National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGL) for Hazardous Substances
Final Meeting 2 Highlights
Green Room, 3rd Floor, Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, D.C.
August 5-7, 1996

INTRODUCTION

The highlights of the meeting are outlined below, and the meeting agenda (Attachment 1) and attendee lists (Attachment 2) are attached.

The highlights for the initial meeting (June 19-21, 1996) were distributed and were approved with minor changes. The final version of NAC Meeting 1 Highlight is attached as Appendix A.

Dr. Roger Garrett welcomed the committee members. Dr. Garrett indicated that in FY 1997 only four committee meetings would be scheduled, thereby allowing adequate time for preparation of the draft AEGL documents and for members to review the draft documents. He emphasized that sound science was the objective and that it would not be compromised for the sake of the schedule. Also he hoped that committee members would not have to be the chemical manager for more than two chemicals. He was pleased that the committee had reached consensus on the proposed fluorine AEGL values from last meeting and considered this a good start.

Following Dr. Garrett's remarks, Dr. Richard Thomas led a discussion on the wording of the AEGL definitions, and some changes were made (see Attachment 3 for revised definitions).

The next order of business was three topical presentations on the use of intraspecies (Mr. Robert Ross, Drs. Jonathan Borak and George Alexeeff, Attachments 4,5,6) and interspecies (Dr. Robert Young, Attachment 7) uncertainty factors (UF). The purpose of these short presentations was to emphasize that the choice of a numerical value for each UF was a chemical-specific decision and that defaults of 10 were not always necessary.

Dr. Borak presented information on sulfur dioxide that suggests that the sensitivity among humans may vary only by a factor of 3 or 4.

Following these presentations, chemical-specific discussions began. The highlights of each discussion are presented below followed by a section on comments and suggestions for improving the AEGL process.

Ammonia, CAS No. 7664-41-7

Chemical manager: Mr. Larry Gephart, Exxon Biomedical Sciences
Author: Dr. Kowetha A. Davidson, ORNL

At NAC Meeting 1, AEGL-1 values were approved but the AEGL-2 &3 values were deferred to meeting 2. Mr. Larry Gephart led the discussion(Attachment 8) and later was expanded by Dr. George Alexeeff (Attachment 9). Two individuals representing industry groups, Dr. Robert Michaels and Mr. Ken Anderson, and Mr. Fred Millar, representing Friends of the Earth, gave presentations/statements. Dr. Michaels (Attachment 10) and Mr. Anderson were concerned that the AEGL values were too low and indicated that additional information was available that would assist the committee. Mr. Millar stated that he thought that a number of industry reports regarding ammonia exposures in the workplace were available. The committee agreed to defer Ammonia to the next meeting to consider additional information that was to be provided by Mr. Ken Anderson by August 26, l996.

Cyanogen Chloride, CAS No. 506-77-4

Chemical manager: Dr. Mark McClanahan, CDC
Author: Dr. Carol Forsyth, ORNL

As summarized by Dr. Forsyth's presentation (Attachment 11), there was a paucity of data on this compound. The information available for analysis was quite out-dated and had been cited from secondary sources. An effort will be made to determine if primary literature does exist, but from the citation trail available, it is doubtful that much will be found. The compound was deferred to the next meeting. The possibility of laboratory tests to fill data gaps was mentioned, but no decision was made.

Methyl Mercaptan, CAS No. 74-93-1

Chemical manager: Dr. Doan Hansen, BNL
Author: Dr. James C. Norris, ORNL

This chemical was introduced by Dr. Doan Hansen (Attachment 12) and revisited because the availability of industrial data that had not been acquired prior to Meeting 1. This information contained data potentially useful for AEGL 1 and 2. The author of the study sent Dr. Norris what he considered relevant portions of the methyl mercaptan toxicology report. After presentation by Dr. Norris (Attachment 13) and some discussion by committee members it was decided that indeed the information looked promising regarding establishing AEGL-1 and AEGL-2 values, but the entire report would be needed to thoroughly consider the situation. Thus, a decision on these values was deferred until the next meeting. Regarding the AEGL-3 values the committee reached a consensus 31, 23, 13, and 10 ppm as the proposed values for 30 min., 1 h, 4 h, and 8 h, respectively (Ballot attached: Appendix B). These values were based on the Tansy et al. (1981) study, which identified a highest nonlethal value of 400 ppm to which an uncertainty factor of 30 (10 for intraspecies and 3 for interspecies) was applied. A factor of 3 instead of 10 was used for interspecies extrapolation

because of the steep dose-response curve. For scaling using the ten Berge equation, *n* was equal to 2.5, which was the value assigned to the structurally related hydrogen sulfide.

Hydrogen Fluoride, CAS No. 7664-39-3

Chemical manager: Mr. Larry Gephart, Exxon Biomedical Sciences
Author: Dr. Sylvia Talmage, ORNL

Mr. Larry Gephart presented a summary of the draft technical support document as shown in Attachment 14. Additional unpublished animal data from studies conducted by the Petroleum Environmental Research Forum (PERF) were presented by Dr. Walden Dalbey of the Mobil Business Resources Corporation (Attachment 15). The PERF studies were conducted with mouth-breathing rats (a potentially more realistic model for the human breathing pattern during exposure to irritant chemicals than nose-breathing rats).

The AEGL-1 values presented in the technical support document were discussed and accepted by the AEGL NAC on August 6, 1996, with the following revisions: the numbers should be rounded to the nearest whole integer and the curve should be flattened. The NAC noted that these are approximate values that reflect the imprecision of the data.

In addition to the AEGL-2 values proposed in the technical support document, additional values from the rat data of the PERF report as they pertain to the AEGL-2 definition were discussed. These values for 10-min. exposures were: 1764 ppm, serious effects; 950 ppm, no serious effects; and 271 ppm, slight local irritation. The 30-min. and 1-h AEGL-2 values were derived from the 10-min. 950 ppm value for no serious effects. This value was divided by an uncertainty factor of 30 (for interspecies and intraspecies differences) and scaled to the different time periods using $C^2 \times t = k$. The 4- and 8-h AEGL-2 values were based on the human exposure study as discussed in the original draft technical support document.

The proposed AEGL-3 values as derived in the technical support document were accepted by NAC (Ballot attached: Appendix C). The following is a summary of proposed values.

Additional discussion focused on the merit of a single 10-min. AEGL value since a 10-min. exposure is characteristic of actual accident emergency situations.

SUMMARY TABLE OF PROPOSED AEGL VALUES FOR HYDROGEN FLUORIDE

Classification	30-min.	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1	2 ppm, 1.6 mg/m^3	2 ppm, 1.6 mg/m^3	1 ppm, 0.8 mg/m^3	1 ppm, 0.8 mg/m^3	Slight eye and nose irritation in humans (Largent 1960, 1961)
AEGL-2	18 ppm, 15 mg/m^3	13 ppm, 11 mg/m^3	10 ppm, 8 mg/m^3	7 ppm, 6 mg/m^3	NOAEL for serious lung effects in rats (PERF 1996)[a]; highest concentration for slight eye and nose irritation and red dening of facial skin in humans (Largent 1960, 1961)[b]
AEGL-3	62 ppm, 51 mg/m^3	44 ppm, 36 mg/m^3	22 ppm, 18 mg/m^3	15 ppm, 13 mg/m^3	Threshold for lethality in mice (Wohlslagel et al. 1976)

[a]30-min. and 1-h AEGL-2 values.
[b]4-h and 8-h AEGL-2 values.

Hydrazine, CAS No. 302-01-2

Chemical manager: Dr. Richard Thomas, I.C.E.H.
Author: Dr. Robert A. Young, ORNL

At Meeting 1, Dr. Thomas indicated that some epidemiological studies needed to be evaluated, and this was done with the result that no additional useful information was found (Attachment 16). Also, a cancer assessment was conducted since the last meeting and showed that the cancer risk would be inconsequential relative to noncancer effects of hydrazine acute exposure. The proposed AEGL values in the following table were presented by Dr. Robert Young, ORNL (Attachment 17) and were accepted by the committee. There were two "no" votes for AEGL-1, one " no"ote for AEGL-2, and none for AEGL-3 (Ballot attached: Appendix D). The AEGL-1 values for the four time periods are the same because the effect of concern was irritancy that is time independent.

SUMMARY TABLE OF PROPOSED AEGL VALUES FOR HYDRAZINE					
Classification	**30 - Min.**	**1-h**	**4-h**	**8-h**	**Endpoint/Reference**
AEGL-1	0.1 ppm, 0.13mg/m^3	0.1 ppm, 0.13mg/m^3	0.1 ppm, 0.13mg/m^3	0.1 ppm, 0.13mg/m^3	Eye and facial irritation in monkeys (House, 1964)
AEGL-2	8 ppm, 10mg/m^3	6 ppm, 8mg/m^3	3 ppm, 4mg/m^3	2 ppm, 3mg/m^3	Nasal lesions in rats (Latendresse et al., 1995)
AEGL-3	47 ppm, 61mg/m^3	33 ppm, 43mg/m^3	17 ppm, 22mg/m^3	12 ppm, 16mg/m^3	Lethality in rats (HRC, 1993)

Comments and Suggestions for Improvements to AEGL Process

The following are comments from the committee members regarding the AEGL process. The order of presentation does not imply a ranking of importance.

1. Preparation of IRIS-like summaries of key studies in table format that contains values, uncertainty factors, and confidence assessment would be helpful.

2. A list of what signs and symptoms constitute the respective AEGL values is needed.

3. In addition to the chemical manager, two committee members should be assigned to each chemical.

4. The rationale for chemical selection needs to be provided.

5. Odor threshold should be considered for establishing AEGL-1 values.

6. Material requiring evaluation should be sent to committee members prior to the meeting and not be distributed at meetings.

7. Each AEGL document should provide the calculations, perhaps in an appendix.

8. Participation by the Office of Research and Development of EPA is needed to ensure overall EPA concurrence.

9. Standardization of decision criteria is needed.

10. Guidelines are needed to determine when and when not to use the Benchmark Dose approach.

11. Committee members' comments to the chemical manager are needed at least two weeks prior to each meeting.

12. Validation of analytical methods is needed.

13. The reason for a "no" vote on a chemical needs to be recorded.

14. Upcoming chemicals should be "advertised" in the *Federal Register* to ensure that all data are obtained and appropriate interest groups are notified.

15. Biology should be more important than models.

This meeting highlight was prepared by Mr. Robert Young and Dr. Po-Yung Lu, ORNL.

LIST of ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.

Attachment 1. NAC/AEGL meeting No. 2 agenda
Attachment 2. Attendee list
Attachment 3. Revised definitions of AEGLs
Attachment 4. Interspecies uncertainty
Attachment 5. An update on sulfur dioxide
Attachment 6. Use of uncertainty and modifying factors for developing threshold-based AEGLs
Attachment 7. Adjustment of interspecies uncertainty factor
Attachment 8. Data analysis of Ammonia
Attachment 9. Benchmark dose level for Ammonia
Attachment 10. Public comment from RAM TRAC Corporation on ammonia
Attachment 11. Data analysis of Cyanogen chloride
Attachment 12. Summary of changes in draft AEGL TSD of Methylmercaptan
Attachment 13. Data analysis of Methylmercaptan
Attachment 14. Data analysis of Hydrogen fluoride
Attachment 15. Summary of PERF project 92-09
Attachment 16. Discussion of issues identified at first NAC./AEGL meeting
Attachment 17. Data analysis of Hydrazine

LIST OF APPENDICES

Appendix A. Revised meeting highlights of NAC/AEGL-1

ATTACHMENT 1

AEGL National Advisory Committee
Aug 5-7, 1996
DRAFT AGENDA

Aug 5

10:00	Introduction (Roger Garrett)
10:15-11:15	Technical Discussion - AEGL Definition (R. Thomas) - Irritants/Sensitive Humans (J. Borak) - Intraspecies Uncertainty Factors - Interspecies Uncertainty Factors
11:15-11:30	Break
11:30-12:00	Ammonia AEGL-3
12:00-1:15	Lunch
1:15-2:45	Ammonia contd. and Cyanogen chloride
2:45-3:00	Break
3:00-5:00	Cyanogen chloride contd. and Methyl mercaptan

Aug 6

9:00-11:00	Methyl mercaptan if necessary and Hydrogen fluoride
11:00-11:15	Break
11:15-12:00	Hydrogen fluoride contd.
12:00-1:15	Lunch
1:15-3:00	Hydrazine
3:00-3:15	Break
3:14-4:00	Hydrazine contd.
4:00-5:00	1,2-Dichloroethylene

Aug 7

9:00-10:00	1,2-Dichloroethylene contd.
10:00-10:10	Break
10:00-12:00	Hydrogen cyanide
12:00-12:15	Conclusion

ATTACHMENT 2

Monday, August 5, 1996

Sign in	Committee
Thomas Tiscornia	DOE
Lynn M Bayles	EPA
[illegible]	[illegible]
George M Rusche	Allied Signal
B.H Brown	ASTHO
[illegible]	OSU
[illegible]	CDC
[illegible]	ATSDR
Sylvia Talmage	ORNL
[illegible]	ORNL
Cheryl Bast	ORNL
[illegible]	ORNL
Kenneth Davidson	ORNL
Greg Colonna	NFPA
Dave Belluck	MDCA
Dean Hansen	BNL/DOE
James [illegible]	ORNL
Robert Michaels	RAM TMC Corp, Schenectady, NY
George Aburoff	Cal/EPA
Thomas J [illegible]	FDA/CFSAN/AFGL
Richard Thomas	TCEH
[illegible]	AAPCC
Fred Wyllys	NWCC
Po-Tung Lin	ORNL
Larry Gephart	Exxon Biomedical
Jonathan Bank	ACOEM

Private Sector

NANCY NICKELL REPORTER PESTICIDE & TOXIC CHEMICAL NEWS		phone 202 986-3812 fax 202 986-7217 nnickel@quaside.mindspring.com	*
JIM SKILLEN	TFI	(202) 608-5910	
CHRIS LEASON	McKENNA & CUNEO (COUNSEL TO TFI)	(202) 496-7102	
Robert A. Venezia	Chem. Manuf. Assoc./Hydrazine	703/741-5639	
Kathlee Bailor	IIAR	202 857-1110	
Sara Thurin Rollins (press)	BNA - Chemical Reg. Reporter	202 452 4584	*
BARRY HOOBERMAN	ENVIRON	703 516-2332	
KENT ANDERSON	IIAR	202 857-1110	
~~Robert~~			
Larry D. Dastin	DuPont	609/540-4576	
Susan Snider	AF&PA	202-463-2589	

* Members of the Press.

TUESDAY August 6, 1996

George M. Rusch

Richard Thomas

Luis Hernandez

[illegible]

Bill [illegible]

Ernena Post

NANCY NICKELL PESTICIDE & TOXIC CHEMICAL NEWS phone 202 986-3812 fax 986-7217 nnickel@quaside.mindspring.com

Sylvia Talmage	ORNL
Cheryl Bast	ORNL
Tagu Aluff	Cal/EPA
Joan Hansen	BNL/DOE
Tom Sobotka	FDA
Larry Gephart	Exxon Biomed
Jim Holler	

Revised wording for AEGLs

(7/23/96)

AEGL-3 is the airborne concentration (expressed as ppm or mg/cu m) of a substance below which it is predicted that the general population, including susceptible but excluding hypersusceptible individuals, could be exposed without experiencing life-threatening effects or death. (Airborne concentrations at or above AEGL-3 represent exposure levels that may cause life-threatening effects or death in the general population.)

AEGL-2 is the airborne concentration (expressed as ppm or mg/cu m) of a substance below which it is predicted that the general population, including susceptible but excluding hypersusceptible individuals, could be exposed without experiencing irreversible or other serious health effects or impairing their ability to escape. (Airborne concentrations at or above AEGL-2 but below AEGL-3 represent exposure levels that may cause irreversible or other serious, long-lasting effects or impair the ability to escape in the general population.)

AEGL-1 is the airborne concentration (expressed as ppm or mg/cu m) of a substance below which it is predicted that the general population, including susceptible but excluding hypersusceptible individuals, could be exposed without experiencing other than mild odor, taste, or other sensory irritations. (Airborne concentrations at or above AEGL-1 but below AEGL-2 represent exposure levels that may produce notable discomfort in the general population.)

Revised wording for AEGLs*

(9/5/96)

AEGL-3 is the airborne concentration (expressed as ppm or mg/cu m) of a substance at or above which it is predicted that the general population, including susceptible but excluding hypersusceptible individuals, could experience life-threatening effects or death. Airborne concentrations below AEGL-3 but above AEGL-2 represent exposure levels that may cause irreversible or other serious, long-lasting effects or impaired ability to escape.

AEGL-2 is the airborne concentration (expressed as ppm or mg/cu m) of a substance at or above which it is predicted that the general population, including susceptible but excluding hypersusceptible individuals, could experience irreversible or other serious, long-lasting effects or impaired ability to escape. Airborne concentrations below AEGL-2 but above AEGL-1 represent exposure levels that may cause notable discomfort.

AEGL-1 is the airborne concentration (expressed as ppm or mg/cu m) of a substance at or above which, it is predicted that the general population, including susceptible but excluding hypersusceptible individuals, could experience notable discomfort. Airborne concentrations below AEGL-1 represent exposure levels that could produce mild odor, taste, or other sensory irritations.

* In reality, the NAC has insisted on a no-effect level for setting AEGLs, whereas the definition calls for a threshold level at which serious effects begin.

ATTACHMENT 4

INTRASPECIES UNCERTAINTY

- The origin of this concept is credited to Lehman and Fitzhugh (1954) who proposed a factor of 10 in early days of regulation of food additives

- The following organizations routinely use a factor of 10

  - U.S. Environmental Protection Agency
  - U.S. Food and Drug Administration
  - Joint Food and Agricultural Organization and World Health Organization Expert Committee on Food Additives
  - United Kingdom Committee on Toxicology

- No real evidence that documents the validity of this value

INTRASPECIES UNCERTAINTY (Continued)

- Some evaluations have suggested values less than 10
  - Renwick (1993) suggests that a factor of 3 or 4 might be more appropriate when pharmacokinetic and pharmacodynamic data are considered
  - Analyzing 490 LD_{50} studies, Weil (1972) showed that a factor of 10 would protect 92% of the animals, a factor of 6, 85% and a factor of 3, 67%
- European Center of Ecotoxicology and Toxicology of Chemicals (Tech. Rep. No. 68, 1995) reviewed previous efforts to define the intraspecies factor and decided to recommend a factor of 3

AN UPDATE on SULFUR DIOXIDE

Jonathan Borak, MD

Prepared for NAC/AEGL
July 27, 1996

Mechanisms of Injury

The pathological effects of sulfur dioxide are dependent upon the availability of cellular and mucosal surface water with which it reacts. Immediate hydrolysis yields sulfurous acid (H_2SO_3) which dissociates to bisulfite (HSO_3^-) and sulfite ($SO_3^=$) ions. The resulting relative proportions of sulfur dioxide, sulfurous acid, bisulfite and sulfite are determined by factors such as pH, temperature and ionic strength (1-4). The concentration of bisulfite ions exceeds that of sulfite at physiological pH and increases as pH declines (5).

Sulfite and bisulfite ions are highly reactive. They attack nucleophilic groups of proteins, DNA and other macromolecules, resulting in nucleophilic substitution and generation of sulfur-containing free radicals (6,7). This process leads to protein denaturation, cellular damage, and clinical inflammation.

Sulfite-mediated inflammation of the nasal and upper respiratory mucosa and resulting increased parasympathetic reflex activity are important initiators of sulfur dioxide-induced bronchoconstriction (1,8,9). Preliminary evidence indicates that bisulfite ions are more potent than sulfite ions (4,10). Prior exposure to inhaled sulfur dioxide enhances airway sensitivity generally to inhaled irritants (11).

It is uncertain to what extent tissue acidification determines toxicity. In exposed animals, severity of bronchospasm was related to lung pH, not sulfite dose (6,12). But this may be due to an increasing proportion and quantity of bisulfite as pH falls, rather than tissue acidification. At sulfur dioxide levels just sufficient to induce bronchospasm in asthmatics (0.6-1.0 ppm), the quantity of hydrogen ions produced during inhalation is substantially less than that required to induce bronchospasm when asthmatics are exposed to acetic acid and other acid mists (4,10).

Clinical Effects

The acute human responses to inhalation of various concentrations of sulfur dioxide in air are presented below in Table I:

TABLE I: HUMAN RESPONSE to SULFUR DIOXIDE INHALATION*

Concentration		Response
400	ppm	Rapid onset of laryngeal and pulmonary edema
150	ppm	Immediate, intolerable irritation
10	ppm	Cough, eye irritation within minutes
<5	ppm	Bronchoconstriction within 15 minutes
<3	ppm	Odor threshold
<1	ppm	Bronchoconstriction in asthmatics

* (13-17)

The most serious effects of sulfur dioxide exposure follow inhalation. Very high concentration exposure (>100-200 ppm) can rapidly cause laryngeal edema, asphyxiation and death. Pulmonary edema can occur several hours after inhalation and be fatal (18,19).

Because of its great water solubility, very little inhaled sulfur dioxide reaches the lungs, particularly in those who nose breathe. Up to 99% of an inhaled dose is scrubbed by the mucosa during nasal breathing (1,20-22). In those who mouth breathe, such as during hyperventilation or strenuous exertion, large amounts of sulfur dioxide can reach the lungs. Toxicity is also enhanced by simultaneous presence of particulates or aerosols (3,23).

In such settings, sulfur dioxide is a potent bronchoconstrictor (1,21). Pretreatment with atropine or sympathomimetics can diminish or prevent sulfur dioxide-induced bronchospasm. A possible role for mast cells degranulation is suggested by the finding that cromolyn can also block onset of bronchospasm following sulfur dioxide exposure (1,8,24).

There is marked individual variability in the severity of reaction to inhalation of low concentrations of sulfur dioxide. Asthmatics, individuals with hyper-reactive airways, smokers and those with chronic respiratory or cardiac disease react to relatively lower concentrations (2,18). Susceptibility may also be increased in people aged >60 years, but reports have not been consistent (25,26).

Asthmatics are particularly sensitive to sulfur dioxide. Declines of >20% in FEV_1 have been documented after inhalation of 0.4-1 ppm for 2-15 minutes (1,16,27-29). The effects of sulfur dioxide exposure are enhanced in normal and asthmatic individuals by moderate exertion (ventilation >40 l/min with mouth breathing), hyperventilation, and use of oral airways (3,30-34). Duration of bronchospasm is generally limited and patients may develop tolerance with prolonged or repeated exposure.

Exposure for 2 hours to low concentrations of sulfur dioxide (0.75 ppm) led to abnormal morphology of nasal mucosal cilia (35). Exposure for several hours to moderate levels (3-5 ppm) caused abnormal bronchial mucus clearance (36-38). Higher doses (500 ppm for 3 hours) caused loss of cilia and altered morphology of bronchial epithelial cells (39). It is has not been determined whether such effects predispose to pulmonary infections.

Chronic pulmonary disease can result from even brief, accidental exposure to high sulfur dioxide concentrations. After lethal exposure in humans, autopsy findings included extensive tracheobronchitis, dense bronchiolar inflammation, hyperplasia of bronchial glands, fibrosis of terminal bronchioles and bronchiolitis obliterans (19,40,41).

Among survivors of accidental high dose exposure, reported chronic pulmonary diseases include chronic bronchitis, bronchial stenosis, bronchiectasis, bronchiolitis obliterans and pulmonary fibrosis (19,40,42-45). Pulmonary function abnormalities were partially reversible over time. Isolated, acute sulfur dioxide exposure has also been reported as a cause of reactive airway dysfunction syndrome (RADS) with chronic airway hyperreactivity, cough, dyspnea and wheeze after inhalation of non-specific pulmonary irritants (44,46-48).

References

1. Gunnison AF, Jacobsen DW: Sulfite hypersensitivity. a critical review. CRC Crit Rev Toxicol 17:185-214, 1987.

2. Simon RA: Sulfite sensitivity. Ann Allergy 56:281-288, 1986.

3. Frank R: SO2-particulate interactions: recent observations. Am J Ind Med 1:427-434, 1980.

4. Lipsett M. Oxides of Nitrogen and Sulfur. In: Hazardous Materials Toxicology, Sullivan JB, Krieger GR (ed). Baltimore: Williams & Wilkins, p.964-972, 1992.

5. Archer VE, Gillam JD: Chronic sulfur dioxide exposure in a smelter. II. Indices of chest disease. J Occup Med 20:88-95, 1978.

6. Gunnison AF, Sellakumar A, Currie D, et al: Distribution, metabolism and toxicity of inhaled sulfur dioxide and endogenously generated sulfite in the respiratory tract of normal and sulfite oxidase-deficient rats. J Toxicol Environ Health 21:141-162, 1987.

7. Neta P, Huie RE: Free-radical chemistry of sulfite. Environ Health Perspect 64:209-217, 1985.

8. Koenig JQ, Marshall SG, Horike M, et al: The effects of albuterol on sulfur dioxide-induced bronchoconstriction in allergic adolescents. J Allergy Clin Immunol 79:54-58, 1987.

9. Nadel JA, Salem H, Tamplin B, et al: Mechanism of bronchoconstriction during inhalation of sulfur dioxide. J Appl Physiol 20:164-167, 1965.

10. Fine JM, Gordon T, Sheppard D: The roles of pH and ionic species in sulfur dioxide- and sulfite-induced bronchoconstriction. Am Rev Respir Dis 136:1122-1126, 1987.

11. Misawa M, Nakano E: Airway constriction by xanthine/xanthine oxidase in guinea pigs in vivo. J Toxicol Environ Health 39:193-205, 1993.

12. Utell MJ: Effects of inhaled acid aerosols on lung mechanics: an analysis of human exposure studies. Environ Health Perspect 63:39-44, 1985.

13. Henderson Y, Haggard HW: Noxious Gases and the Principles of Respiration Influencing their Action. New York: The Chemical Catalog Company, Inc., 1927.

14. Raffle PAB, Lee WR, McCallum RI, et al: Hunter's Diseases of Occupations. London: Hodder and Stoughton, 1987.

15. Waldron HA: Lecture Notes on Occupational Medicine. Oxford: Blackwell Scientific Publishing, 1979.

16. Koenig JQ, Pierson WE, Frank R: Acute effects inhaled SO_2 plus NaCl droplet aerosol on pulmonary function in asthmatic adolescents. Environ Res 22:145-153, 1980.

17. Beliles RP, Beliles EM. Phosphorus, Selenium, Tellurium, and Sulfur. In: Patty's Industrial Hygiene and Toxicology (II/A), Clayton GD, Clayton FE (ed). New York: John Wiley & Sons, p.783-829, 1993.

18. Aleksieva Z. Sulphur compounds. In: Encyclopedia of Occupational Health and Safety, Parmeggiani L (ed). Geneva: International Labour Office, p.2122-2124, 1983.

19. Charan NB, Myers CG, Lakshminarayan S, et al: Pulmonary injuries associated with acute sulfur dioxide inhalation. Am Rev Respir Dis 119:555-560, 1979.

20. Wolff RK: Effects of airborne pollutants on mucociliary clearance. Environ Health Perspect 66:223-237, 1986.

21. Frank NR: Studies on the effects of acute exposure to sulphur dioxide in human subjects. Proc R Soc Med 57:1029-1033, 1964.

22. Speizer FE, Frank NR: The uptake and release of SO2 by the human nose. Arch Environ Health 12:725-728, 1966.

23. Koenig JQ, Pierson WE, Horike M, et al: Bronchoconstrictor responses to sulfur dioxide or sulfur dioxide plus sodium chloride droplets in allergic, nonasthmatic adolescents. J Allergy Clin Immunol 69:339-344, 1982.

24. Myers DJ, Bigby BG, Calvayrac P, et al: Interaction of cromolyn and a muscarinic antagonist in inhibiting bronchial reactivity to sulfur dioxide and to eucapnic hyperpnea alone. Am Rev Respir Dis 133:1154-1158, 1986.

25. Rondinelli RCA, Koenig JA, Marshall SG: The effects of sulfur dioxide on pulmonary function in healthy nonsmoking male subjects aged 55 years and older. Am Ind Hyg Assoc J 48:299-303, 1987.

26. Koenig JQ, Dumler K, Williams PV, et al: Respiratory effects of inhaled sulfuric acid on senior asthmatics and nonasthmatics. Arch Environ Health 48:171-175, 1993.

27. Utell MJ, Frampton MW. Sulfur Dioxide and Sulfuric Acid Aerosols. In: Environmental and Occupational Medicine, Rom WN (ed). Boston: Little, Brown, p.519-527, 1992.

28. Schachter EN, Witek TJ, Beck GJ, et al: Airway effects of low concentrations of sulfur dioxide: Dose-response Characteristics. Arch Environ Health 39:34-42, 1984.

29. Horstman DH, Seal E, Folinsbee LJ, et al: The relationship between exposure duration and sulfur dioxide-induced bronchoconstriction in asthmatic subjects. Am Ind Hyg Assoc J 49:38-47, 1988.

30. Koenig JQ, Pierson WE, Horike M, et al: Effects of SO_2 plus NaCl aerosol combined with moderate exercise on pulmonary function in asthmatic adolescents. Environ Res 25:340-348, 1981.

31. Koenig JQ, Pierson WE, Horike M, et al: Effects of inhaled sulfur dioxide (SO_2) on pulmonary function in healthy adolescents: Exposure to SO_2 alone or SO_2 + sodium chloride droplet aerosol during rest and exercise. Arch Environ Health 37:5-9, 1982.

32. Balmes JR, Fine JM, Sheppard D: Symptomatic bronchoconstriction after short-term inhalation of sulfur dioxide. Am Rev Respir Dis 136:1117-1121, 1987.

33. Linn WS, Avol EL, Peng RC, et al: Replicated dose-response study of sulfur dioxide effects in normal, atopic, and asthmatic volunteers. Am Rev Respir Dis 136:1127-1134, 1987.

34. Roger LJ, Kehrl HR, Hazucha M, et al: Bronchoconstriction in asthmatics exposed to sulfur dioxide during repeated exercise. J Appl Physiol 59:784-791, 1985.

35. Carson JL, Collier AM, Hu S, et al: The appearance of compound cilia in the nasal mucosa of normal human subjects following acute, in vivo exposure to sulfur dioxide. Environ Res 42:155-165, 1987.

36. Wolff RK, Dolovich M, Eng P, et al: Sulfur dioxide and tracheobronchial clearance in man. Arch Environ Health 30:521-527, 1975.

37. Babior BM: Oxygen-dependent microbial killing by phagocytes (second of two parts). N Engl J Med 298:721-725, 1978.

38. Newhouse MT, Dolovich M, Obminski G, et al: Effect of TLV levels of SO_2 and H_2SO_4 on bronchial clearance in exercising man. Arch Environ Health 33:24-32, 1978.

39. Leigh MW, Carson JL, Gambling TM, et al: Loss of cilia and altered phenotypic expression of ciliated cells after acute sulfur dioxide exposure. Chest 101:168, 1992.

40. Murray WA: Bronchial stenosis and atelectasis from sulphur dioxide. Can Med Assoc J 54:599-600, 1946.

41. Galea M: Fatal sulfur dioxide inhalation. Can Med Assoc J 91:345-347, 1964.

42. Greenwald I: Effects of inhalation of low concentrations of sulfur dioxide upon man and other mammals. Arch Ind Hyg Occup Med 10:455-475, 1954.

43. Woodford DM, Coutu RE, Gaensler EA: Obstructive lung disease from acute sulfur dioxide exposure. Respiration 38:238-245, 1979.

44. Harkonen H, Nordman H, Korhonen O, et al: Long-term effects of exposure to sulfur dioxide. Am Rev Respir Dis 128:890-893, 1983.

45. Rabinovitch S, Greyson ND, Weiser W, et al: Clinical and laboratory features of acute sulfur dioxide inhalation poisoning: two-year follow-up. Am Rev Respir Dis 139:556-558, 1989.

46. Brooks SM, Weiss MAF, Bernstein IL: Reactive airway dysfunction syndrome (RADS): Persistent airways hyperreactivity after high level irritant exposure. Chest 88:376-384, 1985.

47. Boulet LP: Increases in airway responsiveness following acute exposure to respiratory irritants; reactive airway dysfunction syndrome or occupational asthma. Chest 94:476-481, 1988.

48. Alford PT, McLees BD, Case LD, et al: Reactive airways dysfunction syndrome (RADS) in workers post exposure to sulfur dioxide (SO2). Chest 94:87S, 1988.

ATTACHMENT 6

Preliminary Draft

Use of Uncertainty and Modifying Factors for Deriving Threshold-Based AEGLs
(Expanded from NRC 1993, p. 88-90.)

To identify a human population threshold, uncertainty factors (UFs) should be applied to NOAELs (NOELs, LOELs, LOAELs, FELs) or to benchmark doses, from the best available study(ies). The application of uncertainty factors reflects various specific recognized uncertainties in extrapolating from animal or human studies and professional judgment, based on the entire data base available on the specific agent. The general uncertainty factor approach is depicted in Figure 1, which exhibits human laboratory animal population distributions.

In the application of uncertainty factors, a factor must be incorporated that approximates the likely range of susceptibilities among humans. As shown in Figure 1, the range of variability from the average human to the susceptible human is approximated to be 10-fold. People at increased risk include those at either extreme of age, those with poor nutritional status, those with preexisting diseases, such as coronary heart diseases or asthma, that are fairly widespread in the general population, those with enhanced hereditary susceptibility, or those who are overexposed because of unusual physical exertion. These subpopulations can be conceptualized as shown in the example in Figure 2. Asthmatics, those with increased bronchial reactivity, can be represented either as the tail of the general population distribution or as a separate subpopulation, implying a bimodal response distribution. The AEGLs do not provide absolute assurance that everyone at risk will be protected under all circumstances, and thus the uncertainty factors should be chosen with the understanding that a few hypersusceptible persons might not be protected.

The AEGL can be derived from the NOAEL (or other effect level) as follows:

$$AEGL = NOAEL/(UF \times MF)$$

where UF is the product of uncertainty factors described below, and MF is the modifying factor.

Generally, a 10-fold UF will be applied when extrapolating from valid experimental results of studies involving appropriate exposures to average healthy humans or to experimental animals. That factor is intended to account for the variation in sensitivity among the human population. This variability is not a true uncertainty. Uncertainty specifically refers to information that is unknown. Human variability is a reflection of the diversity in response in a heterogeneous population. The variation in sensitivity could be due to differences in susceptibility, such as bronchial reactivity, or in exposure. An example of exposure variability is shown in Figures 3a and 3b. These figures describe the average breathing variability per day among children and adults. Variability for short-term exposures, such as one hour, would be greater. For certain airborne substances, such as sulfur dioxide, sulfuric acid or ozone, information may be directly available for the susceptibility of asthmatics. In other cases, it may be possible to identify the potentially sensitive population and focus collection of data. If data are available on a sensitive subpopulation such as asthmatics, the UF might be as low as 1. Reductions in the UF must be science-based and documented in the analysis.

An additional 10-fold UF generally is applied when extrapolation from the valid results of studies on experimental animals because results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to humans, and can be reduced to 3 if pharmacokinetic or human equivalent concentration (HEC) information has been incorporated into the analysis. This UF can also be reduced if information is available indicating, for the endpoint of concern, there is little variability among species and there is evidence indicating that humans would be likely to respond similarly to animals. The scientific basis for reducing this uncertainty factor should be documented and describe why the average human is unlikely to be 10-fold more sensitive than laboratory animals.

Intermediate factors (between 1 and 10) may be applied when the data are very strong and relevant animal-to-human extrapolation factors have been derived, when limited data are available for a sensitive human subpopulation, and when dosimetric adjustments have been made on the basis of species considerations. The derivation of the animal-to-human extrapolation factors should be explained and documented in the AEGL analysis. The intermediate factor is usually 3 - i.e., the geometric mean of 1 and 10, rounded to one significant figure.

An additional 10-fold UF may be introduced when deriving a level from a LOAEL or FEL instead of a NOAEL. That factor is intended to account for the uncertainty in extrapolating a NOAEL from a LOAEL.

Professional judgment must be used to determine another UF, the MF, which is more than 0 and less than 10. The magnitude of the MF depends on the professional assessment of the scientific uncertainties of the study and data base that are not explicitly treated by the UF (e.g., the completeness of the overall data base and the number of species tested). This factor may be less than 1, i.e., 0.3, when the data are better than average quality and allow for utilization of a benchmark dose or a categorical regression approach. The basis for this professional judgment used should be explicitly provided in the analysis.

In selecting UFs for deriving AEGLs, it is important to recognized that the intent is to avoid unnecessary conservatism that might result in exposure levels with little or no biological plausibility. An example of that would be the application of several levels of uncertainty to a concentration of an agent that produced irritation in an appropriate and in an adequate animal inhalation study. Although it is desirable to consider uncertainty around varying sensitivities and extrapolations, it is not practical to establish an inflexible system of UFs that simply become multiplicative in their application. Therefore, UFs must be determined case by case. Of course, the determinations would be associated closely with the quantity and quality of the data and the end points in question. In the case of the AEGL-2, uncertainty factors must be balanced against the risk associated with likely risk management actions that might be taken, such as shelter-in-place or evacuation. Large uncertainty factors, (i.e., 1000 to 3000) which might be appropriate

for chronic exposure guidance or in emergency planning applications might be associated with increased risk to the community in the application of the AEGL-2. For example, an overly conservative AEGL-2 may lead to evacuation or shelter-in-place at an exposure level that would not result in health consequences. Furthermore, such actions may cause undue panic and other adverse consequences.

To address these concerns, a case-by-case evaluation should be made of available scientific information to determine if there is a scientific basis for reducing the UFs. The following outline may assist in the analysis. (1) Identify the best available study(ies) to establish the AEGL (i.e., 1, 2, and 3). (2) Apply the standard UF procedure as described above, including application of intermediate factors, if appropriate. Check if dosimetric adjustments and the UFs have been properly applied and reflect the overall quality of the data set. (3) Assess the relationship between the three levels with the UFs applied. If a less severe level is higher than the more severe level, determine the source of the difference. In some cases, a more severe effect may occur at lower concentrations. For example, an AEGL-2 effect based on developmental toxicity (a more severe effect) may be lower than an AEGL-1 based on sensory irritation (a less severe effect). In such a case, the AEGL-1 would not be reported because irritation, while less severe, is not the most sensitive effect. (4) Using professional judgment and the information database available, determine which of the three levels has the least uncertainty in the estimate. Determine if the relationship between the levels reflects the available literature. (5) Identify any available chronic reference concentrations (RfCs) for comparison. Check the relationship of the AEGLs to any available chronic RfC adopted by U.S. EPA. An RfC should be consistent with the AEGLs; i.e., if any AEGL is below an RfC, then either the data considered by one of the standards were incomplete, or too large an uncertainty factor was incorporated into the AEGL. Comparisons to occupational standards are inappropriate since they are not designed to protect the general public, may be based on historical industrial practice instead of health-based information, and may be developed for different purposes.

Preference for a More Quantitative NOAEL

It has long been recognized, that there are two major problems with the use of NOAELs (or LOAELs, etc.) in deriving reference levels. First, NOAELs do not readily account for the number of animals used in the study. A second major problem with the use of NOAELs is that the slope of the dose-response curve for the critical toxic effect is generally ignored in the estimation of the reference level. Thus, in some cases, the use of some other procedure for quantitative risk assessment for noncancer endpoints might have greater validity and less uncertainty. The current UF method was designed as a threshold-based method using NOAELs and LOAELs. A procedure that reduces the total uncertainty of the evaluation would improve the NOAEL approach. Two such procedures are the benchmark dose and the categorical regression analysis methods.

The benchmark dose (BD) procedure has certain advantages over the NOAEL approach. The BD makes use of the sample size in the study. This is reflected in the magnitude of the confidence interval. The guidance value is derived from the lower confidence limit of the benchmark dose calculation. The BD exploits the shape (steepness) of the dose-response curve in the experimental range but does not depend strongly on the particular mathematical model used, because the model is not followed below the 1% response level. That is, at the 1% level, the BD calculation does not vary substantially when different extrapolation models are used. EPA's "Guidelines for Developmental Toxicity Risk Assessment" (EPA, 1991) recommend that a BD be calculated to supplement the NOAEL or LOAEL used in determine a reference dose for developmental toxicity. However, one unresolved issue with the BD procedure is the size of the UF that should be applied to any particular BD to account for variation in sensitivity among members of a population. The use of the lower confidence limit accounts for some variation in the population, especially if the study is based on human data. This problem will be addressed as more experience is gained with the BD procedure. Presently, it is suggested that when the BD procedure is used for developing AEGLs and the total UF product is greater than 3, a modifying factor of 0.3 should be used. This would reflect one's greater confidence in the data and would reduce overall uncertainty associated with the AEGL. The level 0.3 is chosen as an intermediate

factor between 0.1 and 1.0. This would be the geometric mean of 1 and 0.1 rounded to one significant digit. This appears to be a useful approach for acute inhalation exposures but may not be applicable to other situations.

The categorical regression analysis (CRA) approach also has advantages over the NOAEL approach. CRA uses results from multiple studies and calculates a statistical lower bound over time for a predefined severity level. In this approach, health effects are assigned to severity categories based on evaluation of the reported information and consideration of biological and statistical significance. The actual response rate per dose group is not used in the regression, it may be used to help classify the severity of the response. The logistic regression model is applied with the severity code as the dependent variable and the exposure concentration and duration as the independent variables. This approach allows for the incorporation of both quantal and qualitative data and it enables the simultaneous analysis of many studies. The result of the analysis produces a concentration-by-duration profile for any desired probability level either as a point estimate or a confidence limit. Since the approach incorporates time-to-response information, an empirical time extrapolation is calculated and an additional time extrapolation approach does not need to be included. If the human data available are insufficient to extrapolate over time, animal data can also be incorporated into the model to calculate the slope for extrapolation. The size of the UF that should be applied to any particulate CRA result is unclear at present. The use of the lower confidence limit accounts for some variation in the population, especially if the analysis is based on humans. Thus, it is presently suggested on a trail basis when the CRA procedure is used for developing AEGLs and the total UF is greater than 3, a modifying factor of 0.3 should be used. This would reflect one's greater confidence in the data and will reduce overall uncertainty associated with the AEGL. The level of 0.3 is chosen as an intermediate factor between 0.1 and 1.0. This would be the geometric mean of 1 and 0.1 rounded to one significant digit.

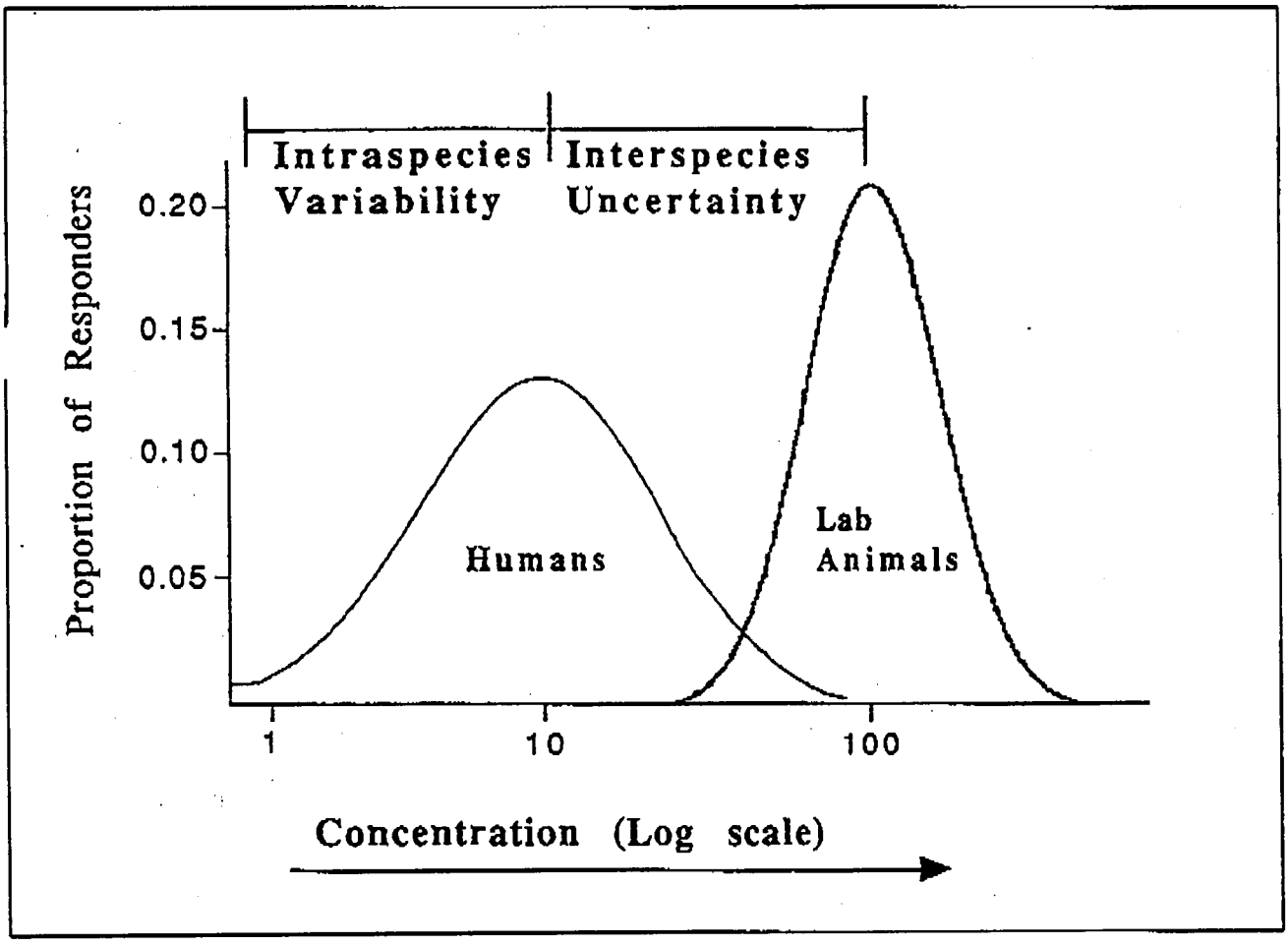


Figure 1. Hypothetical response of human and laboratory animal populations to a toxic agent. The uncertainty and variability are those generally assumed by the U.S. EPA and the NRC.

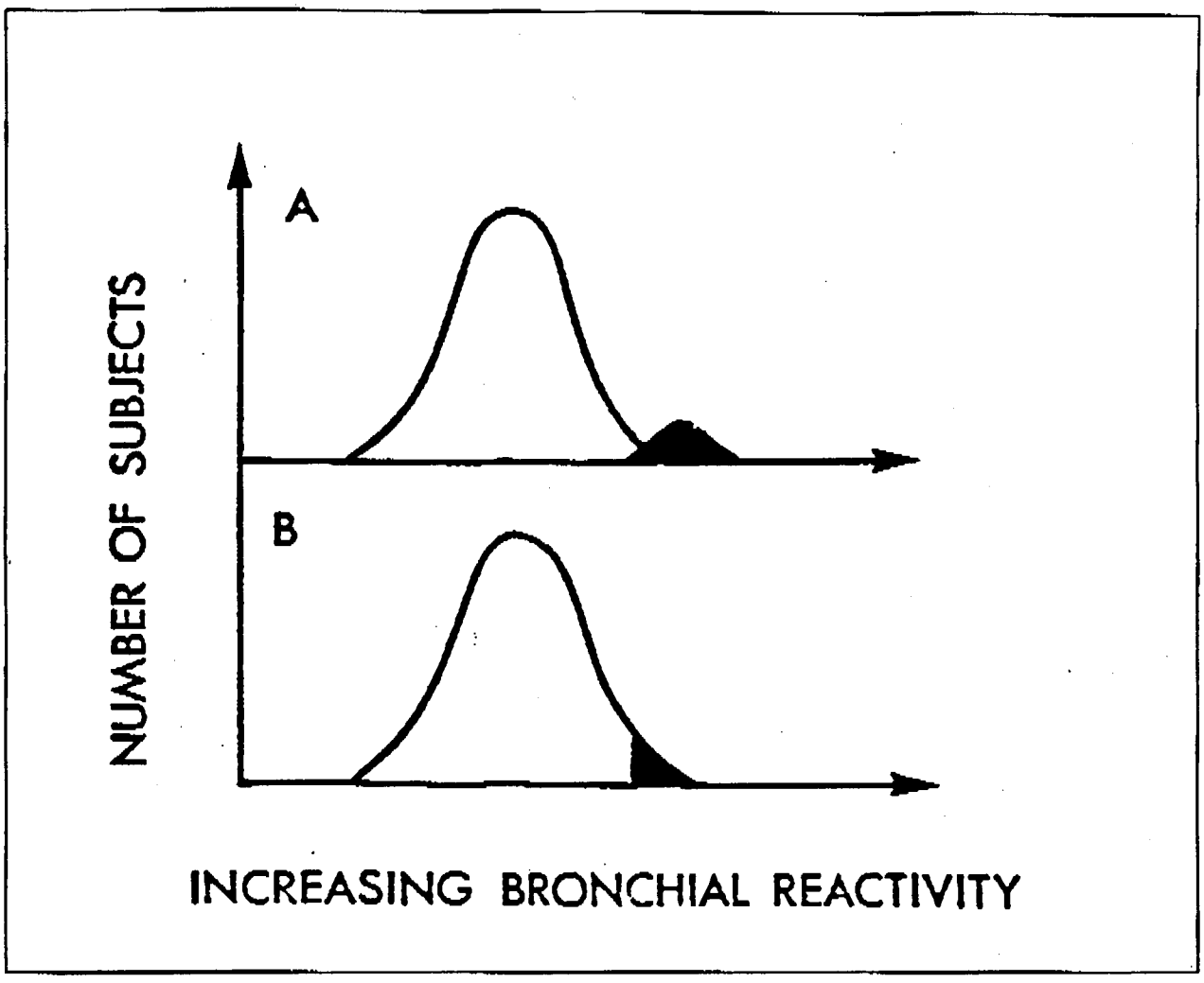


Figure 2. Hypothetical population distributions of nonspecific bronchial responsiveness (reproduced from Crockcroft et al., 1983, Chest 5:751-754). Graph A depicts a bimodal response distribution. Graph B depicts the presence of a sensitive subpopulation at the tail of the distribution.

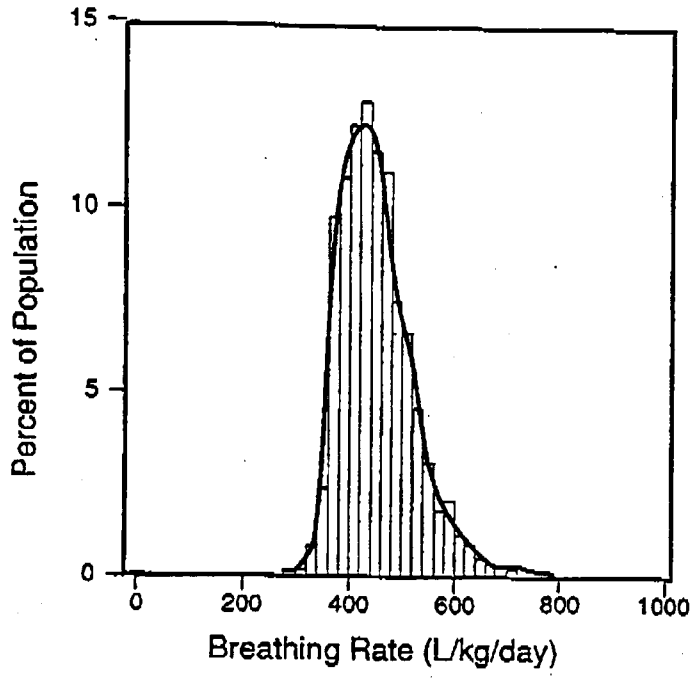


Figure 3a. Child daily breathing rates based on minute ventilation and activity patterns.

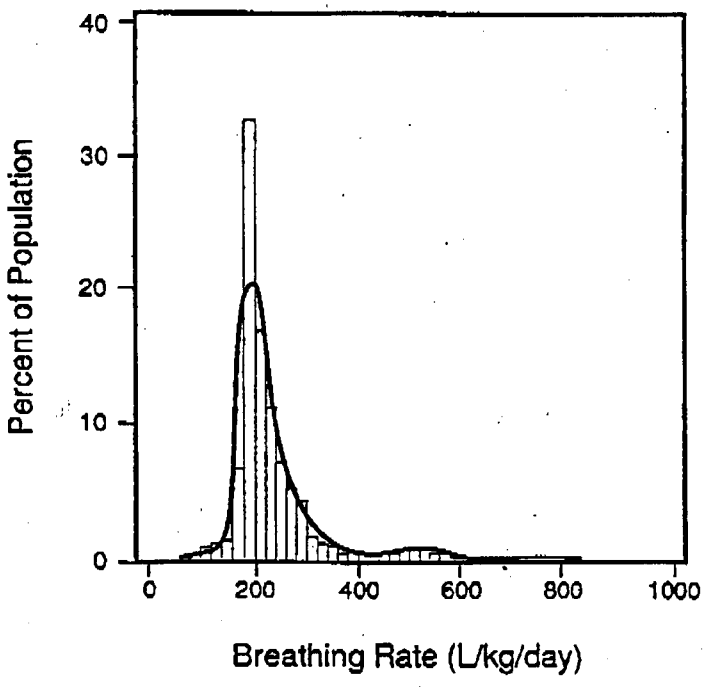


Figure 3b. Adult daily breathing rate based on minute ventilation and activity patterns.

ATTACHMENT 7

ADJUSTMENT OF INTERSPECIES UNCERTAINTY FACTOR

- DO NOT LIMIT EVALUATION TO "KEY STUDIES"

- EVALUATE ADDITIONAL DATA RELEVANT TO CHEMICAL AND SPECIES

- TWO COMPONENTS OF INTERSPECIES DIFFERENCES CAN BE ADDRESSED (RENWICK, 1993)
  - TOXICOKINETIC COMPONENT
  - TOXICODYNAMIC COMPONENT

ASSOCIATION OF FOOD AND DRUG OFFICIALS

re: food additives hazards

- "ANIMALS ARE, FOR THE MOST PART, MORE RESISTANT TO TOXIC CHEMICALS THAN MAN"

- HUMANS 10 TIMES MORE SENSITIVE THAN RATS; 4 TIMES MORE SENSITIVE THAN DOGS

- CONSIDERABLE VARIABILITY AMONG SPECIES; SUSCEPTIBILITY CHANGES FROM ONE SUBSTANCE TO ANOTHER
  MICE < RATS < DOGS

- "100-FOLD MARGIN OF SAFETY" IS A GOOD TARGET BUT NOT AN ABSOLUTE YARDSTICK AS A MEASURE OF SAFETY

ATTACHMENT 8

AMMONIA AEGLS

L. A. Gephart

AMMONIA AEGLS

- AEGL 1 AND 2
  - Tentative agreement on values at June, 96 meeting

	30 Minute	1 Hour	4 Hour	8 Hour
AEGL 1 (Reversible, Nondisabling)	25	25	25	25
AEGL 2 (Disabling, Irreversible	140	100	50	25

- AEGL 3
  - Use study in mice Kapeghian et al. as starting point
  - 30 minute and 1 hour AEGL values proposed
    - Discussion on using 1-hour data to set 4- and 8-hour values
    - Discussion on use of LC_{10} vs. lowest non lethal concentration vs. BD
    - Discussion on UFs
  - Propose alternative approaches for deriving AEGL 3 values at August meeting

RESULTS OF 1-HOUR
LC_{50} STUDY IN MICE BY KAPEGHIAN

Concentration (PPM)	Mortality	Percent	
4860	12/12	100	
4860	10/12	83.3	
4490	8/12	66.6	
4220	5/12	41.6	
3950	3/12	25.0	(Lowest lethal concentration)
3440	0/12	0	(Highest non lethal concentration)
2130	0/12	0	
1390	0/12	0	
1190	0/12	0	

LC_{50} 4230 ppm, 95% C.I. 4070-4400 ppm, (Litchfield & Wilcoxin method, 1949)

ALTERNATE APPROACH 1

- USE REGRESSION COEFFICIENTS* PUBLISHED BY TEN BERGE ET AL. (1986), WHICH ARE SPECIFIC FOR THE DATA IN MICE REPORTED BY KAPEGHIAN, TO DERIVE LC_{01} VALUES

- SCALE RESULTS FROM 1-HOUR TO 30 MINUTES, 4-HOURS, 8-HOURS USING THESE COEFFICIENTS

Exposure Time	LC_{01} Concentration (PPM)
30 Minutes	4104
1-Hour	2932
4-Hour	1484
8-Hour	1067

- APPLY INTER-SPECIES UNCERTAINTY FACTOR OF 1
  - Data from mice, the most sensitive species, used as starting point
  - Of data in mice, most sensitive study chosen
  - Data in cats are not relevant

ALTERNATE APPROACH 1 - (Continued)

- APPLY INTRA-SPECIES UNCERTAINTY FACTOR OF 3
  - Glottis closure results indicate 3x variation in sensitivity
  - No pharmacokinetic component to ammonia induced acute toxicity
  - Direct acting agent

- APPLY ADDITIONAL MODIFYING FACTOR OF 2 TO 4-HOUR AND 8-HOUR VALUES, SINCE WE EXTRAPOLATING BEYOND OUR EXPERIMENTAL RANGE FOR THESE TIME FRAMES

Exposure Time	Concentration (PPM)
30 Minutes	1368
1-Hour	977
4-Hour	247[a]
8-Hour	178[a]

[a] Includes 2x modifying factor

ALTERNATE APPROACH 2

- START WITH THE HIGHEST CONCENTRATION NOT PRODUCING LETHALITY (3440 PPM) AND SCALE TO OTHER TIME FRAMES

Exposure Time	Concentration (PPM)
30 Minutes	4865
1-Hour	3440
4-Hour	1720
8-Hour	1216

- APPLY INTER-SPECIES UF OF 1, INTRA-SPECIES UF OF 3, AND MODIFYING FACTOR OF 2 (FOR 4- AND 8-HOUR EXPOSURE DURATIONS)

Exposure Time	Concentration (PPM)
30 Minutes	1621
1-Hour	1146
4-Hour	287
8-Hour	203

ALTERNATE APPROACH 3

- USE TEN BERG REGRESSION COEFFICIENTS TO DERIVE LC_{01} VALUES, SCALE TO OTHER TIME FRAMES
- APPLY HUMAN EQUIVALENT CONCENTRATION FACTOR OF 2.5
  - Based on regional gas dose ratio, which is the ratio of minute volume / surface area of the pulmonary region for mice and humans
- APPLY INTER-SPECIES UF OF 1, INTRA-SPECIES UF OF 3, AND MODIFYING FACTOR OF 2 FOR 2- AND 8-HOUR VALUES

Exposure Time	Concentration (PPM)
30 Minutes	3420
1-Hour	2932
4-Hour	625
8-Hour	445

- IF INCLUDE INTER-SPECIES UF OF 3 INSTEAD OF 1

Exposure Time	Concentration (PPM)
30 Minutes	1140
1-Hour	977
4-Hour	208
8-Hour	148

Table 1. Animal Lethality Maximum Likelihood Estimate and Benchmark Dose Levels for Ammonia

Species	Time (min.)	MLE_{01} (ppm)	BD_{01} (ppm)	MLE_{05} (ppm)	BD_{05} (ppm)	MLE_{10} (ppm)	BD_{10} (ppm)	Reference
Mouse	60	3692	2965	4006	3406	4184	3659	1
Mouse	60	3435	3070	3664	3366	3792	3533	2
Mouse	10	6008	4504	6965	5624	7537	6328	3
Rat	60	5452	4184	5999	4908	6312	5337	1
Rat	60	7759	258[a]	9590	861[a]	10737	1632[a]	4
Rat	40	11524	3685	13637	5977	14915	7728	4
Rat	20	20568	14694	22545	17687	23675	19508	4
Rat	10	25685	20066	29027	24348	30983	26935	4

1 MacEwen & Vernot (1972)

2 Kapeghian et al. (1982)

3 Silver & McGrath (1948)

4 Appelman et al. (1982)

[a] The greater than 10-fold difference between the MLE and the BD suggests substantial uncertainty or variability in the data set for extrapolation to the BMD.

Table 3. Factors for Developing AEGL-3 Values for Ammonia Based on 1-Hour Exposure Mouse Lethality Data from Kapeghian et al. (1982).

Species	BD_{01}[a] (ppm)	BD_{05} (ppm)	BD_{10} (ppm)	HEC[b,c]	(MF)[d]	Interspecies[e] (UF)	Intraspecies[f] (UF)
Mouse	3070	3366	3533	2.5	0.3	3	10

[a] Calculated by log-probit and using the 95% lower confidence limit.

[b] NOAEL equivalents are multiplied by HEC values and divided by MF and UF values.

[c] HEC value calculated by .....

[d] MF of 0.3 used since data represent a high quality data set among a series of high quality studies for lethal assessment and allowed for BD analysis with a 95% lower confidence limit.

[e] Interspecies adjustment factor of 3 used since HEC adjustment utilized.

[f] Standard assumption to protect sensitive individuals. Elderly may be particularly sensitive due to glottis closure.

Table 4. Proposed AEGL Values for Ammonia[a] Based on Benchmark Doses (95% LCL) and Categorical Regression Analysis (95% LCL) at the 1%, 5%, and 10% MLE Levels

Approach	30 min			1 hour			4 hour			8 hour		
	1%	5%	10%	1%	5%	10%	1%	5%	10%	1%	5%	10%
BD	1206	1322	1388	853	935	981	426	468	491	302	331	347
CRA												

[a] Mouse lethality data from Kapeghian et al. (1982), for 1 hour exposure.

RAM TRAC Corporation

Robert A. Michaels, PhD, CEP, President
Toxicology & Risk Assessment Consulting

ATTACHMENT 10

Comments of Robert A. Michaels, PhD, CEP to the *National Advisory Committee on Acute Exposure Guideline Levels* on AEGL Values for Ammonia

5 August 1996

RAM TRAC Corporation

Project Director:

Robert A. Michaels, PhD, CEP
Board Certified Environmental Assessor
Chair, ABCEP Certification Review Board
Elected Life Member, NY Academy of Sciences
Admitted Member, American College of Toxicology
Admitted Member, Society of Toxicology

EXECUTIVE SUMMARY

These comments seek to assist NAC AEGL to appropriately define the AEGL-1, 2, and 3 parameters; and to derive their appropriate values for ammonia. A summary table (next page) compares values recommended by RAM TRAC, NAC AEGL, and its contractor, Oak Ridge National Laboratory (ORNL). ERPG *(Emergency Response Planning Guideline)* values are also tabulated. RAM TRAC recommends adopting higher AEGL-2 and AEGL-3 values and adding a five-minute value. The comments technically support the recommendations.

RAM TRAC AEGL-3 values are based upon reconstruction of the Potchefstroom, South Africa ammonia release accident of 1974, in which 18 people died and many more survived. Detailed air modeling has demonstrated a five-minute no-mortality concentration of 33,737 ppm. RAM TRAC's recommended AEGL-3 values are based upon application of an uncertainty factor of two to this benchmark. ORNL and NAC AEGL derived their recommendations based upon applying a safety factor of 20 to $LC_{0.1}$ (one-per-thousand mortality) values derived from a rat bioassay. However, the portion of the safety factor applied to protect sensitive subpopulations (probably 10) is redundant, and the values derived from this study probably should be tenfold higher. In that case, RAM TRAC's proposed values are the more stringent.

RAM TRAC AEGL-2 values are based upon application of a factor of 10 to derive an IDLH *(Immediately Dangerous to Life or Health)* value from an LC_{50} value for sensitive subpopulations. ORNL and NAC AEGL recommended AEGL-2 values were based upon the need to preserve people's ability to escape from a chemical release. A study of volunteers exposed to ammonia revealed 'intolerable' concentrations, forming the numerical basis for ORNL and NAC AEGL values. However, another study of volunteers revealed significantly higher toleration of ammonia, with neither incapacitation nor lasting effect. Further, the NIOSH IDLH parameter is defined as a concentration below which employee escape within 30 minutes will not be impaired. The NIOSH procedure for deriving the IDLH uses a preliminary value equal to one tenth the 30-minute LC_{50} value. RAM TRAC's value applies this procedure to ORNL's 30-minute LC_{50} value for sensitive subpopulations, reflecting the need to protect members of the general population rather than just 'healthy workers'.

AEGL values are related directly to the cost of emergency planning. The cost of emergency planning is roughly proportional to the emergency planning area, which varies as the square of the emergency planning radius, which in turn is proportional (roughly) to the AEGL value. Thus, proposing an unnecessarily stringent AEGL value translates to increasing the emergency planning zone radius linearly, while increasing the emergency planning area and cost exponentially. Consequently, the credibility of the *Community Emergency Planning Program* and of NAC AEGL itself depend upon the reasonableness of the AEGL values finally adopted.

Comparison of AEGL Recommendations*

AEGL	criterion	source	recommended values (ppm-v)**				
			5 min.	30 min.	1 hour	4 hours	8 hours
3	lethality	RAM TRAC	16,869	6,887	4,870	2,435	1,722
		ORNL	*4,164*	1,700	1,200	300	200
		NAC AEGL	*3,429*	1,400	990	250	200
		ERPG-3	*3,464*	*1,414*	1,000	*500*	*354*
2	irreversible injury	RAM TRAC	1,704	696	492	246	174
		ORNL	*490*	200	150	75	50
		NAC AEGL	*343*	140	100	50	35
		ERPG-2	*693*	*283*	200	*100*	*71*
1	discomfort	RAM TRAC	...	...	...	...	...
		ORNL	*122*	50	35	25	25
		NAC AEGL	*61*	25	25	25	25
		ERPG-1	*87*	*35*	25	*13*	*9*

*acronyms:
RAM TRAC. RAM TRAC Corporation, Schenectady, New York;
ORNL. Oak Ridge National Laboratory, Tennessee;
NAC AEGL. National Advisory Committee on Acute Exposure Guideline Levels;
ERPG-1, 2, 3. Emergency Response Planning Guidelines of the American Industrial Hygiene Association (AIHA).

**Italicized values were calculated based upon the Ten Berge equation: C^n x T = K, where C is concentration, T is time, K is a constant, and n is a constant which is equal to 2 for ammonia.

CONTENTS

INTRODUCTION

The purpose of these comments is to critically evaluate Acute Exposure Guideline Levels (AEGLs) for ammonia advanced by NAC AEGL and/or its contractor, the Oak Ridge National Laboratory (ORNL; 11). The scope of the comments includes the following issues:

–1. **AEGL-1, 2, and 3 definitions.** Using the National Research Council *"Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances"* (10) and other documents (1-9, 11-23), these comments examine NAC AEGL's definition of the AEGL-1, 2, and 3 parameters. They critically evaluate whether or not the definitions are appropriate in the context of emergency planning, and whether or not the parameters actually derived conform with their prescribed definitions.

–2. **AEGL-1, 2, and 3 derivation methods.** These comments critically examine the methods prescribed for deriving AEGL-1, 2, and 3 parameter values; and evaluate whether or not the derivations actually applied by NAC AEGL and/or ORNL (11) are consistent with prescribed derivation methods; and

–3. **AEGL-1, 2, 3 calculations.** These comments critically examine proposed AEGL-1, 2, and 3 parameter values; and evaluate whether they have been calculated correctly.

METHODS

These comments have been prepared based upon examination and evaluation of the definition of the three AEGL parameters, the proposed guidance for their derivation, and the numerical calculation of ammonia AEGL values resulting from application of the guidance. Extensive review of the primary and secondary toxicology literature on ammonia supports this critical evaluation. Extensive and detailed literature evaluations and citations were provided in a separate document titled *"Acute Inhalation Risks Potentially Posed By Anhydrous Ammonia,"* as fully cited in this comment document (13) and distributed to NAC AEGL. The cited document also has been submitted to the journal *Environmental Health Perspectives* for peer review and possible publication.

FINDINGS AND CONCLUSIONS

AEGL-1, 2, and 3 Definitions

AEGLs vs. CEELs. In implementing its charge to develop AEGLs, NAC AEGL provided participants and interested parties with guidelines prepared by the Committee on Toxicology of the National Research Council (NRC; 10). However, the guidelines developed by NRC are for *Community Emergency Exposure Levels* (CEELs), not AEGLs. Apparently, neither NAC AEGL nor NRC has publicly elucidated the relationship between AEGLs and CEELs implied by application of CEEL guidelines for AEGL development. Paul Tobin, U. S. EPA Designated Federal Official for NAC AEGL, has indicated that

AEGLs are the new name for CEELs. However, examination of the definitions of each parameter reveal differences, including potentially substantive differences:

CEEL-1: *"the concentration of an airborne substance (such as a gas, vapor, or aerosol) for an exposure lasting 1-8 hr below which direct toxic effects are unlikely to lead to discomfort in the exposed population (including susceptible but excluding hypersusceptible individuals) and above which discomfort becomes increasingly common"* (10, page 10);

AEGL-1: *"the exposure concentration (ppm) of an airborne substance below which exposed persons might complain of odor, taste, slight or mild sensory irritation, but above which exposed persons might request assistance although their condition does not impair escape, produce disablement or result in permanent or long-lasting effects"* (11, page vi).

CEEL-2: *"the concentration of an airborne substance (such as a gas, vapor, or aerosol) for an exposure lasting 1-8 hr below which escape is not impaired and direct toxic effects are unlikely to lead to disability in the exposed population (including susceptible but excluding hypersusceptible individuals) and above which disability becomes increasingly common"* (10, page 10);

AEGL-2: *"the concentration below which direct toxic effects are unlikely to lead to disability, permanent or long-lasting effects, but above which impairment of escape or permanent or long-lasting effects occur"* (11, page vi);

CEEL-3: *"the concentration of an airborne substance (such as a gas, vapor, or aerosol) for an exposure lasting 1-8 hr below which death or life-threatening effects are unlikely in the exposed population (including susceptible but excluding hypersusceptible individuals) and above which death or life-threatening effects become increasingly common"* (10, page 10);

AEGL-3: *"the exposure concentration (ppm) below which death or life-threatening effects are unlikely (including susceptible but excluding hypersusceptible individuals), but above which life-threatening effects occur immediately or soon after exposure"* (11, page vi).

Durations of Exposure. Currently, NAC AEGL has proposed AEGL values corresponding to exposure durations of 30 minutes, one hour, four hours, and eight hours. However, NRC guidelines indicate the need for AEGL values for shorter-term exposures:

> *"... several public and private groups have established exposure limits for some substances and some exposures..., these limits are not easily or directly translated to the kind of limits required for emergency exposures, which typically involve exposure at high levels but of short duration, usually less than 1 hour, and only once in a lifetime"* (10, page 1).

The accident in which 18 people were killed following an ammonia tank failure in Potchefstroom, South Africa in 1974 involved significant but transient elevation of ammonia levels, for a period within 10 minutes.

AEGL-1, 2, and 3 Derivation Methods

Proportion of population to be protected against mortality. NRC guidelines state the following:

> *"CEELs should indicate exposures that would be thresholds for the occurrence of (1) death or life-threatening effects, (2) disability, or (3) discomfort in the population. At such a threshold concentration, a small proportion of the population might exhibit effects... Precision in defining 'a small proportion' is impossible and unnecessary..."* (10, page 21; emphasis added).

This statement undermines the guidelines for establishing AEGLs by allowing virtually any degree of control to preclude mortality rates from exceeding, for example, one person in a million ($LC_{0.0001}$) to one person in two (LC_{50}). Even a zero-risk requirement can be accommodated within the NRC guidance on this issue.

AEGL-1, 2, and 3 Calculations

AEGL-2

Human data relevant to AEGL-2. ORNL (11) based its recommended AEGL-2 values upon human data derived primarily from the study by Verberk (1977; 23). Specifically, ORNL chose a one-hour value calculated at 156 ppm via the Ten Berge equation, and downwardly rounded to 150 ppm. At this concentration, Verberk reported that volunteers experienced irritation of the eyes, nose, throat, and chest. ORNL selected this value based upon protection against impairment of a subject's ability to escape (disablement) rather than causation of severe and irreversible injury.

Verberk (1977; 23) exposed two groups of eight volunteers to ammonia at levels of 50, 80, 110, and 140 ppm for up to two hours. An 'expert' group consisted of individuals previously exposed to ammonia, whereas a 'non-expert' group consisted of individuals lacking such experience. Half of each group were smokers. At 15-minute intervals, individuals rated odor, eye irritation, nose irritation, throat irritation, urge to cough, chest irritation, and general discomfort on an increasing scale of zero to five, where a rating of zero was 'no sensation', one was 'just perceptible', two was 'distinctly perceptible', three was 'nuisance', four was offensive', and five was 'unbearable'. Four non-expert subjects exposed to 140 ppm terminated their exposure between 30 minutes and one hour, and none remained for two hours.

Animal data relevant to AEGL-2. ORNL states that Barrow, *et al.* (1978) predicted rapid incapacitation of humans at an ammonia concentration near 303 ppm, which halved breathing rates of mice (11). This prediction is refuted by clinical tests of human volunteers (Silverman, *et al.* 1949, 14; Verberk 1977, 23; studies discussed later).

AEGL-3

Human data relevant to AEGL-3. MULDER AND VAN DER ZALM. ORNL's *Preliminary Draft* (11) indicates the absence of primary human studies available for deriving AEGL-3, except Mulder and Van der Zalm (1967; 9) reporting death of an individual following exposure to 10,000 ppm. However, Mulder and Van der Zalm is a Dutch article which was clearly mistranslated and misconstrued. It does, indeed, cite a 10,000-ppm lethality value (which originated from Henderson and Haggard in 1927; 5), but for the purpose of refuting it: the victim was exposed to *"multiple times 10,000 ppm,"* according to the authors. Indeed, the victim's exposure level appears to have been, at least sporadically, to the full 300,000-ppm saturated vapor displaced from inside the tank he was refilling, while failing to wear respiratory protection. Further, death of the victim six hours after exposure may have been attributable, not to the inexorable effects of ammonia, but to the victim's failure to seek medical attention for three hours while continuing to work. Therefore, death from fatal heart failure six hours postexposure was perhaps avertable, further undermining the 10,000-ppm lethality concentration proposed by Henderson and Haggard.

WHAZAN VS. HGSYSTEM. NAC AEGL's contractor, ORNL, reports (11) that Pedersen and Selig estimated a 30-minute human LC_{50} for ammonia of 11,500 ppm based upon probit analysis (12). However, this value was derived using the WHAZAN air dispersion model, and would have been higher if based upon use of the HGSYSTEM model. This demonstrates that mortality rates in industrial ammonia releases occurred at higher ammonia levels than suggested by the decade-old WHAZAN model. The underestimation is primarily attributable to the inability of the WHAZAN model to account for the initially heavier-than-air density of cryogenically cooled ammonia prior to its

equilibration with ambient temperature (8). For the Potchefstroom, South Africa accident reconstruction, RAM TRAC has estimated a five-minute LC_{50} of 83,322 ppm (13). Using the Ten Berge equation (16, 17), this is equivalent to a 30-minute LC_{50} of 34,016 ppm [calculation: $C^n \times T = (83{,}322)^2 \times 5$, assuming n = 2 for ammonia; C = 34,016 at T = 30].

LETHAL CONCENTRATIONS FOR SENSITIVE SUBPOPULATIONS. ORNL (11) uses a separate regression equation published by Pedersen and Selig (12) to estimate a human 30-minute LC_{50} for sensitive subpopulations. The value calculated by ORNL is 6,955 ppm. ORNL also calculates $LC_{1.0}$ and $LC_{0.1}$ values for members of the general population vs. sensitive subpopulations (ORNL Table 8, page 31; 11). ORNL then draws an unsupported conclusion:

> *"There is very little difference between the estimate for the two populations suggesting that this method may not be protective for sensitive individuals"* (11, page 29; emphasis added).

A better conclusion, supported by the data, is that members of the general population are not much more resistant to ammonia than members of sensitive subpopulations. The *ad hoc* conclusion drawn by ORNL could just as easily have been reversed: that the probit method *underestimates* the resistance of members of the general population, suggesting the need to multiply the higher concentrations tolerable to members of the general population by three rather than divide the lower concentrations by three. Either way, *and contrary to the dose-response equations,* the 'correction' *arbitrarily and without basis* increases the spread between the responses to a given dose of the two types of population.

Animal data relevant to AEGL-3. MOUSE LETHALITY CONVERSIONS TO HECs. The ORNL preliminary draft calculates the $LC_{0.1}$, LC_{01}, and LC_{10} for mice and rats based upon published studies (11). However, conversions of mouse lethality concentrations to human equivalent concentrations (HECs) is performed incorrectly. That is, mouse lethality concentrations were divided by a mouse-to-human conversion factor, but should have been multiplied by that factor instead. The factor was 2.5, whereas a factor of 2.7 should have been used (18). Thus, the values for mice are underestimated by a factor of $2.5 \times 2.7 = 6.75$.

REDUNDANT APPLICATION OF UNCERTAINTY FACTORS. To derive AEGL-3 values, ORNL divided the rat 30-minute and one-hour $LC_{0.1}$ values by an uncertainty factor of 20 to extrapolate from animals to humans and from the general human population to sensitive subpopulations. The portion of the composite uncertainty factor applied to protect sensitive subpopulations (probably 10) is redundant in the case of an $LC_{0.1}$. The $LC_{0.1}$ is defined as the concentration lethal to 0.1 percent of exposed individuals (0.001 mortality rate). Thus, the concentration has already been diminished by a factor which will protect all but one person in a thousand. This represents protection of sensitive (but perhaps not hypersensitive) subpopulations. The $LC_{0.1}$ for sensitive subpopulations represents an $LC_{<0.1}$ for the entire population. Assuming that the lifetime risk of a catastrophic chemical release is one per thousand, then protection of the public to a lifetime risk level of one per million requires use of the $LC_{0.1}$ for the entire population. Dividing the $LC_{0.1}$ by an uncertainty factor of 10 would impose a more stringent acceptable risk standard, probably equivalent to a zero-risk standard.

RECOMMENDATIONS

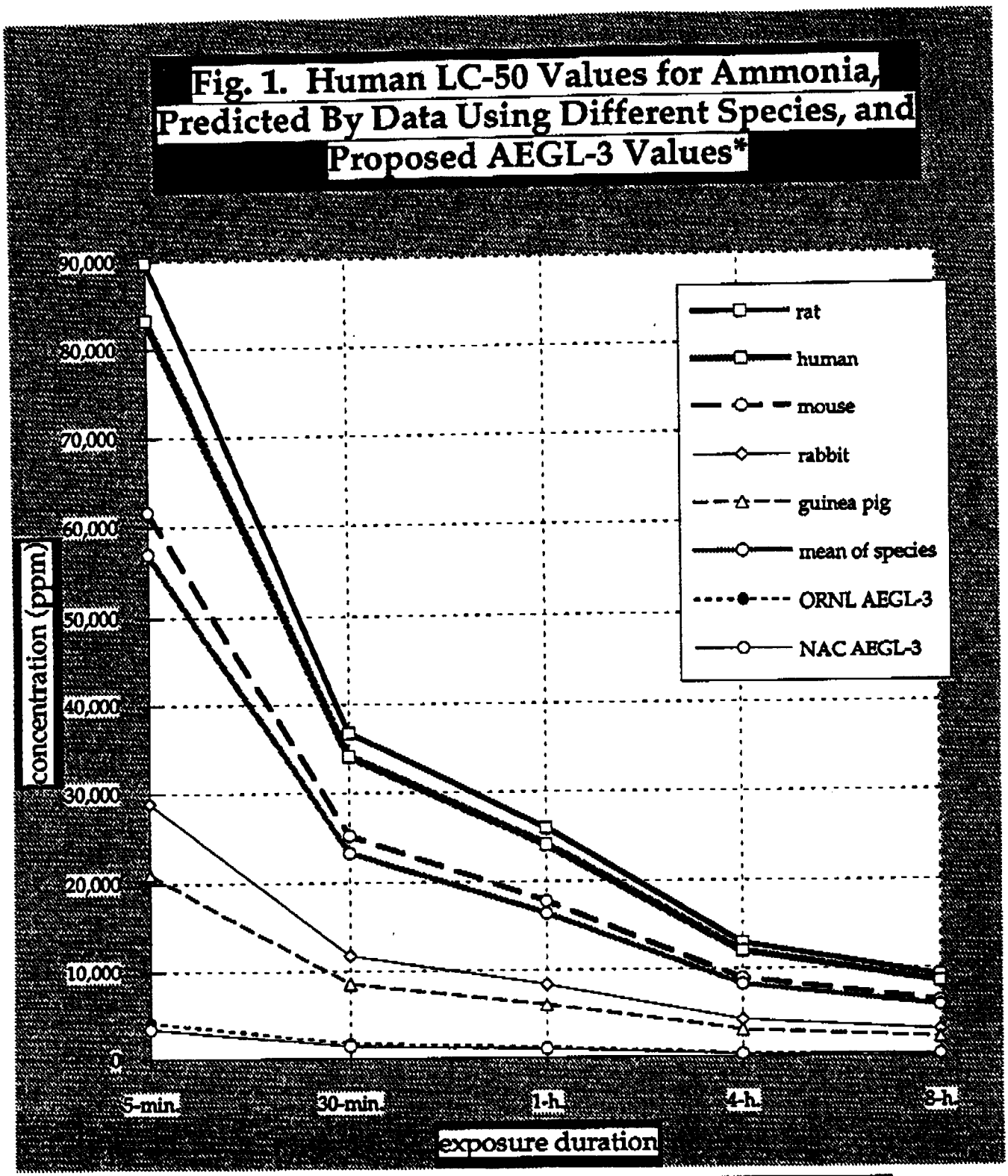
AEGL-1, 2, and 3 Definitions

AEGLs vs. CEELs. NAC AEGL should clearly elucidate the relationship between AEGLs and CEELs, guidelines for development of which were applied to developing AEGLs. Definitions should be more precise, and differences of definition should be reconciled and eliminated to avoid ambiguity. The CEEL-1, CEEL-2, and CEEL-3 definitions should be corrected to include exposures of up to eight hours, rather than *"1-8 hr"* as presently formulated.

AEGL durations of exposure. AEGL definitions should emphasize shorter time frames, such as five minutes and 30 minutes. This will be consistent with NRC's statement that relevant exposure levels usually will be less than one hour. NAC AEGL should add five minute AEGL-1, AEGL-2, and AEGL-3 values. Figure 1 illustrates the relationship of five-minute, 30-minute, one-hour, four-hour, and eight-hour LC_{50} values for several species, along with AEGL-3 values recommended by NAC AEGL and its contractor, ORNL.

AEGL-2 definition. The definition of AEGL-2 should focus upon protecting against irreversible injury and impairment of escape. However, the phraseology includes *"disability, permanent or long-lasting effects,"* which can be misinterpreted to include unintended outcomes. 'Disability' might infer the types of conditions for which occupational injuries are compensated, irrespective of whether they might affect an individual's ability to escape, and irrespective of whether the disability is temporary. 'Irreversible or long-lasting effects' might include mild effects, such as cosmetically significant scarring. The definition should be modified to include the concept of severity of the effect(s) to be prevented by the AEGL-2 level of protection.

RAM TRAC Corporation



*Data source: RAM TRAC. Acute Inhalation Risks Potentially Posed By Anhydrous Ammonia. Schenectady, New York. 99 pp. 31 May 1996.

AEGL-3 definition. AEGL-3 protects against *"death or life-threatening effects."* The meaning of death is clear, whereas life-threatening effects would seem to include diverse effects, such as depression possibly leading to suicide, tachycardia possibly leading to fatal heart attack, bronchoconstriction possibly leading to fatal asthma attack, vertigo possibly leading to fatal falling injury, and so forth. The definition of AEGL-3 should clearly reflect the intent of NRC guidelines:

> *"Except for death, these graded categories of effect are not sharply demarcated, but each merges into adjacent categories... Death or life-threatening effects are the most severe effects for which an exposure index can be provided; they are easily defined and are used by society to judge the severity of accidents"* (10, page 21).

All deaths are preceded, at least briefly, by *"life-threatening effects."* AEGL-3 should be defined unambiguously to protect against people dying. Death can be NRC's only intended effect, if it is *"easily defined"* as indicated above. Any other intended effect(s) would predominantly overlap with AEGL-2, which protects against permanent or long-lasting effects, inasmuch as many if not most effects which are *"life-threatening"* also are potentially *"permanent or long-lasting."*

Finally, *"life-threatening effects"* may represent a generic phrase which usually means 'potentially fatal effects of delayed onset, most notably, cancer.' Assuming that is the intended meaning of *"life-threatening effects,"* the phrase can be eliminated if the definition is revised to mean *"the exposure concentration below which immediate or delayed lethality is unlikely to occur."* This phraseology refocuses the AEGL-3 definition on lethality.

AEGL-1, 2, and 3 Derivation Methods

Proportion of population to be protected against mortality. Regulatory agencies have expressed concern about mortality risks to the public in a lifetime (70-year) risk range of one per million (10^{-6}) to one per hundred thousand (10^{-5}). In the context of community emergency planning, presumably this same risk range will be relevant. However, in the context of community emergency planning, the risk to life must be partitioned into two components: the risk of a chemical release, and the risk of death or other levels of adverse effect following a chemical release. To control lifetime mortality risks to, say, one per million (the $LC_{0.0001}$), the product of these two components must equal 10^{-6}. This means that AEGL-3 values should be set at a level significantly above the $LC_{0.0001}$.

Unfortunately, the probability of a release is not a constant, but is highly variable among facilities. Indeed, some facilities generate releases several times annually, whereas others may never generate releases. However, releases of a type and magnitude potentially producing mortality beyond the facility property line are relatively rare. As an approximation, a reasonable value for the probability of a lethal release over a period of 70 years of facility operation in a community might be one per thousand (10^{-3}). This leaves an equal one-per-thousand (10^{-3}) residual risk of mortality following such a release. This residual risk corresponds to the $LC_{0.1}$, which would seem to represent an appropriate concentration, exceedance of which would be subject to emergency planning to prevent the mortality from occurring.

AEGL-1, 2, and 3 Calculations

AEGL-2

Human data relevant to AEGL-2. VERBERK STUDY. ORNL (11) based its recommended AEGL-2 values upon human data derived primarily from the study by Verberk (1977; 23), in which four non-expert subjects exposed to 140 ppm terminated their exposure between 30 and 60 minutes, and none remained for 120 minutes. However, this study must be viewed in the context of voluntary exposure. Clearly, volunteers terminating their exposure perceived it as 'intolerable' in that context. However, they were unlikely to be close to incapacitation or to suffering severe and irreversible injury. With respect to a gas that can be detected by its odor, such as ammonia, most volunteers presumably would be inclined to allow a wide berth between their voluntary exposure levels vs. levels which would injure them.

SILVERMAN, ET AL. STUDY. ORNL's estimation that incapacitation might result at levels just higher than 140 ppm (at 30 minutes) used in the study by Verberk is contradicted by a study by Silverman, *et al.* (1949; 14) using a significantly higher concentration. Silverman, *et al.* exposed seven volunteers to airborne ammonia at 500 ppm for 30 minutes. The authors reported the following:

> *"[t]he most significant physiologic change in response to ammonia was the increase in respiratory minute volume, amounting to 50 to 250 per cent over control values."*

However, ORNL (Table 10, page 35) asserts that only two of seven volunteers tolerated exposure. This assertion is misleading. According to the authors:

> *"only two subjects were able to continue nasal breathing throughout the 30-minute exposure, the others changing*

> *to mouth breathing on account of nasal dryness and irritation."*

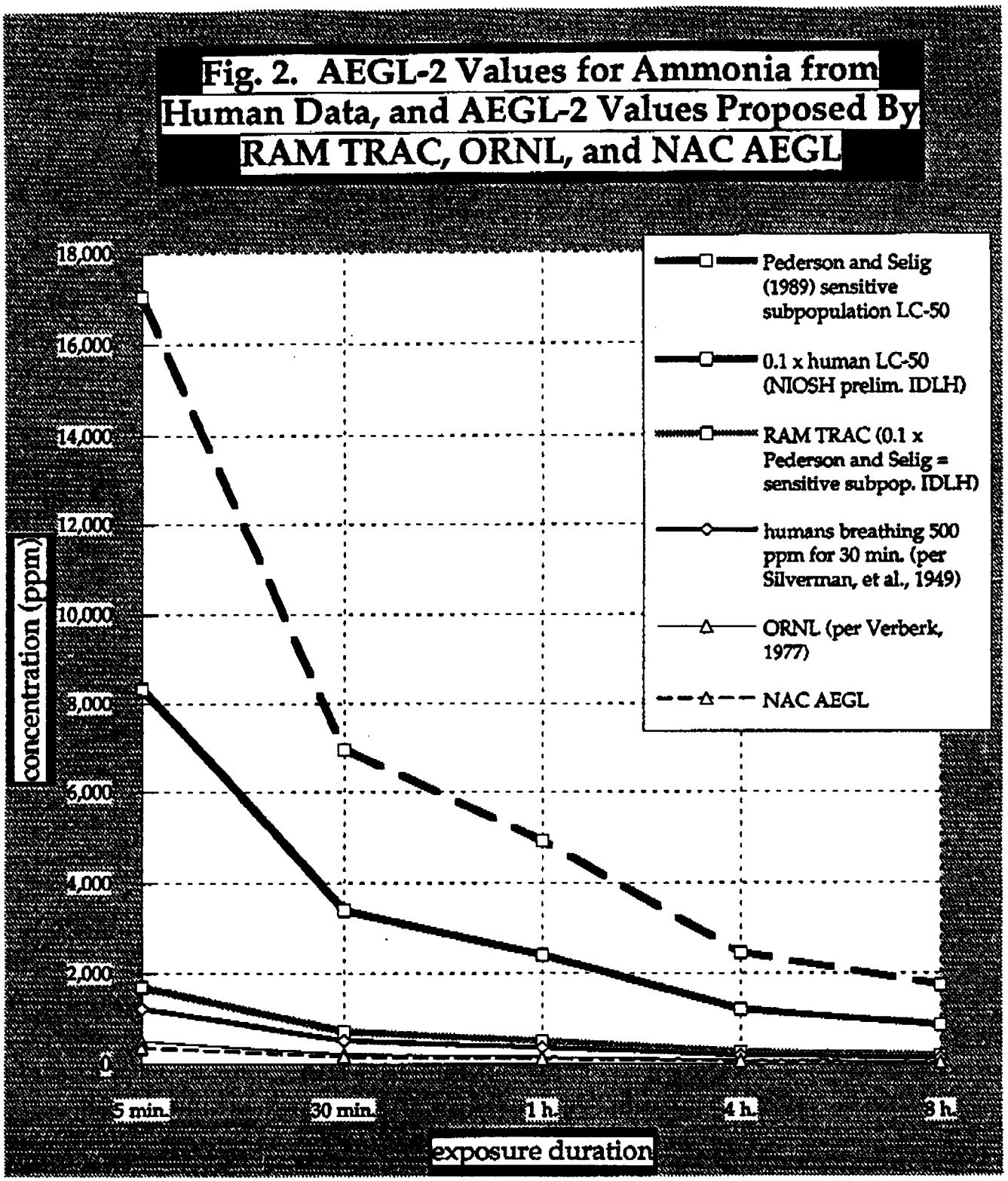
The Silverman, *et al.* article demonstrates that people were not incapacitated by 30 minutes of exposure to ammonia at 500 ppm. Far from it: they voluntarily allowed their exposure to continue for 30 minutes.

AEGL-2 VALUES BASED UPON SILVERMAN, ET AL. At a minimum, ORNL's recommended AEGL-2 values should be upwardly revised based upon the Silverman, *et al.* study described earlier. This would produce AEGL-2 values of 1,224 ppm at five minutes, 500 ppm at 30 minutes, 354 ppm at one hour, 177 ppm at four hours, and 125 ppm at eight hours. However, even these values would underestimate the appropriate AEGL-2 value, as shown below.

AEGL-2 VALUES BASED UPON NIOSH IDLH PROCEDURES. ORNL's basis for deriving AEGL-2 values was impairment of the ability to escape. This is the same criterion used by NIOSH to develop IDLH values, where the IDLH is defined as the level above which escape within 30 minutes might be impaired. The NIOSH procedure for developing IDLH values is to develop an initial value based upon one tenth of the 30-minute LC_{50} value. The human five-minute LC_{50} based upon reconstruction of the Potchefstroom accident is 83,322 ppm (8, 12, 13), which would yield a five-minute IDLH value of 8,332 ppm. This value may be time-adjusted using Ten Berge's equation to derive IDLH values for different time frames, as follows: 8,332 ppm at five minutes, 3,402 ppm at 30 minutes, 2,405 ppm at one hour, 1,202 ppm at four hours, and 850 ppm at eight hours. The resulting IDLH values are below lethality levels proposed by Henderson and Haggard in 1927, which clearly underestimate the lethality parameter. AEGL-2 values may be derived from this value or from sensitive subpopulation regression coefficients published by Pederson and Selig. The latter procedure is recommended by RAM TRAC (see below).

Animal data relevant to AEGL-2. ORNL should modify its prediction of human incapacitation at 30-minute exposure levels near 303 ppm.

RAM TRAC recommendations for AEGL-2. AEGL-2 values for the general public, which may differ from 'healthy workers' in sensitivity to ammonia, may be derived by the procedure outlined above, using Pederson and Selig's regression coefficients for sensitive subpopulations (12). ORNL calculated a 30-minute LC_{50} (of 6,955 ppm) for sensitive subpopulations. Sensitive subpopulation AEGL-2 values may be derived directly as 0.1 times the sensitive subpopulation LC_{50}, that is, AEGL-3 = 695.5 ppm at 30 minutes. For all time frames, AEGL-2 is 1,704 ppm at five minutes, 696 ppm at 30 minutes, 492 ppm at one hour, 246 ppm at four hours, and 174 ppm at eight hours. Figure 2 illustrates the relationship of RAM TRAC recommended AEGL-2 values to other AEGL-2 recommendations.



AEGL-3

Human data relevant to AEGL-3. MULDER AND VAN DER ZALM. NAC AEGL should require its contractor, ORNL, to revise its *Preliminary Draft* (11) to indicate the significance of the Mulder and Van der Zalm report. The significance is that a person was demonstrably exposed, at least sporadically, to all or a high fraction of the 300,000-ppm saturated vapor displaced from the tank he was refilling, yet was able to return to work for three hours. His death may have been avertable with timely medical intervention. Whether or not this is the case, however, the report casts doubt upon the 10,000-ppm lethality concentration set forth by Henderson and Haggard (1927; 5) and contemporary sources which cite their report.

WHAZAN VS. HGSYSTEM. NAC AEGL should require ORNL, to revise its *Preliminary Draft* (11) to upwardly adjust the estimated human 30-minute LC_{50} of 11,500 ppm based upon the WHAZAN model to 34,016 ppm based upon the HGSYSTEM model.

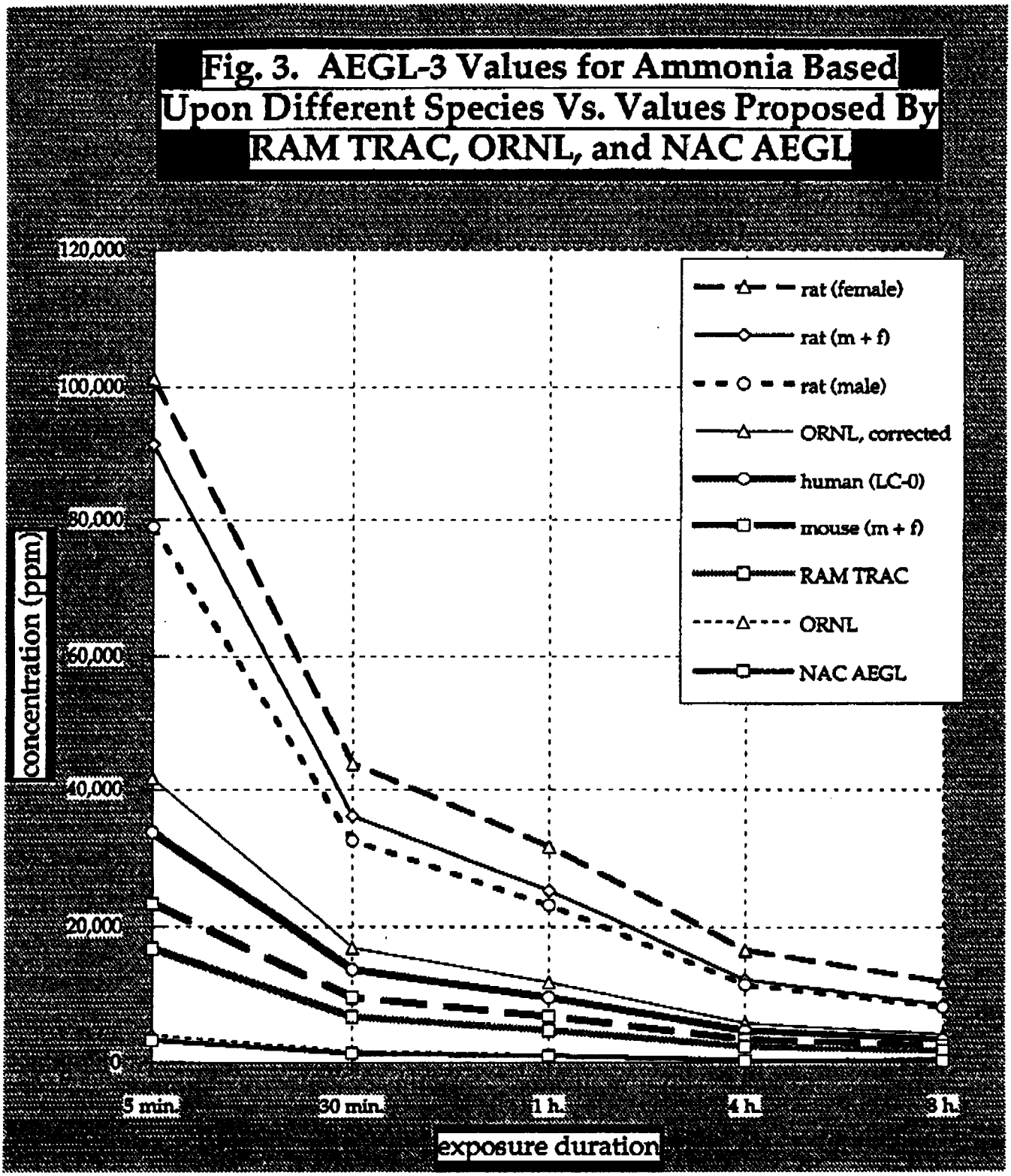
LETHAL CONCENTRATIONS FOR SENSITIVE SUBPOPULATIONS. Calculating a separate 30-minute LC_{50} (of 6,955 ppm) for sensitive subpopulations and then applying safety and/or uncertainty factors to that parameter is redundant. ORNL should eliminate estimates based upon this redundant and biased procedure.

Animal data relevant to AEGL-3. MOUSE LETHALITY CONVERSIONS TO HECs. ORNL should correct human equivalent concentrations (HECs) derived from mouse $LC_{0.1}$, LC_{01}, and LC_{10} values by multiplying them each by 6.75.

REDUNDANT APPLICATION OF UNCERTAINTY FACTORS. ORNL should multiply its proposed 30-minute and one-hour AEGL-3 values by a factor of 10 to remove the redundant uncertainty factor to protect sensitive subpopulations. Such protection is intrinsic to using an $LC_{0.1}$ for AEGL-3 derivation. The resulting values are 17,000 ppm at 30 minutes, and 12,000 ppm at one hour. Use of ORNL's procedure of applying Ten Berge's equation results in a five-minute AEGL-3 value of 41,641 ppm, a four-hour AEGL-3 value of 6,000 ppm, and an eight-hour value of 4,242 ppm. The latter two values are ten-fold higher than those proposed by ORNL.

RAM TRAC recommendations for AEGL-3. RAM TRAC estimated a five-minute LC_0 (no mortality) value of 33,737 ppm based upon the Potchefstroom accident reconstruction (8, 12, 13). Application of an uncertainty factor of two would generate a suite of appropriate AEGL-3 values. They are: 16,869 ppm at five minutes, 6,887 ppm at 30 minutes, 4,870 ppm at one hour, 2,435 ppm at four hours, and 1,722 ppm at eight hours. Figure 3 illustrates the relationship of RAM TRAC recommended AEGL-3 values to other AEGL-2 recommendations.

NAC AEGL credibility. AEGL values are related directly to the cost of emergency planning. The cost of emergency planning is roughly proportional to the emergency planning area, which varies as the square of the emergency planning radius, which in turn is proportional (roughly) to the AEGL value. Thus, proposing an unnecessarily stringent AEGL value translates to increasing the emergency planning zone radius linearly, but the emergency planning area and cost exponentially. Consequently, the credibility of the Community Emergency Planning Program and of NAC AEGL itself depend upon the reasonableness of the AEGL values finally adopted.



LITERATURE CITED

1. **AIHA.** *Emergency Response Planning Guidelines: Ammonia.* Fairfax, Virginia; American Industrial Hygiene Association, 3 pp., 1988;

2. **American Thoracic Society.** *Guidelines as to what constitutes an adverse respiratory health effect, with specific reference to epidemiologic studies of air pollution.* American Reviews of Respiratory Disease, 131:666-8, 1985;

3. **ATSDR.** *Toxicological Profile for Ammonia.* Atlanta, Georgia; Agency for Toxic Substances and Disease Registry, 125 pp., December 1990;

4. **ATSDR.** *Minimal Risk Levels for Priority Substances and Guidance for Derivation.* Atlanta, Georgia; Agency for Toxic Substances and Disease Registry. Notice. Federal Register, 61(101):25,873-82, 23 May 1996;

5. **Henderson, Y., and H. W. Haggard.** *Noxious gases and the principles of respiration influencing their action.* American Chemical Society Monograph Series. New York City, Chemical Catalogue Company, Inc.; 87:113-26, 1927;

6. **Holness, D. L., J. T. Purdham, and J. R. Nethercott.** *Acute and chronic respiratory effects of occupational exposure to ammonia.* American Industrial Hygiene Association Journal, 50:646-50, 1989;

7. **Institution of Chemical Engineers.** *Ammonia Toxicity Monograph*.Rugby, Warwickshire, UK; 27 pp., 1988;

8. **Mudan, K.; and K. Mitchell.** *Report on the Potchefstroom, South Africa Ammonia Incident*. Columbus, Ohio; Four Elements, Inc.; 15 pp., March 1996;

9. **Mulder, J. S., and H. O. Van Der Zalm.** *Een gaval van dodelijke ammoniakvergiftiging (Fatal case of ammonia poisoning).* Tijdschrift Voor Sociale Geneeskunde (Rotterdam, The Netherlands), 45:458-60, 1967;

10. **NRC.** *Guidelines for Developing Community Exposure Levels for Hazardous Substances.* Washington, DC; National Research Council Committee on Toxicology, 109 pp., 1993;

11. **ORNL.** *Acute Exposure Guideline Levels (AEGLs) for Ammonia.* Tennessee, Oak Ridge National Laboratory, K. A. Davidson, Project Director; preliminary draft, 45 pp., April 1996;

12. **Pederson, F., and R. S. Selig.** *Predicting the consequences of short-term exposure to high concentrations of gaseous ammonia.* Journal of Hazardous Materials, 21:143-59, 1989;

13. **RAM TRAC.** *Acute Inhalation Risks Potentially Posed By Anhydrous Ammonia.* Robert A. Michaels, PhD, CEP; Project Director. Schenectady, New York; RAM TRAC Corporation, 99 pp. including appendices (29 pages), 31 May 1996;

14. **Silverman, L., J. L. Whittenberger, and J. Muller.** *Physiological response of man to ammonia in low concentrations.* Journal of Industrial Hygiene and Toxicology, 31:74-8, 1949;

15. **Smyth, H. F., Jr.** *Improved communication: hygienic standards for daily inhalation.* American Industrial Hygiene Association Quarterly, 17(2):129-85, 1956;

16. **Ten Berge, W. F., and M. V. van Heemst.** *Validity--and accuracy--of a commonly used toxicity-assessment model in risk analysis.* Fourth International Symposium on Loss Prevention and Safety Promotion in the Process Industries. Volume 1: *Safety In Operations and Processes.* European Federation of Chemical Engineering Publication Series, No. 33, Vol. 1, pp. I-1 to I-12, 1983;

17. **Ten Berge, W. F., A. Zwart, and L. M. Appelman.** *Concentration-time mortality response relationship of irritant and systemically acting vapours and gases.* Journal of Hazardous Materials, 13:301-9, 1986;

18. **U. S. EPA.** *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry.* Washington, DC; Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, EPA/600/8-90/066F, i. p., October 1994;

19. **U. S. EPA.** *Generic Guidance Risk Management Program (RMP) for Ammonia Refrigeration Facilities.* Draft prepared by Science Applications International Corporation (Reston, Virginia), 8 pp. plus appendices, January 1996;

20. **U. S. EPA.** *Offsite Consequence Analysis Guidance.* Draft. Washington, DC; U. S. Environmental Protection Agency, 113 pp., 22 January 1996;

21. **U. S. EPA.** *Risk Management Plan (RMP) Data Elements--Draft Instructions (for data elements listing in Docket No. A-91-73 Category VIII-A-3a).* Washington, DC; U. S. Environmental Protection Agency, 29 pp., 22 January 1996;

22. **U. S. EPA.** *National Advisory Committee for Acute Exposure Guideline Levels (NAC/AEGL).* Federal Register, 61(111):29.095; 7 June 1996;

23. **Verberk, M. M.** *Effects of ammonia in volunteers.* International Archives of Occupational and Environmental Health, 39:73-81, 1977.

ATTACHMENT 11

CYANOGEN CHLORIDE - KEY REFERENCES

Flury, F. and Zernik, F. **1931**. Noxious Gases, Vapors, Mists, Smoke and Dust Particles, Springer Verlag, Berlin, pp. 350-354.

Hartung, R. 1994. Cyanides and Nitriles. In: Patty's Industrial Hygiene and Toxicology, 4th ed. G.D. Clayton and F.E. Clayton, Eds. John Wiley and Sons, Inc., New York, pp. 3119-3172.

NDRC. **1946**. National Defense Research Committee. Hydrogen cyanide and cyanogen chloride. In: Preparation and Evaluation of Potential Chemical Warfare Agents. Summary Technical Report of Division 9, NDRC, vol. 1, part 1, chapter 2. Office of Scientific Research and Development, Vannevar Bush, Director. NDRC Chairman, James B. Conant; Division 9 Chief, W.R. Kirner. Washington, D.C. pp. 7-16.

TABLE 8: AEGL-1 VALUES FOR CYANOGEN CHLORIDE (ppm [mg/m^3])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-1	0.13 [0.32]	0.07 [0.18]	0.02 [0.05]	0.01 [0.03]

TABLE 9: AEGL-2 VALUES FOR CYANOGEN CHLORIDE (ppm [mg/m^3])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-2	0.26 [0.65]	0.14 [0.35]	0.04 [0.11]	0.02 [0.06]

TABLE 10: AEGL-3 VALUES FOR CYANOGEN CHLORIDE (ppm [mg/m^3])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-3	1.60 [4.02]	0.88 [2.20]	0.26 [0.66]	0.14 [0.36]

Summary of Proposed AEGL Values					
Classification	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1	0.13 [0.32]	0.07 [0.18]	0.02 [0.05]	0.01 [0.03]	Eye and respiratory irritation in humans (Hartung, 1994; Flury and Zernik, 1931)
AEGL-2	0.26 [0.65]	0.14 [0.35]	0.04 [0.11]	0.02 [0.06]	Intolerable irritation in humans (Hartung, 1994)
AEGL-3	1.60 [4.02]	0.88 [2.20]	0.26 [0.66]	0.14 [0.36]	Lethality in humans (Hartung, 1994)

EFFECTS OF CYANOGEN CHLORIDE		
Concentration	**Duration**	**Effect**
1 [2.51]	?	minimum irritating
20 [50.2]	?	intolerable
159 [400]	10 minutes	probably fatal

Jacobs, M.B. 1942. War Gases: Their identification and decontamination. Interscience Publishers, New York.

TABLE 2. EFFECTS OF CYANOGEN CHLORIDE ON HUMANS		
Concentration (ppm [mg/m^3])	**Duration (min)**	**Response**
1 [2.51]	10	lowest irritant level
2 [5.02]	10	intolerable
20 [50.2]	1	intolerable
48 [120]	30	fatal
159 [399]	10	fatal

TABLE 3: $L(Ct)_{50}$ AND LC_{50} VALUES OF CYANOGEN CHLORIDE IN DOGS			
Exposure time (min)	**Number of animals**	**$L(Ct)_{50}$ (mg-min/m^3)**	**LC_{50} (mg/m^3)**
1	26	3800	3800
3	18	4200	1400
7.5	26	4500	600
10	26	5000	500
30	14	6000	200

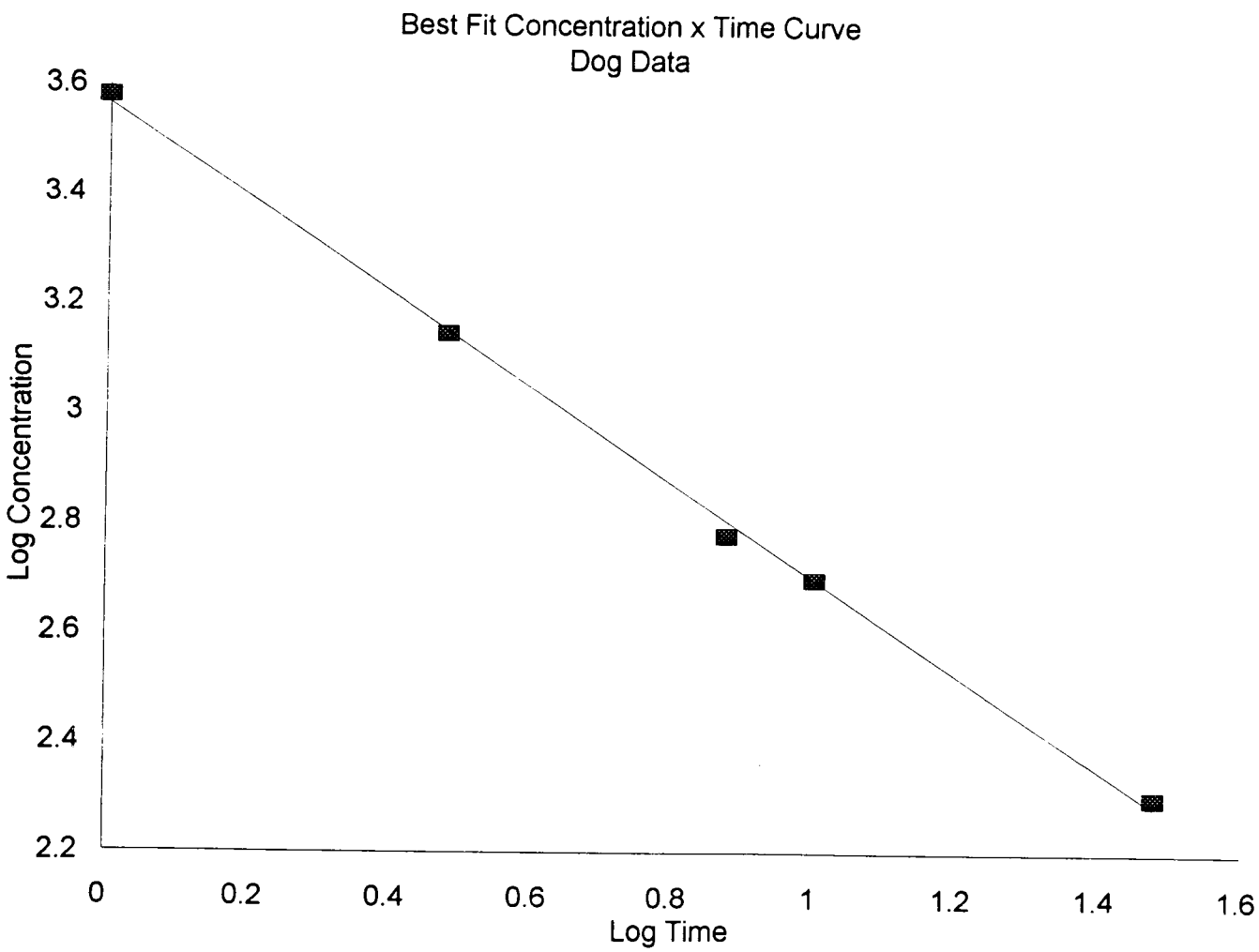

Best Fit Concentration x Time Curve
Dog Data
Log Concentration
3.6
3.4
3.2
3
2.8
2.6
2.4
2.2
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
Log Time

TABLE 4: $L(Ct)_{50}$ AND LC_{50} VALUES OF CYANOGEN CHLORIDE IN RATS		
Exposure time (min)	**$L(Ct)_{50}$ ($mg\text{-}min/m^3$)**	**LC_{50} (mg/m^3)**
1	13,000	13,000
2	9400	4700
3	5400	1800
7.5	6300	840
30	9000	300

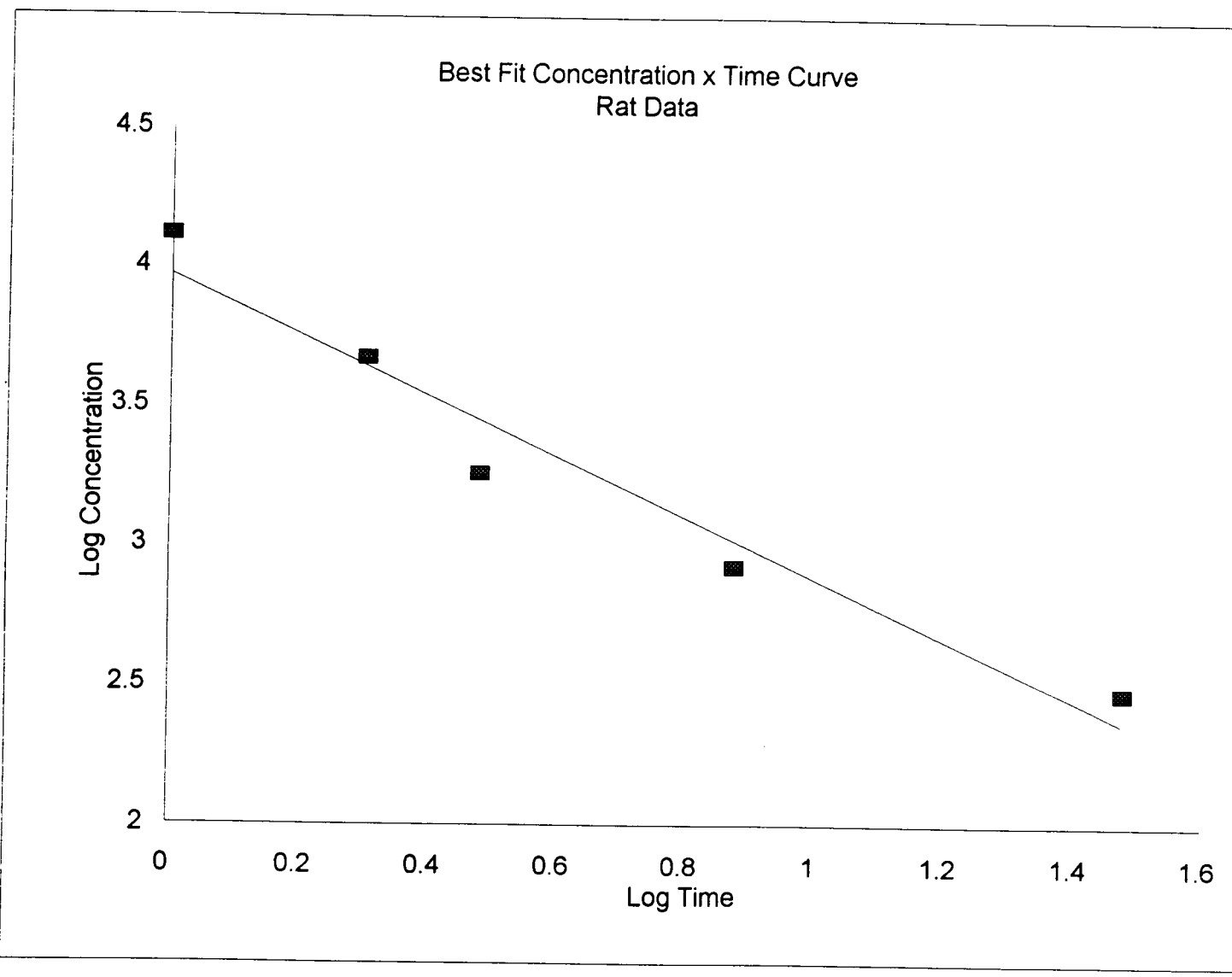
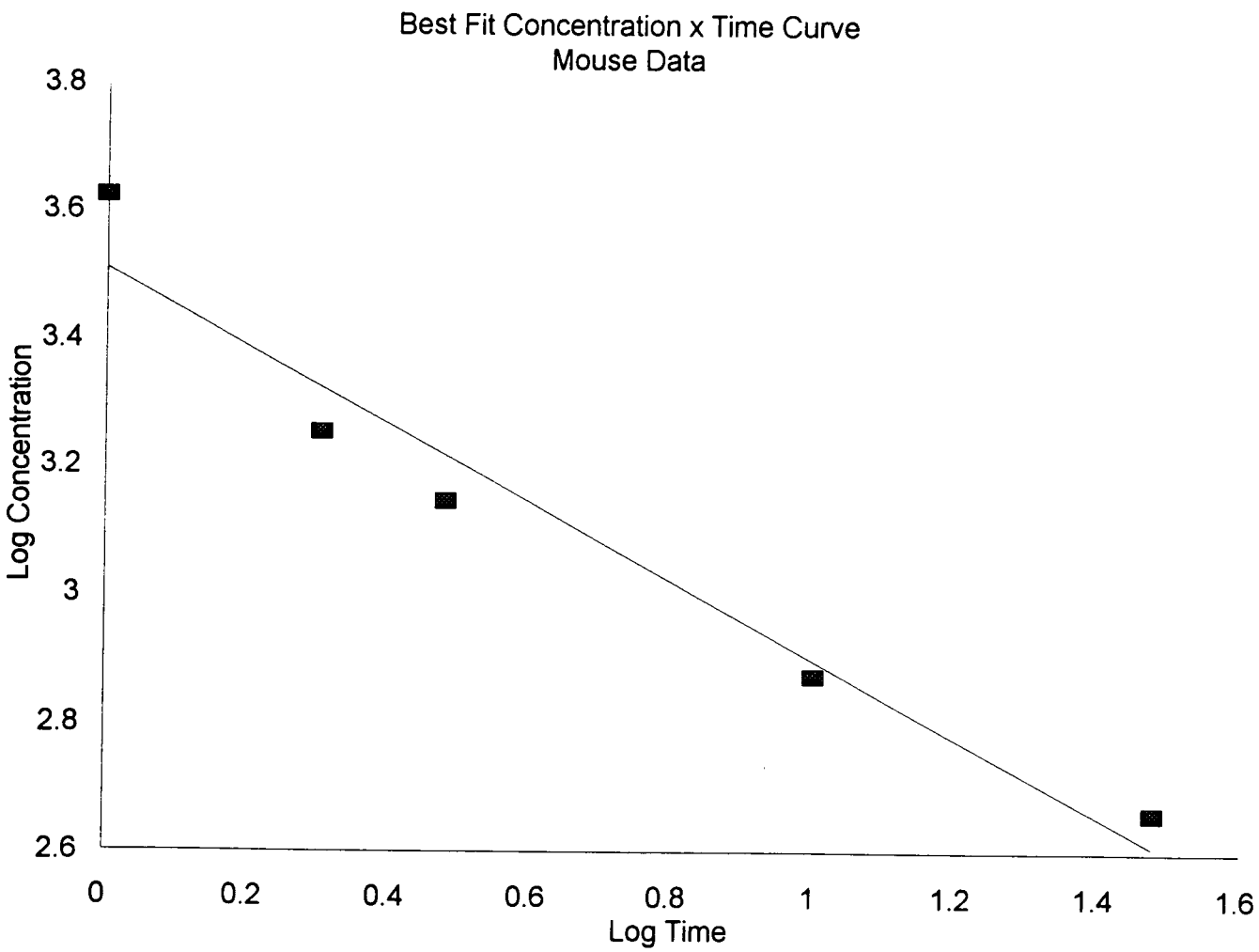

Best Fit Concentration x Time Curve
Rat Data
4.5
4
3.5
3
2.5
2
Log Concentration
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
Log Time

TABLE 5: $L(Ct)_{50}$ AND LC_{50} VALUES OF CYANOGEN CHLORIDE IN MICE		
Exposure time (min)	**$L(Ct)_{50}$ ($mg\text{-}min/m^3$)**	**LC_{50} (mg/m^3)**
1	4200	4200
2	3600	1800
3	4200	1400
10	7500	750
30	13,800	460


Best Fit Concentration x Time Curve
Mouse Data
Log Concentration
3.8
3.6
3.4
3.2
3
2.8
2.6
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
Log Time

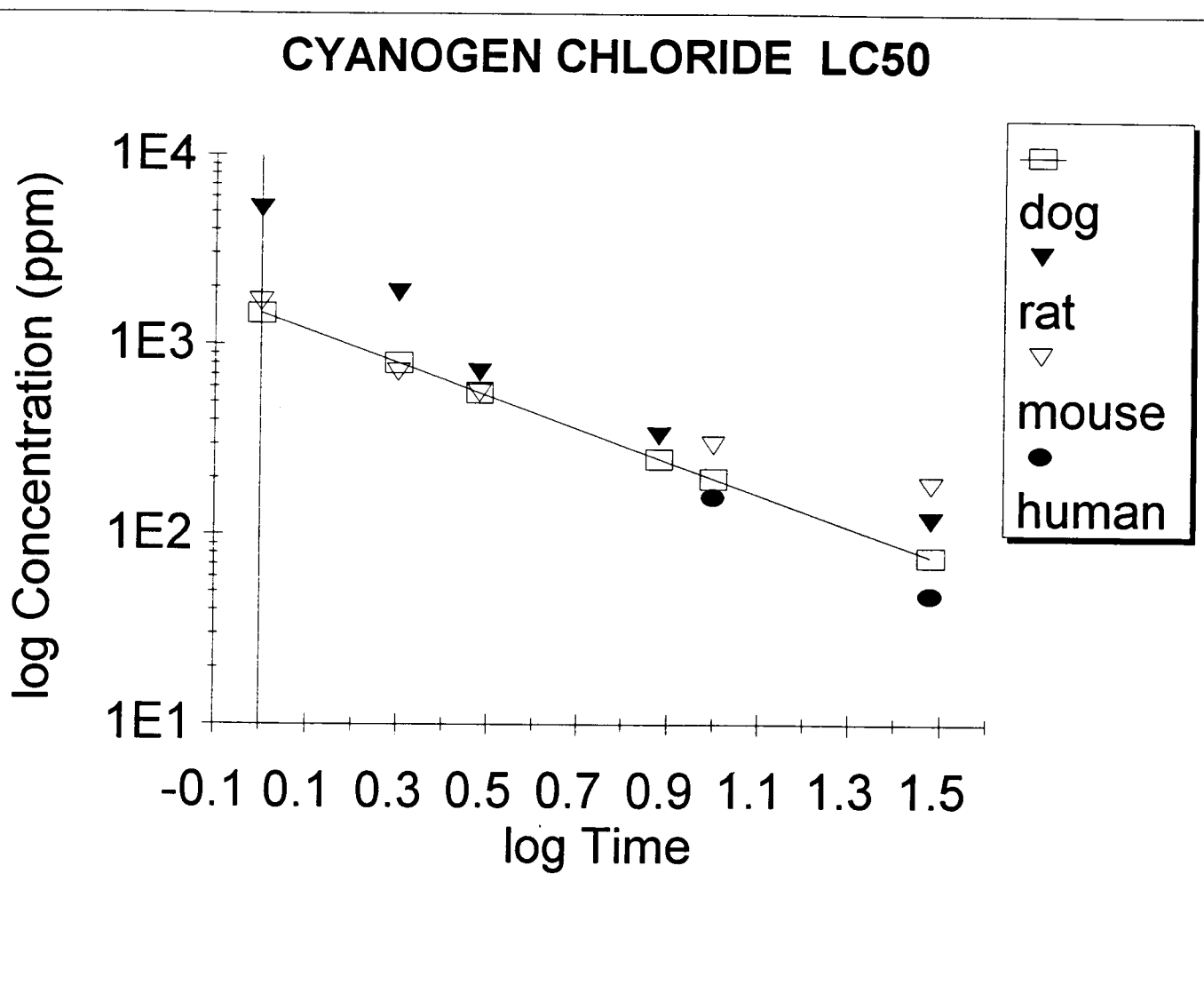

CYANOGEN CHLORIDE LC50
log Concentration (ppm)
1E4
1E3
1E2
1E1
-0.1 0.1 0.3 0.5 0.7 0.9 1.1 1.3 1.5
log Time
dog
rat
mouse
human

TABLE 7: REGRESSION ANALYSES OF ANIMAL DATA					
Species used	**Y-intercept**	**slope**	**R^2**	**n**	**k**
dog	3.565	-0.868	0.999	1.153	12858.85
rat	3.968	-1.085	0.950	0.921	4525.15
mouse	3.510	-0.610	0.951	1.638	563459.1

TABLE 6: EFFECTS OF ACUTE INHALATION OF CYANOGEN CHLORIDE ON VARIOUS ANIMAL SPECIES

Species	Concentration (ppm [mg/m^3])	Duration	Effect	Reference
Monkey	1753 (4400)	1 minute	LC_{50}	NDRC, 1946
Dog	80 (200) 48 (120) 319 (800) 20 (50) 120 (300)	30 minutes 6 hours 7.5 minutes 20 minutes 8 minutes	LC_{50} fatal fatal recovered recovered	NDRC, 1946 Flury and Zernik, 1931 Flury and Zernik, 1931 Flury and Zernik, 1931 Flury and Zernik, 1931
Cat	2390 (6000) 40 (100) 120 (300)	1 minute 18 minutes 3-3.5 minutes	LC_{50} death after 9 days fatal	NDRC, 1946 Flury and Zernik, 1931 Flury and Zernik, 1931
Rat	5179 (13,000) 120 (300)	1 minute 30 minutes	LC_{50} LC_{50}	NDRC, 1946 NDRC, 1946
Mouse	80 (200) 1673 (4200) 183 (460)	5 minutes 1 minute 30 minutes	tolerated by some LC_{50} LC_{50}	Hartung, 1994 NDRC, 1946 NDRC, 1946
Goat	717 (1800) 996 (2500)	2 minutes 3 minutes	LC_{50} death after 70 hours	NDRC, 1946 Flury and Zernik, 1931

ATTACHMENT 12

CHANGES IN THE METHYL MERCAPTAN AEGL DRAFT DOCUMENT		
Task	**Explanation**	**Action Taken**
1.Compare the ten Berge equation to the Wilson equation.	Equations are equivalent.	Incorporated the ten Berge reference.
2.Obtain a translation of the Horiguchi (1960) paper for more details.	A verbal description was obtained, and written sections will be provided in the future. The exposure concentrations were from nomimal determinations. Food and water were provided during the exposure. The postobservation period was for 24 hours.	Data retained in the draft.
3.Obtain a translation of the Pichler (1918) paper. How was methyl mercaptan analyzed? Was the methodology valid? Were additional analog chemicals tested?	A translation was obtained. No analytical measurements were performed. Four and one half days after the initial incident, 3 grams of ethyl mercaptan were missing from a vial that was discovered to be leaking.	Reference removed from the draft.
4.Determine if there are definitive reasons for "dismissing" the results Seluzhitsky (1972) other than the values were low.	A translation was obtained. The exposure concentrations were not in the document.	Reference removed from the draft.
5.Can the subchronic results of Tansy et al. (1981) be incorporated for setting the AEGL-2 value?	Observations of the animals during the initial portion of the study were not provided.	No action.
6.For the scaling of AEGL-3 values, use 400 ppm instead of 600 ppm from the Tansy et al. (1981) paper.	The AEGL definitions were changed to comply with using the 600 ppm for AEGL-3.	No action.
7.The nausea and vomiting for ethyl mercaptan should be used to set AEGL-2 values and not AEGL-1 values.	Exposure concentration was not validated from the Pichler paper.	Reference removed from the draft.
8.What are the IDLH values for structurally related chemicals?	Since the ethyl mercaptan information was removed from the draft, IDLH values were not obtained.	No action.
9.An uncertainty value of 10 should be used instead of 3.		Incorporated 10 instead of 3. AEGL-3 values reduced.
10.Mail a copy of the Tansy et al. (1981) paper to Dr. George Alexeeff.		Mailed to Dr. George Alexeeff.
11.Determine the AEGLs from the Benchmark methodology.	Dr. Dan Guth was to perform these calculations.	No action.
12.Reassess the AEGL-1 values based on the above tasks.		AEGL-1 values were not determinable since the Pichler reference was omitted.

Methyl Mercaptan

	0.5 Hr	1 Hr	4 Hr	8 Hr	Exp. Conc. (Effect) [species]	UF (inter x intra)
AEGL 1	3 ppm	2 ppm	1 ppm	1 ppm	112 ppm (Shallow breathing) [mouse]	10 x 10
AEGL 2	10 ppm	7 ppm	4 ppm	3 ppm	374 ppm (Shallow breathing & hypoactivity) [mouse]	10 x 10
AEGL 3	31 ppm	23 ppm	13 ppm	10 ppm	400 ppm (Highest nonlethal concentration) [rat]	10 x 3
AEGL 3	28 ppm	21 ppm	12 ppm	9 ppm	363 ppm (Benchmark Dose)	

ATTACHMENT 14

HF AEGLS

L. A. Gephart

HF

- COLORLESS, FUMING GAS (OR LIQUID) WITH HIGH WATER SOLUBILITY

- USES: FLUORINATING AGENT IN ORGANIC AND INORGANIC REACTIONS, CATALYST IN ALKYLATION AND POLYMERIZATION REACTIONS, PRODUCTION OF FLUORINE AND ALUMINUM FLUORIDE, ADDITIVE IN LIQUID ROCKET PROPELLANTS, GLASS ETCHING

- PRIMARY TOXICITY CONCERN FOR ACUTE INHALATION EXPOSURE: SEVERE IRRITATION
  - Lower concentrations scrubbed in nasal passages, upper respiratory tract
  - Higher concentrations reach deep lung producing necrosis, pulmonary edema

- TOXICITY CONCERNS FOR REPEATED EXPOSURES: RENAL EFFECTS, OSTEOFLUORISOS

- DATA FROM SIMULATED ACCIDENTAL CATASTROPHIC RELEASES FROM COMPRESSED GAS CYLINDERS INDICATE CRITICAL EXPOSURE DURATIONS ARE IN THE RANGE OF 2-10 MINUTES

HUMAN DATA

- LETHAL EFFECTS
  - No actual data due to ethical considerations

- "SERIOUS EFFECTS" (TABLE 2)
  - 3 Older studies, with limitations
    - Exposure levels were either low and repeated or higher but brief
    - Effects were less serious than indicated by definition of AEGL-2
    - Small number of people used and all are assumed to be healthy adults
    - Differences in HF collection and analysis methods
  - 3 Accident exposure reconstruction studies, with limitations
    - Uncertainty in exposure estimates
    - Lack of controls
    - Problems with symptom survey / reporting

- MINIMAL / NO EFFECTS
  - 2 Studies in workers exposed repeatedly to HF, flouride
    - No respiratory effects observed at moderate exposure levels
    - Combined exposure to HF / fluorides limits usefulness

TABLE 2
SUMMARY OF IRRITANT EFFECTS IN HUMANS

Concentration (PPM)	Exposure Time	Effects	Reference
1.42	6 hours / day, 15 days	No noticeable effect (single subject)	Largent 1960, 1961
2.59-4.74 (avg.) 0.9-8.1 (range)	6 hours / day, 10-50 days	Slight irritation of the skin, nose, and eyes; sour taste in mouth	Largent 1960, 1961
~5.76 (avg.) 4.2-9.1 (range)	6 Hours	Irritant effect followed by accommodation	Collings et al. 1951
32	3 Minutes	"tolerated" with discomfort' mild irritation of eyes and nose	Machle et al. 1934
61	~1 Minute	Eye and nasal irritation	Machle et al. 1934
122	~1 Minute	Marked eye and respiratory irritation, skin irritation, highest concentration tolerated for > 1 minute	Machle et al. 1934

[a]Exposure to gaseous HF and silicon tetrafluoride.

ANIMAL DATA

- ACUTE LETHALITY DATA (TABLE 4)
  - Good data base for exposure durations of 5-60 minutes
  - Limited data for 4-8 hours
  - Differences in results partially due to differences in analytical methods
  - Lethality data tend to follow $C^2 \times T = K$ (Alexeeff, Ten Berge)

- ACUTE SERIOUS EFFECTS DATA (TABLE 3)
  - Limited data, mostly from clinical observations in LC_{50} studies*
    - Exception: Study by Stavert

* Excluding data from the PERF HF toxicity studies

TABLE 4
SUMMARY OF ACUTE LETHAL INHALATION DATA IN LABORATORY ANIMALS

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Rat	4,970	5 Minutes	LC_{50}	Rosenholtz et al. 1963
Rat	14,640[b] 10,700[b]	5 Minutes	LC_{50}	Haskell Laboratory 1988a, 1988b
Rat	12,440	5 Minutes	LC_{10}	Higgins et al. 1972
Rat	18,200	5 Minutes	LC_{50}	Higgins et al. 1972
Rat	25,690	5 Minutes	LC_{100}	Higgins et al. 1972
Rat	2,689	15 Minutes	LC_{50}	Rosenholtz et al. 1963
Rat	6,620[b] 1,020[c]	15 Minutes	LC_{50}	Haskell Laboratory 1988a, 1988b
Rat	2,042	30 Minutes	LC_{50}	Rosenholtz et al. 1963
Rat	2,890[b] 1,020[c]	30 Minutes	LC_{50}	Haskell Laboratory 1988a, 1988b
Rat	1,307	60 Minutes	LC_{50}	Rosenholtz et al. 1963
Rat	1,108	60 Minutes	20% Mortality	Wohlslagel et al. 1976
Rat	1,395	60 Minutes	LC_{50}	Wohlslagel et al. 1976
Rat	2,300	60 Minutes	LC_{50}	Haskell Laboratory 1990
Rat	1,630[b] 540[c]	60 Minutes	LC_{50}	Haskell Laboratory 1988a, 1988b
Rat	190	6 Hours	LC_{100}	Morris and Smith 1982
Mouse	6,247	5 Minutes	LC_{50}	Higgins et al. 1972
Mouse	11,010	5 Minutes	LC_{100}	Higgins et al. 1972
Mouse	342	60 Minutes	LC_{50}	Wohlslagel et al. 1976
Guinea Pig	>1,220-1,830	5 Minutes	Death in a Significant Number of Animals	Machle et al. 1934
Guinea Pig	4,327	15 Minutes	LC_{50}	Rosenholtz et al. 1963
Rabbit	>1,220-1,830	5 Minutes	Death in a Significant Number of Animals	Machle et al. 1934

a LC_{50} and LC_{100} values were obtained at 3 hours post exposure (Morris and Smith 1982), 7 days post exposure (Higgins et al. 1972); 14 days post exposure (Rosenholtz et al. 1963, Wohlslagel et al. 1976, Haskell Laboratory 1988a, b).

b Tested at relative humidity of <10%.

c Tested at relative humidity of 40-50%.

HF SAMPLING / ANALYTICAL CONSIDERATIONS

- **BEST METHOD (DUPONT, 1990):**
  - Use glass impingers fitted with teflon inlet / outlet
  - Sample at air flow rate of 1.2 - 1.6 L / minute
  - Collect into 0.1 N NaOH
  - Dilute 1:1 with buffer
  - Analyze with fluoride specific ion electrode

- **OLDER METHODS**
  - Use of all glass impingers: HF levels 25% lower than actual
  - Use of low air flow rates: HF levels 12% lower than actual

SUMMARY OF SAMPLING / ANALYTICAL METHODS IN HF STUDIES

Study	Sampling and Analysis Method
Haskell Lab 1988, 1989	Collection into 0.1 n NaOH using glass impingers, diluted 1:1 with total ionic strength adjusting buffer (TISAB). Analysis using fluoride specific ion electrode.
Haskell Lab, 1990	As above except impinger inlets and outlets were coated with teflon.
Higgins et al., 1972	Collection into "aqueous reagent solutions" and measurement via specific ion electrode
Largent, 1960, 1961	Unknown
Machle et al., 1934	Collection into NaOH using a glass apparatus. Analysis using titration with Nitric acid and phenol red.
Machel and Evans, 1940	Unknown but likely as above.
Morris and Smith, 1990	Similar to Haskell 1988-9 except collection was directly into TISAB.
Rosenholtz et al., 1963	Collection into gas bottles, or, 0.2 N NaOH solutions. Analyses via the "volumetric method."
Stavert et al., 1991	As per Haskell Lab, 1988-1989
Wohlslsag et al, 1976	Collection into "gas scrubber column with known amounts of aqueous reagent absorber." Analysis using specific ion electrodes.

AEGL 1

- **USE MILD IRRITATION OF THE EYES, RESPIRATORY TRACT IN HUMANS EXPOSED TO HF AT 2 PPM FOR 6 HRS / DAY FR 10-50 DAYS (LARGENT) AS STARTING POINT**
  - Include UF of 3 to protect sensitive individuals
  - Scale to 30-minutes, 1, 4, and 8-hours using $C^2 \times t = k$

	30 Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (PPM)	2.3	1.6	0.8	0.6

AEGL 2

- **USE MILD IRRITATION AND REDDENING OF THE SKIN AND FACE IN HUMANS EXPOSED TO HF AT CONCENTRATIONS AS HIGH AS 8 PPM FOR 6 HRS / DAY FOR 10-15 DAYS (LARGENT) AS STARTING POINT**
  - **No UF included because the effects notes were not serious and the exposures were repeated**
  - **Scale to appropriate time frames using $C^2 \times t = k$**

	30 Minute	1-Hour	4-Hour	8-Hour
AEGL-2 (PPM)	28	20	10	7

AEGL 3

- **USE 1-HOUR LC_0 IN MICE REPORTED BY WOHLSLAGEL (263 PPM) AS STARTING POINT**
  - **Apply intra-species UF of 3**
    - **Direct acting agent**
    - **Metabolic differences are not important**
  - **Apply inter-species UF of 2**
    - **Data for most sensitive species used**
    - **HF exposure levels are likely low due to analytical method used**
  - **Scale to appropriate time frames using $C^2 \times t = k$**

	30 Minute	1-Hour	4-Hour	8-Hour
AEGL-3 (PPM)	62	44	22	15

PROPOSED HF AEGLS

	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	~~2.3~~ 2	~~1.6~~ 2	~~0.8~~ 1	~~0.6~~ 1
AEGL-2	~~26~~	~~20~~	~~10~~	~~7~~
AEGL-3	62	44	22	15

ATTACHMENT 15

SUMMARY OF PERF PROJECT 92-09

PRESENTED TO AEGL ADVISORY COMMITTEE

AUGUST, 1996

Walden Dalbey, Ph.D., DABT
Mobil Business ResourcesCorporation

OBJECTIVES OF PERF PROJECT

- PROVIDE TOXICITY DATA (WITH DOSE-RESPONSE) ON POTENTIAL HEALTH EFFECTS FROM AIRBORNE HF WITH 2-MINUTE AND 10-MINUTE EXPOSURES
    - EMPHASIS ON NONLETHAL EFFECTS
- PERFORM A LIMITED NUMBER OF EXPOSURES AT 60 MIN FOR COMPARISON TO EXISTING ERPGs

NOSE-BREATHING VS MOUTH-BREATHING RATS

- NASAL LESIONS EXPECTED WITH NOSE-BREATHING
- HUMANS LIKELY TO BREATHE AT LEAST PARTIALLY THROUGH MOUTH DURING EXPOSURE
- THEREFORE, MOUTH-BREATHING MODEL WAS USED FOR EXPOSURES OF RATS TO HF
- CONSERVATIVE MODEL
    - DIRECT DELIVERY OF HF TO TRACHEA
    - NO ALTERATION OF BREATHING BY SENSORY IRRITATION

EXPERIMENTAL DESIGN

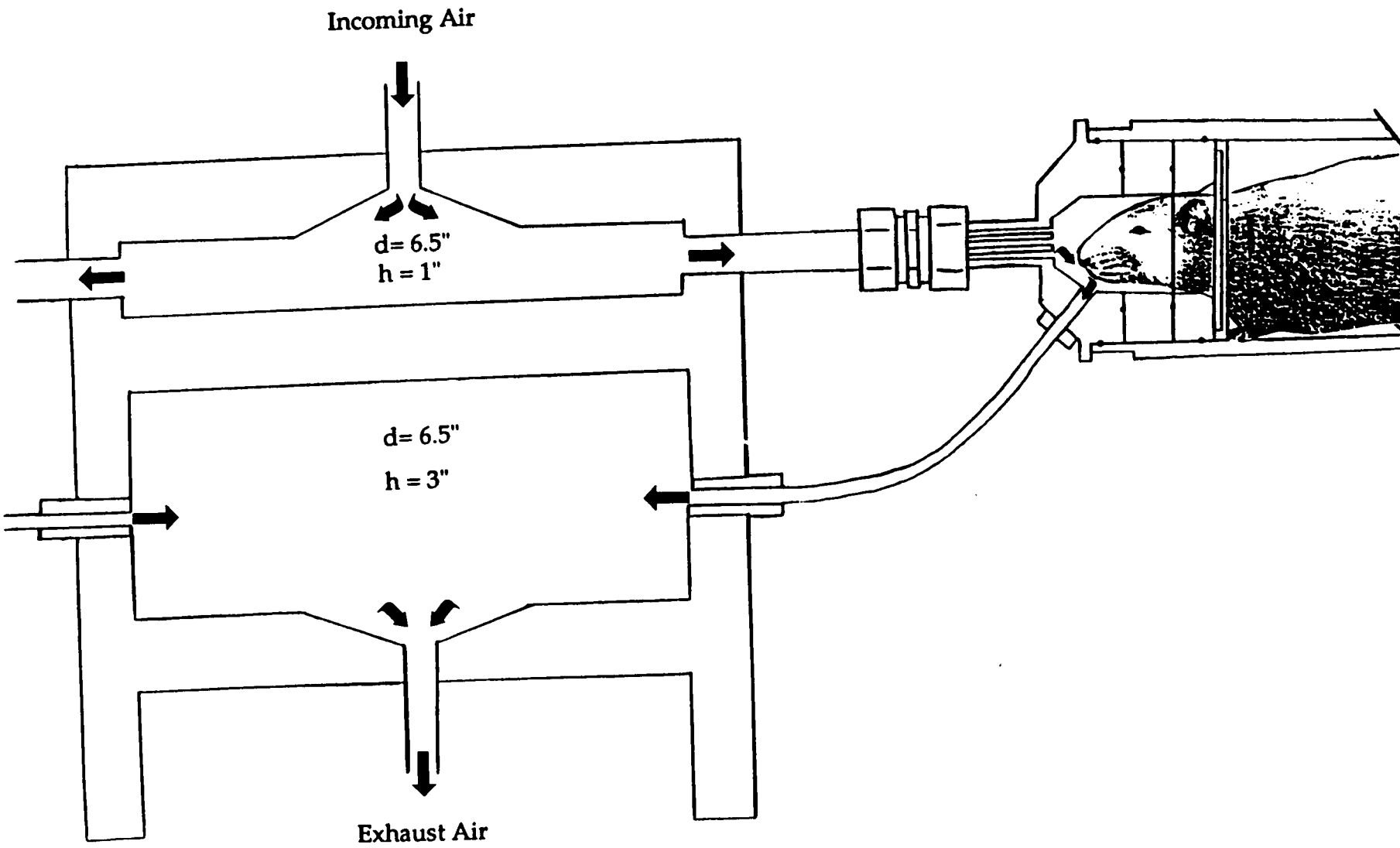
	DURATION OF EXPOSURE TO HF		
ppm x min	2 Min.	10 Min.	60 Min
~1,200	O - 593 ppm	N - 135 ppm	Q - 20 ppm
~2,800	L - 1589 ppm	K - 271 ppm	M - 34 ppm J - 48 ppm
~9,500	E - 4887 ppm	B - 950 ppm	
~14,000	G - 6392 ppm	I - 1454 ppm (recovery)	
~17,000	D - 8621 ppm	F - 1669 ppm A - 1764 ppm	
38,470		*R - 3847 ppm**	
~70,000		*T - 7014 ppm**	*U - 1224 ppm*
122,340			*S - 2039 ppm*

Underlined: NB

* MB and NB exposed simultaneously

Italics: Lethality exposures with limited endpoints and 2-week observations

Exposure Cylinder Used for HF



ENDPOINTS FOLLOWING EXPOSURE TO HF

- NASAL RESISTANCE (NB GROUPS)

- PULMONARY FUNCTION: PULMONARY RESISTANCE, LUNG VOLUMES, QUASISTATIC PRESSURE-VOLUME CURVES, MAXIMAL FORCED EXHALATION, CARBON MONOXIDE DIFFUSING CAPACITY

- BRONCHOALVEOLAR LAVAGE: LAVAGED CELLS, LDH, G-6-PDH, ALK. PHOS., ACID PHOS., β-GLUCURONIDASE, MYELOPEROXIDASE, PROTEIN, ALBUMIN, SIALIC ACID

- HEMATOLOGY AND SERUM CHEMISTRY

- STANDARD NECROPSY AND 7 ORGAN WEIGHTS

- HISTOPATHOLOGY OF RESPIRATORY TRACT AND MAJOR ORGANS

CONCENTRATION-RELATED CHANGES WITH MOUTH-BREATHING

- NECROSIS, INFLAMMATION, AND FIBRINOPURULENT EXUDATE IN TRACHEA AND BRONCHI; INFLAMMATION IN ALVEOLAR REGION

- BAL: INCREASED PROTEIN, SIALIC ACID, MPO, LDH, PMNs

- PULMONARY FUNCTION
  - DECREASED TLC, VC, IC
  - APPARENT GAS TRAPPING
  - DECREASED FLOW DURING FORCED EXHALATION
  - INCREASED PULMONARY RESISTANCE
  - DECREASED Dlco ONLY WITH HIGHEST PPM (2-MIN)

- INCREASED WEIGHT OF LUNG LOBE

- RECOVERY BY 14 WEEKS AFTER EXPOSURE

NOSE-BREATHING: NECROSIS AND ACUTE INFLAMMATION IN THE NOSE

RESULTS OF EXPOSURES OF MOUTH-BREATHING RATS FOR 60 MINUTES

- 20 PPM: NO TREATMENT-RELATED ADVERSE EFFECTS

- 48 PPM: NO TREATMENT-RELATED ADVERSE EFFECTS

ADDITIONAL MORTALITY STUDIES

- MORTALITY WAS MUCH GREATER WITH MB THAN WITH NB GROUPS

- RESULTS WITH NB RATS WERE WITHIN RANGE OF PUBLISHED DATA

DERIVATION OF TENTATIVE "SHORT-TERM EXPOSURE VALUE" FOR 10 MIN

- BASED ON SAME DEFINITION AS ERPG-2

- SERIOUS EFFECTS DEFINED AS PRONOUNCED FUNCTIONAL OR BIOCHEMICAL ALTERATIONS OR AS PRONOUNCED MORPHOLOGIC LESIONS

- 1,764 PPM SELECTED AS CAUSING SERIOUS EFFECTS

- 950 PPM WAS NEXT LOWER CONCENTRATION GIVING NO SERIOUS EFFECTS

- THRESHOLD OF SERIOUS EFFECTS ESTIMATED AS THE MEAN OF THESE TWO CONCENTRATIONS (1,357 PPM)

- THRESHOLD DIVIDED BY UNCERTAINTY FACTOR TO EXTRAPOLATE TO PEOPLE, RESULTING IN STEV OF 130 PPM

ATTACHMENT 16

ISSUES IDENTIFIED AT FIRST MEETING

I. **Identify Additional Information on Acute Effects**

1. Huntington Research Center Report - Acute Inhalation Study, 1993
2. Industrial Practice - Low Concentration Exposures for AEGL-1

II. **Identify Additional Epidemiologic Information**

1. Roe, 1978

   Wald, 1984 - Reexamination of Roe
2. French Producers Study - Status

III. **Conduct a Carcinogenicity Calculation for Acute Exposure**

Review the Support for the Calculation for Hydrazine

ATTACHMENT 17

HYDRAZINE AEGL DERIVATION

PRESENTATION OVERHEADS

National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGL) for Hazardous Substances

NAC AEGL Meeting #2
August 5-7, 1996

PROPOSED AEGL VALUES FOR HYDRAZINE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint(Reference)
AEGL-1 (Nondisabling)	0.6 ppm	0.4 ppm	0.2 ppm	0.1 ppm	Eye and facial irritation in monkeys (House, 1964)
AEGL-2 (Disabling)	6 ppm	4 ppm	2 ppm	1 ppm	Body weight reduction, hepatotoxicity in rats; route-to-route extrapolation required (Becker et al., 1981)
AEGL-3 (Lethality)	16 ppm	11 ppm	6 ppm	4 ppm	Lethality in mice (Jacobson et al., 1955)

PROPOSED AEGL VALUES FOR HYDRAZINE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint(Reference)
AEGL-1 (Nondisabling)	0.3 ppm	0.2 ppm	0.1 ppm	0.1 ppm	Eye and facial irritation in monkeys (House, 1964)
AEGL-2 (Disabling)	8 ppm	6 ppm	3 ppm	2 ppm	Nasal lesions (Latendresse et al., 1995)
AEGL-3 (Lethality)	47 ppm	33 ppm	17 ppm	12 ppm	Lethality in rats (HRC, 1993)

TABLE 10. AEGL-1 FOR HYDRAZINE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-1	0.3 [0.4]	0.2 [0.3]	0.1 [0.1]	0.1 [0.1]

Key study: House (1964). Monkeys exposed continuously by inhalation to 0.4 ppm (0.52 mg/m^3) exhibited flushing of the face and eye irritation.

Scaling: $C^2 \times t = k$ (ten Berge, 1986)

Uncertainty factors: 3 for interspecies variability (hydrazine appears to be equally irritating to all species)
3 for intraspecies variability (not protecting hypersusceptible individuals)

DERIVATION OF AEGL-2 VALUES FROM DIFFERENT DATA SETS				
Time Point	Weatherby & Yard (1955); dogs, UF = 30[a] muscular incoord.. weakness	Keller et al. (1988) rats; UF = 30[a] maternal toxicity during gestation	Kulagina (1962) rats; UF = 30[a]; altered behavior	Latendresse et al.(1995) rats (UF = 30) nasal lesions[b]
30 min	0.4 ppm	24 ppm	1 ppm	8 ppm
1 hr	0.2 ppm	16 ppm	1 ppm	6 ppm
4 hr	0.1 ppm	8 ppm	0.4 ppm	3 ppm
8 hr	0.1 ppm	6 ppm	0.3 ppm	2 ppm

a UF of 30 includes 10 for interspecies variability and 3 for intraspecies variability; UF of 9 includes 3 for interspecies (RGDR dosimetric adjustment accounts for some variability) and 3 for intraspecies variability.

b Dosimetric conversion (RGDR, U.S. EPA, 1994) performed because effects were in the nasopharyngeal region. UF of 30 inlcudes 10 for interspecies (dosimetric conversion does not necessarily account for species variability in response) and 3 for intraspecies variability.

TABLE 11. AEGL-2 FOR HYDRAZINE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-2	8 [1]	6 [8]	3 [4]	2 [3]

Key study: Latendresse et al. (1995). Rats exposed for 1 hr to 750 ppm hydrazine exhibited nasal lesions. Lesions reversible upon cessation of exposure.

Dosimetric Conversion: RGD methodology (U.S. EPA, 1994); extrathoracic region

Scaling: $C^2 \times t = k$ (ten Berge, 1986)

Uncertainty factors: 10 for interspecies variability
3 for intraspecies variability (not protecting hypersusceptible individuals)

DERIVATION OF AEGL-3 VALUES FROM DIFFERENT DATA SETS				
Time Point	Jacobson (1955) Rat; lethality; UF = 90[a]	Keller et al. (1988) Rat; embryolethality; UF = 30	BMD_{05} (OEHHA draft) (MacEwen and Vernot, 1975, 1981); UF = 30[b]	HRC (1995)[c] Rat; lethality; UF = 30
30 min	5 ppm	8 ppm	34 ppm	47 ppm
1 hr	3 ppm	5 ppm	24 ppm	33 ppm
4 hr	2 ppm	3 ppm	12 ppm	17 ppm
8 hr	1 ppm	2 ppm	9 ppm	12 ppm

[a] UF of 90 includes 10 for interspecies variability, 3 for intraspecies variability and 3 for uncertainty in estimating lethality threshold.

[b] UF of 30 includes 10 for interspecies and 3 for intraspecies variability.

[c] UF of 30 includes 10 for interspecies variability and 3 for intraspecies variability. Dosimetric conversion (RGDR, U.S. EPA, 1994) performed because effects were in the pulmonary region; based upon estimated LC_1.

TABLE 14. AEGL-3 FOR HYDRAZINE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-3	47 [61]	33 [43]	17 [22]	12 [15]

Key study: HRC 1993. Rat inhalation (nose-only) LC_{50} study. LC_{01} of 0.4 mg/l (444.4 mg/m^3) estimated from data using method of Litchfield and Wilcoxon

Dosimetric Conversion: RGD methodology (U.S. EPA, 1994); pulmonary region

Scaling: $C^2 \times t = k$ (ten Berge, 1986)

Uncertainty factors: 10 for interspecies variability
3 for intraspecies variability (not protecting hypersusceptible individuals)

CANCER ASSESSMENT OF HYDRAZINE

- Key study: MacEwen et al. (1981)

- Cancer assessment for acute inhalation exposure to hydrazine was conducted following the NRC methodology for EEGLs, SPEGLs and CEGLs (NRC, 1986).

- Virtually safe dose (VSD) $d = 2 \times 10^{-4}\ \mu g/m^3$

- Calculate 24-hr exposure:

$$d \times 25{,}600 = 5.1\ \mu g/m^3$$

- Maximal additional risk contributed by uncertainties regarding stages of the carcinogenic process [Crump and Howe, 1984]):

$$\frac{\text{24-hr exposure}}{2.8} = \frac{5.1\ \mu g/m^3}{2.8} = 1.82\ \mu g/m^3$$

CANCER ASSESSMENT OF HYDRAZINE

- Maximal additional risk contributed by uncertainties regarding stages of the carcinogenic process [Crump and Howe, 1984]):

$$\frac{\text{24-hr exposure}}{2.8} = \frac{5.1\ \mu g/m^3}{2.8} = 1.82\ \mu g/m^3$$

- For a 1×10^{-4} risk, the extent of risk based on the 24-hr exposure concentration becomes:

$$1.82\ \mu g/m^3 = \frac{1 \times 10^{-4}}{1 \times 10^{-6}\ \text{(risk at d)}}$$
$$= 1.82 \times 10^2\ \mu g/m^3 \text{ or } 0.2\ mg/m^3$$

- If the exposure is limited to a fraction (f) of a 24-hr period, the fractional exposure becomes 1/f x 24 hrs (NRC, 1985).

24-hr exposure	=	0.2 mg/m³ (0.2 ppm)
8-hr	=	0.6 mg/m³ (0.5 ppm)
4-hr	=	1.2 mg/m³ (0.9 ppm)
1-hr	=	4.8 mg/m³ (3.6 ppm)
0.5 hr	=	9.6 mg/m³ (7.3 ppm)

- For interspecies variability, it is suggested that this uncertainty be increased to 100:

24-hr exposure	=	0.002 mg/m³ (0.002 ppm)
8-hr	=	0.01 mg/m³ (0.01 ppm)
4-hr	=	0.01 mg/m³ (0.01 ppm)
1-hr	=	0.05 mg/m³ (0.04 ppm)
0.5 hr	=	0.09 mg/m³ (0.07 ppm)

CANCER ASSESSMENT OF HYDRAZINE

- Maximal additional risk contributed by uncertainties regarding stages of the carcinogenic process [Crump and Howe, 1984]):

$$\frac{\text{24-hr exposure}}{2.8} = \frac{0.09\ \text{mg/m}^3}{2.8} = 0.03\ \text{mg/m}^3$$

- For a 1×10^{-4} risk, the extent of risk based on the 24-hr exposure concentration becomes:

$$0.03\ \text{mg/m}^3 = \frac{1 \times 10^{-4}}{1 \times 10^{-6}\ \text{(risk at d)}}$$
$$= 3\ \text{mg/m}^3$$

- If the exposure is limited to a fraction (f) of a 24-hr period, the fractional exposure becomes 1/f x 24 hrs (NRC, 1985).

24-hr exposure	=	3 mg/m^3 (2.3 ppm)
8-hr	=	9 mg/m^3 (6.8 ppm)
4-hr	=	18 mg/m^3 (13.7 ppm)
1-hr	=	72 mg/m^3 (55 ppm)
0.5 hr	=	144 mg/m^3 (109 ppm)

- For interspecies variability, it is suggested that this uncertainty be increased to 100:

24-hr exposure	=	0.03 mg/m^3 (0.02 ppm)	2
8-hr	=	0.09 mg/m^3 (0.07 ppm)	7
4-hr	=	0.18 mg/m^3 (0.13 ppm)	13
1-hr	=	0.72 mg/m^3 (0.55 ppm)	55
0.5 hr	=	1.4 mg/m^3 (1.1 ppm)	110

CANCER ASSESSMENT OF HYDRAZINE

- Key study: Vernot et al. (1985)

Administered Dose (ppm)	Human Equivalent Dose[a] (mg/kg/day)	Tumor Incidence[b]
0	0	0/146
0.05	0.001	2/96
0.25	0.007	1/94
1.0	0.03	9/97
5.0	0.14	58/98

- Cancer assessment for acute inhalation exposure to hydrazine was conducted following the NRC methodology for EEGLs, SPEGLs and CEGLs (NRC, 1986).

- Virtually safe dose (VSD) $d = 4 \times 10^{-6}$ mg/m^3

- Calculate 24-hr exposure:

$$\text{24-hr exposure} = d \times 25{,}600$$
$$= (4 \times 10^{-6} \text{ mg/m}^3) \times 25{,}600 \text{ days}$$
$$= 0.09 \text{ mg/m}^3$$

National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGL) for Hazardous Substances
Final Meeting 1 Highlights
Green Room, 3rd Floor, Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, D.C.
June 19-21, 1996

INTRODUCTION

The highlights of the meeting are outlined below, and the meeting agenda (Attachment 1) and attendee list (Attachment 2), and acronym list (Appendix) are attached.

Dr. Roger Garrett (U.S. EPA) provided an historical overview of the project including establishment of the Federal Advisory Committee Act (FACA) and the National Advisory Committee for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances under FACA; the genesis of AEGLs from and along with other inhalation guidelines; the process by which AEGLs are developed, reviewed, and published; and the role of the chemical manager in the AEGL evaluation process. Dr. Garrett also discussed the National Academy of Science's (NAS) "Guidelines for Developing Community Emergency Exposure Levels (CEELs) for Hazardous Substances," which is to be used as guidance for deriving AEGLs. He pointed out that CEELs and AEGLs are identical and that values were renamed AEGLs to reflect their more generic application. Chemical managers will serve as liaisons among committee members and attempt to resolve scientific issues, seek a consensus of the committee members, frame scientific issues for upcoming committee meetings, present the draft AEGL values and issues at the meeting, and engage in follow-up activities.

Dr. Garrett introduced Dr. Paul Tobin (EPA), the assigned "Designated Federal Officer" (DFO) for this FACA committee, and the chair of the AEGL committee, Dr. George Rusch (AlliedSignal). Dr. Tobin gave an orientation regarding guidance for AEGL development. The organizations that may participate include AAPCC, ACOEM, AFL-CIO, ATSDR, CDC, DOE, DOT, DoD, EPA, FEMA, ICEH, NFPA, NESCAUM, OSHA, STAPPA/ALAPCO, AlliedSignal, Exxon and state agencies. In addition, discussions continue with regard to participation by FDA and NIOSH. He emphasized the need for numbers by these and other participants (e.g., chemical companies, manufacturers, and the state of Pennsylvania for its incineration program). Without the development of these values, evacuation guidelines may be set by persons who are not scientifically trained. The AEGL values will also help eliminate some of the overlap among agencies currently developing guidelines.

Dr. Rusch gave a brief introduction to the committee and requested that the members be provided bylaws before the next meeting.

To provide AEGL members with a comprehensive background and the scientific principles involved in developing CEELs, Dr. John Doull (University of Kansas Medical Center, retired) reviewed the process presented in the "Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances."

Several questions were asked before the committee members began their review of the draft. (Answers were prepared after the meeting and provided by the EPA project officer, the DFO, the AEGL chair, and Oak Ridge National Laboratory [ORNL] staff.)

Q. Can more time be given to the committee members reviewing the drafts prior to the meeting?
A. Ideally, 6 weeks will be given between the committee members receiving the drafts and the meetings. However, it will require several meetings before this amount of time can be provided.

Q. How will the uncertainty factors be used?
A. A special task group will be reviewing this issue and will provide some information at the next meeting.

Q. Can the references be provided to the committee members?
A. The chemical manager will receive a full set of key references, and additional references can be provided by request. Committee members can request the ORNL staff to provide articles from the draft document's reference check list.

REVIEW OF DRAFT DOCUMENTS

Fluorine
CAS No. 7782-41-4

Chemical manager: Dr. Ernest Falke, EPA
Author: Dr. Sylvia Talmage, ORNL

Dr. Ernest Falke presented an overview of the draft technical support document and the revised AEGL values. (Attachment 3 is a copy of the slides used in that presentation.)

He emphasized the similarity in response (particularly the LC_{50} values but also the irritant effects) to fluorine among four tested species -- rat, mouse, guinea pig, and rabbit -- and the steepness of the dose-response curve. The mouse data for mild and severe lung congestion were used to derive the AEGL-2 and AEGL-3 values, respectively. These data are 67 ppm for 30 minutes and 30 ppm for 60 minutes (very mild lung congestion) and 75 ppm for 60 minutes (severe lung congestion). Because the irritant and LC_{50} concentrations among species were nearly identical, indicating that irritation and lethality are a function of the concentration of fluorine in the air, no scaling factor among species was applied. The data were divided by a factor of 3 for differences in human sensitivity and by a factor of 2 to account for the fact that the data set was from one laboratory and not confirmed elsewhere. At the suggestion of a committee member, the AEGL-2 values will be compared with values derived from a human exposure to 25 ppm for 5 minutes that resulted in slight irritation of the eyes. Also, at the suggestion of a committee member, the revised AEGL-1 values, initially based on a slight irritant effect to humans at an intermittent exposure to 10 ppm for a total of 30 minutes, were recalculated based on no effects during continuous exposure to 10 ppm for 15 minutes. The resultant values were divided by 3 to account for differences in human sensitivity. All values were scaled from the test time periods to other time periods by the formula derived from the animal test data: $C^n \times t = k$, where C is the concentration, n is approximately 2, t is time in minutes, and k is a constant. The values accepted by the majority of the committee members are summarized in the following table. Two committee members concurred with the AEGL values developed by NAC but with comments. These comments will be prepared and become an integral part of the technical support document.

SUMMARY TABLE OF AEGL VALUES					
Classification	**30 Minutes**	**1 Hour**	**4 Hours**	**8 Hours**	**Endpoint (Reference)**
AEGL-1	2 ppm ($4\ mg/m^3$)	2 ppm ($3\ mg/m^3$)	1 ppm ($1\ mg/m^3$)	1 ppm ($1\ mg/m^3$)	no effect in humans (Keplinger and Suissa, 1968)
AEGL-2*	11 ppm ($17\ mg/m^3$)	5 ppm ($8\ mg/m^3$)	2 ppm ($4\ mg/m^3$)	2 ppm ($3\ mg/m^3$)	mild lung congestion-mice (Keplinger and Suissa, 1968)
AEGL-3	19 ppm ($29\ mg/m^3$)	13 ppm ($19\ mg/m^3$)	6 ppm ($9\ mg/m^3$)	4 ppm ($6\ mg/m^3$)	severe lung congestion-mice (Keplinger and Suissa, 1968)

*AEGL-2 values for 30 and 60 minutes were based on separate data points.

Methyl Mercaptan
CAS No. 74-93-1

Chemical manager: Dr. Doan Hansen, BNL
Author: Dr. James C. Norris, ORNL

Dr. Hansen presented an overview of the draft. Attachment 4 is a copy of the slides used in that presentation.

After discussion of the draft completion of the following actions was determined to be needed before the document could be forwarded.

1. Compare the results from the ten Berge and the Wilson equations.
2. Obtain a translation of the Horiguchi (1960) paper for more details.
3. Obtain a translation of the Pickler (1918) paper.
   How was methyl mercaptan analyzed?
   Was the methodology valid?
   Were additional analog chemicals tested?
4. Determine if there are definitive reasons for "dismissing" the results of Seluzhitsky (1972) other than the low values.
5. Can the subchronic results of Tansy et al. (1981) be incorporated for setting the AEGL-2 value?
6. For the scaling of AEGL-3 values, use 400 ppm instead of 600 ppm from the Tansy et al. (1981) paper.
7. The nausea and vomiting for ethyl mercaptan should be used to set AEGL-2 values and not AEGL-1 values.
8. What are the IDLH values for structural related chemicals?
9. Should an uncertainty factor of 10 be used instead of 3?
10. Mail a copy of the Tansy et al. (1981) paper to George Alexeeff.

11. Determine the AEGL values from the benchmark methodology. (Dr. Daniel Guth, EPA, committed to perform these calculations).

The draft document for methyl mercaptan will be reconsidered at the next meeting to fully evaluate comments from outside participants.

Hydrazine
CAS No. 302-01-2

Chemical manager: Dr. Richard Thomas, ICEH
Author: Dr. Robert A. Young, ORNL

Dr. Richard Thomas presented an overview of the draft. Attachment 5 is a copy of the slides used in that presentation.

After discussion of the draft, completion of the following actions was determined to be needed before the document could be forwarded.

1. Review 2 or 3 epidemiological studies mentioned by Dr. Richard Thomas.
2. Incorporate maternity toxicity for AEGL-2 and embryonic toxicity for AEGL-3.
3. Perform cancer calculations.
4. Incorporate the vapor density value.
5. Perform C^n x $t = k$, where $n = 2$.
6. Obtain additional information on acute exposures in animal studies and human experience.

Ammonia
CAS No. 7664-41-7

Chemical manager: Mr. Larry A. Gephart, Exxon Biomedical Sciences
Author: Dr. Kowetha A. Davidson, ORNL

Mr. Larry Gephart presented an overview of the draft. Attachment 6 is a copy of the slides used in that presentation.

Dr. Daniel Guth analyzed the ammonia data using categorical regression and presented his results.

Dr. George Alexeeff analyzed the ammonia data using a benchmark approach and presented his results.

Dr. Robert A. Michael (RAM TRAC Corp.) presented an overview of the report "Acute Inhalation Risks Potentially Posed by Anhydrous Ammonia," dated May 31, 1996 (Attachment 7).

The AEGLs agreed upon by the committee are listed below.

SUMMARY TABLE OF AEGL VALUES FOR AMMONIA

Classification	30 Minutes	1 Hour	4 Hours	8 Hours	Endpoint (Reference)
AEGL-1	25 ppm (17 mg/m^3)	25 ppm (17 mg/m^3)	25 ppm (17 mg/m^3)	25 ppm (17mg/m^3)	odor (no reference)
AEGL-2*					
AEGL-3*					

*To be determined.

Committee recommendations included recalculating the HEC values and describing the different approaches used for deriving AEGL values for ammonia at the next meeting.

CLOSING COMMENTS

Dr. George Rusch requested comments regarding the format and results of the meeting. Listed below are those comments:

1. A wide range of technical issues were discussed.
2. The quality of ORNL's documents was excellent, and ORNL was responsive to the chemical managers' needs.
3. A good exchange of ideas and information took place.
4. The interaction between committee members and document authors is a critical step in the AEGL developmental process.
5. Having different perceptions from the committee members was helpful.
6. The diversity of backgrounds, interests, and disciplines of the committee members facilitated the committee's task.
7. In a short time period, a number of values were generated.
8. AEGL values should be based on "good" science.
9. The chemical managers provided needed support.
10. Voting was a valuable part of the process.
11. The selection of the first four chemicals provided a diverse number of problems.
12. The Chair did an exceptional job.
13. The DFO's support was excellent.
14. The cooperation of all the committee members was appreciated in dealing with governmental delays.
15. The efforts of Dr. Roger Garrett were appreciated.
16. It was great not to have any telephones.
17. The leadership of Drs. Garrett, Tobin, and Rusch was appreciated.
18. Broad coverage of issues aided in understanding.
19. The committee was supportive to all speakers.

ACTION ITEMS

- Issues on the use of uncertainty factors (such as intraspecies differences). ORNL will coordinate with Drs. Alexeeff, Borak, Gephart, and Guth on a progress report to be presented at the next meeting.
- Definitions of AEGLs are to be reviewed. ORNL will work with Dr. Thomas for clarified

definitions.
- EPA will be responsible for distributing bylaws to the committee members.

NAC/AEGL FUTURE MEETINGS

- NAC AEGL Meeting 2: August 5, 6, and 7 in Washington, D.C.
- NAC AEGL Meeting 3: September 17, 18, and 19 in Washington, D.C.
- All chemicals scheduled for review should be distributed to the committee.
- The documents need to be distributed earlier.

Dr. Po-Yung Lu (ORNL) will coordinate the hotel and room reservations and will notify the committee members.

The meeting was adjourned at 1:00 pm.

The minutes of the meeting were prepared by Dr. Po-Yung Lu , ORNL.

ACRONYMS

AAPCO	Association of American Pesticide Control Officials
ACOEM/ACEP	American College of Occupational Environmental Medicine/ American College of Energy Physicians
AFL-CIO	American Federation of Labor & Congress of Industrial Organizations
ATSDR	Agency for Toxic Substances & Disease Registry
BNL	Brookhaven National Laboratory
CDC	Center for Diseases Control
DoD	Department of Defense
DOE	Department of Energy
DOT	Department of Transportation
EPA	Environmental Protection Agency
FEMA	Federal Emergency Management Agency
FDA	Food and Drug Administration
ICEH	International Center for the Environment and Health
NESCAUM	North Eastern States for Coordinated Air Use Management
NFPA	National Fire Protection Association
NIOSH	National Institute of Safety and Health
ORNL	Oak Ridge National Laboratory
OSHA	Occupational Safety and Health Administration
STAPPA/ALAPCO	State and Territorial Air Pollution Program Administrators/ Association of Local Air Pollution Control Officials

LIST OF ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.

Attachment 1. NAC meeting 1 agenda
Attachment 2. Attendee list
Attachment 3. Data analysis for Fluorine
Attachment 4. Data analysis for Methylmercaptan
Attachment 5. Data analysis for Hydrazine
Attachment 6. Data analysis for Ammonia
Attachment 7. Public comment on Ammonia by RAM TRAC Corporation