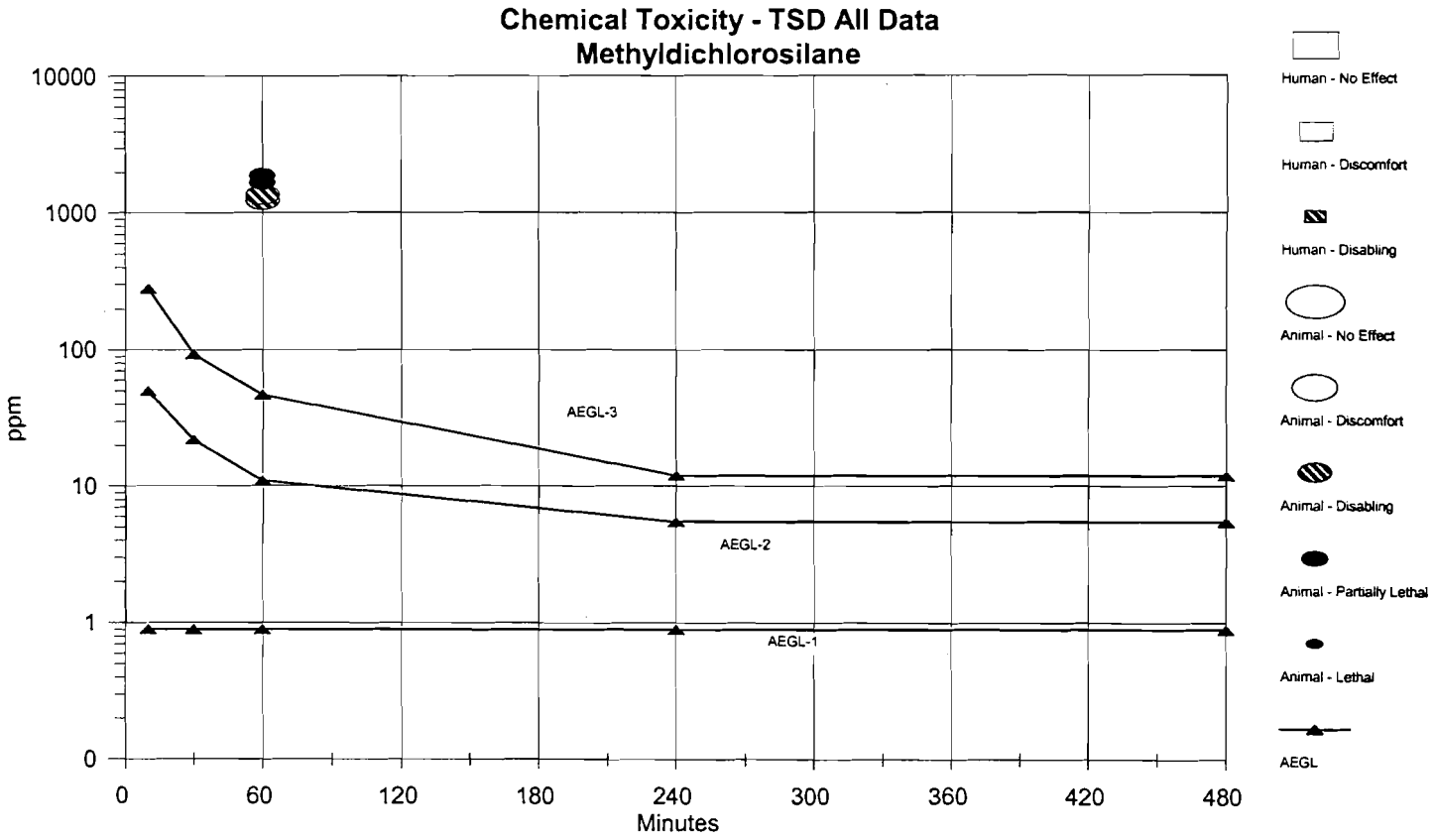
The 4-hr value was adopted as the 8-hr value to obtain values consistent with the total data base.

Uncertainty Factors:

Interspecies = 10 (data from only one species)

Intraspecies = 3 (Utilizing a value of 10 would yield would yield AEGL-3 values approaching or below the AEGL-2 values)

Relational Comparison of AEGL Values for Methyldichlorosilane					
Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm
AEGL-2	50 ppm	22 ppm	11 ppm	5.5 ppm	5.5 ppm
AEGL-3	280 ppm	93 ppm	47 ppm	12 ppm	12 ppm


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

Comparison of AEGL-3 Values for Methyldichlorosilane with AEGL Values for Hydrogen Chloride					
Classification	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**
Methyldichlorosilane AEGL-3	280 ppm	93 ppm	47 ppm	12 ppm	12 ppm
Hydrogen Chloride AEGL-3	620 ppm	210 ppm	100 ppm	26 ppm	26 ppm
Hydrogen Chloride AEGL-3 ÷2	310 ppm	105 ppm	50 ppm	13 ppm	13 ppm
HCl: Methyldichlorosilane AEGL-3 Ratio	2.2 : 1	2.2 : 1	2.1 : 1	2.1 : 1	2.1 : 1

ACUTE EXPOSURE GUIDELINE LEVELS FOR DIKETENE (CAS NO. 674-82-8)

PRESENTED BY
KOWETHA DAVIDSON
ORNL STAFF SCIENTIST

CHEMICAL MANAGER
WARREN JEDERBERG

NAC/AEGL MEETING, Research Triangle Park, NC
April 12-14, 2005

1

DIKETENE
CAS NO. 674-82-8

COMMON SYNONYMS: Acetyl ketene, ketene dimer

PHYSICAL CHARACTERISTICS:

- light colored or colorless non-hygroscopic liquid
- Vapor pressure: 10 mm Hg at 24.3°C
- Vapor density: 2.9 (air = 1)
- Soluble in common organic solvents; insoluble in water
- Conversion: 1 ppm = 3.44 mg/m^3

2

OTHER INFORMATION

- **Uses:** production of pigments, toners, pesticides, food preservatives, and pharmaceutical intermediates
- **ODOR:** Pungent
- **ODOR THRESHOLD:** 5.5 – 11.6 ppb
- **LOA:** 0.14 ppm (140 ppb)

3

HUMAN DATA

- No data on humans exposed to lethal concentrations
- Effects at non-lethal concentrations
  - 0.58 ppm, 1 min: irritating to eyes (conjunctiva) and mucosa of the nose and throat
  - 3.2-6.1 ppb, unknown duration: threshold for ocular sensitivity to light
  - 2.9-5.5 ppb, unknown duration: threshold for electrical activity of the brain

The toxicological significance of the tests for ocular sensitivity to light and electrical activity of the brain is uncertain.

4

ANIMAL DATA

Lethality Data (Acute Inhalation Exposure)

Study: Katz, 1987

Five male and five female CRL:CD®rats were exposed diketene vapor at concentrations of 250, 500, or 750 for 1 hour and observed for 14 days.

Exposure Conditions:

420-L stainless and glass chamber

10-13 air changes/hour

Chamber atmosphere analyzed 4-5 times using an infrared analyzer

Analytical concentrations: 271, 466, and 778 ppm, respectively

Parameters evaluated:

Mortality, clinical signs, and gross lesions

Results:

5

Parameter	Exposure concentration (ppm)					
	250	500	750	250	500	750
	Males			Females		
No. exposed	5	5	5	5	5	5
Mortality	0	2	4	0	1	3
LC50	548 ppm for male rats; 689 ppm for females; 612 ppm combined sexes					
Lacrimation	5	5	5	5	5	5
Porphyrin discharge	0	2	2	0	2	3
Gasping	5	5	5	5	5	5
Rales	1	1	1	0	1	0
Wheezing	1	0	0	0	1	2
Poor condition	0	0	4	0	0	1

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ANIMAL DATA (CONT.)

Lethality data (acute inhalation study)
Study: Wooster et al., 1947
Exposure duration: 10 minutes, 15 day observation period
Mice:
- 194 ppm: 0/4 deaths
- 580 ppm: 0/30 deaths
- 870 ppm: 1/20 deaths (pulmonary edema)

Guinea pigs:
- 194 ppm: 3/3 died (pulmonary edema)

Rats and Rabbits
- 194 ppm: 0/4 rats and 0/3 rabbits died

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OTHER DATA

- No data were found on neurotoxicity, developmental/ reproductive toxicity, genetic toxicity, or carcinogenicity of inhaled diketene in experimental animals.
- No data were found on metabolism or disposition
- Mechanism of toxicity: Diketene is an irritant
- Structure/activity relationships: The dimeric diketene is similar to but less toxic than ketene, and the toxicity of ketene is similar to that of phosgene
- The most sensitive species appears to be the guinea pig.

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AEGL-1 DERIVATION

- Human study: Fel'dman, 1967
- POD = 0.58 ppm (mild irritation to eyes, nose, & throat) after 1 minute
- UF = 3: interspecies = 1; intraspecies = 3
- Diketene is an irritant & mode-of-action is not expected to differ among individuals in the population
- Time scaling: default: n = 1 scaling to a longer duration (10 min.)
- Scaling to 30 minutes and 1, 4, and 8 hours would reduce AEGL values below the odor threshold for almost all individuals including the most sensitive

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AEGL-1 values for diketene [ppm (mg/m^3)]				
10 min.	30 min.	1 hour	4 hours	8 hours
0.019 [0.065]	0.019 [0.065]	0.019 [0.065]	0.019 [0.065]	0.019 [0.065]

10

AEGL-2 DERIVATION

The experimental data from animal studies were not appropriate for deriving AEGL-2 values

- AEGL-2 values were derived by reducing AEGL-3 values by a factor of 3

The exposure-response curve was relatively steep

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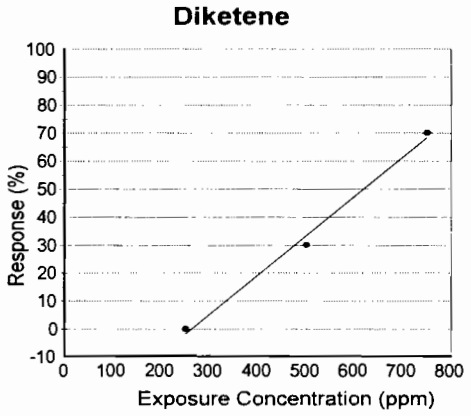
Rat data (Katz, 1987)

240 ppm – 0% mortality

500 ppm – 30% mortality

750 ppm – 70% mortality



12

AEGL-2 values for diketene [ppm (mg/m^3)]				
10 min.	30 min.	1 hour	4 hours	8 hours
10 [34]	7.0 [24]	5.7 [20]	1.4 [4.8]	0.70 [2.4]

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AEGL-3 DERIVATION

- Study: Katz, 1987 [1-h inhalation study in rats]
- POD = $BMCL_{05}$ = 170 ppm
- UF = 10: interspecies = 3; intraspecies = 3
- Diketene is an irritant & mode-of-action is not expected to differ considerably among species or individuals in the population
- Time scaling: default: n = 3 when scaling to a shorter duration; n = 1 when scaling to a longer duration

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AEGL-3 values for diketene [ppm (mg/m^3)]				
10 min.	30 min.	1 hour	4 hours	8 hours
31 [107]	21 [72]	17 [58]	4.3 [15]	2.1 [7.2]

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Summary of AEGL Values [ppm(mg/m^3)]					
Classification	**10 min**	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1 (Nondisabling)	0.019 [0.065]	0.019 [0.065]	0.019 [0.065]	0.019 [0.065]	0.019 [0.065]
AEGL-2 (Disabling)	10 [34]	7.0 [24]	5.7 [20]	1.4 [4.8]	0.70 [2.4]
AEGL-3 (Lethal)	31 [107]	21 [72]	17 [58]	4.3 [15]	2.1 [7.2]

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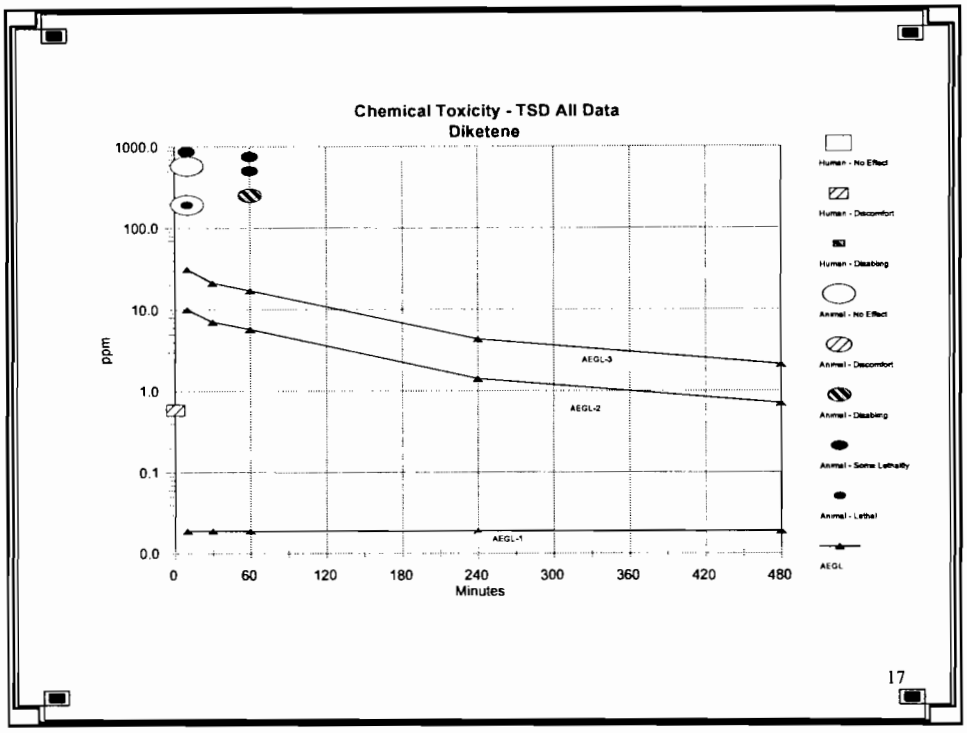

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AEGL-1 DERIVATION WORK SHEET

	10 min	30 min	1 h	4 h	8 h
Study: POD = UF = N =					
Comments					
Study: POD = UF = N =					
Comments					

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AEGL-2 DERIVATION WORK SHEET

	10 min	30 min	1 h	4 h	8 h
Study: POD = UF = N =					
Comments					
Study: POD = UF = N =					
Comments					

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AEGL-3 DERIVATION WORK SHEET

	10 min	30 min	1 h	4 h	8 h
Study: POD = UF = N =					
Comments					
Study: POD = UF = N =					
Comments					

20