National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 6 Highlights
Green, 3rd Floor, Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, D.C.
June 9-11, 1997

INTRODUCTION

George Rusch (NAC/AEGL Chair) opened the meeting and reflected on the fact this meeting represented the first anniversary of the convening of the NAC/AEGL. The highlights of the meeting are described below and the meeting agenda (Attachment 1) and attendee list (Attachment 2) are affixed. The NAC- 5 highlights were approved without changes (Appendix A).

Prior to discussion of AEGL priority chemicals, Roger Garrett (Program Director) addressed several issues of importance to NAC/AEGL functions: (1) standing operating procedures for the NAC/AEGL, (2) attendance at NAC/AEGL meetings, (3) status of NAC/AEGL products for the Federal Register and, (4) NAC/AEGL member responsibilities.

(1) Standing Operating Procedures (SOP) Workgroup for the NAC/AEGLs

Roger Garrett announced the formation of a workgroup to develop guidance procedures for the NAC/AEGL. He urged the SOP workgroup to start the planning and priorization immediately and have a progress report in the next meeting.

(2) Meeting Attendance

Roger stressed the importance of attendance at NAC/AEGL meetings as well as concern regarding arrival/departure inconsistencies. It is imperative to have full attendance throughout the duration of the meeting for optimum productivity and performance of the NAC/AEGL.

(3) Federal Register Submissions

Roger Garrett reviewed the process and progress pertaining to the AEGLs submitted to the Federal Register. Ten chemicals are currently ready for submission and it is expected that several more will be ready for submission following the deliberations of this meeting.

(4) NAC Member Responsibilities

Roger Garrett expressed concern that all NAC/AEGL members should be active as chemical managers and reviewers as well as providing input on draft TSDs to ORNL in a timely fashion, and coordinating document review during the NAC/AEGL meetings.

TECHNICAL DISCUSSIONS

Uncertainty Factor Workgroup Report (Richard Thomas)

The workgroup has had three teleconferences, the first being an organizational effort, the second noting background information on the various uncertainty factors used in the development of AEGLs, and the third addressing significant figure and rounding issues. The discussions on rounding and significant figures culminated in a motion to use two significant figures regardless of the relationship to the decimal point (Attachment 3).

Chemical-Specific Issues - Final Review of Proposed AEGLs

Arsine

Robert Young provided a brief overview of the AEGLs for arsine and a justification for recommending that AEGL-1 values for this chemical are not appropriate (Attachment 4). The justification was based upon the known steep dose-response for arsine and its mechanism of action (hemolysis) that may result in little margin between nontoxic exposures and lethal exposures, and the fact that toxicity may occur below the odor threshold. A motion to replace the AEGL-1 values of 0.1 ppm for arsine with "Not Appropriate" was unanimously approved (Appendix B).

Cyanogen chloride

Mark McClanahan affirmed that data for this chemical are limited and that commercial production can not be verified (the chemical appears to exist only as an intermediate in chemical processes). It was the consensus of the NAC [motion made by T. Hornshaw, seconded by R. Thomas: YES:27, NO:0] that the existing AEGL values be removed from the document and replaced with the narrative to the effect of "Information is inadequate for AEGL derivation. The NAC does not have commercial production data and, therefore, does not currently perceive the necessity to derive AEGLs" (Appendix C).

Hydrogen cyanide

Ernie Falke briefly reviewed pertinent information including the Wexler et al. 1947 report (Attachment 5). He stated that it is necessary to state if the dose used in this study was a bolus administration. The use of n=1 rather than n=2 for the ten Berge equation was also noted. An elaboration on justification of uncertainty factors is also needed. Three options were proposed regarding this document: (1) leave document as is, (2) re-evaluate the data, or (3) search for more data. George Rusch suggested that the document be revisited and that kinetic data be evaluated to provide insight into the route-to-route extrapolation issue.

Hydrogen fluoride

Sylvia Talmage summarized the issues (Attachment 6) pertaining to the AEGL derivation for this chemical: (1) inconsistencies in data usage, (2) inconsistencies in uncertainty factor application (i.e., 10 was used but 3 may be more appropriate), and (3) adjustment of the toxicity endpoint. Because some of the suggested changes were large and the NAC needed to refamiliarize themselves with the TSD, George Rusch recommended that this chemical be tabled until the next meeting whereupon relevant issues will be revisited.

Methyl mercaptan

Doan Hansen provided a brief overview (Attachment 7) of odor threshold, an important issue for this chemical. Following discussion regarding odor threshold and derivation of the AEGL-1 values, it was the consensus of the NAC to expand the rationale for the AEGL-1 values. The AEGL-2 and AEGL-3 values will remain unchanged.

AEGL PRIORITY CHEMICALS

Ammonia
CAS Reg. No. 7664-41-7

Chemical Manager: Larry Gephart , Exxon Biomedical
Staff Scientist: Kowetha Davidson, Oak Ridge National Laboratory

Larry Gephart provided an introduction and general update regarding the comments on proposed AEGLs from external reviews and interested parties (Attachment 8). Kowetha Davidson summarized the current status of the ammonia AEGLs, their respective data sets, and derivations (Attachment 9). Robert Michaels (Ram Trac Corp.) reiterated previous concerns regarding several issues (e.g., inconsistencies between proposed AEGL-3 values and actual lethality levels, assumption of n=2 in the ten Berge equation, mice as an appropriate model species, concerns regarding human equivalent concentrations, concerns regarding AEGL-2 values being reduced with exposure duration) (Attachment 10). Representatives for The Fertilizer Institute (TFI), Chris Leason and Barry Hooberman, provided comments on previous draft AEGL values (e.g., selection of endpoints) and comments regarding responsibilities of the NAC to respond to external comments on a previous draft of the ammonia technical support document (Attachment 11). Paul Tobin (Designated Federal Officer) responded that the legal responsibilities regarding mode and method of response are outside of the NACs' purview. Several NAC members noted that review of the Environ and Ram Trac reports simply represented alternate interpretations of data. Discussions focusing on specific AEGLs followed. AEGL-3 discussions focused on the use of an estimated lethality threshold as opposed to a NOAEL, and also the application of an uncertainty factor for individual variability (10 vs 3). It was the consensus of the NAC that the LC_{01} was appropriate for deriving the AEGL-3 and that a UF of 3 was justified for accounting for individual variability. The AEGL-3 values as shown in the summary table were appproved [motion made by E. Falke, seconded by R. Thomas: YES:23, NO:3, ABSTAIN:5]. The AEGL-2 discussions considered the relevance of the selected endpoint and its severity as applicable to AEGL-2. The NAC discussed the 1-hour exposure concentrations (110 or 140 ppm) associated with different levels of effects (baseline values) and the n-value (n = 2 or 4) for the $C^n \times t = k$ equation. The following table shows the baseline values and the resulting AEGL values extrapolated over the relevant time points (UF=1):

	AEGL values considered by the NAC				
Baseline values	5-min	30-min	1-hour	4-hours	8-hours
110 ppm; n=2	380 ppm	160 ppm	110 ppm	55 ppm	38 ppm
110 ppm; n=4	200 ppm	130 ppm	110 ppm	78 ppm	65 ppm
140 ppm; n=2	480 ppm	220 ppm	140 ppm	70 ppm	50 ppm
110 ppm; n=2 (60 -min)	380 ppm	160 ppm	110 ppm	110 ppm	110 ppm

It was also proposed that 110 ppm be used for all time points. It was the consensus of the NAC the AEGL-2 be based upon a 60-min exposure to 110 ppm resulting in unbearable eye irritation, odor, and nasopharyngeal irritation [motion made by S. Barbee, seconded by L. Koller: YES:18, NO:7, ABSTAIN:2]. The AEGL-2 values for 5 minutes and 30 minutes were based on ten Berge's equation where n=2, and the 1-, 4-, and 8-hour values were flatlined at 110 ppm (Appendix D).

SUMMARY OF PROPOSED AEGL VALUES FOR AMMONIA					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1 [a,b]	25 ppm 17 mg/m^3	25 ppm 17 mg/m^3	25 ppm 17 mg/m^3	25 ppm 17 mg/m^3	odor
AEGL-2 [b]	160 ppm 112 mg/m^3	110 ppm 77 mg/m^3	110 ppm 77 mg/m^3	110 ppm 77 mg/m^3	severe eye irritation, odor, nasopharyngeal irritation
AEGL-3 [b]	1600 ppm 1119 mg/m^3	1100 ppm 769 mg/m^3	550 ppm 385 mg/m^3	390 ppm 273 mg/m^3	LC_{01} in mice

[a] AEGL-1 values previously adopted by the Committee were not changed.
[b] Proposed 5-min AEGL-3 of 3800 ppm (2675 mg/m^3), 5-min AEGL-2 of 380 ppm (266 mg/m^3), and 5-min AEGL-1 of 25 ppm (17 mg/m^3) were also approved, respectively.

Toluene 2,4-& 2,6-diisocyanates
CAS Reg. Nos. 91-08-7 and 584-84-9

Chemical Manager: **Steve Barbee, Olin Corporation**
Chemical Reviewers: **Jonathan Borak, ACOEM**
Doan Hansen, Brookhaven National Laboratory
Staff Scientist: Carol Forsyth, Oak Ridge National Laboratory

Steve Barbee reviewed the AEGL values for TDI from the last NAC deliberation (Attachment 12). Discussions followed regarding endpoints for AEGL-2. The endpoint of reversible pulmonary inflammation (Duncan et al., 1962) was supported by human data (Henschler et al., 1962). For AEGL-1, discussions revolved around data showing changes in airway resistance (FEV_1) in asthmatics and other signs/symptoms (chest tightness, cough, dyspnea, headache) reported by Bauer (1985). The proposed AEGL-1 and AEGL-2 values shown in the table below were approved by the NAC [motion made by Z. Post, seconded by L. Koller: AEGL-1, YES:26, NO:2, ABSTAIN:1; motion made by Z. Post, seconded by L. Koller: AEGL-2 YES:28, NO:0, ABSTAIN:1] (Appendix E). For AEGL-1, it was noted that a statement be added to the technical support document indicating that the proposed values will not be protective for isocyanate-sensitized individuals. The proposed AEGL-3 values were approved at NAC Meeting No. 5.

SUMMARY OF PROPOSED AEGL VALUES FOR 2,4 AND 2,6 TDI					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	0.02 ppm 0.14 mg/m^3	0.02 ppm 0.14 mg/m^3	0.01 ppm 0.07 mg/m^3	0.01 ppm 0.07 mg/m^3	FEV_1 changes and clinical signs
AEGL-2	0.2 ppm 1.42 mg/m^3	0.1 ppm 0.71 mg/m^3	0.06 ppm 0.43 mg/m^3	0.06 ppm 0.43 mg/m^3	pulmonary histopathologic changes
AEGL-3[a]	0.92 ppm 6.6 mg/m^3	0.65 ppm 4.6 mg/m^3	0.32 ppm 2.3 mg/m^3	0.23 ppm 1.6 mg/m^3	lethality threshold estimated from 4-hr LC_{50} for mice

[a] AEGL-3 values were approved at NAC Meeting No. 5, June 9-11, 1997.

Chlorine trifluoride
CAS Reg. No. 7790-91-2

Chemical Manager: **Kyle Blackman, FEMA**
Chemical Reviewers: **Robert Benson, U.S. EPA**
Nancy Kim, New York State Dept. of Health
Mark McClanahan, CDC
Staff Scientist: Sylvia Talmage, Oak Ridge National Laboratory

Kyle Blackman made brief introductory remarks about chlorine trifluoride (Attachment 13) followed by an overview by Sylvia Talmage of the derivation of AEGL values for this chemical (Attachment 14). Following discussion, the following values were approved by the NAC/AEGL: AEGL-1 [motion made by E. Falke, seconded by J. Hinz: YES:24, NO:4, ABSTAIN:1]; AEGL-2 [motion made by E. Falke, seconded by J. Hinz: YES:26, NO:2, ABSTAIN:1]; AEGL-3 [motion made by E. Falke, seconded by J. Hinz: YES:26, NO:2, ABSTAIN:1] (Appendix F).

SUMMARY OF PROPOSED AEGL VALUES FOR CHLORINE TRIFLUORIDE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	0.70 ppm 2.7 mg/m^3	0.35 ppm 1.3 mg/m^3	0.09 ppm 0.34 mg/m^3	0.04 ppm 0.15 mg/m^3	threshold for notable discomfort
AEGL-2	6.2 ppm 24 mg/m^3	3.1 ppm 12 mg/m^3	0.77 ppm 2.9 mg/m^3	0.39 ppm 1.5 mg/m^3	strong irritation - dog
AEGL-3	27 ppm 103 mg/m^3	14 ppm 53 mg/m^3	3.4 ppm 13 mg/m^3	1.7 ppm 6.5 mg/m^3	threshold for lethality (LC_{01}) - mouse

Ethylenimine
CAS Reg. No. 151-56-4

Chemical Manager: **Mark McClanahan, CDC**
Chemical Reviewers: **Loren Koller, OSU**
Richard W. Niemeier, NIOSH
Staff Scientist: Kowetha Davidson, Oak Ridge National Laboratory

Mark McClanahan presented introductory material and Kowetha Davidson presented an overview of AEGL derivations for ethylenimine (Attachment 15). Following discussions regarding the concentration measurement in the human data sets and how to address the carcinogenicity issues, Steve Barbee proposed AEGL-2 and AEGL-3 values based upon respiratory effects and lethality endpoints, respectively, with a total uncertainty factor application of 10 (3 for intraspecies variability and 3 for interspecies variability). The proposed AEGL values were approved by the NAC/AEGL: AEGL-1 [motion made by S. Barbee, seconded by M. McClanahan: YES:26, NO:1, ASBSTAIN:1]; AEGL-2 [motion made by S. Barbee, seconded by M. McClanahan: YES:23, NO:4, ABSTAIN:1]; AEGL-3 [motion made by S. Barbee, seconded by M. McClanahan: YES:24, NO:3, ABSTAIN:1]. The TSD for ethylenimine should note the carcinogenicity issue as well as the possibility of delayed effects at AEGL levels (Appendix G).

SUMMARY OF PROPOSED AEGL VALUES FOR ETHYLENIMINE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	NR	NR	NR	NR	
AEGL-2	9.8 ppm 5.5 mg/m^3	4.6 ppm 2.6 mg/m^3	1.0 ppm 0.56 mg/m^3	0.47 ppm 0.26 mg/m^3	respiratory difficulty - guinea pig
AEGL-3	18 ppm 10 mg/m^3	9.6 ppm 5.5 mg/m^3	2.8 ppm 1.6 mg/m^3	1.5 ppm 0.84 mg/m^3	lethality threshold - rat

NR: No recommendation

Diborane
CAS Reg. No. 19287-45-7

Chemical Manager: **Jim Holler, ATSDR**
Chemical Reviewers: **George Rogers, AAPCC**
Robert Benson, U.S. EPA
Staff Scientist: Claudia Troxel, Oak Ridge National Laboratory

Claudia Troxel presented an overview of the derivation of AEGLs for diborane (Attachment 16). Following a very brief discussion, a motion was made by D. Hansen and seconded by W. Bress to approve values for AEGL-2 and AEGL-3, and adopt a "Not Appropriate" status for AEGL-1 (no sensory irritation and AEGL-2 values are below the odor threshold). The motion carried and the following proposed values were approved: AEGL-1 [YES:26, NO:2, ABSTAIN:1]; AEGL-2 [YES:22, NO:6, ABSTAIN:1]; AEGL-3 [YES:27, NO:1, ABSTAIN:1] (Appendix H).

SUMMARY OF PROPOSED AEGL VALUES FOR DIBORANE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	NA	NA	NA	NA	
AEGL-2	2.0 ppm 2.2 mg/m^3	1.0 ppm 1.1 mg/m^3	0.25 ppm 0.28 mg/m^3	0.13 ppm 0.14 mg/m^3	multifocal and/or diffuse epithelial degeneration in terminal bronchi
AEGL-3	7.3 ppm 8.0 mg/m^3	3.7 ppm 4.1 mg/m^3	0.92 ppm 1.0 mg/m^3	0.46 ppm 0.51 mg/m^3	LC_{01} - mouse

NA: Not appropriate

Allylamine
CAS Reg. No. 107-11-9

Chemical Manager: **Loren Koller, OSU**
Chemical Reviewers: **Mark McClanahan, CDC**
Robert Hazen, New Jersey
Staff Scientist: Sylvia Milanez, Oak Ridge National Laboratory

Sylvia Milanez provided an overview of the derivation of proposed AEGLs for allylamine (Attachment 17). The AEGL-3 values based upon lethality in rats were accepted as originally proposed in the TSD [motion made by L. Gephart, seconded by Z. Post: YES:25, NO:0, ABSTAIN:1]. Loren Koller led discussions regarding the selection of the exposure concentrations, endpoints, and uncertainty factors with which to derive the AEGL-2 values for allylamine. Following discussions, four options were presented: (1) base all AEGL-2 values on the RD_{50}, (2) use an irritation threshold in human subjects for the 30-min and 1-hour values, and cardiotoxic effects in rats (40 ppm for 8 hours, UF=100) for the 4- and 8-hour values, (3) use an 8-hour exposure to 40 ppm (cardiotoxicity, UF=100), or (4) use the values as originally proposed in the draft TSD based upon decreased body weight gain in rats at 10 ppm, UF=30). A poll of the Committee appeared to favor the originally proposed values or those based upon the third option. The NAC/AEGL approved the AEGL-2 values based upon cardiotoxicity following an 8-hour exposure to 40 ppm [motion made by Z. Post, seconded by J. Hinz: YES:22, NO:2] (Appendix I). Because the odor threshold is at or above the 4- and 8-hour AEGL-2 values, it was the consensus [motion made by E. Falke, seconded by R. Thomas: YES:17, NO:7] of the NAC/AEGL that AEGL-1 values be considered inappropriate for allylamine (Appendix I). The AEGLs for allylamine are summarized in the following table.

SUMMARY OF PROPOSED AEGL VALUES FOR ALLYLAMINE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	NA	NA	NA	NA	
AEGL-2	11 ppm 25 mg/m^3	4.7 ppm 11 mg/m^3	0.91 ppm 2.1 mg/m^3	0.40 ppm 0.93 mg/m^3	cardiotoxicity following 8-hr exposure to 40 ppm
AEGL-3	40 ppm 94 mg/m^3	18 ppm 42 mg/m^3	3.5 ppm 8.1 mg/m^3	2.3 ppm 5.4 mg/m^3	lethality (LC_{01}) in rats exposed for 1, 4, or 8 hrs

NA: Not appropriate

Hydrogen chloride
CAS Reg. No. 7647-01-6

Chemical Manager: **John Hinz, USAF**
Chemical Reviewers: **Larry Gephart, Exxon Biomedical**
Nancy Kim, New York State Health Department
Staff Scientist: Cheryl Bast, Oak Ridge National Laboratory

An overview of hydrogen chloride issues from the perspective of the U.S. Air Force Rocket Emissions Workgroup was provided by John Hinz (Attachment 18). It was emphasized that HCl exposure is a pertinent issue relative to rocket launches (ground cloud exposures to mission-critical personnel, on-base personnel

distant to the launch site, and civilian off-base population), and that such exposure potential occurs with regularity as opposed to the single accident scenarios normally assumed for AEGL application. Cheryl Bast reviewed the limited data available for derivation of AEGLs as well as the derivation of the AEGLs proposed in the draft TSD (Attachment 19). Following discussion, it was unanimously agreed that the AEGL-1 be set at 1.8 ppm for all time points [motion made by D. Hansen, seconded by S. Barbee: YES:25, NO:0]. For AEGL-2, discussions focused on incidences of histopathologic findings in the rats from the Stavert et al. (1991) study and that the proposed 1-hour AEGL-2 was higher than the ERPG and SPEGL. Following discussions regarding uncertainty factor applications, AEGL-2 values were approved by the Committee [motion made by W. Bress, seconded by R. Benson: YES:23, NO:1]. AEGL-3 values were accepted as originally presented in the TSD [motion made by L. Koller, seconded by D. Hansen: YES:16, NO:5]. The values for HCl are shown in the following table. (Appendix J)

SUMMARY OF PROPOSED AEGL VALUES FOR HYDROGEN CHLORIDE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	1.8 ppm 2.7 mg/m^3	1.8 ppm 2.7 mg/m^3	1.8 ppm 2.7 mg/m^3	1.8 ppm 2.7 mg/m^3	no effect level in humans (exercising asthmatics)
AEGL-2	43 ppm 64 mg/m^3	22 ppm 33 mg/m^3	5.4 ppm 8.0 mg/m^3	2.7 ppm 4.0 mg/m^3	histopathology in rats
AEGL-3	210 ppm 313 mg/m^3	104 ppm 155 mg/m^3	26 ppm 39 mg/m^3	13 ppm 19 mg/m^3	1-hr rat LC_{50}

ADMINISTRATIVE ISSUES

Meeting Commencement and Adjournment

It was the consensus of the NAC/AEGL that the meeting will continue to start at 10:00 a.m. the first day but that commencement will be 8:00 a.m. for days 2 and 3. Adjournment on day 3 will be at 12:30 p.m.

General Comments

In an open comment session, George Rusch requested comments from the committee. These included but were not limited to:

- a need for clear presentation of how AEGL values are derived
- a need for carefully developed standard operating procedures that allow for time- and cost-effective document preparation and approval of values
- need for a cover memo on document revisions to note major changes and a date on each draft
- a need to identify research needs where appropriate
- improvement in the meeting facility audio equipment and in visual aids used by presenters
- necessity of focusing on science vs policy procedures
- availability of a table/chart of NAC areas-of-expertise
- NAC should avoid dogmatic views and excessive focus on methodologies rather than human health issues
- the formation of separate groups for chemical-specific evaluations
- availability of chemical-specific experts as *ad hoc* participants at NAC/AEGL meetings
- a need to focus on cancer assessments for acute exposures

- Paul Tobin emphasized that the copies of TSDs in the foyer of the meeting room are for visitors/observers and NOT for NAC/AEGL members. Members are to bring their own copies to the

meeting

- For the standing operating procedures, some attention should be given to endpoints for AEGLs, application and interpretation of dispersion models and dose reconstruction, carcinogenicity and reproductive toxicity issues, disposition of Federal Register comments, and recourse if data are inadequate for AEGL derivation

Standing Operating Procedures (SOP) Workgroup

A workgroup to assist in the development of AEGL technical support document (TDS) was announced by Roger Garrett. The Standing Operating Procedures (SOP) Workgroup, chaired by Ernest Falke (U.S. EPA), will consist of George Alexeeff (CALEPA), Steven Barbee (Olin Corp.), David Belluck (MN Pollution Control), George Rogers (AAPCC), Kenneth Steel (DoD), and Robert Young (ORNL). George Rusch and Roger Garrett will serve as advisors. Based on an open discussion with the NAC/AEGL members, chaired by George Rusch on Tuesday, June 10, 1997, regarding the focus of the workgroup, a list of important areas releated to the development of AEGL values was compiled. This list has been orgnized into three major categories that are to be addressed initially by the workgroup. These include: (1) development of information and data for TSDs, (2) calculation of AEGL values, and (3) format and content of TSDs (Attachment 20). A 30-minute organizational meeting of the workgroup was held on Wednesday, June 11, prior to the regular NAC/AEGL priority chemical review session. An effort will be made to focus on item No. 3 and to identify specific areas in item No. 2 that may be more easily addressed. Areas that were not considered to be of immediate concern to the workgroup were justification for chemical selection, review of AEGLs, membership, chemical manager roles, and identification of studies to fill data gaps.

Action Item: members of the SOP Workgroup will provide comments/thoughts on initial issues to Ernest Falke by June 28.

Future Meeting Dates

The following meeting dates were tentatively scheduled:
Meeting No. 7 - September 23-25, 1997
Meeting No. 8 - December 8-10, 1997

The date and location of the March and June 1998 meetings were briefly discussed but no decisions made.

The meeting highlights were prepared by Robert Young and Po-Yung Lu, ORNL.

Areas to be Addressed by SOP Workgroup

1. Development of Information and Data for TSDs.
   a. Possible approaches to supplements to literature/data searches
   b. Guidelines/criteria for quality ranking of papers/data and confidence in studies
   c. Possible use or graphs to evaluate/utilize data
   d. Archives - who, how long, where

2. Calculations of AEGL Values
   a. Refinement of AEGL-1 definition (possibly AEGL-2 also)
   b. Endpoints for selection of AEGL levels (and their significance, including significance of odor & behavioral criteria)
   c. Dose extrapolation techniques
   d. Guidelines/criteria for use of NOAELs and LOAELs
   e. Guidelines/criteria for uncertainty factors
   f. Guidelines/criteria for modifying factors
   g. Guidelines/criteria for time scaling (algorithm and short to long term scaling)
   h. Guidelines/criteria for exposure data, exposure assumptions, and exposure models
   I. Guidelines/criteria for scientific rationale
   j. Policy for known and suspect carcinogens
   k. Scientific basis for decision
   l. Endpoints - key ones - priority
   m. What constitutes insufficient information
   n. Fetotoxicity, Ca risk

3. Format and Content of TSDs
   a. Format for summary table
   b. Consistency of data tables
   c. Potential inclusion of special data/info (e.g., chemical structure, relevant P/C properties, uses, etc.)
   d. Guidelines/criteria for presentation of scientific rationale
   e. Guidelines/criteria for describing/presenting calculations
   f. Potential inclusion of graphic descriptions of data
   g. Format/consistency in developing revised TSDs
   h. Guidelines/criteria for consistent description of data

LIST OF ATTACHMENTS

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

1. NAC /AEGL Meeting No. 6 Agenda
2. NAC/AEGL Meeting No. 6 Attendee List
3. Consensus of Operating Procedures - Richard Thomas
4. Data analysis of Arsine - Bob Young
5. Data analysis of Hydrogen cyanide - Ernie Falke
6. Data analysis of Hydrogen fluoride - Sylvia Talmage
7. Data analysis of Methylmercaptan - Doan Hansen
8. Ammonia AEGL Update - Larry Gephart
9. Data analysis of Ammonia -Kowetha Davidson
10. Public comment from RAM TRAC - Robert Michaels
11. Public comment from ENVIRON - Chris Leason and Barry Hooberman
12. Threshold for Sensitization - Steve Barbee
13. ClF3 hydrolysis products - Kyle Blackman
14. Data analysis of ClF3 - Sylvia Talamge
15. Data analysis of Ethylenimine - Kowetha Davidson
16. Data analysis of Diborane - Claudia Troxel
17. Data analysis of Allylamine - Sylvia Milanez
18. HCl: An Air Force-based Perspective - John Hinz
19. Data analysis of HCl - Cheryl Bast
20. SOP Workgroup Report

LIST OF APPENDICES

A. Approved NAC/AEGL- 5 Meeting Highlights
B. Ballot for Arsine
C. Ballot for Cyanogen chloride
D. Ballot for Ammonia
E. Ballot for TDI
F. Ballot for ClF3
G. Ballot for Ethelenimine
H. Ballot for Diborane
I. Ballot for Allylamine
J. Ballot for Hydrogen chloride

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

Ariels Rios Building, 3rd Floor, Green Room
1200 Pennsylvania Avenue, N.W., Washington, D.C.

NAC-6

Agenda

Monday, June 9, 1997

10:00 - 10:15	AM	Introduction and approval of NAC-5 highlights
10:15 - 10:30		Uncertainty Factor Subcommittee report (Richard Thomas)
10:30 - 11:30		Final Review of AEGLs: ▸ Arsine ▸ Cyanogen chloride ▸ Hydrogen cyanide ▸ Hydrogen fluoride ▸ Methyl mercaptan
11:30 - 12:00		Ammonia (Larry Gephart/Kowetha Davidson)
12:00 - 1:00	PM	**Lunch**
1:00 - 2:30		Ammonia (continued)
2:30 - 2:45		**Break**
2:45 - 3:45		Toluene 2,4- & 2,6-diisocyanates (Steve Barbee/Carol Forsyth)
3:45 - 5:00		Chlorine trifluoride (Kyle Blackman/Sylvia Talmage)

Tuesday, June 10, 1997

8:30 - 10:30	AM	Hydrogen chloride (John Hinz/Cheryl Bast)
10:30 - 10:45		**Break**
10:45 - 11:15		Dimethyldichlorosilane (Ernie Falke/Cheryl Bast)
11:15 - 12:30		Ethylenimine (Mark McClanahan/Kowetha Davidson)
12:30 - 1:30	PM	**Lunch**
1:30 - 2:45		Diborane (Jim Holler/Claudia Troxel)
2:45 - 3:00		**Break**
3:00 - 4:15		Allylamine (Loren Koller/Sylvia Milanez)
4:15 - 5:30		Carbon tetrachloride (Bill Bress/Bob Young)

Wednesday, June 11, 1997

8:30 - 9:15	AM	Carbon tetrachloride (continued)
9:15 - 11:15		Methyl-, iso-Propyl-, Propyl-chloroformates (Ernie Falke, Doan Hansen/Cheryl Bast)
11:15 - 11:30		**Break**
11:30 - 1:00	PM	Administrative issues
1:00		Adjournment

Attachment 2

ATTENDANCE SHEET

SUBJECT: NAC/AEGL

DATE: June 9, 1997 LOCATION: Ariel Rios - Green Room

TIME: 10:00 AM —

Name	Signature	Organization	Phone Number
Thomas J. Sobotka	[signature]	FDA/CFSAN	301 594-5881
Robert Hazen	[signature]	NJDEP	609 292-8294
Marion Ehrich	[signature]	Virginia Tech	540-231-4938
Patricia Talcott	[signature]	UI/WSU	208-885-7081
Loren Koller	[signature]	Oregon State University	541 737 5547
Zarena Post	[signature]	Tx Natural Resource Conserv. Commission	512-239-1332
Bill Bress	[signature]	ASTHO	802-863-7220
Doan Hansen	[signature]	BNL/DOE	516 344-7535
Larry Gephart	[signature]	Exxon	908 874-4581
Jonathan Borak	[signature]	ACOEM	203-777-6611
Richard Thomas	[signature]	SCEH	703-734-1454
Ernest V. Falke	[signature]	USEPA	(202) 260-3433
Roger L. Garrett	[signature]	US EPA	202-260-4302
Luz Claudio	[signature]	Mt Sinai	212 241 7625
John P. Hinz	[signature]	USAF	(210) 536-6136
M Gerald OTT	[signature]	BASF	(201) 426-6997
Nancy Nickell	[signature]	SELF (reporter)	(202) 986-3812 / 201 fax
Robert Michaels	[signature]	RAM TRAC Corp.	518-785-0976
Daniel R. Kuespert	[signature]	IIAR	202-857-1110
Daniel M. Woltering	[signature]	ENVIRON	703-516-2300
Barry Hooberman	[signature]	ENVIRON	703-516-2332

Maxyne Hodges

ATTENDANCE SHEET

SUBJECT:

LOCATION: Ariel Rios - Green Room

DATE:
TIME:

Name	Signature	Organization	Phone Number
Richard Thomas			
Kallas Dan			
NANCY NICKELL	NN	Freelance Reporter	Ph (202) 986-3812 Fax " " 2017
Green			
John S. Morawetz	John S. Morawetz	ICWUC	513-621-8882
George Rusch	[illegible]	Allied Signal	201-455-3672
Larry Geplart	[illegible]	Exxon Biomed.	908 874 4581
George Cushmac		DOT	202-366-4493
Tom Sobotka	Tom Sobotka	FDA	301-594-5885
JIM HOLLER	Jim Holler	ATSDR	404-639-6208
SYLVIA TALMAGE	Sylvia Talmage	ORNL	423-576-7758
Bill Bress	Bill Bress	VA DOH	802-893-1180
M G OTT	M G Ott	BASF	201 426-6997
ROBERT YOUNG	Robert Young	ORNL	(423) 574-4573
Sylvia Milanez	Sylvia Milanez	ORNL	423 576 2964
Claudia M Troxel	Claudia M Troxel	ORNL	423 574-8784
Bob Hazen	[illegible]	NJDEP	609 292 8244
SJ Barbee	SJ Barbee	Olin	203-495-8550
Roger Garrett			
Bob Hazen			
Andrew Jaques	Andrew Jaques	API	202-682-8563
Cheryl Bast	Cheryl Bast	ORNL	423-574-7581
DAVE DELLARCO	V. a Dellarco	MPCA	612-296-7874
Glenn Leach	Glenn Leach	ARMY	410-671-3980
Robert Michaels	Robert Michaels	RAM TRAC Corp	518-785-0976

ATTENDANCE SHEET

SUBJECT:

DATE:
TIME:

LOCATION: Ariel Rios - Green Room

Name	Signature	Organization	Phone Number
MARK A. McCLANAHAN	Mark McClanahan	CDC	770-488-7297
JIM HOLLER	Jim Holler	ATSDR	404-639-6308
GLENN LEACH	Glenn Leach	U.S. Army - CHPPM	410-671-3980
Kenneth R. Still	[illegible]	US NAVY	937-255-6058 X202
GEORGE CUSHMAC	George Cushmac	US DOT	202-366-4493
STEVEN BARBEE	[illegible]	Olin Corp	203-495-8550 x5455
WILLIAM PELELKO	William Pelelko	U.S. EPA	202-260-5904
Nancy Kim	Nancy Kim	NYS - Health	518-458-6435
Bob Benson	Robert Benson	USEPA - Region 8	303-312-7070
TOM HORNSHAW	Thomas C. Hornshaw	IL EPA	217-785-0830
George Alexeeff	George Alexeeff	Cal/EPA	510-540-3324
DAVE Bellaci	D. A. Bellaci	MPCA	612-296-7874
KYLE BLACKMON	Kyle W. Blackmon	FEMA	202/646-4676
Paul Tobin	Paul Tobin	EPA	202 260-1736
GEORGE RUSCH	[illegible]	Allied Signal	201-455-3672

Mahfuz Hodge

ATTENDANCE SHEET

SUBJECT:

DATE:
TIME:

LOCATION: Ariel Rios - Green Room

Name	Signature	Organization	Phone Number
Lynn Beasley	Lynn M Beasley	EPA Superfund	703 603 9088
Dan Wolkerin	Dan Wolkerin	ENVIRON	703 516 2300
BARRY HOOKSTRA		ENVIRON	703-516-2372
John Hinz		USAF/Brooks AFB	(210)536-6136
JIM SKILLEN	Jim Skillen	TFI	(202)608-5910
CHRIS LEADON		McKenna/Cum	202.496.7102
Kowetha A. Davidson		ORNL	423/574-7799
Sylvia S. Talmage	S.S. Talmage	ORNL	423-576-7758
Po-Yung Lu	Po Yung Lu	ORNL	423-574-7803
Carl A. Mazzola	Carl A Mazzola	Stone & Webster	706-650-0939

Consensus Operating Procedure

Number 1

Treatment of AEGL Values

Significant Figures

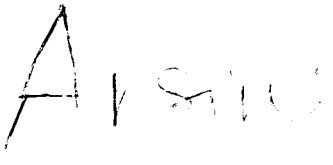
Significant figures are the digits necessary to express the results of a measurement to the precision with which it is made. Precision is the variability among replicate measurements. By consensus, the National Advisory Committee for Acute Exposure Guideline Levels (NAC/AEGL) has agreed to express all AEGL values in no more than two significant figures and one significant figure to the right of the decimal. Thus, an AEGL value of 0.354 ppm will be rounded to 0.4 ppm and a value of 2.828 ppm will be rounded to 2.8 ppm. The committee may also agree to round this value further to 3 ppm, when the data indicate that one significant figure is appropriate.

Rounding Values

The Committee has agreed by consensus, to use the standard accepted procedure of rounding down when a numeric value is between 1 and 4 and round up when the value is between 5 and 9. Thus, 1.44 ppm will be rounded to 1.4 ppm and 1.46 ppm will be rounded to 1.5 ppm.

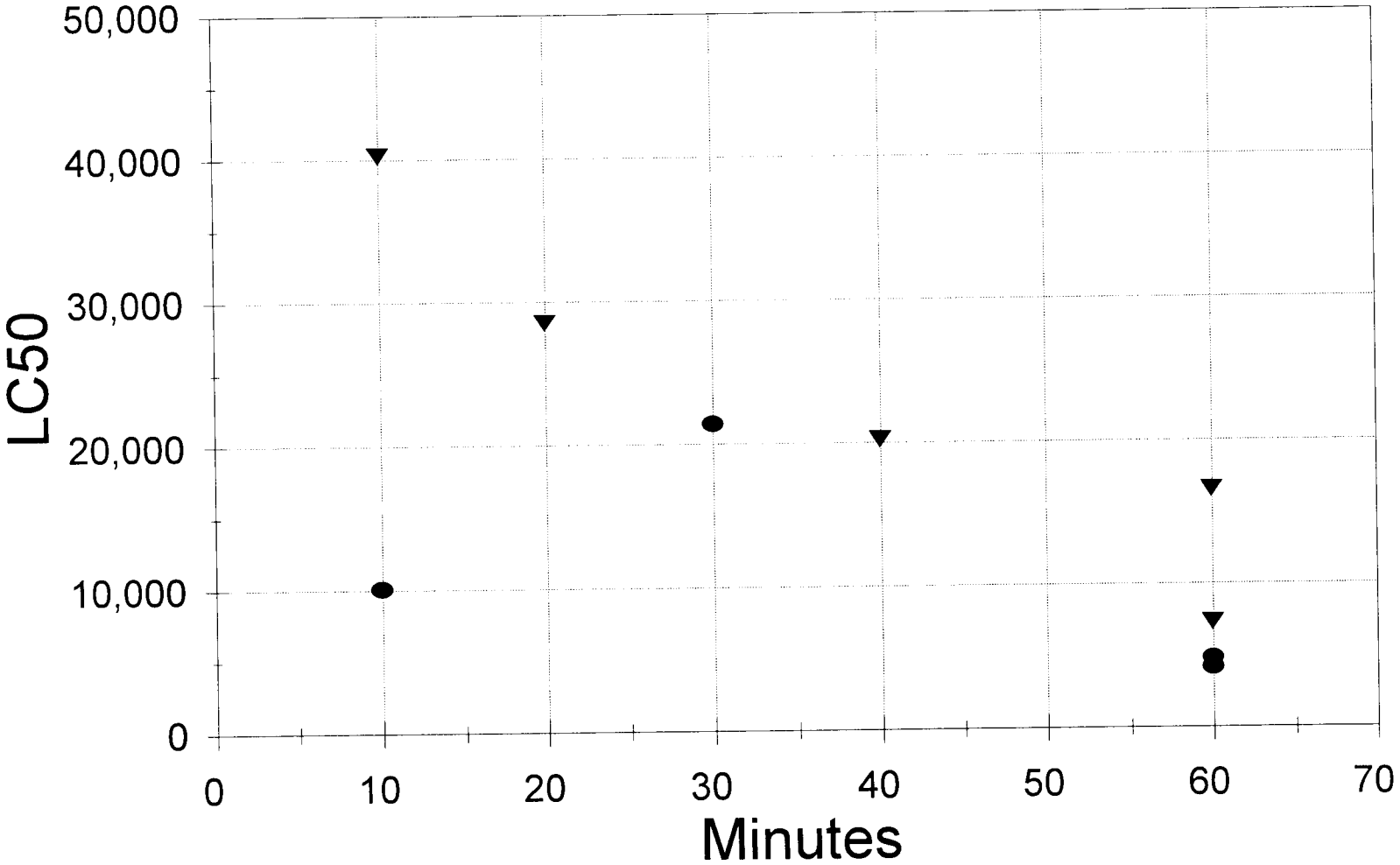
The AEGL-1 values (0.1 ppm for all time points) may not be scientifically justifiable. The available data (both quantitative and qualitative assessments) indicate a very steep exposure-response curve for arsine. Data from studies in rodents affirm that there is little margin between exposures that cause little or no toxicity and those that are lethal. The currently proposed AEGLs reflect this; all AEGL values are between 0.1 and 0.7 ppm and the 4-hr and 8-hr AEGL-2 values are the same as the AEGL-1 values. Considering the mechanism of arsine toxicity (hemolysis that may rapidly and irreversibly culminate in renal failure and death) and the fact that toxicity in animals and humans has been demonstrated at concentrations at or below the odor threshold (0.5 ppm), it seems appropriate to refrain from setting AEGL-1 values. This, in fact, is consistent with what was done with methylhydrazine and dimethylhydrazine which also exhibited toxicity at or below the odor threshold.

With respect to these concerns, it is proposed that the arsine AEGL-1 values for all time points be considered not applicable. An AEGL-1 for arsine would be difficult to justify scientifically.



SUMMARY OF PROPOSED AEGL VALUES FOR ARSINE					
Classification	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	0.1 ppm 0.3 mg/m^3	0.1 ppm 0.3 mg/m^3	0.1 ppm 0.3 mg/m^3	0.1 ppm 0.3 mg/m^3	No-effect level for hematological changes in mice (Blair et al., 1990) and the fact that toxic effects are known to occur below the odor threshold of 0.5 ppm.
AEGL-2 (Disabling)	0.24 ppm 0.8 mg/m^3	0.17 ppm 0.5 mg/m^3	0.1 ppm 0.3 mg/m^3	0.1 ppm 0.3 mg/m^3	Absence of significant hematological alterations in mice consistent with the known continuum of arsine toxicity (Peterson and Bhattacharyya, 1985)
AEGL-3 (Lethality)	0.7 ppm 2.2 mg/m^3	0.5 ppm 1.6 mg/m^3	0.25 ppm 0.8 mg/m^3	0.18 ppm 0.6 mg/m^3	Estimated threshold for nonlethality in mice (Peterson and Bhattacharyya, 1985)

LETHALITY DATA FOR RATS AND MICE



Attachment 5

Revision of Proposed Hydrogen Fluoride AEGLs

June 1997

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Larry Gephart

Attachment 6

HYDROGEN FLUORIDE

INCONSISTENCIES IN THE USE OF DATA

Inconsistency: For derivation of the 10-minute AEGL-2, the mean of a no-effect (950 ppm) and a lethal concentration (1/20 deaths at 1764 ppm) of orally-cannulated rats was used (1300 ppm), whereas the no-effect 950 ppm concentration was used to derive the 30-minute and 1-hour AEGL-2 values.

Change: Use the 10-minute 950 ppm no-effect concentration to derive the 10-minute AEGL-2. Result is 95 ppm instead of 130 ppm.

The combined interspecies and intraspecies uncertainty factor of 10 (3 and 3) remains the same.

HYDROGEN FLUORIDE

INCONSISTENCIES IN THE USE OF UNCERTAINTY FACTORS

Inconsistency: Used interspecies uncertainty factor of 10 (rat was not the most sensitive species) and intraspecies uncertainty factor of 3 for 30-minute and 1-hour AEGL-2. However, hydrogen fluoride was delivered directly to the trachea (a conservative model that mimics human mouth breathing), thus bypassing the scrubbing action of the nasal passages. In addition, the endpoint was a no-effect concentration (950 ppm for 10 minutes). Interspecies and intraspecies uncertainty factors of 3 and 3 are generally used for irritant gases.

Change: Use total uncertainty factor of 10 (3 and 3). Results are 30-minute and 1-hour AEGL-2 values of 55 and 39 ppm instead of 18 and 13 ppm.

HYDROGEN FLUORIDE

ADJUSTMENT OF ENDPOINT

Inconsistency: For AEGL-3, used LC_0 for mouse (263 ppm for 1 hour) when data allowed calculation of an LC_{01}, the accepted threshold for lethality.

Change: Use LC_{01} (200 ppm) instead of LC_0 (263 ppm).

HYDROGEN FLUORIDE

BACKUP STUDIES TO THE AEGL-2 AND AEGL-3 VALUES

AEGL-2

Mouse RD_{50} = 151 ppm (0.1 x RD_{50} = 15 ppm)

0.1 x RD_{50} can be tolerated for hours with some irritation (Alarie)

AEGL-3

All of the animal data support the new AEGL-3 values:

Nose-breathing animals

monkey, 1-hour LC_0 of 690 ppm/10 = 69 ppm (MacEwen and Vernot, 1970)
rat, 1 hour no lung lesions of 1630 ppm/10 = 163 ppm (Haskell, 1989)
rat, 1 hour respiratory distress of 1224 ppm/10 = 122 ppm (Dalbey, 1996)
rat, 1 hour LC_0 of 1087 ppm/10 = 109 ppm (Wohlslagel et al. 1976)
guinea pig, 30 minutes no deaths, 1377/10 = 138 ppm (Rosenholtz et al., 1963)
guinea pig, 30 minutes no deaths, 1220/10 = 122 ppm (Machle et al., 1934)
rabbit, 30 minutes no deaths 1220/10 = 122 ppm (Machle et al., 1934)

Orally-cannulated rats:

1700 ppm for 10-minutes = 1/20 deaths
1700/10, scaled, = 1-hour value of 69 ppm

HYDROGEN FLUORIDE

INCONSISTENCIES IN THE USE OF UNCERTAINTY FACTORS (con't)

Inconsistency: Used interspecies uncertainty factor of 2 for the 30-minute and 1-, 2-, 4-, and 8-hour AEGL-3 values (based on the LC_0 of 263 ppm for the mouse, the most sensitive species).

Change: Use interspecies uncertainty factor of 1 because mouse is 2-4 times more sensitive than rat; if we use UF of 2 or 3, the AEGL-3 values will be below the AEGL-2 values. Use 1-hour mouse LC_{01} (200 ppm) instead of mouse LC_0 (263 ppm). Results are 30-minute and 1-, 4-, and 8-hour AEGL-3 values of 94, 67, 33, and 24 ppm.

HYDROGEN FLUORIDE

SUMMARY OF REVISED PROPOSED AEGL VALUES					
Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	2 ppm (1.6 mg/m^3)	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)
AEGL-2 (Disabling)	95 ppm (78 mg/m^3)	55 ppm (45 mg/m^3)	39 ppm (32 mg/m^3)	10 ppm (8 mg/m^3)	7 ppm (6 mg/m^3)
AEGL-3 (Lethal)	170 ppm (139 mg/m^3)	94 ppm (77 mg/m^3)	67 ppm (55 mg/m^3)	33 ppm (27 mg/m^3)	24 ppm (20 mg/m^3)

HYDROGEN FLUORIDE

SUMMARY OF ORIGINAL PROPOSED AEGL VALUES					
Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	2 ppm (1.6 mg/m^3)	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)
AEGL-2 (Disabling)	130 ppm (107 mg/m^3)	18 ppm (15 mg/m^3)	13 ppm (11 mg/m^3)	10 ppm (8 mg/m^3)	7 ppm (6 mg/m^3)
AEGL-3 (Lethal)	170 ppm (139 mg/m^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)

5.1 Human Data Relevant to AEGL-1

Katz and Talbert (1930) exposed human subjects to one inhalation of methyl mercaptan via a nosepiece at a range of concentrations (n=6 for each nominal concentration). The subjects rated methyl mercaptan odor intensity as follows:

Intensity	Description	Concentration (ppm)
0	no odor	0.0030
1	threshold	0.041
2	faint	0.57
3	median, easily noticeable	7.9
4	strong	110
5	most intense	1,500

Wilby (1969) exposed 34 observers to methyl mercaptan at 12 concentrations representing a one hundred fold range in concentrations. Odorometers were used to blend (dilute) standard concentrations (standard concentrations verified by gas chromatograph). For each subject an odor recognition threshold was determined on the basis of three trials. The mean odor threshold concentration for methyl mercaptan was 0.00099 ppm with a standard deviation of 0.00072 ppm and a coefficient of variation of 0.72. No other effects were noted.

Williams (1977) used the Dynamic Triangle Olfactometer, an instrument which measures odor thresholds by dilution and steady state flow, to determine odor thresholds by means of ED50s. Here the ED50 represents the effective dilution at which 50% of subjects can detect the odor. Using an unspecified number of subjects, the odor threshold for methyl mercaptan was determined to be 1.5E10-7 ppm. No other health effects were noted.

Nishida (1979) exposed 8-11 humans (18-40 y.o.) to a series of chemicals including methyl mercaptan. Subjects rated odors on a scale of 0 to 8, where 0=no smell at all and 8=extremely strong. A PPT50 (defined as perceptive threshold to 50% of population) was determined for methyl mercaptan and used to obtain an odor detection level of 0.019 ppm (range of 0.010-0.430 ppm). No other health effects were noted.

Kangas (1984) collected air samples from kraft mills and sulfite mills (pulp industry) and reported methyl mercaptan concentrations ranging from 0 to 15 ppm for 13-15 workers. Some subjects reported clinical symptoms (seven had lack of mental concentration capacity versus only one of the controls), however, workers were simultaneously exposed to hydrogen sulfide, dimethyl sulfide and dimethyl disulfide. It is difficult to attribute symptoms to methyl mercaptan alone or at any concentration level.

5.2 Animal Data Relevant to AEGL-1

There is little animal data relevant for deriving an AEGL-1 for methyl mercaptan. Selyuzhitskii (1972, translation) derived the MPC of 0.0005 mg/m3 (0.000025 ppm) for methyl mercaptan, where MPC is the Maximum Permissible Concentration. This value (i.e., the MPC) is

based on odor. The authors defined MPC as being above the threshold concentration but below the "irritating concentration" in man. The authors determined LC50s for rats and mice, however, relevant experimental parameters were not stated and the study should not be strongly considered.

5.3 Derivation of AEGL-1

Odor is the health effect noted in humans exposed experimentally or empirically to low concentrations of methyl mercaptan, as cited above. The determination of an odor threshold, particularly for use with AEGL-1, should include sensitive members of the population but not be restricted to hypersensitive members. The use of ten Berge (1986) and other scaling factors may not be appropriate for odor data (since odor is a sensation rather than a cumulative dose response effect).

An AEGL-1 value of 0.5 ppm was derived for all AEGL-1 time periods. An AEGL-1 of 0.5 ppm is above the experimentally determined odor thresholds, thus including hypersensitive and sensitive individuals, and existing occupational exposure limits (ACGIH TLV = 0.5 ppm and OSHA PEL = 0.5 ppm) have not resulted in the occurrence of other acute adverse health effects other than nuisance odor, thus indicating that exposures to these concentrations in the healthy working population are not harmful and presumably in the general public as well.

Additional References:

Selyuzhitskii, G.V., "Test Data, Substantiating Maximum Permissible Concentrations of Methyl Mercaptan of Dimethyl Sulfide and Dimethyl Disulfide," Gig. Tr. Prof. Zabol., 16(6):46-47, 1972.

J. Kangas, P. Jappinen, and J. Avolainen, "Exposure to Hydrogen Sulfide, Mercaptans and Sulfur Dioxide in Pulp Industry,"Am. Ind. Hyg. Assoc. J. 45(12):787-790 (1984).

Nishida, K., M. Yamakawa and T. Honda, "Experimental Investigations on Combined Actions of Components Mixed in Odorous Gas," Mem. Fac. Eng., Kyoto Univ. 41, part 4, 552-565. Code A.

Williams, F.D., J.F. Emele and M.C. Alford 1977, "The Application of the Dynamic Triangle Olfactometer to the Evaluation of Oral Odor," Chem. Senses Flavour 2:497-502.

Katz, S.H. and E.J. Talbert 1930, "Intensities of Odors and Irritating Effects of Warning Agents for Inflammable and Poisonous Gases," (U.S. Bureau of Mines, Technical Report no. 480.) Washington D.C.: U.S Dept. Of Commerce. Code A.

Wilby, F.V., "Variation in Recognition Odor Threshold of a Panel," Air Pollut. Control Assoc. 19:96-100. Code A (1969).

AMMONIA AEGL UPDATE - JUNE 1997

- REVIEWED COMMENTS
  - Public
  - AEGL Committee
  - Our own
- CONSIDERED NEW INFORMATION
  - Mouse LC50 by Vernot
  - Occupational exposure on poultry workers
  - Accident reconstruction data
- REVISED TECHNICAL SUPPORT DOCUMENT COMMENTS
  - AEGL 3 and 2 rationales
  - Text: many changes
  - Expanded discussion on confidence / uncertainties

ACUTE EXPOSURE GUIDELINE LEVELS FOR AMMONIA

PREPARED BY

KOWETHA A. DAVIDSON
OAK RIDGE NATIONAL LABORATORY

PRESENTED AT THE NAC/AEGL MEETING, WASHINGTON, D.C., JUNE 9 - 10, 1997

Attachment 9

AEGL-3 VALUES FOR AMMONIA
Reference: MacEwen and Vernot, 1972 **(I)**; Kapeghian et al., 1982 **(II)**
Test Species/Strain/Sex/Number: CF1or ICR strain/males/10 or 12 per group
Exposure Route: Inhalation **Concentration**: 0, 3600, 4550, 5720 ppm **(I)** 0, 1190, 1340, 2130, 3440, 3950, 4220, 4490, 4860 ppm **(II)** **Duration**: 1 hour exposure; 14-day observation
Effects: **(I)**: deaths: 0/10, 3/10, and 9/10 at 3600 ppm, 4500 ppm, and 5720 ppm; clinical signs: nasal and eye irritation, labored breathing, gasping, convulsions; low body weight gain **(II)**: deaths: 0/12, 3/12, 5/12 , 8/12, and 12/12 and 10/12 at ≤3440, 3950, 4220, 4490, and 4860 ppm; clinical signs: eye and nasal irritation, hypoactivity, labored breathing, ataxia, convulsions; weight loss
AEGL Toxicity Endpoint/Concentration: lethality (LC_{01} determined by probit analysis): 3374 and 3317 ppm
Time Scaling: $C^n \times t = k$, where C = concentration, t = time, k = constant, and n = 2 (ten Berge et al., 1986)

AEGL-3 VALUES FOR AMMONIA (Continued)

Uncertainty Factors/Rationale: total UF = 3

UF = 1 for interspecies sensitivity because of unusual sensitivity of mouse to chemical irritants; humans data showing 500 ppm for 30 minutes is not lethal; humans assumed to be no more sensitive than the mouse

UF = 3 for intraspecies sensitivity to protect elderly, children, and individuals with heart disease and asthma and because the response to irritants is not expected to vary markedly among individuals in the population

Modifying factor:

1 – multiple studies in mouse showed similar LC_{50} values

5 minutes	30 minutes	1 hour	4 hours	8 hours
3800 ppm 2657 mg/m^3	1600 ppm 1119 mg/m^3	1100 ppm 769 mg/m^3	550 ppm 385 mg/m^3	390 ppm 273 mg/m^3

Comments:

both studies used to derive the AEGL-values were well-conducted; more than the minimal – number of animals required for lethality studies were used; there was a clear dose-response for mortality; exposure concentrations were determined analytically; necropsy was performed on animals in both studies, and Kapeghian et al. conducted microscopic examination on some tissues; no deaths, clinical signs of toxicity, or gross findings were reported in a study on rats exposed repeatedly for 8 hours/day to 1100 ppm; dogs and rabbits showed mild to moderate eye and respiratory tract irritation.

AEGL-2 VALUES FOR AMMONIA

Reference: Verberk et al., 1977

Test Species/Strain/Sex/Number:
Human subjects/males and females/8 expert and 8 nonexpert subjects

Exposure Route: Inhalation
Concentration: 50, 80, 110, and 140 ppm
Duration: 2-hour exposure

Effects: odor, eye, nose, throat, and chest irritation, urge to cough, and general discomfort

AEGL Toxicity Endpoint/Concentration: Irritation: eyes and respiratory tract, urge to cough

Time Scaling:
$C^n \times t = k$, where C = conc., t = time, k = constant, and n = 2 (ten Berge et al., 1986)

Uncertainty Factors/Rationale: total UF = 1
Subjective responses of nonexpert subjects judged to be representative of normal individuals and effects reported were judged to be somewhat less serious than those described in the definition of AEGL-2

Modifying factor:
1 – values based on human experiment

5 minutes	30 minutes	1 hour	4 hours	8 hours
480 ppm (336 mg/m^3)	**200 ppm (140 mg/m^3)**	**140 ppm (98 mg/m^3)**	**70 ppm (49 mg/m^3)**	**50 ppm (35 mg/m^3)**

Comments:
Values were based on a study in humans; responses were based on personal perception of each subject but were considered to be valid indications of the effects.

AEGL-1 FOR AMMONIA				
5 minutes	30 minutes	1 hour	4 hours	8 hours
25 ppm (18 mg/m^3)	**25 ppm (18 mg/m^3)**	**25 ppm (18 mg/m^3)**	**25 ppm (18 mg/m^3)**	**25 ppm (18 mg/m^3)**

Reference: Pierce, 1994; MacEwen et al., 1970

Comments: This AEGL value is based on odor threshold; there were no data showing irritation at this concentration, but data for higher concentrations suggest that irritation would be minimal at 25 ppm

Uncertainty factors: Not applicable

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

Compilation of Previous RAM TRAC Comments Still Requiring Response Regarding Draft Oak Ridge National Laboratory Ammonia Support Documents Submitted to NAC AEGL

9 June 1997

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

RAM TRAC Comments on Draft ORNL Ammonia Document Requiring Response

page	line	RAM TRAC comment	importance	appropriate ORNL correction
3	3	ORNL failed to include data regarding a well-documented ammonia accident which occurred in Florida on 5 December 1996, despite receiving a report of this accident.	Environ (1997) reported that an employee driving a fork lift under a tank containing 42 tons of pressurized anhydrous ammonia clipped a tank nipple, and was directly exposed to the ammonia.	ORNL should state that the individual survived without permanent lung damage, despite exposure to ammonia at 390,000 to 400,000 ppm (5-min TWA = 89,400 ppm, assuming 15-second exposure duration).
3	7	ORNL should report an accident in Beaumont, Texas on 11 April 1973 in which an individual was exposed to a stream of pressurized anhydrous ammonia at 1,400 psi, which threw him backward approximately 12-15 feet.	The individual was hospitalized for 13 or 14 days, with injuries primarily to his skin and eyes. He now must wear eyeglasses (trifocal prescription OD 1.25, 0.25, 0.05; OS 1.0, 0.25, 0.05).	ORNL should report this accident, including the escape of the individual along a 100-foot escape route.
3	9	ORNL wrongly implies that we can derive no useful information about the concentration of ammonia to which the deceased was exposed in the Mulder and Van der Zalm (1967) report.	The deceased, wearing no respiratory protection, was manually filling a tank of 25-percent ammonia, displacing vapors saturated at a concentration of 330,000 ppm.	Acknowledge refutation of 10,000-ppm as a 5- to 10 minute lethality value. ORNL has verbally agreed that the report indicates exposure of the deceased to "many times 10,000-ppm."
6	31	ORNL states incorrectly that RAM TRAC's Potchefstroom accident analysis used gross mortality rates in accident zones where some people were indoors. RAM TRAC deemed these values to be unsuitable for for AEGL-3 derivation.	RAM TRAC's use of the 37,737-ppm accident zone at Potchefstroom to derive a zero-mortality ammonia concentration is correct, inasmuch as many people were outdoors, and none died.	Correct misleading statement.
7	7	ORNL states incorrectly that indoor ammonia concentrations were predicted by RAM TRAC and/or by HGSYSTEM.	The zero-mortality value was based solely upon non-lethal exposure of people outdoors.	Correct misleading statement.
7	15	ORNL erroneously criticizes RAM TRAC for using Haber's rule for "extrapolating from TWA ammonia conc. ... to 5-min. exposure scenarios."	RAM TRAC reported five-minute TWA ammonia concentrations in the standard way, from concentration data, which does not involve Haber's or Ten Berge's rules.	Remove two sentences about Haber vs. Ten Berge, who address toxic effects of exposures of varied duration. They do not alter TWAs!
7	23	ORNL cites Henderson and Haggard (1943), but should cite H&H (1927). The 'data' are even older, from an era when ammonia producers vied to sell ammonia as a war gas to military buyers with an interest in gases exhibiting high toxic potency.	Henderson and Haggard was explicitly refuted, most notably by Mulder and Van der Zalm (1967), as acknowledged by ORNL.	Correct misleading statements.

15, 16	16, 21	ORNL erroneously claims that "decreased reflex activity of the glottis suggests that protection of the airways in elderly people may be decreased..."	Ammonia would be admitted in a narrow band of concentration to the lungs of older, but not younger, people, but not necessarily with differential harm.	State the other, equally plausible suggestion that elderly people may have a higher threshold of susceptibility than younger people.
16	10	ORNL repeats erroneous claims, refuted above, which would undermine the Potchefstroom accident analysis.	RAM TRAC's AEGL-3 derivation was based upon multiple sources. The most stringent was Potchefstroom, which produced an LC-0 value used for AEGL derivation. The LC-0 is not subject to ORNL's complaints about LC-50 values.	Correct or remove misleading statements.
22	6	ORNL erroneously claims that "the relationship of any concentration and time corresponding to a mortality rate can be expressed as $C^n \times T = K$..."	This statement is too general. It assumes agreement on values of the probit constants b_0, b_1, and b_2 (where $b_1/b_2 = n$).	Address uncertainties associated with not knowing b_0.
22	7	ORNL assumes the probit parameter, b_0, equals -47.8 for mice and humans. However, this parameter is highly variable, even among mouse studies.	The concentration associated with a fixed pair of t and n values in the probit equation responds exponentially to a change in b_0.	Quantify the effect upon AEGL-3 of changing the b_0 value (ORNL's q, which ORNL assumes equals -47.8, without evidence).
22	9	ORNL erroneously assumes that n = 2.02 for rodents and humans.	This assumption is wrong for rodents, and produces over 10 times the number of actual deaths of people at Potchefstroom.	Address uncertainties in the value of n for rodents and humans, and reconcile n = 2 with 97-percent survival at Potchefstroom.
26	6	ORNL misleadingly cites Barrow's prediction from sensory irritation testing of nose-breathing mice that ammonia at the RD-50 would be "rapidly incapacitating to humans."	Barrow (p. 81) states that sensory irritants decrease respiratory rate by acting on the nasal mucosa, not the lower respiratory tract. EPA (1994, p. 2-39) states that "[t]he relationship of sensory irritation to airway irritation is unknown."	Adopt EPA policy on deriving RFCs: "the suitability of the sensory irritation [RD-50] test results is limited to serving as an indication of the potential for respiratory tract irritation" (p.2-39).
26	12	ORNL, citing Barrow, equates a mouse RD-50 of 303 ppm to humans, but EPA states: "dose-response assessment of the sensory irritation [RD-50] test is not recommended" (EPA 1994, p. 2-39).	EPA (1994, p. 2-39): "evaluation of the sensory irritation test ... found that quantitative evaluation with respect to human data was not possible due to ... factors, including .... intra- and interspecies inconsistencies in response."	Acknowledge that Silverman's report of *increased* breathing rates in volunteers refutes Barrow's RD-50 prediction, at least for humans breathing ammonia at up to 500-ppm concentration.

28	6	ORNL presents some lethality data, but excludes lethality data (previously provided by RAM TRAC) suggesting higher tolerance in cats, guinea pigs, and rabbits.	Ammonia lethality occurs at higher exposure levels than suggested by ORNL AEGL-3 values. Such tolerance is ubiquitous among all five species tested. Humans are unlikely to be more sensitive than smaller species having narrower respiratory passageways.	ADD: cat: 60-min. LC-50 = 10,000 ppm (Boyd, et al. 1944); guinea pig: 9-min. LC-LO = 22,612 ppm (Environment Canada 1981); rabbit: 60-min. LC-50 = 10,000 ppm (Boyd, et al., 1944); 60-min. LC-LO = 7,000 ppm (Environment Canada 1981)
35	5, 30	ORNL states uncertainties limiting the usefulness of industrial accident reconstructions, and erroneously concludes that such data are therefore inappropriate for AEGL-3 derivation.	ORNL's unwillingness to scale ammonia concentrations used in animal bioassays to human equivalent concentrations (HECs) enhances the importance of air modeling to infer human exposure levels.	Acknowledge that air modeling is central to the RMP Program, and that uncertainties in air modeling and interspecies extrapolation are of comparable magnitude. Use both.
35	7	ORNL erroneously equates uncertainties associated with WHAZAN and HGSYSTEM.	WHAZAN is primitive compared with HGSYSTEM, which makes use of a decade of advances in computing and software development.	ORNL should upwardly revise results from WHAZAN to HGSYSTEM, which better models the density evolution of cryogenically released ammonia.
35	10	ORNL faults HGSYSTEM for not estimating indoor ammonia levels, but this is irrelevant because survivable levels were estimated from outdoor levels which people outdoors survived.	RAM TRAC's use of the 37,737-ppm zone as a zero-mortality concentration at Potchefstroom is correct, inasmuch as all people outdoors in this zone survived.	Correct misleading statement.
35	14	In criticizing use of the HGSYSTEM model for its inability to model multiple sources of release, ORNL confuses sources with release points.	Two sources contributed to the total ammonia release at Potchefstroom, but only one release point: the failed bullet tank.	Correct misleading statement.
35	22	ORNL, citing Mazzola, incredibly states that the "Benign Bubble hypothesis cannot be proven in the absence of 3-dimensional wind field data."	ORNL (and Mazzola) completely misunderstand 'benign bubble', which is not a hypothesis requiring proof, but an uncertainty factor which accords with ORNL's concern (lines 8-9) about using atmospheric concentrations as surrogates for exposure.	Correct misleading statement.
36	15-22	Accepting Ten Berge's statement that mice are more sensitive than other mammals, including humans, ORNL illogically prefers mouse data over rat data.	Ten Berge's statement suggests that humans are likely to differ less from rats than from mice, notwithstanding a 2.3-fold difference between the two rat studies.	Acknowledge that the higher rat LC-50 values confirm the greater sensitivity of mice to ammonia, and that the difference between the two rat LC-50 values does not preclude using them.

37	1	ORNL's derivation of AEGL-3 values fails to scale concentrations lethal to rodents to human equivalent concentrations (HECs).	A HEC scaling factor for irritant gases multiplies concentrations to which mice or rats are exposed by a factor of 2.7.	ORNL should apply a HEC scaling factor of 2.7 to adjust respiratory doses received by rodents to respiratory doses received by people *from the same ammonia concentration.*
37	2	ORNL's AEGL-3 assumptions about the toxic potency of ammonia would have killed approximately 200 people outdoors at Potchefstroom, but the death rate was more than an order of magnitude lower.	ORNL's assumptions cannot be true	Reconcile survival of nearly all present at Potchefstroom with the equations: mouse = human and $c^n t = K$, with n = 2.02.
38	32	ORNL incredibly states that ammonia concentrations which cause people to cough must be regarded as potentially lethal.	ORNL illogically argues that people killed by ammonia coughed; therefore, people who cough from ammonia may die.	Withdraw this nonsense.
40	14	ORNL repeats its misleading characterization of exposures in the Verberk study as "intolerable."	"Intolerable" in the Verberk study was a poor choice of descriptor for volunteers, who reported intolerability of ammonia by tolerating it, without incapacitation.	Acknowledge, in light of 500-ppm exposures in the Silverman study, that the Verberk study does not suggest an upper limit of ammonia exposure causing irreversible effect or incapacity to escape.
40	23	ORNL inappropriately derives AEGL-2 levels based upon concentrations considered *"intolerable"* by volunteers.	AEGL-2 is defined as an exposure level causing *irreversible effect* or *incapacity to escape.*	Follow the AEGL-2 definition.
41	10	ORNL misleadingly states that only 2/7 subjects tolerated 500-ppm ammonia via nose breathing.	People are primarily mouth breathers, and the remaining volunteers tolerated 500-ppm ammonia without ill effect.	Correct misleading statement.
40	28	ORNL misleadingly cites Barrow's prediction from sensory irritation testing of nose-breathing mice that ammonia at the RD-50 would cause "rapidincapacitation in humans."	Barrow (p. 81) states that sensory irritants decrease respiratory rate by acting on the nasal mucosa, not the lower respiratory tract. EPA (1994, p. 2-39) states that "[t]he relationship of sensory irritation to airway irritation is unknown."	Adopt EPA policy on deriving RFCs: "the suitability of the sensory irritation [RD-50] test results is limited to serving as an indication of the potential for respiratory tract irritation" (p.2-39).
40	28	ORNL, citing Barrow, equates the mouse RD-50 of 303 ppm to humans, but EPA states: "dose-response assessment of the sensory irritation [RD-50] test is not recommended" (EPA 1994, p. 2-39).	EPA (1994, p. 2-39): "evaluation of the sensory irritation test ... found that quantitative evaluation with respect to human data was not possible due to ... factors, including .... intra- and interspecies inconsistencies in response."	Acknowledge that Silverman's report of *increased* breathing rates in volunteers refutes Barrow's RD-50 prediction, at least for humans breathing ammonia at up to 500-ppm concentration.
42	17	ORNL applies the Ten Berge equation with n = 2 to non-lethal effects, downwardly biasing AEGL-2 values.	Ten Berge, et al. (1986, p. 301) advocated use of $c^n t$ with $n \neq 1$ *"for predicting the mortality response."*	Use Haber's rule as a default equation for nonlethal response.

42	20	ORNL justifies using Ten Berge's equation for non-lethal effects because ammonia at 100 ppm failed to injure people breathing it for two to six hours.	Ten Berge's criterion for using the c" t term was the occurrence of an adverse effect (mortality), not the failure of an effect to occur.	Correct this *non-sequitur*.
42	19	Diminishing AEGL-2 values beyond 30 minutes, except where a toxic effect is demonstrated, violates NAC AEGL procedure.	Thirty-minute AEGL-2 values should not be diminished for longer exposure because escape is assumed to have already occurred within 30 minutes.	Do not reduce AEGL-2 values beyond 30 minutes.
42	29	ORNL misleadingly asserts that volunteers breathing ammonia at140 ppm for 30 minutes experienced an "unbearable" urge to cough.	This means the volunteers coughed, not that the exposure causing them to cough was unbearable or intolerable.	Correct the misleading statement.
43	16	ORNL illogically argues that the decision of 4/8 volunteers to terminate their exposure to ammonia at 140 ppm before 1 h means that serious lower respiratory effects were looming.	Volunteers may terminate their exposures for many reasons which would operate well before imminent injury loomed.	Correct this misleading deduction.
47	3	ORNL incorrectly states that *"quantitative human data were not available for deriving the AEGL-3 values."*	This statement is wrong. Available accident reconstruction data are directly applicable to the short time frames of ammonia accident exposures.	Correct this misleading statement.
56	1	ORNL fails to adjust ammonia concentrations derived from the WHAZAN model based upon more modern models, such as HGSYSTEM.	WHAZAN is primitive compared with HGSYSTEM, which makes use of a decade of advances in computing and software development.	ORNL should upwardly revise results from WHAZAN to HGSYSTEM, which better models the density evolution of cryogenically released ammonia.
56	7	ORNL erroneously reports values of the probit paramater, b_0, as positive numbers. They are negative.	The concentration associated with a fixed pair of t and n values in the probit equation responds exponentially to a change in b_0.	Any incorrect probit calculations should be corrected as appropriate.
58	4	ORNL miscalculates 5-min. TWA values for the Potchefstroom accident	Ten Berge's equation is inapplicable to calculating TWA values.	Ten Berge and Haber use TWA values as inputs to predict the potency of exposures of different duration. They do not alter the calculation of TWA exposure levels.

literature cited:

Barrow, C. S.; Y. Alarie, and M. F. Stock. *Sensory irritation and incapacitation evoked by thermal decomposition products of polymers and comparisons with known sensory irritants.* Archives of Environmental Health, 33:79-88, March/April 1978;

Environ. Letter to NAC AEGL from Jim Skillen (The Fertilizer Institute, Washington, DC), transmitting letter report from R. B. Kapuscinski re *AEGL Values for Ammonia,* including *Attachment A: Dose Reconstruction Modeling for Recent Ammonia Accident,* 8 pp.,14 February 1997;

Mazzola, C. A. *Potchefstroom Dose Reconstruction: Inherent Uncertainties that Significantly Limit Effective Application to Human Health Standards Process.* Stone & Webster Engineering Corporation, 32 pp., May 1997;

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;

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RAM TRAC. *Acute Inhalation Risks Potentially Posed By Anhydrous Ammonia.* Schenectady, New York; RAM TRAC Corporation, RA Michaels, Project Director, 99 pp., 31 May 1996;

RAM TRAC. *Comments of Robert A. Michaels, PhD, CEP to the National Advisory Committee on Acute Exposure Guideline Levels on AEGL Values* for Ammonia. Schenectady, New York; RAM TRAC Corporation, RA Michaels, Project Director, 28 pp., 5 August 1996;

RAM TRAC. *Residual Issues of Ammonia Emergency Planning: Comments By Robert A. Michaels to the National Advisory Committee on Acute* Exposure Guideline Levels. Schenectady, New York; RAM TRAC Corporation, RA Michaels, Project Director, 19 pp., 15 November 1996;

RAM TRAC. *Supplemental Comments By Robert A. Michaels to the National Advisory Committee on Acute Exposure Guideline Levels for Ammonia.* Schenectady, New York; RAM TRAC Corporation, RA Michaels, Project Director, 19 pp., 15 November 1996;

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;

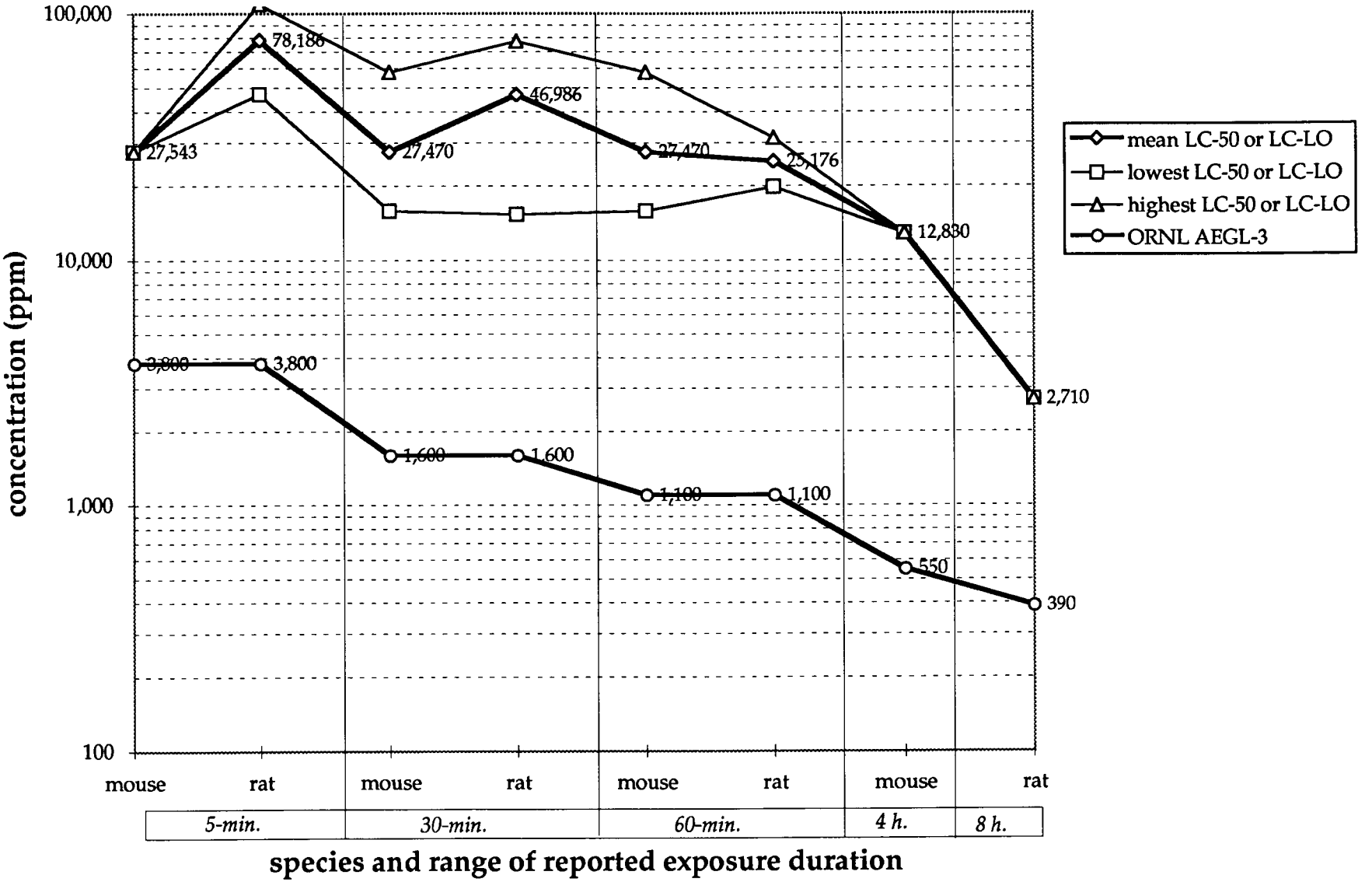
Ten Berge, W. F.; A. Zwart, and L. M. Appelman. *Concentration-time mortality response relationship of irritant and systemically acting vapours and gases.* Journal of Hazardous Materials, 13:301-9, 1986;

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

RAM TRAC Corporation

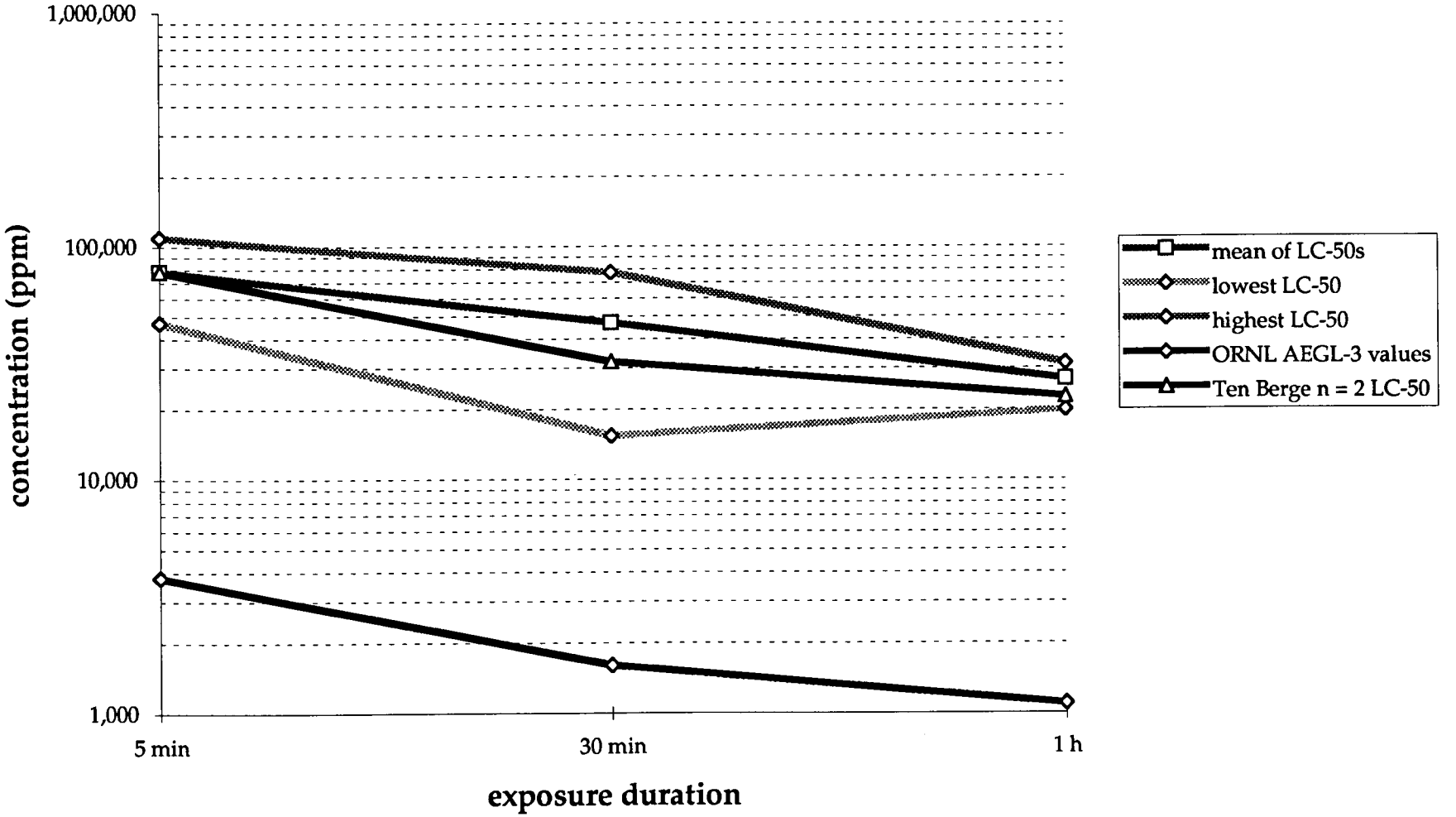
Human Equivalent

Concentrations of Airborne Ammonia Lethal To Mice and Rats



RAM TRAC Corporation

Human Equivalent Ammonia Concentrations Lethal To Rats



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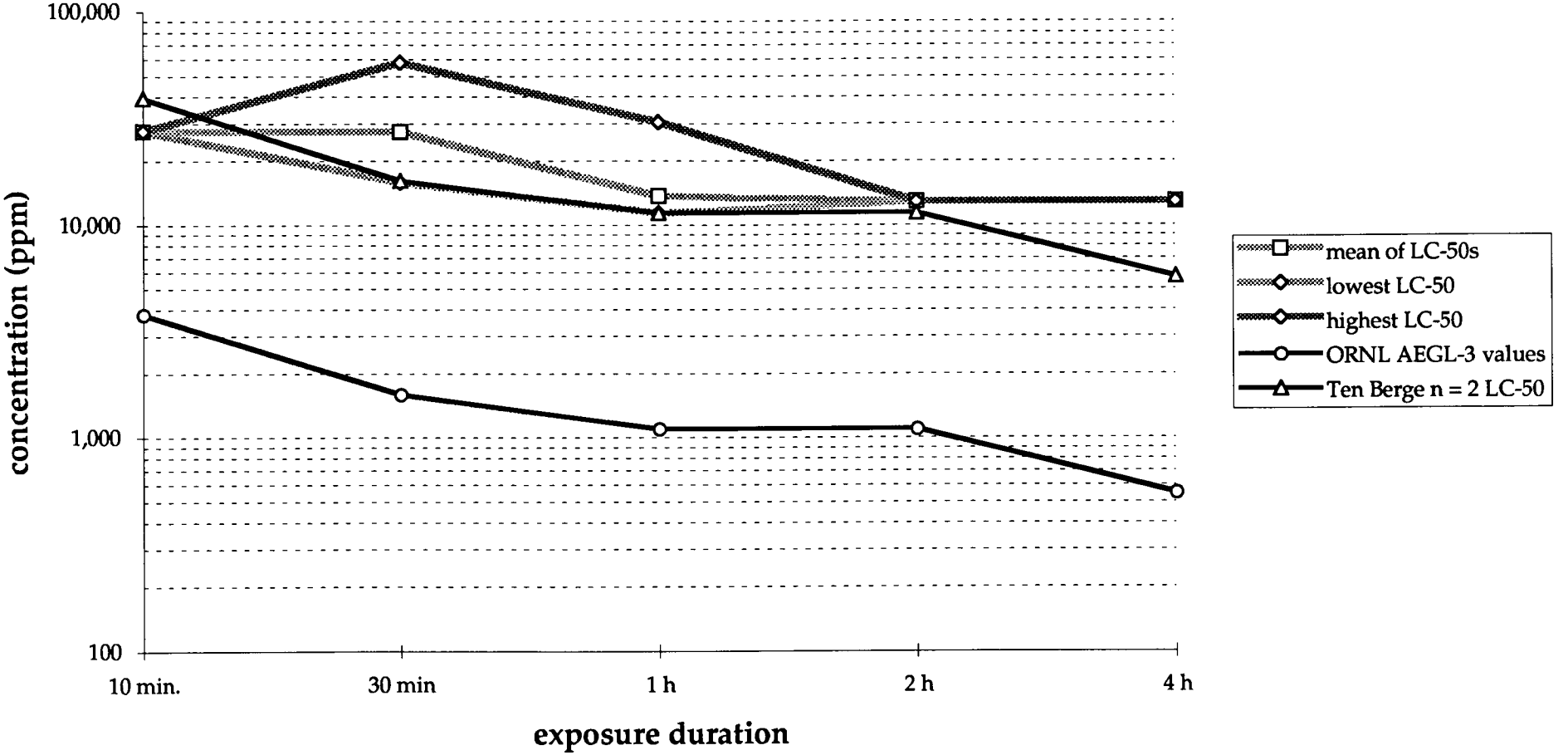
RAM TRAC Corporation

Human Equivalent

Concentrations of Airborne Ammonia Lethal To Mice



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Averting Bhopal-type disasters differs from establishing acceptable exposure levels.

"In the Bhopal disaster of 1984, 2,000 residents living near a chemical plant were killed and approximately 20,000 more suffered irreversible damage to their eyes and lungs following an accidental release of methyl isocyanate... This tragedy served to focus international attention on the need for governments to identify hazardous substances and to assist local communities in planning how to deal with emergency exposures.

As a first step, ... EPA has identified 366 EHSs [Extremely Hazardous Substances], [but existing] ***workplace or ambient air quality ... limits are not easily or directly translated into 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"*** (page 1, emphasis added).

source:
National Research Council Committee on Toxicology. *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances.* Washington, DC; National Academy Press, 109 pp., 1993.

Rat data are more relevant to humans than mouse data.

"These findings suggest that experiments using mice do not provide an appropriate basis for predicting quantitatively the mortality response in humans" (page 308, emphasis added).

source:
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;

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Appropriateness of Species As a Model for Humans

"This subject area has been reviewed (Hakkinen and Witschi, 1985) and various mammalian species **(rat, hamster, and rabbit)** have been identified as appropriate species for extrapolation from several perspectives" (page 80, emphasis added).

source:
National Research Council Committee on Toxicology. *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances.* Washington, DC; National Academy Press, 109 pp., 1993.

The mouse RD-50 cannot be used to set AEGL-3 values for humans.

A test for sensory irritation in laboratory animals was developed [the RD-50], *based on the premise that if sensory irritation can be prevented then systemic effects will be prevented as well...* [However...]

[t]he relationship of sensory irritation to airway irritation is unknown... An ***evaluation of the sensory irritation test ... found that quantitative evaluation with respect to human data was not possible*** *due to ... factors, including .... intra- and interspecies inconsistencies in response*

For these reasons, the suitability of the sensory irritation test results is limited to serving as an indication of the potential for respiratory tract irritation" (pages 2-38 to 2-39; emphasis added).

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

ORNL failed to consider the Farmland accident, one of two accidents in which an individual survived direct exposure to pressurized anhydrous ammonia.

TFI [The Fertilizer Institute] recently provided ENVIRON with data regarding an accident that occurred on December 5, 1996 at the Farmland Hydro L. P.'s Green Bay plant in Bartow, Florida in which a worker was exposed to a release of anhydrous ammonia from a pressurized storage tank. Although the worker was hospitalizied for 19 days, he survived. Attachment A is a tabular summary of the modeling analysis conducted by Koogler & Associates to reconstruct potential off-site exposures. Five dispersion models were employed to predict ground level concentrations from the release, which was estimated to involve 284,000 pounds of ammonia over a two-hour period...

If the "no lethal effects threshold concentrations" follow the ten Berge equation [with n=2]... this corresponds to a 5-minute allowable concentration of 89,400 ppmv. This is supported by the 5-minute LC_0 (no mortality threshold concentration) that is based upon dose reconstruction modeling for the 1974 accident in Potchefstroom, South Africa (33,737 ppmv (Michaels 1996), which is of comparable magnitude. These data provide a basis for setting AEGL-3 values substantially higher than those proposed by [ORNL 1996ab)] and even those recommended by ENVIRON in its December 1996 report... (emphasis added).

source:

Environ. Letter to NAC AEGL from Jim Skillen (The Fertilizer Institute, Washington, DC), transmitting letter report from R. B. Kapuscinski re AEGL Values for Ammonia, including Attachment A: Dose Reconstruction Modeling for Recent Ammonia Accident, 8 pp.,14 February 1997

ORNL violates AEGL-3 criterion: lethality vs. coughing.

"No verified lethal concentrations for ammonia were found in the available literature. However, Silverman, et al. *(1949) reported that 1,000 ppm induced an immediate urge to cough. Legters (1980) noted that coughing may indicate that the absoptive (scrubbing) capacity of the upper respiratory tract has been exceeded and that ammonia is penetrating to the lower respiratory passages. Data presented in Section 2.1 of this report showed that death in humans exposed to ammonia is associated with damage to the lower respiratory tract, and data presented in Section 2.2.1 showed effects caused by ammonia on the lower respiratory tract that would be lethal without prompt medical attention. Therefore, concentrations of ammonia that exceed the scrubbing capacity of the upper respiratory tract and cause coughing, which indicate lower respiratory effects, have lethal potential"* (page 38, emphasis added).

source:
ORNL. *DRAFT Acute Exposure Guideline Levels (AEGLs) for Ammonia.* Oak Ridge, Tennessee; Oak Ridge National Laboratory, 61 pp., 2 June 1997.

ORNL fails to adjust concentrations to which animals were exposed to human equivalent concentrations (HECs).

Cross-Species Extrapolation:
Specific Dose Adjustment

> *"The extrapolation of quantitative animal data to humans, whether for threshold toxicity or for assumed non-threshold toxicity (e. g., genotoxic carcinogens) requires cross-species extrapolation.* (pages 90-91, emphasis added).

source:
National Research Council Committee on Toxicology. *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances.* Washington, DC; National Academy Press, 109 pp., 1993.

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> *"The RfC methodology requires conversion by dosimetric adjustment of the NOAELs and LOAELs observed in laboratory animal experiments... to human equivalent concentrations (HECs)... The dosimetric conversion to an HEC is necessary before the different adverse effects in the data array can be evaluated and compared"* (page 1-4, emphasis added).

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

ORNL violates AEGL-2 criteria: irreversible or long-term effects, or incapacity to escape.

"Reversible effects may become irreversible and irreversible effects may become lethal due to delays in medical treatment as well as to continued exposure. For these reasons, the AEGL-2 levels for ammonia are based on the concentrations considered to be "intolerable" rather than those causing irreversible or long-term effects" (page 40, emphasis added).

source:
ORNL. *DRAFT Acute Exposure Guideline Levels (AEGLs) for Ammonia.* Oak Ridge, Tennessee; Oak Ridge National Laboratory, 61 pp., 2 June 1997.

ORNL violates NAC AEGL policy by diminishing AEGL-2 values beyond 30 minutes.

"The recommended AEGL-2 values for 5-minute and 30-minute exposures are 480 and 200 ppm (rounded values) based on the Ten Berge, et al. *(1986) equation (C^n x t = k, where n = 2, and k is a constant).* ***Using the same equation, the recommended AEGL-2 values for 4- and 8-hour exposures are 70 ppm and 50 ppm,*** *respectively. It is noted that the data reported by Ferguson,* et al. *(1977) appear to support the use of C^n x t = k where n = 2 for extrapolating to longer time frames. In this study, human volunteers tolerated repeated 2- to 6-hour ammonia exposures at concentrations of up to 100 ppm without experiencing serious effects"* (page 42; emphasis added).

source:

ORNL. *DRAFT Acute Exposure Guideline Levels (AEGLs) for Ammonia.* Oak Ridge, Tennessee; Oak Ridge National Laboratory, 61 pp., 2 June 1997.

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"The results show that the product of concentration and exposure time (ct) is not always a good parameter ***for predicting the mortality response*** *(Haber's rule). On the contrary, the term $c^n t$, in which the exponent n is different from 1, often predicts the response very well"* (page 301; emphasis added).

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.

ENVIRON

June 9, 1997

To members of the National Advisory Committee for AEGLs:

The new revision of the draft document *Acute Exposure Guideline Levels (AEGLs) for Ammonia* (dated July, 1997) contains the latest recommendations of the National Advisory Committee (NAC) for AEGLs and reviews the background information used to derive these values. In the course of the Committee's deliberations, ENVIRON Corporation has submitted comments on behalf of The Fertilizer Institute on several occasions with regard to the derivation of AEGL levels for ammonia. Several areas of concern in this latest document, many of which were previously noted by ENVIRON in reviews of earlier AEGL background documents, have been identified by ENVIRON and the following discussion, prepared on behalf of The Fertilizer Institute, summarizes these concerns and their implications for deriving appropriate AEGL values.

Comments Regarding AEGL-1 Values

- AEGL-1 levels should not be based upon odor threshold concentrations. They should be based upon thresholds for *notable discomfort* in accordance with the NAC's definitions. In the case of ammonia, airborne concentrations associated with discomfort are greater than odor threshold concentrations.

  As summarized in the new draft document:

  > "Experimental studies on human volunteers showed that *slight irritation* occurs at 30 ppm (10 minutes), *moderate irritation* to the eyes, nose, throat, and chest occurs at 50 ppm (30 minutes to 2 hours), *highly intense irritation* occurs at 110 ppm (30 minutes to 2 hours), *unbearable irritation* occurs at 140 ppm (30 minutes to 2 hours), and *excessive lacrimation and irritation* at 500 ppm."

  There are no data cited in the new draft document that demonstrate any adverse effects at the proposed level of 25 ppm. By definition, the AEGL-1 level is an effect level (airborne concentration *at or above* which the individuals could experience *notable discomfort*). The lack of data showing effects that meet the AEGL-1 definition at 25 ppm would appear to preclude its use as the AEGL-1 value. The available data suggests that the *moderate irritation* observed at 50 ppm is consistent with the AEGL-1 definition.

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Comments Regarding AEGL-2 Values

- The definition for AEGL-2 cites "*irreversible or other serious, long-lasting effects or impaired ability to escape*." Yet, the recommended AEGL-2 values are based upon the Verberk study, in which the observed effects were *nondisabling and reversible*.

  The most serious effects observed in the Verberk study occurred following exposures to 140 ppm ammonia for between 30 minutes and 1 hour when four subjects termed their exposure "unbearable" and left the exposure chamber. Clearly, there was no impaired ability to escape under these conditions. Several tests of respiratory function were conducted on the exposure subjects; there was no evidence of adverse effects from these measures. Thus, there were no effects observed in this study that meet the definition for AEGL-2 effects. The new draft document even states that intolerable or unbearable concentrations "are likely to be lower than those causing irreversible damage to the respiratory tract." Again, it is important to note that the AEGL-2 definition is an effect level (airborne concentration *at or above* which the individuals could experience irreversible or other serious, long-lasting effects or impaired ability to escape). It is therefore inappropriate to use the results of the Verberk study to set AEGL-2 values.

  Furthermore, if sufficient and appropriate data on humans do not exist for establishing a true "effects threshold concentration" for disabling effects following ammonia exposure, then, consistent with NRC guidance, the NAC should not propose AEGL-2 values when there is not a sound scientific basis to do so.

- There is no technical basis for the application of the ten Berge equation to non-lethal responses in any species.

  The proposed AEGL-2 values in the new draft document are based on the ten Berge equation ($C^n \times t = k$, where $n = 2$ and k is a constant), applied to the results of Verberk for 140 ppm and a 1-hour exposure. The ten Berge equation was developed using only lethality data. The new draft document provides no rationale for the use of ten Berge extrapolations on non-lethal toxicity endpoints. The appropriateness of such extrapolations has not been established.

The failings of the ten Berge extrapolation for non-lethal effects is illustrated by deriving a 2-hour AEGL-2 value using the same procedures employed in the proposed recommendations. The 2-hour AEGL-2 is 100 pm, a level at which the same effects should be observed as those reported for the 1-hour exposure to 140 ppm. However, Verberk exposed subjects to 110 ppm for 2 hours and *did not* observe the same "unbearable" irritation reported in the 140 ppm/1-hour exposure group.

Comments Regarding AEGL-3 Values

- Human dose-response data from accidents are relevant to AEGL-3 values and should be strongly considered.

  Although there are substantial uncertainties associated with the accident reconstruction models (e.g., gas dispersion models), this does not entirely negate the usefulness of the human data. Such uncertainties have not precluded the use of these models in other exposure assessment contexts. For example, gas dispersion models are an important component of accidental release analyses that will be required under USEPA's RMP rule and are also included in USEPA technical guidance documents that describe refined approaches for determining the maximum impact distance in the case of an accident. Yet, the new draft document discounts all of the human data in determining AEGL-3 values. Even if the data derived from models of accidental exposures to humans is inadequate to function as the sole basis for deriving AEGL-3 values, these data may play an important and invaluable role as a "biological check" of the AEGL-3 values based on animal data.

  For example, the "zero lethality" (LC_{01}) concentration predicted by Pedersen and Selig probit equation for vulnerable individuals is 3,356 ppm for a 1-hour exposure. This value is about three times higher than the proposed AEGL-3 value based on mouse data, but is similar to AEGL-3 values based on rat data.

- If animal data are to be used in developing AEGL-3 values, they should be based upon the rat data of Appleman et al. (1982).

  Earlier drafts of the background document concluded that the data generated from the rat

studies of Appleman et al. are more appropriate for extrapolating lethal doses in humans, primarily because the data set was more complete in that multiple exposure concentrations and multiple exposure durations were incorporated into the test protocols. The new draft document now asserts that the mouse data are more appropriate for deriving AEGL-3 levels due to the more sensitive lethality response observed in mice compared to rats. There are two areas of concern with this conclusion:

- Mice may be disproportionately sensitive to the lethal effects of irritants. ten Berge et al. (whose work is cited extensively in generating AEGL levels), studied the lethality of several irritants in a range of animal species and concluded that the conspicuous sensitivity of mice renders data on lethal doses in mice not appropriate for predicting mortality in humans.

- The new draft document cites increased confidence in the mouse data because of the similarity between two mouse studies in their 1-hour LC_{50} estimates. One problem with this approach is that it ignores the other mouse LC_{50} data reported in the document; data that is not consistent with the former two studies. A second problems is that, unlike the rat data, the mouse studies were conducted at only one exposure duration. Given that the data from the single exposure duration will be
- extrapolated to several exposure durations in deriving AEGL-3 values, additional uncertainty is incorporated into the derived values from using the single duration mouse data.

- Differences in dose delivered to the target tissue in humans versus rats (for a given exposure concentration) should be taken into account (i.e., human equivalent concentrations).

In earlier versions of the draft document, the regional gas dose ratio (RGDR) approach outlined by the USEPA was used to account for species differences. For example, the increased sensitivity of the mouse to irritants may be a function of its respiratory physiology, ventilation rate, etc. In the new draft document, all references to this approach are gone, with no rationale for why such a correction for interspecies differences, one that is consistent with EPA policy, is no longer relevant.

- There is not a sound scientific basis for AEGL-3 values for exposure durations greater than one hour. Consistent with NRC guidance, the NAC should not propose AEGL-3 values when there is not a sound scientific basis to do so.

  At best, the ten Berge equation is applicable to a limited range of exposure durations, concentrations, and species. There is no scientific basis for its application to humans for exposure durations greater than one hour. Although the text in the new draft document is in agreement with the above statement, the tables in the new draft document listing the recommended AEGLs still contain AEGL-3 values for 4- and 8-hour exposures.

In its previous comments, ENVIRON has discussed the inconsistent use of uncertainty factors in extrapolating animal data to humans and expressed concern over unnecessary conservatism in the use of such factors. It is therefore important to note that the NAC has appeared to develop a more uniform and appropriate approach towards the use of uncertainty factors, as evidenced by the new draft document, and should be commended for doing so.

We hope that the members of the NAC will take these comments into their deliberations. ENVIRON believes that the implementation of these comments will result in the best scientifically justifiable AEGL values. Please give me a call if you have any questions regarding any of these issues. I can be reached at 703-516-2315.

Very truly yours,

Daniel M Woltering

for Joseph V. Rodricks, Ph.D.
Principal

cc: The Fertilizer Institute

ClF_3 hydrolysis products

- Limited water
  - $ClF_3 + H_2O \Rightarrow 2HF + \frac{1}{2} ClO_2F + \frac{1}{2} ClF$
  - Subsequent formation of Cl_2, O_2 & ClO_3F

- Excess water
  - $2ClF_3 + 3H_2O \Rightarrow 6HF + Cl_2 + 3/2O_2$
  - Formation of small amounts of ClO_3F

Proposed Chlorine Trifluoride AEGLs

June 1997

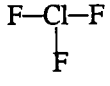
ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Kyle Blackman

Chemical Reviewers:
Robert Benson
Nancy Kim
Mark McClanahan

Attachment 14

CHLORINE TRIFLUORIDE

- **STRUCTURE:** 

- **PRODUCTION:** Several metric tons per year

- **USES:** Nuclear fuel processing, fluorinating agent, incendiary, rocket propellant, pyrolysis inhibitor

- **TOXICITY CONCERNS:** Extreme irritant

- **AVAILABLE DATA:**
  No data on human exposures

  Inhalation studies with monkey, dog, rat, mouse for several exposure durations

CHLORINE TRIFLUORIDE

AEGL-1

Dogs and rats exposed to 1.17 ppm for 6 hours (Horn and Weir, 1956)
- Rats: no effects during 6 hours
- Dogs: sensory irritation (nasal discharge) usually within 45 minutes
  - notable discomfort (lacrimation) after 3 hours of exposure
  - not clear effect occurred on first day

Uncertainty factors
- 3 for interspecies (dog was a sensitive species)
- 3 for intraspecies (effect of irritant gas does not differ greatly among individuals)

Proposed AEGL-1 Values

30 Minutes	1 Hour	4 Hours	8 Hours
0.70 ppm	0.35 ppm	0.09 ppm	0.04 ppm

CHLORINE TRIFLUORIDE

Chemistry:

Rapid hydrolysis in moist air: ClOF, ClF, ClO_2F, ClO_3F, ClO_2, Cl_2, and HF

Toxicity of hydrolysis products:

ClO^- anions relatively nontoxic

Hydrolysis products of concern are HF and ClO_2

Toxicity approximately equivalent to HF or ClO_2 on the basis of the number of equivalents of HF or Cl produced
- Dost et al., 1974
- MacEwen and Vernot, 1970

Scaling across time:

$C^1 \times t = k$ (based on two lethality studies with two exposure durations)

CHLORINE TRIFLUORIDE

AEGL-2

Dogs and rats exposed to 5.15 ppm for 6 hours (Horn and Weir, 1955)
- Rats: no effects during 6 hours
- Dogs: strong irritation (salivation, lacrimation, rhinorrhea, coughing, sneezing) reversible by next morning

Uncertainty factors
- 3 for interspecies (dog was a sensitive species)
- 3 for intraspecies (effect of irritant gas does not differ greatly among individuals)

Proposed AEGL-2 Values

30 Minutes	1 Hour	4 Hours	8 Hours
6.2 ppm	3.1 ppm	0.77 ppm	0.39 ppm

Comparison of Chlorine Trifluoride Values with Hydrogen Fluoride:

Chemical	30-Minute AEGL-1	1-Hour AEGL-1
Hydrogen fluoride	2 ppm	2 ppm
Chlorine trifluoride	0.70 ppm	0.35 ppm
3 x Chlorine trifluoride	2.1 ppm	1.1 ppm

AEGL SUMMARY FOR CHLORINE TRIFLUORIDE

SUMMARY OF PROPOSED AEGL VALUES				
Classification	Exposure Duration			
	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	0.70 ppm (2.7 mg/m^3)	0.35 ppm (1.3 mg/m^3)	0.09 ppm (0.34 mg/m^3)	0.04 ppm (0.15 mg/m^3)
AEGL-2 (Disabling)	6.2 ppm (24 mg/m^3)	3.1 ppm (12 mg/m^3)	0.77 ppm (2.9 mg/m^3)	0.39 ppm (1.5 mg/m^3)
AEGL-3 (Lethal)	27 ppm (103 mg/m^3)	14 ppm (53 mg/m^3)	3.4 ppm (13 mg/m^3)	1.7 ppm (6.5 mg/m^3)

CHLORINE TRIFLUORIDE

AEGL-3

Mouse most sensitive species based on LC_{50} values (MacEwen and Vernot, 1970)
LC_{01} of 135 ppm calculated by probit analysis

Uncertainty factors
3 for interspecies (mouse was a sensitive species)
3 for intraspecies (effect of irritant gas does not differ greatly among individuals)

Proposed AEGL-3 Values

30 Minutes	1 Hour	4 Hours	8 Hours
27 ppm	14 ppm	3.4 ppm	1.7 ppm

ACUTE EXPOSURE GUIDELINE LEVELS FOR
ETHYLENIMINE

PREPARED BY

KOWETHA A. DAVIDSON
OAK RIDGE NATIONAL LABORATORY

Attachment 15

PRESENTED AT THE NAC/AEGL MEETING, WASHINGTON, D.C., JUNE 9 - 10, 1997

Table 2. Summary of Lethal and Nonlethal Effects on Ethylenimine in Humans

Conc. (ppm)	Exposure Time	Effects	Comments	Reference
Unknown	<5 min	vomiting, eye irritation, severe respiratory effects (pulmonary edema and destruction of tracheo-bronchial tree), death	death may have been caused by aggressive steroid therapy	Gresham and West, 1975
235 - 353 ppm (estimated)	1½ to 2 h	severe vomiting, lacrimation, eye irritation, photophobia, hemoglobinemia, eosinophilia, extensive respiratory irritation	eye effects delayed by 1½ to 3 h and other effects delayed 3 to 7 h; residual effects 3 months after exposure; also exposed to NH_3, isopentane, and *N*-ethylethylenimine	Weightman and Hoyle, 1964
unknown	not reported	reddening, blistering, swelling of scrotum; no evidence of testicular effects	protective equipment prevented exposure to the eyes and respiratory tract	Theiss et al., 1971
unknown	unknown	skin sensitization	occurred in a laboratory worker	Carpenter et al., 1948
unknown	unknown	severe dermatitis, nose and throat irritation, conjunctivitis	effects on eyes, nose, and throat were transient	Carpenter et al., 1948
one drop on tongue, ca. 50 μL	NR, prob. only sec.	inflammation and edema of the epit. of the oral cavity, inflammation of the eyes	inhalation exposure was possible, but negligible; study showed insidious nature of ethylenimine	Danehy and Pflaum, 1938
liquid on skin	not reported	necrotizing painless burns to hand; no other effects	this study involved skin contact with liquid ethylenimine	Weightman and Hoyle, 1964

Table 3. Effects of Acute Exposure to Ethylenimine in Wistar Rats			
Exposure duration (min.)	Exposure Concentration (ppm)	Mortality response	LC_{50}[a] (ppm)
5	100, 250, 500, 1000, 4000	0/6, 0/6, 1/6, 1/5, 4/6	2558
10	500, 1000, 2000, 4000	2/6, 4/6, 1/6, 5/6	1407
15	100, 250, 500, 1000, 2000, 4000	0/6, 1/6, 3/6, 5/6, 5/6, 6/6	545
30	500, 1000, 2000	5/6, 6/6, 5/5	could not be determined
60	100, 250, 500	0/6, 2/6, 6/6	268
120	50, 100, 250	0/6, 1/6, 3/6	259
240	25, 50, 100, 250	0/6, 2/5, 6/6, 6/6	58
480	25, 50	1/6, 5/6	35

Source: Carpenter et al., 1948
[a]LC_{50} values calculated by probit analysis.

Table 4. Mortality in Mice Exposed to Ethylenimine Vapor for 10 Minutes		
Concentration		Mortality (%)
mg/L	ppm	
2.1	1176	3/20 (15)
2.3	1288	3/20 (15)
2.9	1624	7/20 (35)
3.3	1848	3/20 (15)
3.4	1904	10/20 (50)
3.5	1960	4/20 (20)
3.7	2072	9/20 (45)
4.2	2352	13/20 (65)
6.1	3416	18/20 (90)
LC_{50} value = 2236 ppm		

Source: Silver and McGrath, 1948

- **Nonlethal Effects**
  - no systemic effects from 4-hour exposure of shaved guinea pig to 4000 ppm
- **Carcinogenicity**
  - no inhalation studies available
  - evidence of carcinogenicity in mice and rats by subcutaneous injection or oral dosing
  - quantitative data not available for calculating risk values
- **Genotoxicity**
  - no inhalation studies available
  - very reactive monofunctional direct alkylating agent
  - mutagenic in all test systems investigated
  - test systems investigated include bacteria, fungi and plants, insects, mammalian cells in vitro, and mice by intraperitoneal injection (dominant lethality)
- **Metabolism/Disposition/Kinetics**
  - small amount of a parenteral dose converted to CO_2; excreted primarily in urine; metabolites unidentified
  - distributed to all tissues; highest specific activity in liver, cecum, spleen, kidneys, intestines, and bone marrow

Table 5. Effects of Acute Exposure to Ethylenimine in Guinea Pigs

Exposure duration (min.)	Exposure Concentration (ppm)	Mortality response	LC_{50}[a] (ppm)
5	250, 500, 1000, 4000	0/6, 0/6, 0/6, 4/6	2906
10	2000, 4000	1/12, 6/6	2824
15	250, 500, 1000, 2000	0/6, 0/6, 0/6, 6/6	1283
30	100, 250, 500, 1000	0/6, 0/6, 5/6, 6/6	364
60	25, 100, 250, 500	0/12, 1/6, 2/6, 6/6	235
120	50, 100, 250, 500	0/6, 1/6, 5/6, 6/6	158
240	10, 25, 50, 100, 250	0/6, 2/5, 2/6, 6/6, 6/6	45
480	10, 25, 50	0/6, 2/6, 6/6	27

Source: Carpenter et al., 1948
[a]LC_{50} values calculated using probit analysis.

AEGL-3 VALUES FOR ETHYLENIMINE (Continued)			
30 minutes	1 hour	4 hours	8 hours
59 ppm (33 mg/m^3)	**32 ppm (18 mg/m^3)**	**9 ppm (5 mg/m^3)**	**5 ppm (3 mg/m^3)**
Comments: Both the rat and guinea pig studies were judged acceptable or adequate for deriving AEGL-3 values was similar; there were no obvious weaknesses except the use of calculated exposure concentrations rather than analytically measured concentrations.			

AEGL-3 VALUES FOR ETHYLENIMINE
Reference: Carpenter et al., 1948
Test Species/Strain/Sex/Number: rat/Wistar/male/5 or 6 per group
Exposure route: Inhalation **Concentration**: 25 and 50 ppm **Duration**: 8 hours
Effects: death: 1/6 and 5/6; extreme respiratory difficulty; occurred after 3 hour at 25 ppm
AEGL Toxicity Endpoint/Concentration: Lethality (LC_{01} determined by probit analysis of rat data; 480-minute exposure
Time Scaling: $C^n \times t = k$; n = 1.12 (derived from rat data)
Uncertainty Factors/Rationale: total UF = 3 UF = 1 for interspecies sensitivity because the mechanism of action is not expected to vary depending on species and the LC_{50} values for mice, rats, and guinea pigs vary only slightly suggesting very little interspecies variability; evidence suggest that humans may be less sensitive than rodents. UF = 3 for intraspecies variability because effects may not be noticeable until after exposure; the very reactive nature of the chemical suggests that individuals may respond similarly; therefore, the response of population subgroups may not vary considerably.
Modifying Factor: 1 Lethality studies in 3 species

AEGL-2 VALUES FOR ETHYLENIMINE (Continued)			
Modifying Factor: MF = 2 because quantitative data are not available to estimate the cancer risk associated with inhalation exposure to ethylenimine.			
30 minutes	1 hour	4 hours	8 hours
16 ppm **(9 mg/m^3)**	**7.6 ppm** **(4.2 mg/m^3)**	**1.7 ppm** **(1 mg/m^3)**	**0.78 ppm** **(0.4 mg/m^3)**
Comments: The AEGL-2 values are below the irritancy threshold for humans (100 ppm).			

AEGL-2 VALUES FOR ETHYLENIMINE
Reference: Carpenter et al., 1948
Test Species/Strain/Sex/Number: Guinea pigs/mixed sex/5 or 6 per group
Exposure Route: Inhalation **Concentration**: 10, 25, 50, 100, and 250 ppm **Duration**: 240 minutes
Effects: Death: 0/6, 2/5, 2/6, 6/6, and 6/6; no clinical effects at 10 ppm; extreme respiratory difficulty at 25 - 250 ppm, but it did not occur until 3 hours at 25 ppm; eye irritation at 100 and 250 ppm; prostration after 3 hours at 150 ppm; gross and microscopic lung effects; tubular necrosis and cloudy swelling in kidneys.
AEGL Toxicity Endpoint/Concentration: lethality (LC_{01} determined by probit analysis of guinea pit data; 240-minute exposure
Time Scaling: $C^n \times t = k$; n = 0.91(derived from guinea pig data)
Uncertainty Factors/Rationale: total UF = 3 UF = 1 for interspecies sensitivity because the mechanism of action is not expected to vary depending on species and the LC_{50} values for mice, rats, and guinea pigs vary only slightly suggesting very little interspecies variability; evidence suggest that humans may be less sensitive than rodents. UF = 3 for intraspecies variability because effects may not be noticeable until after exposure; the very reactive nature of the chemical suggests that individuals may respond similarly; therefore, the response of population subgroups may not vary considerably.

AEGL-1 VALUES FOR ETHYLENIMINE			
30 minutes	1 hour	4 hour	8 hour
No values derived			
Rationale: no specific warning properties regarding odor (similar to ammonia and 2 ppm odor threshold or sensory irritation (insidious, i.e. no effects during exposure) AEGL-2 values for 4- and 8-hour exposures are below odor detection level no benefit to public to propose AEGL-1 values below odor detection and irritancy levels			

DIBORANE AEGLs

Jim Holler
Claudia M. Troxel

DIBORANE

- **PROPERTIES**
  Highly unstable, colorless gas
  Rapidly hydrolyzes in water

- **PRODUCTION**
  U.S. capacity:
  45 metric tons/year
  produced on demand (40 lb min.)
  Dopants (BF_3, diborane, arsine, phosphine etc.):
  predicted 9% average annual growth rate between 1994-1999

- **AVAILABLE DATA**
  Case reports of human exposure
  Nonlethal and lethal studies in variety of animal species

DIBORANE

- **ANALYTICAL METHODS**

NIOSH recommends:

Collection on charcoal/particulate filter
Reagent: hydrogen peroxide
analytical method: plasma emission spectroscopy

Toxic gas monitor was used in more recent toxicity studies

HUMAN DATA

- **LETHAL EFFECTS:**

none recorded

- **SUBLETHAL EFFECTS:**

Odor threshold: determined in human subjects to be 2-4 mg/m^3 (1.8-3.6 ppm)

Accidents/Case Reports:

No data on exposure concentrations
Signs and symptoms of acute exposure:
chest tightness, nonproductive cough, dyspnea, precordial pain, fatigue, and wheezing
Symptoms developed shortly after exposure and generally disappeared within a week.

SUMMARY OF LC_{50} INHALATION VALUES IN LABORATORY ANIMALS			
Species	Conc. (ppm)	Exposure Time	Reference
Rat	159-182	15 min	Krackow, 1953
Rat	50	4 h	Krackow, 1953
Rat[b]	40, 42	4 h[a]	Jacobson and Lawson, 1962
Rat[c]	65	4 h[a]	Jacobson and Lawson, 1962
Rat[d]	80, 74	4 h[a]	Jacobson and Lawson, 1962
Mouse	29	4 h[a]	Jacobson and Lawson, 1962
Mouse	31.5	4 h[a]	Uemura et al., 1995

[a] LC_{50} values were obtained 14 days post exposure.
[b] 2 month EBF rat
[c] 5 month EBF rat
[d] 5 month Wistar (CRDL) rat

SUMMARY OF ACUTE LETHAL INHALATION DATA IN LABORATORY ANIMALS				
Species	Conc. (ppm)	Exp. Time	Death (No. died/No. exp)	Reference
Dog	350	15 min	edema	Kunkel et al., 1956
Dog	40-125	2-2½	edema (2/3)	Kunkel et al., 1956
Rat	158-446	1 h	(22/24)	Comstock et al., 1954
Rat	159	2 h	(3/6)	Comstock et al., 1954
Rat	228	2 h	(6/6)	Comstock et al., 1954
Rat	47	4 h	(2/6)	Comstock et al., 1954
Rat	60-140	4 h	(46/54)	Comstock et al., 1954
Mouse	15	8 h	lung damage (1/10)	Uemura et al., 1995
Rabbit	unknown	until death	edema	Kunkel et al., 1956
Hamster	50-1000	until death	edema	Stumpe, 1960

AEGL ENDPOINT

Panbronchiolitis-like lesions in animals:

"multi-focal and/or diffuse inflammatory epithelial degeneration exclusively located in the region of the respiratory bronchioles"

Most sensitive and reproducible endpoint

Concentration/duration-response

In humans:

Characterized by chronic inflammation

Nonspecific inflammatory response
etiology not known, can occur following respiratory viral infections such as influenza, measles

SUMMARY OF SUBLETHAL INHALATION DATA IN LABORATORY ANIMALS

Species	Conc. ppm	Duration	Effects[a]	References
Rat	0.9 9.2	4h	**3 Days post-exposure:** BALF: Beginnings of inflammatory process in lung accompanied by cell injury Serum: α_1-antitrypsin activity increased in the 9.2 ppm group. Histopathology: Diffuse panbronchiolitis-like obstructive changes in the 9.2 ppm group.	(Nomiyama, 1995)
Rat	20	4h	**Immediately after, 1 day, 3 days, or 14 days post-exposure:** BALF: Indicated inflammatory process and cell damage initially, returning to normal by 14 days post-exposure except a significant decrease in α_1-antitrypsin by 14 days. Histopathology: Bronchial polymorphonuclear neutrophil infiltration immediately after exposure, becoming milder by 1 and 3 days post-exposure. Panbronchiolitis-like obstructive changes 3 days post-exposure; returning to normal by 14 days post-exposure.	(Nomiyama, 1995)

[a] Diborane delivered by exposure in chamber

SUMMARY OF SUBLETHAL INHALATION DATA IN LABORATORY ANIMALS (con't)

pecies	Conc. (ppm)	Duration	Effects[a]	References
louse	1	1, 2, 4, 8 h	**3 Days post-exposure:** Lung weight: Decreased in 1h 4h, 8h groups. Histopathology: No changes.	(Nomiyama et al., 1995)
louse	5	1, 2, 4, 8 h	**3 Days post-exposure:** Lung weight: Increased in 8h group. Histopathology: Duration-response relationship for diffuse panbronchiolitis-like obstructive changes (0/10, 4/10, 9/10, 10/10, respectively).	(Nomiyama et al., 1995)
ouse	15	1, 2, 4, 8 h	Observations: all groups: face washing, restlessness; 4 and 8 h groups: ruffled fur, systemic tremors **3 Days post-exposure:** Weights: Liver, kidney, spleen, thymus, b.w. decreased, Lung, trachea weights increased (4h, 8h groups most affected). Histopathology: Duration-response relationship for diffuse panbronchiolitis-like lesions (8/10, 10/10, 10/10, 10/10, respectively); longer exposed mice had cellular infiltration in bronchioles, congestion, edema, bleeding.	(Uemura et al., 1995)
ouse	15	4h	Observations: face washing, restlessness; 3 day and 14 day post-exposure groups also had ruffled fur, hypoactivity. **Immediately, 1 day, 3 days, or 14 days post-exposure:** Weights: Lung wts increased in all groups; b.w. decreased 1 day post-exposure. Histopathology: Polymorphonuclear neutrophil infiltration of bronchiolar lumens immediately after exposure; macrophages in alveolar and bronchiolar lumen immediately after, becoming more prominent 1 and 3 days post-exposure. Diffuse panbronchiolitis-like lesions present 1 day, more severe by 3 days, post-exposure. Edema and congestion 1 and 3 days post-exposure. 2 wk post-exposure: panbronchiolitis lesions replaced by peribronchiolar thickening; subepithelial inflammatory cellular infiltration.	(Uemura, 1996)

borane delivered by exposure in chamber

Nomiyama, T., et al. (1995). No-observed-effect level of diborane on the respiratory organs of male mice in acute and subacute inhalation experiments.

10 male ICR mice/group, exposed to **0, 1, or 5 ppm** for **1, 2, 4, or 8 hours**; sacrificed 3 days after exposure

Increased lung weight in 8 hour group (117%)

DPB-LIKE CHANGE					
Conc.	**Control**	**1 h**	**2 h**	**4 h**	**8 h**
1 ppm	0/10	0/10	0/10	0/10	0/10
5 ppm	0/10	0/10	4/10	9/10	10/10

Uemura, T., et al. (1995). Acute and subacute inhalation toxicity of diborane in male ICR mice.

10 male ICR mice/group, exposed to **15 ppm** for **1, 2, 4, or 8 hours**, control to filtered air for 8 hours; sacrificed 3 days after exposure

Absolute and relative lung weight: significantly increased at 2, 4, or 8 hours of exposure:
absolute: 125%, 129%, 142% of control, respectively
relative: 134%, 154%, 165% of control, respectively

MICROSCOPIC LESIONS IN LUNGS					
Finding	**Cont**	**1 h**	**2 h**	**4 h**	**8 h**
DPB-like lesion	0	7.5	10	10	10
Congestion	0	9	9.5	10	10
Edema	0	0	1	4.5	10
Bleeding	0	3	4	6.5	10
Macrophages in alveolus	0	3	4	8	5
Cellular infiltration in resp. bronchioles	0	7.5	10	10	10

Uemura, T. (1996). Development of pulmonary lesions following acute exposure to diborane in male ICR mice.

40 mice, 10 male ICR mice/group, were exposed to **15 ppm** diborane for **4 hours**. One group was sacrificed immediately after, 1 day, 3 days, or 14 days after exposure.

Absolute and relative lung weight significantly increased in all exposed groups: absolute: 126% to 154% of controls
relative: 130 % to 156% of controls

MICROSCOPIC LESIONS IN LUNGS					
Finding	**Time after exposure**				
	Cont	**imm.**	**1 D**	**3 D**	**14 D**
PMN neutrophils at bronchiolus	0	10	5	0	0
Macrophages in alveolus	0	2	9	9	0
DPB-like lesion	0	0	10	10	0
Edema and congestion	0	0	10	10	0
Peribronchiolar thickening	0	0	0	0	10
Subepithelial inflam. cellular infiltration	0	0	0	0	10

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

- Based on regression analysis of EC_{50} values derived from studies by Nomiyama et al. (1995) and Uemura et al. (1995)
  - 1, 2, and 4 hour exposures to 1, 5, or 15 ppm diborane
  - panbronchiolitis-like lesions as the endpoint for toxicity

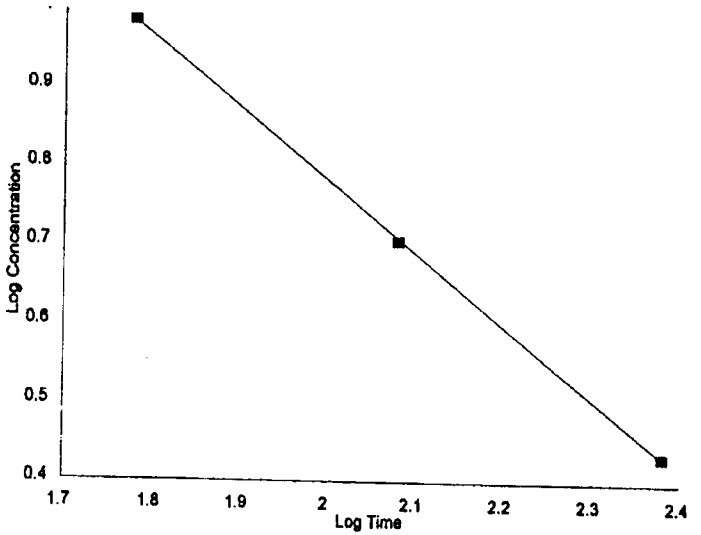


FIGURE 1. Regression Plot of EC_{50}s : Concentration vs. Time

AEGL-1 (ppm)			
30 minutes	1 hour	4 hours	8 hours
1.6	0.8	.2	0.1

- **Reference:** Nomiyama, T., et al. 1995. No-observed-effect level of diborane on the respiratory organs of male mice in acute and subacute inhalation experiments.

- 10 ICR male mice/exposure group

- **Concentration/Time Selection/Rationale:** exposure to 1 ppm for 8 hours produced no adverse effects

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: 10
  - Interspecies: 3 - species to species extrapolation; mouse is the most sensitive species; protective endpoint
  - Intraspecies: 3 to protect sensitive individuals: the mechanism of toxicity not expected to vary significantly between individuals

- **Time scaling:** $C^n \times t = k$ where $n = 1$

SUPPORTING DATA

AEGL-1 (ppm)			
30 minutes	1 hour	4 hours	8 hours
1.0	0.5	.0125	0.062

Reference: Nomiyama et al., 1995.

Next lower NOAEL of 5 ppm for 1 hour

UF = 10

n = 1

AEGL-2 (ppm)			
30 minutes	1 hour	4 hours	8 hours
2.0	1.0	0.25	~~0.12~~ 0.13

- **Reference:** Nomiyama, T., et al. 1995. No-observed-effect level of diborane on the respiratory organs of male mice in acute and subacute inhalation experiments.

- 10 ICR male mice/exposure group

- **Concentration/Time Selection/Rationale:** 4/10 animals exposed to 5 ppm for 2 hours developed panbronchiolitis-like lesions by 3 days postexposure (LOAEL).

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: 10
  Interspecies: 3 - species to species extrapolation; mouse is the most sensitive species; protective endpoint
  Intraspecies: 3 to protect sensitive individuals: the mechanism of toxicity not expected to vary significantly between individuals

- **Time scaling:** $C^n \times t = k$ where $n = 1$

SUPPORTING DATA

AEGL-2 (ppm)			
30 minutes	1 hour	4 hours	8 hours
3.0	1.5	0.38	0.19

Reference: Uemura et al., 1995.

Next higher LOAEL of 15 ppm for 1 hour

UF = 10

n = 1

AEGL-3 (ppm)			
30 minutes	1 hour	4 hours	8 hours
7.3	3.7	0.92	0.46

- **Reference:** Uemura, T., et al. 1995. Acute and subacute inhalation toxicity of diborane in male ICR mice.

- 10 ICR male mice/exposure group

- **Concentration/Time Selection/Rationale:**
  A 4-hour LC_{01} was estimated by probit analysis using the data given in the LC_{50} study

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: 10
  Interspecies: 3 - species to species extrapolation; mouse is the most sensitive species; protective endpoint
  Intraspecies: 3 to protect sensitive individuals: the mechanism of toxicity not expected to vary significantly between individuals

- **Time scaling:** $C^n \times t = k$ where $n = 1$

Decision by the committee:

SUMMARY OF PROPOSED AEGL VALUES FOR DIBORANE (ppm [mg/m³])					
Classification	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**
AEGL-1	NA	NA	NA	NA	
AEGL-2	2.0 [2.2]	1.0 [1.1]	0.25 [0.28]	0.13 [0.14]	LOAEL for pulmonary changes in mice (Nomiyama et al., 1995)
AEGL-3	7.3 [8.0]	3.7 [4.1]	0.92 [1.0]	0.46 [0.51]	LC_{01} estimated from a 4-hour LC_{50} in mice (Uemura et al., 1995)

Attachment 17

overheads used 6/10/97

Proposed AEGLs for ALLYLAMINE

June 1997

ORNL Staff Scientist:
Sylvia Milanez

Chemical Manager:
Loren Koller

Chemical Reviewers:
Mark McClanahan
Robert Hazen

ALLYLAMINE

- STRUCTURE: $H_2C=C-CH_2-NH_2$
- USES: Industrial vulcanization of rubber; synthesis of products including ion exchange resins, mercurial diuretics, sedatives, and antiseptics.
- TOXIC EFFECTS: Severe respiratory, eye, and skin irritant; induces cardiac and vascular lesions in laboratory animals at high doses
- USEFUL STUDY DATA:
  - Human: One sensory irritation study; one occupational exposure study
  - Animal: Several rat LC_{50} studies; mouse acute lethality study; monkey, rat, mouse, and rabbit single and/or multiple exposure studies

Hine et al., 1960
Rat study

Nominal conc. (ppm)	Exp. time (hr)	Morta-lity	Time of death (from exp. start)	LC_{50} (ppm)	LC_{01} (ppm)
1000	1	1/5	4 hours	1933	533
1500		1/5	4 hours		
2250		3/5	2-4 hours		
3380		5/5	2-4 hours		
133	4	0/5	-	286	104
200		0/5	-		
300		3/5	2-4 hours		
450		5/5	2-4 hours		
89	8	0/5	-	177	69.2
133		0/5	-		
200		4/5	8-24 hours		
300		5/5	8-24 hours		

$k = 0.8458$

for $c^n t = k$

HUMAN DATA - ALLYLAMINE

- Incomplete studies (no time or conc. given): occupational or accidental exposure, odor threshold of panel (Hart, 1939; Guzman et al., 1961; Shell Oil Co., 1992; Summer, 1971).

- No worker detection or complaints from 4 hrs/day exposure to <0.1 - 0.2 ppm allylamine; co-exposure to diallylamine (≤0.3 ppm) and triallylamine (≤0.6 ppm) (Shell Oil Co., 1992).

- Volunteers exposed for 5 minutes to 2.5, 5, 10, or 14 ppm allylamine rated eye and nose irritation, pulmon. discomfort, CNS effects, and olfactory cognition (Hine et al., 1960).

AEGL-1 FOR ALLYLAMINE (Shell Oil Co., 1992)			
30 minute	**1 hour**	**4 hours**	**8 hours**
0.78 ppm (1.8 mg/m^3)	0.34 ppm (0.80 mg/m^3)	0.07 ppm (0.16 mg/m^3)	0.03 ppm (0.07 mg/m^3)

UF = 3

AEGL-2 DERIVATION

Key Study: Hine et al., 1960; Guzman et al., 1961
Study design: Long-Evans rat, 15 males/conc.;
Exposure: 7 hrs/day, 50 days @ 0, 5, 10, 20, or 40 ppm (5d/wk)
Results:

5 ppm - no effects
10 ppm - lowered weight gain
20 ppm - lowered weight gain, loss of body fat, 1/9 examined had cardiovascular lesions
40 ppm - emaciated, dull fur, enlarged hearts, pneumonia, rust-colored lungs, cardiovascular lesions (8/8 examined) ; 5/15 died (NG)

AEGL-2 FOR ALLYLAMINE (10 ppm, 7 hrs)			
30 min.	**1 hour**	**4 hours**	**8 hours**
7.5 ppm ($18\ mg/m^3$)	3.3 ppm ($7.8\ mg/m^3$)	0.65 ppm ($1.5\ mg/m^3$)	0.28 ppm ($0.67\ mg/m^3$)

UF=30

AEGL-3 DERIVATION

Key Study: Hine et al., 1960
Study design: Long-Evans rat, 5 males/dose, 10 days observation
Results: All treated rats appeared "depressed," and had eye and respiratory irritation. Lacrimation and bloody nasal discharge were seen at higher concentrations (NS). Rats dying had stomachs distended with air, fluid-filled lungs with hemorrhage, and pulmonary edema. Survivors had no notable pathologies.

AEGL-3 FOR ALLYLAMINE, based on LC_{01} values at 1, 4, 8 hours; 30-min. scaled from 1-hr exposure			
30 minute	**1 hour**	**4 hours**	**8 hours**
40 ppm (94 mg/m^3)	18 ppm (42 mg/m^3)	3.5 ppm (8.1 mg/m^3)	2.3 ppm (5.4 mg/m^3)

UF=30

Nominal conc. (ppm)	Exp. time (hr)	Morta-lity	Time of death (from exp. start)	LC_{50} (ppm)	LC_{01} (ppm)
1000	1	1/5	4 hours	1933	533
1500		1/5	4 hours		
2250		3/5	2-4 hours		
3380		5/5	2-4 hours		
133	4	0/5	-	286	104
200		0/5	-		
300		3/5	2-4 hours		
450		5/5	2-4 hours		
89	8	0/5	-	177	69.2
133		0/5	-		
200		4/5	8-24 hours		
300		5/5	8-24 hours		

$k = 0.8458$
for $c^n t = k$

SUMMARY OF AEGL VALUES FOR ALLYLAMINE					
Classification	**30 minutes**	**1 hour**	**4 hours**	**8 hours**	**Endpoint (Reference)**
AEGL-1 (Non-disabling)	0.78 ppm (1.8 mg/m^3)	0.34 ppm (0.80 mg/m^3)	0.07 ppm (0.16 mg/m^3)	0.03 ppm (0.07 mg/m^3)	No detection by workers; 0.2 ppm, 4 hrs (Shell Oil Co., 1992)
AEGL-2 (Disabling)	7.5 ppm (18 mg/m^3)	3.3 ppm (7.8 mg/m^3)	0.65 ppm (1.5 mg/m^3)	0.28 ppm (0.67 mg/m^3)	Lower weight gain; pre-cardiotox., (Hine et al., 1960; Guzman, 1961)
AEGL-3 (Lethal)	40 ppm (94 mg/m^3)	18 ppm (42 mg/m^3)	3.5 ppm (8.1 mg/m^3)	2.3 ppm (5.4 mg/m^3)	Lethality (LC_{01}) in rats (Hine et al., 1960)

AEGL-1 UF = 3

AEGL-2 UF = 30

AEGL-3 UF = 30

AEGL VALUES FOR ALLYLAMINE CALCULATED USING ALTERNATE VALUES FOR *N*				
n- value	**30 min.**	**1 hour**	**4 hours**	**8 hours**
AEGL-1 (ppm)				
n = 0.8458	**0.78**	**0.34**	**0.07**	**0.03**
n = 1	0.53	0.27	0.07	0.03
n = 2	0.19	0.13	0.07	0.05
AEGL-2 (ppm)				
n = 0.8458	**7.5**	**3.3**	**0.65**	**0.28**
n = 1	4.7	2.3	0.58	0.29
n = 2	1.2	0.88	0.44	0.31
AEGL-3 (ppm)				
n = 0.8458	**40**	**18**	**3.5**	**2.3**
n = 1	36	18	3.5	2.3
n = 2	25	18	3.5	2.3

POTENTIAL AEGL-1 VALUES FOR ALLYLAMINE					
30 min.	**1 hr**	**4 hrs**	**8 hrs**	**UF**	**Endpoint (Reference)**
0.20	0.09	0.02	0.01	3	Human sensory irritation; 5 min. exposure to 5 ppm (Hine et al., 1960)
0.78	**0.34**	**0.07**	**0.03**	**3**	**No worker complaints from 4 hrs/day exposure for many days (Shell Oil Co., 1992)**
0.79	0.35	0.07	0.03	3	Mouse RD_{50} study (0.01 x RD_{50}) (Gagnaire et al, 1989; 1993)

Extrapolation was performed using $C^n \times t = k$, n=0.8458 (ten Berge et al., 1986). **The study used for AEGL-1 derivation is in bold.**

30'	1hr	4hrs	8hr
3.8	1.7	0.32	0.14

(AEGL-2 key study).
UF = 30, based on Hine 1960 Gregman 1961
using 5ppm NOEL for rats exposed 7hrs/day for 50d.

POTENTIAL AEGL-2 VALUES FOR ALLYLAMINE: SINGLE EXPOSURE STUDIES					
30 min.	**1 hr**	**4 hrs**	**8 hrs**	**UF**	**Endpoint (Reference)**
0.4	0.13	0.03	0.02	3	Human sensory irritation; exposed 5 min. to 10 ppm (Hine et al., 1960)
8	3.5	0.68	0.3	3	Mouse RD_{50} study (0.1 x RD_{50}) (Gagnaire et al., 1989; 1993)
10	4.5	0.87	0.38	30	Tracheally cannulated mice, respiration changes; 59 ppm for 2 hrs (Gagnaire et al., 1993)
52	23	4.4	2.0	30	Rat, "depressed,"eye and nasal irritation; 4 hr at 133 ppm (Hine et al. 1960) [**LC_0** in key AEGL-3 study]
80	35	6.9	3.0	30	Rat, cardiovascular changes; 14 h at 60 ppm (Guzman et al., 1961)
103	45	8.8	3.9	30	Rat, myocardial lesions; 16 h at 40 ppm (Guzman et al., 1961)
131	58	11	4.9	30	Rat, myocardial lesions; 40 h at 50 ppm (Guzman et al., 1961)
147	65	13	5.5	30	Rat, areas of cardiomyopathy; 48 h at 20 ppm (Guzman et al., 1961)

Extrapolated using $C^n \times t = k$, where n=0.8458 (ten Berge et al.,1986).

POTENTIAL AEGL-2 VALUES FOR ALLYLAMINE: MULTIPLE EXPOSURE STUDIES					
30 min.	**1 hr**	**4 hrs**	**8 hrs**	UF	**Endpoint (Reference)**
7.5	**3.3**	**0.65**	**0.28**	**30**	**Rat lowered weight gain, 10 ppm, 7 hrs/day, 50 days (5d/wk) (Hine et al., 1960; Guzman et al., 1961)**
15	6.7	1.3	0.57	30	20 ppm: 1/9 cardiovascular toxicity, fat loss; **LC_0** for 40 ppm
16	6.9	1.3	0.59	30	Rhesus monkey, rat, rabbit; no heart lesions, 40 ppm for 4 hr/day for 73 days (5 d/wk). (Guzman et al., 1961)
17	7.5	1.5	0.64	30	Mouse, no histol. changes in nose, trachea or lungs; 27 ppm 6 hr/day for 4-14 d (5 d/wk). (Zissu, 1995)
25	11	4.9	0.95	30	Rat, increased relative heart weight, 40 ppm for 6 hr/day for 120 days; **LC_0** for 80 ppm. (Lynch et al., 1989)
30	13	2.6	1.1	30	Rat, cardiovascular changes; 40 ppm, 7 hr/day for 10, 20, 30, or 40 days. (Guzman et al., 1961)
63	28	5.4	2.4	30	Rat, irritation and cardiovascular effects; 100 ppm, 6 hr/day for 10 d.; **LC_0** for 150 ppm (Lynch et al.,1983)

Extrapolated using $C^n \times t = k$, where n=0.8458 (ten Berge et al., 1986).
The study used for AEGL-3 derivation is in bold.

Note: A single exposure (i.e. one-day, continuous) was used for AEGL-2 calculations

POTENTIAL AEGL-3 VALUES FOR ALLYLAMINE					
30 min.	**1 hr**	**4 hrs**	**8 hrs**	**UF**	**Endpoint (Reference)**
30	13	2.6	1.1	30	Rat lethality (5/15), 7 hr/d @40 ppm, 50 days (5d/wk); emaciated, red lungs, pneumonia, 8/8 cardiovasc. lesions (Hine 1960; Guzman 1961)
35	16	3.0	1.3	30	Rat lethality (1/1) after 8 hrs at 40 ppm; had cardiovascular lesions
39	17	3.3	1.5	30	Rat lethality (1/8; no cardiotox.); 4 hr at 100 ppm (Guzman et al.,1961)
40	**18**	**3.5**	**2.3**	**30**	**Rat lethality LC_{01} values for 1, 4, and 8-hr exp. (pulmonary edema, stomachs distend. w. air); 30-min scaled from 1 hr (Hine et al., 1960)**
94	42	8.1	3.6	30	F-344 rat lethality (6/10; cardiovasc. effects); 150 ppm for 6 hrs/day for 10 days (5 d/wk) (Lynch et al.,1983)
50	22	4.3	1.9	30	F-344 rat lethality (22/100; cardiac necrosis); 80 ppm for 6 hr/d, 5 d/wk up to 24 wks (Lynch et al., 1989)
160	70	14	6.0	30	Mouse lethality (30/30 nasooral irritation, cyanosis, convulsions, etc.); 10-min LC_{01} values used (Hart, 1939)

Extrapolated using $C^n \times t = k$, where n=0.8458 (ten Berge et al., 1986). **The study used for AEGL-3 derivation is in bold.**

TABLE 4. CARDIOTOXIC EFFECTS IN RATS AFTER A SINGLE ALLYLAMINE EXPOSURE (Guzman et al.,1961)

Expo. time (hrs)	Conc. (ppm)	Total no. rats	Number of rats sacrificed @ given time[1]	Comments and Results
0	0	5	all @ 14 days	Control group; no heart lesions
4	100	8	2 @ 4 days 2 @ 5 days **1 death @ 5 d** 3 @ 7 days	No lesions at day 4 or in rat that died on day 5; lesions possibly seen at 5 days, one myocardial lesion at 7 days
8	40	1	**Died at 8 hrs**	Cardiac and vascular lesions
14	60	4	1 @ 18 hours 1 @ 2 days 2 @ 8 days	Myocardial lesions in all rats
16	40	20	11 @ 8-17 hrs 4 @ 7 days 5 @ 14 days	No lesions seen; minor vascular changes (round cell infiltration,vessel wall edema)
20	50	3	1 @ < 20 hours 2 @ 8 days	Myocardial lesions in all rats
24	100 (6h), 60 (18h)	3	2 @ < 24 hrs 1 @ 2 days	Myocardial lesions in all rats, severity increased at 2 days
32	40	5	all @ 3 days	Well established heart lesions in 2/5 rats
48	20	18	2 @ 2 days 6 @ 4 days 6 @ 7 days 4 @ 13 days	Several small areas of infarcted cardiopathy seen at days 2, 4 and 7 only

[1]Calculated from the beginning of the exposure period. All animals died by sacrifice except as noted.

- HCl -
An Air Force-based Perspective

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Toxicologist
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Brooks AFB, TX 78235

AGENDA

- HCl & Rockets - what rockets?
- USAF/SG Policy Guidance
- Tools for the Launch Commander
- What's REWG?
- REWG's recommendations

- Dr. C. Bast's review

HCl & ROCKETS

- Combustion product from solid fuel
  - Solid fuel in "strap-on" boosters
  - Ammonium / aluminum perchlorate and binder
- HCl production (lb.) - ground cloud

Minuteman III	2,300	dry
Peacekeeper	4,700	dry
Delta II	14,000	?
Titan IV	58,000	?
Space Shuttle	184,000 (total)	wet

LAUNCH COMMANDER TOOLS

- 3 Tier concept - similar to Cal EPA "Hot Spots" levels

  Tier 3 (Level 1) - IDLH, mission-critical personnel

  Tier 2 (Level 2) - EEGL, on-base personnel away from launch site

  Tier 1 (Level 3) - SPEGL, civilian population (including sensitives!) off-base
- Dispersion and risk models

  REEDM =Rocket Exhaust Emissions Dispersion Model

  LATRA =Launch Area Toxic Risk Assessment Model

USAF/SG POLICY & GUIDANCE

- Public Law 81-60

  Launch operations will "be no more dangerous than conventional aircraft flying overhead."

- Range Safety Requirements (AF policy)

  "the general public will not suffer an adverse effect"

  "risk to the public ... is minimized to the greatest degree possible"

- USAF Surgeon General

  Guidance to launch centers - health-based GO/NO GO criteria, per both law and policy.

  SPACECOM/SG requested AL/OE support ->REWG created.

WHAT's REWG?

- Rocket Emissions Work Group
  - *Ad hoc* advisory panel to SPACECOM/SG's office, from military, government contractors & industry
- Mission
  - Review exposure limits
  - Characterize potential exposure groups
  - Validate/amend tiers, suggest dose/response functions
  - Recommendations to SPACECOM/SG

ACCOMPLISHMENTS

- 3-tiered approach OK with asthmatics as surrogates
- D/R curves - anchor on sensitives, upper end to be legally defendable
- Tier values: Tier 3 = 50 ppm (IDLH)
  Tier 2 = 5 ppm (EEGL as IDLH/10)
  Tier 1 = 2 ppm (TWA for 1hr, C = 10)
- Tier 3 rationale predicated on
  Stevens et al (1.8 ppm for 3/4 hr) & law and AF policy
- National Research Council - Committee On Toxicology - completing review, report due soon.

1

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2 AGENDA

- HCl & Rockets - what rockets?
- USAF/SG Policy Guidance
- Tools for the Launch Commander
- What's REWG?
- REWG's recommendations

- Dr. C. Bast's review

3 HCl & ROCKETS

- Combustion product from solid fuel
  - Solid fuel in "strap-on" boosters
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  Guidance to launch centers - health-based GO/NO GO criteria, per both law and policy.
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- Mission
  - Review exposure limits
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  - Recommendations to SPACECOM/SG

7 ☐ ACCOMPLISHMENTS

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- D/R curves - anchor on sensitives, upper end to be legally defendable
- Tier values: Tier 3 = 50 ppm (IDLH)
  Tier 2 = 5 ppm (EEGL as IDLH/10)
  Tier 1 = 2 ppm (TWA for 1hr, C = 10)
- Tier 3 rationale predicated on

  Stevens et al (1.8 ppm for 3/4 hr) & law and AF policy
- National Research Council - Committee On Toxicology - completing review, report due soon.

Attachment 19

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR HYDROGEN CHLORIDE

June, 1997

ORNL Staff Scientist:
Cheryl B. Bast

Chemical Manager:
John Hinz

Reviewers:
Larry Gephart
Nancy Kim

PROPOSED AEGL VALUES FOR HYDROGEN CHLORIDE

Classification	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	2.7 [4]	1.4 [2.1]	0.3 [0.45]	0.2 [0.3]	No-effect-level in exercising human asthmatics (Stevens et al., 1992)
AEGL-2 (Disabling)	130 [194]	65 [97]	16 [24]	8 [12]	Histopathology in rats (Stavert et al., 1991)
AEGL-3 (Lethality)	210 [313]	104[155]	26 [39]	13 [19]	1-Hour rat LC_{50} (Wohlslagel et al., 1976; Vernot et al., 1977)

ISSUES

Should AEGL-1 values be flat-lined?

Is an additional uncertainty/modifying factor needed due to the relatively sparse data base?

Is an additional uncertainty factor needed for Reactive Airway Dysfunction Syndrome?

" The exact incidence of RADS, either in the community or among victims of inhalation accidents, is still unknown. An evaluation based on data from poison control centers indicated that RADS is uncommon, with only 6% of victims of (generally mild) inhalation injury exhibiting symptoms for more than 2 weeks."
(Nemery, 1996)

AEGL-1 FOR HYDROGEN CHLORIDE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-1	2.7 [4]	1.4 [2.1]	0.3 [0.45]	0.2 [0.3]

Species: Human (exercising asthmatics)
Concentration: 1.8 ppm Hydrogen Chloride
Time: 45 minutes
Endpoint: No effect

n = 1

Uncertainty Factor = None

(Flat Line ?)

AEGL-2 FOR HYDROGEN CHLORIDE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-2	130 [194]	65 [97]	16 [24]	8 [12]

Species: Rat
Concentration: 1300 ppm Hydrogen Chloride
Time: 30 minutes
Endpoint: Severe nasal or pulmonary histopathology

n = 1

Uncertainty Factor = 10

Interspecies = 3 (species used is more sensitive than primate)

Intraspecies = 3 (mechanism is irritation and is not expected to vary greatly between individuals)

AEGL-3 FOR HYDROGEN CHLORIDE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-3	210 [313]	104 [155]	26 [39]	13 [19]

Species: Rat
Endpoint: 1-Hr. LC_{50} x ⅓

n = 1

Uncertainty Factor = 10

Interspecies = 3 (species used is more sensitive than primate)

Intraspecies = 3 (mechanism is irritation and is not expected to vary greatly between individuals)

PROPOSED AEGL VALUES FOR HYDROGEN CHLORIDE				
Classification	30-min	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	2.7 [4]	1.4 [2.1]	0.3 [0.45]	0.2 [0.3]
AEGL-2 (Disabling)	130 [194]	65 [97]	16 [24]	8 [12]
AEGL-3 (Lethality)	210 [313]	104[155]	26 [39]	13 [19]

ERPG Values (AIHA, 1989): ERPG-1: 3 ppm
ERPG-2: 20 ppm
ERPG-3: 100 ppm

NIOSH REL (CDC/NIOSH,1994): 5 ppm ceiling

OSHA PEL (CDC/NIOSH, 1994): 5 ppm ceiling

IDLH (CDC/NIOSH, 1994): 50 ppm

SPEGL (NRC, 1987): 1 ppm

ALTERNATIVE AEGL-2 VALUES (ppm) FOR HYDROGEN CHLORIDE
(Total UF = 10, unless otherwise indicated)

SPECIES	Endpoint/exposure	30 min	1 hr	4 hr	8 hr	Reference
Guinea pig-exercising	LOEL for incapacitation; 140 ppm, 16.5 min (UF =3)*	26	13	3	2	Malek & Alarie, 1989
Guinea pig	Pulmonary irritation; 320 ppm, 18 min	19	10	2	1	Burleigh-Flayer et al., 1985
Rat	Histopathology; 4200 ppm, 15 min.	210	105	26	13	Kaplan et al., 1993b
Rat	Severe nasal (nose breathers) or pulmonary (mouth breathers) effects; 1300 ppm, 30 min	130	65	16	8	Stavert et al., 1991
Mouse	RD_{50} x 0.1; 309 ppm; UF =3**	160	80	20	10	Barrow et al., 1984
Baboon	5000 ppm; 15 min.	250	125	31	16	Kaplan et al., 1988; 1993a
Baboon	2780 ppm; 5 min	46	32	6	3	Kaplan, 1987

*UF= 3; 10 for animal to human, none for species sensitivity since animals were exercising
**UF= 3; Animal to human accounted for in RD_{50} manipulation

ALTERNATIVE AEGL-3 VALUES (ppm) FOR HYDROGEN CHLORIDE
(Total UF = 10, unless otherwise indicated)

SPECIES	Endpoint/exposure	30 min	1 hr	4 hr	8 hr	Reference
Guinea pig	NOEL for death; 162 ppm, 30 min	16	8	2	1	Malek & Alarie, 1985
Guinea pig	NOEL for death; 320 ppm, 30 min	32	16	4	2	Burleigh-Flayer et al., 1985
Guinea pig	histopathology; 500 ppm, 15 min	25	13	3	1.6	Kaplan et al., 1993b
Rat	30 min-LC_{50} (x 0.3); 4700 ppm	157	78	19	9.8	Darmer et al., 1974
Rat	1 hr-LC_{50} (x 0.3); 3124 ppm	210	104	26	13	Wholslagel et al., 1976; Vernot et al., 1977
Rat	1 hr-LC_{0}; 1813 ppm	360	180	45	23	Wholslagel et al., 1976; Vernot et al., 1977
Mouse	30 min-LC_{50} (x 0.3); 2600 ppm	87	43	11	5	Darmer et al., 1974
Mouse	1 hr-LC_{50} (x 0.3); 1108 ppm	74	37	9	5	Wholslagel et al., 1976; Vernot et al., 1977
Mouse	30 min-LC_{50} (x 0.3); 10,137 ppm	300	150	38	2	Anderson & Alarie, 1980
Mouse-trachea cannulated	30 min-LC_{50} (x 0.3); 1095 ppm	37	18	5	2	Anderson & Alarie, 1980
Mouse	RD_{50} x 1; 309 ppm; UF = 3*	1648	824	206	103	Barrow et al., 1984
Baboon	long-term pulmonary function effects; 10,000 ppm; 15 min.	500	250	63	31	Kaplan et al., 1988; 1993a
Baboon	11,400 ppm; 5 min	189	95	24	12	Kaplan, 1987

*UF= 3; Animal to human accounted for in RD_{50} manipulation

Areas to be Addressed by SOP Workgroup

1. Development of Information and Data for TSDs.
   a. Possible approaches to supplements to literature/data searches
   b. Guidelines/criteria for quality ranking of papers/data and confidence in studies
   c. Possible use or graphs to evaluate/utilize data
   d. Archives - who, how long, where

2. Calculations of AEGL Values
   a. Refinement of AEGL-1 definition (possibly AEGL-2 also)
   b. Endpoints for selection of AEGL levels (and their significance, including significance of odor & behavioral criteria)
   c. Dose extrapolation techniques
   d. Guidelines/criteria for use of NOAELs and LOAELs
   e. Guidelines/criteria for uncertainty factors
   f. Guidelines/criteria for modifying factors
   g. Guidelines/criteria for time scaling (algorithm and short to long term scaling)
   h. Guidelines/criteria for exposure data, exposure assumptions, and exposure models
   I. Guidelines/criteria for scientific rationale
   j. Policy for known and suspect carcinogens
   k. Scientific basis for decision
   l. Endpoints - key ones - priority
   m. What constitutes insufficient information
   n. Fetotoxicity, Ca risk

3. Format and Content of TSDs
   a. Format for summary table
   b. Consistency of data tables
   c. Potential inclusion of special data/info (e.g., chemical structure, relevant P/C properties, uses, etc.)
   d. Guidelines/criteria for presentation of scientific rationale
   e. Guidelines/criteria for describing/presenting calculations
   f. Potential inclusion of graphic descriptions of data
   g. Format/consistency in developing revised TSDs
   h. Guidelines/criteria for consistent description of data

Appendix A

National Advisory Committee (NAC)

for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 5 Highlights
Green Room, 3rd Floor, Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, D.C.
March 17-19, 1997

INTRODUCTION

George Rusch, Chair, opened the meeting. The highlights of the meeting are described below and the meeting agenda (Attachment 1) and attendee list (Attachment 2) are attached. The NAC-4 highlights were approved with minor changes (Appendix A).

The following agenda items were briefly discussed. Project Director Roger Garrett made abbreviated remarks on the AEGL project, including interactions among chemical managers, chemical reviewers, and ORNL staff scientists. He noted that the first 15 chemicals are essentially finished and ready for publication in the Federal Register for public comment but more time is needed to review them for consistency. Designated Federal Officer Paul Tobin described strategies for prioritizing the chemicals nominated by various organizations for development of AEGLs (Attachment 3) and distributed the candidate priority chemical list as of March 1997. Although the list will remain fluid, it needs to be finalized as organizations need to know for attendance at meetings and also for testing considerations. Chemicals on the list can be ordered according to several factors including toxicity and production or by the organizations' priority list in which case some chemicals suggested by each organization (AIHA, ATSDR, DoD, etc.) could be included on the list. Thus far 78 chemicals appear on the list. The chosen chemicals are not based on spill data. Comments on the list are due by March 28 to Paul. Jonathan Borak noted that some of the listed chemicals are not appropriate for acute exposures. To date (4/8/97), the final chemical priority list has been completed and is available to NAC members (Attachment 4).

Paul will continue pursuing OSHA monitoring data. He reported that the AEGL internet site is under development; the Federal Register will carry an announcement of the proposed AEGL values. There will be an AEGL symposium at the 214th annual meeting of the American Chemical Society in Las Vegas in September 1997. Any NAC members interested in participating in the symposium should contact Po-Yung or Paul.

George Alexeeff commented on the absence of representatives from EPA ORD and environmental groups on the committee. Roger Garrett noted that these groups had been contacted but there was no response at this time. George Alexeeff also commented that the benchmark dose and human equivalent concentrations were not presently used in the AEGL derivations.

TECHNICAL DISCUSSIONS

Protocol of Acute Inhalation Toxicity Study Outline (George Rusch)
Thomas Sobotka suggested that neurotoxicity should be part of the Technical Support Document outline. In the present documents, neurotoxicity, if relevant, is discussed under the Lethal and/or Nonlethal Toxicity sections.

Uncertainty Factor Subcommittee Report (Richard Thomas)
As a result of two conference calls which included discussions of Ernest Falke's "Living Document" Richard Thomas noted that there is much consistency in the use of uncertainty factors (UFs) among chemicals at this point. However, justification for use of specific UFs is still needed in some of the documents. Richard will prepare a brief consensus or summary for the committee; additional comments from committee members should be given to the chemical managers.

"Living Document" (Ernest Falke)
Ernest Falke has compiled critical data used in deriving AEGL values (e.g. species, critical effect, reference, scaling procedures, UF application, etc.); these summary sheets were distributed to committee members prior to the meeting. His comments were directed to rounding off in a uniform manner, leveling values across time, and combined UFs (Attachment 5). He recommended that rounding off should be to two significant figures. Although this might indicate a greater degree of precision than the data indicates, the values are needed by modelers who will use the numbers for dispersion models (at the AEGL-2 level). For leveling values across an AEGL level, several approaches can be used: leveling across all time periods versus using two levels (i.e., one for the 30-minute and 1-hour and another for the 4- and 8-hours time periods). Leveling should probably be addressed on a chemical-by-chemical basis. Uncertainty factors of 3 and 10 have generally been used in the completed AEGL documents and should continue to be used unless there is overwhelming support for a lack of species differences. For the use of combined interspecies and intraspecies UFs, Ernie suggested that 3 x 3 = 10 as 3 is really 3.16, the geometric mean of 10; furthermore, 3 x 10 = 30. Discussion among the committee ensued followed by the following 3 proposals: (1) a boilerplate statement should be added to the documents indicating that "all AEGL values are rounded to 2 significant figures unless the data indicate otherwise. This policy is not meant to imply a greater degree of precision than the data allows." A statement for inclusion in the preface or summary will be crafted and submitted to the committee. (2) For two UFs of 3 use a single UF of 10 because 3 = 3.16 and 3.16 x 3.16 = 10. Also 3 x 10 = 30. (3) Use empirical data to derive the exponent "*n*" in $C^n \times t = k$; if data for derivation of *n* are lacking, use the ten Berge default value of 2. The 3 proposals were adopted by the committee.

Action Item: Chemical managers and ORNL staff scientists are to comply with the rounding off and uncertainty factor proposals. If changes to the AEGL values are small, they should be adjusted without further committee action. If substantial changes occur for any of the values, they should be brought to the committee's attention via e-mail.

10-minute AEGL for compressed gases (George Rusch)
Because 10-minute exposures are not needed for all chemicals, it was decided that these would be developed based on need by a specific group or manufacturer and the availability of short-term exposure data as it is difficult to go from long-term to short-term exposures with a degree of certainty.

Status of cyanogen chloride (Mark McClanahan)
Due to the paucity of data and relatively small volume shipment containers (40 lbs), it was decided to defer further action until additional data is located. Only two manufacturers were located (Attachment 6). Paul Tobin noted that Ciba-Geigy (Novarttis) and Sandoz (Degussa) are interested in AEGLs to develop their risk management plans.

Compilation of associated adverse health effects of AEGL-2 and -3 (Larry Gephart)
Larry Gephart defined some endpoints associated with each AEGL level (Attachment 7). The use of cancer and teratogenic effects for AEGL-2 and -3 endpoints was discussed.

Additional Items
David Belluck noted the need for a Standard Operating Procedures (SOP) document. It was suggested that this could either be a broadening of the scope of the UF committee or the UF committee report could feed into the SOP document. Richard Thomas will summarize procedures used in the present documents.

George Alexeeff presented highlights from the Society of Toxicology meeting pertinent to UFs from his poster and that of McLaren/Hart-ChemRisk. The presentation was a stochastic evaluation of acute inhalation thresholds from published LOAELs and involved data on UFs (for interspecies, intraspecies, and LOAEL to NOAEL extrapolation). George evaluated the distribution of LOAEL to NOAEL ratios and considered the importance of severity of effect (i.e., irritation, irreversible, or lethal). The ratios were used to estimate UFs when extrapolating from LOAELs to NOAELs within and between effect levels. In general, an UF of 3-5 would encompass the 95th percentile within an effect level, but an UF of 10 is necessary to encompass the 95th percentile when going from a lethal level to the highest NOAEL (Attachment 8). Abstracts from these posters and others in the symposium were distributed to NAC members prior to the meeting. Expanded abstracts of Alexeeff et al., Gillis et al., and Schmidt et al. were presented to the UF subcommittee (Appendix B).

The question arose as to whether there is an AEGL-1 for arsine. After checking the ballots, Paul Tobin indicated that a level 1 for arsine (0.1 ppm across all time periods) had been approved by the committee. Later, it was brought to the committee's attention that the exponent *n* (in $C^n \times t = k$) for scaling across time for HCN should be 2.7 instead of 2. It was decided that HCN would be revisited accordingly after the public comment period.

AEGL PRIORITY CHEMICALS

Phosgene
CAS Reg. No. 75-44-5

Chemical Manager: **William Bress, Vermont Department of Health**
Chemical Reviewers: **David Belluck, Minnesota Pollution Control Agency**
Larry Gephart, Exxon Biomedical
Staff Scientist: **Jim Norris, ORNL**

Bill Bress introduced the chemical and noted its use and effects in World War I (Attachment 9). Jim Norris suggested that an AEGL-1 level not be developed due to the lack of data meeting the definition of AEGL-1. A proposed AEGL-2 level was based on an inhalation study with rats in which there was increased lung weight and proteins in the lavage fluid; combined inter- and intraspecies uncertainty factors of either 30 or 100 were suggested (Attachment 10). The proposed AEGL-3 was based on a lethality study with sheep and a combined uncertainty factor of 100. Jonathan Borak suggested that more recent papers were available to cite for the mechanism of action. One paper, Rinehart and Hatch (1964), as noted in the ERPG document, was discussed as being a paper of interest for setting the AEGL-3 values. Jim agreed to acquire the paper (the paper had been previously ordered, but the citation was wrong). However, he noted that another Rinehart paper presented only the CT product and not the specific exposure times and concentrations. George Alexeeff presented an overview of studies from the document for consideration in setting AEGL-1 levels (Attachment 11). Experimental details were provided by Jim for not using the other studies mentioned in the draft document. The committee requested that these studies be incorporated in a manner to support the usage of the sheep data. Further action on phosgene was postponed until the June meeting.

Ethylene oxide
CAS Reg. No. 75-21-8

Chemical Manager: **Kyle Blackman, FEMA**
Chemical Reviewer: **George Alexeeff, California EPA**
Staff Scientist: **Kowetha Davidson, ORNL**

Kyle Blackman introduced ethylene oxide and presented several issues of concern (Attachment 12). Kowetha Davidson discussed an additional developmental toxicity study published since the preliminary summary distributed at the December 1996 meeting. She then presented the proposed values for each AEGL level (Attachment 13). The proposed AEGL-3 values were based a LC_{01} derived from the NTP mouse study and using an uncertainty factor of 3 for intraspecies variability, 1 for interspecies variability, and the $C \times t = k$ (Haber's law) equation for extrapolating across time frames. There was much discussion on the use of the mouse data vs rat data, the use of Haber's law vs ten Berge' equation ($c^n \times t = k$) for time frame extrapolation, the use of 1 for the interspecies uncertainty factor, and use of a NOEL for lethality vs the LC_{01}. Bob Snyder was

concerned about the role of epoxide hydrase in the metabolism of ethylene oxide; he would like to see more information on metabolism in the document. The committee chose to use the rat data by Jacobson et al. (1956) for deriving the AEGL-3 values, an LC_{01} rather than a NOEL for lethality, an *n*-value of 1.2 based on a regression analysis of the rat data for time frame extrapolation, and uncertainty factors of 3 for intraspecies and interspecies extrapolation (total UF = 10). The AEGL-3 values approved by the committee are as follows: 360, 200, 63, and 35 ppm for 30-minute, 60-minute, 4-hour, and 8-hour exposure durations, respectively (Appendix C).

The proposed values for AEGL-2 were based on a developmental toxicity study using rats (BRRC, 1993), which showed a LOEL of 50 ppm for 6-hour/day exposures during organogenesis; an uncertainty factor of 3 for intraspecies variability and 1 for interspecies sensitivity was applied, and Haber's law was used to extrapolate across the different time frames (Attachment B). There was considerable discussion on the use of the developmental toxicity study for deriving the AEGL-2 values. George Rogers pointed out that growth retardation is not a relevant endpoint for acute exposures as it is due to chronic exposure. William Snellings (Product Safety Division, Union Carbide Corporation) presented data in which he compared the results of several developmental toxicity studies including one from his laboratory (Attachment 14). The discussion then focused on using other studies to derive the AEGL-2 values. A subchronic toxicity study (13 weeks) and a single exposure study in rats were considered. The single exposure study showing neurotoxicity, diarrhea, and eye and respiratory tract irritation in rats exposed to 1000 ppm for 4 hours (Embree et al., 1977) was selected for deriving AEGL-2 values. Kowetha Davidson pointed out that dominant lethality was observed in this study. The committee voted to used the Embree et al. (1977) study applying an uncertainty factor of 30 (3 for intraspecies variability and 10 for interspecies sensitivity) and ten Berge's equation, where $n = 1.2$, for extrapolation across time frames. An interspecies uncertainty factor of 10 was applied because there is little difference between lethality and the observed neurotoxicity, i.e. the concentration resulting in neurotoxicity was close to the lethal threshold.

The AEGL-2 values approved by the committee are as follows: 190, 110, 33, and 19 for 30-minute, 60-minute, 4-hour, and 8-hour exposure durations, respectively (Appendix C). These values are backed up by a subchronic toxicity study in rats exposed 500 ppm 6 h/day, 3 days/week that did not show neurotoxicity until 5 weeks into the study; these values were considered to be protective of reproductive and developmental outcomes.

The proposed AEGL-1 values for ethylene oxide presented by the ORNL staff scientist were based on a NOEL for developmental toxicity (Snellings et al., 1982) (Attachment 13). The committee discussed the relevancy of deriving AEGL-1 values for ethylene oxide considering the definition for AEGL-1. The odor detection level for ethylene oxide is 260 ppm or greater. Toxic effects are expected to occur below the odor detection level and below the concentration expected to cause sensory irritation. The committee voted not to derive AEGL-1 values.

The derived values are shown in the table below.

SUMMARY OF PROPOSED AEGL VALUES FOR ETHYLENE OXIDE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	ND[a]	ND	ND	ND	Not relevant
AEGL-2	190 ppm 342 mg/m^3	110 ppm 198 mg/m^3	33 ppm 59 mg/m^3	19 ppm 34 mg/m^3	Neurotoxicity
AEGL-3	360 ppm 648 mg/m^3	200 ppm 360 mg/m^3	63 ppm 113 mg/m^3	35 ppm 63 mg/m^3	Lethality

[a] Not determined due to lack of data.

2,4- and 2,6-Toluene diisocyanate (TDI)
CAS Reg. Nos. 91-08-7 and 584-84-9

Chemical Manager: **Steven Barbee, Olin Corporation**
Chemical Reviewers: **Jonathan Borak, ACOEM**
Doan Hansen, Brookhaven National Laboratory
Staff Scientist: **Carol Forsyth, ORNL**

After an introduction by Steven Barbee (Attachment 15), Carol Forsyth presented the data (Attachment 16). AEGL-3 levels were based on a 4-hour LC_{50} of 9.7 ppm in the mouse. The committee requested that a better explanation of the UFs used be added to the paper. A UF of 3 was applied to estimate the LC_0 and a UF of 10 was applied which includes 3 for inter- and 3 for intra-species variation. Values for the 30-min, 1-, and 8-hour time points were extrapolated using ten Berge with a default of $n = 2$. The committee directed that statements be added to the effect that while there may be individuals presensitized to TDI, it is impossible to predict the rate of sensitization in the general population. Therefore, there may be individuals that have a strong reaction to TDI and the AEGL values may not be protective of these individuals. The committee might have considered lower values for AEGL-3, but did not know how to quantify the numbers of presensitized individuals. The AEGL-3 values are presented in the table below. Because of the response of several asthmatics to tested concentrations in the studies used to derive AEGL-1 and -2 values, it was proposed and passed that discussion of AEGL-1 and -2 values be tabled until the physicians on the committee are present (Appendix D).

SUMMARY OF PROPOSED AEGL VALUES FOR 2,4- and 2,6-TOLUENE DIISOCYANATE[a]					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-3	0.92 ppm 6.6 mg/m^3	0.65 ppm 4.6 mg/m^3	0.32 ppm 2.3 mg/m^3	0.23 ppm 1.6 mg/m^3	Lethality

[a] These values may not be protective of individuals presensitized to the chemical.

Aniline
CAS No. 62-53-3

Chemical Manager: **Robert Snyder, Environmental and Occupational Health Sciences**
Chemical Reviewer: **George Rodgers, AAPCC**
Staff Scientist: **Sylvia Talmage, ORNL**

Robert Snyder presented a historical perspective of exposure to aniline in the workplace. Data for derivation of AEGLs including inhalation data in rats, metabolism, the formation of methemoglobin (the relevant endpoint) over time, the calculation of the exponent *n* from exposures at different times, relative species sensitivity based on oral studies, and the potential greater sensitivity of infants and cardiac patients relative to healthy adults were presented by Sylvia Talmage (Attachment 17). The AEGL-1 was based on an exposure of rats to 100 ppm for 8 hours which resulted in a peak methemoglobin level of 22%. The 100 ppm value was divided by an interspecies uncertainty factor of 10 (results of oral studies and levels of methemoglobin reductase levels in red blood cells suggested that humans are much more sensitive than rats) and an intraspecies uncertainty of 10 (anecdotal data suggested that infants are much more sensitive than adults) and scaled to the other time periods using $C^1 \times t = k$ (*n* was based on LC_{50} studies at different time points). The AEGL-2 was based on the same study in which rats exposed to a level of 150 ppm for 8 hours reached a peak hemoglobin level of 41%. The same uncertainty factors and scaling procedure as used for the AEGL-1 were applied. The AEGL-3 was based on the same study with rats, but because no exposures resulted in a methemoglobin level relevant to the definition of the AEGL-3, the graph concentration versus methemoglobin level at 8 hours was extended to attain a concentration resulting in a methemoglobin level of approximately 70-80%, the defined threshold for death. The same uncertainty factors and scaling procedure as used for the AEGL-1 were applied. The values approved by the NAC appear in the table below. Because aniline is absorbed through the skin, a skin notation will be added to the table (Appendix E).

SUMMARY OF PROPOSED AEGL VALUES FOR ANILINE[a]

Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	16 ppm 61 mg/m^3	8 ppm 30 mg/m^3	2 ppm 7.6 mg/m^3	1 ppm 3.8 mg/m^3	Methemoglobin formation (22%)
AEGL-2	24 ppm 91 mg/m^3	12 ppm 46 mg/m^3	3 ppm 11 mg/m^3	1.5 ppm 5.7 mg/m^3	Methemoglobin formation (41%)
AEGL-3	40 ppm 152 mg/m^3	20 ppm 76 mg/m^3	5 ppm 19 mg/m^3	2.5 ppm 9.5 mg/m^3	Methemoglobin formation (70%)

[a] Cutaneous absorption may occur; direct skin contact with the vapor or liquid should be avoided.

isoPropyl chloroformate,
CAS Reg. No. 108-23-6

Chemical Manager: **Doan Hansen, Brookhaven National Laboratory**
Chemical Reviewers: **Ernest Falke, EPA**
Zarena Post, Texas Natural Resource Conservancy
Staff Scientist: **Cheryl Bast, ORNL**

Doan Hansen discussed the paucity of data for this chemical and the problem of using an RD_{50} that approaches the LC_{50} to set an AEGL-3 (Attachment 18). Cheryl Bast presented the data on isopropyl chloroformate and its two isomers, methyl and propyl chloroformate (Attachment 19), and asked the committee's advice on proceeding with the calculation of values. Data on the three chloroformate isomers will be summarized and sent to committee members for their evaluation.

Hydrochloric acid will be reviewed at the next meeting because the committee needs more time to handle comments.

The next meeting (6th NAC AEGL meeting) will be held June 9, 10, and 11 in the same place. The NAC-7 meeting may be considered in conjunction with the ACS Symposium in September 1997, to be held in Las Vegas.

Meeting highlights were compiled by Sylvia Talmage and Po-Yung Lu, ORNL.

LIST OF ATTACHMENTS

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

1. NAC Meeting No. 5 Agenda
2. NAC Meeting No. 5 Attendee List
3. DFO report - Paul Tobin
4. Final chemical priority list - Paul Tobin
5. Issues of AEGL draft documents - Ernie Falke
6. General comments on cyanogen chloride - Mark McClanahan
7. AEGL endpoints - Larry Gephart
8. Data analysis of SOT posters relevant to UFs - George Alexeeff
9. General comments on Phosgene - Bill Bress
10. Data analysis of proposed AEGL values for Phosgene - Jim Norris
11. Animal toxicities of Phosgene - George Alexeeff
12. General comments on ethylene oxide - Kyle Blackman
13. Data analysis of proposed AEGL values for Ethylene oxide - Kowetha Davidson
14. Developmental toxicity studies of Ethylene oxide - William Snellings
15. General comments on 2,4- and 2,6-Toluene diisocyanate (TDI) - Steve Barbee
16. Data analysis of TDI data - Carol Forsyth
17. Data analysis of derivation of AEGLs for Aniline - Sylvia Talmage
18. Introduction of isoPropyl chloroformate - Doan Hansen
19. Data summaries of isoPropyl chloroformate and Methyl and Propyl chloroformate - Cheryl Bast

LIST OF APPENDICES

A. NAC-4 Highlights
B. Expanded abstracts of UFs by Alexeeff et al. from the SOT meeting
C. Ballott for Ethylene oxide
D. Ballott for 2,4- and 2,6-Toluene diisocyanate (TDI) - AEGL-3 only
E. Ballott for Aniline

Date of AEGL NAC meeting: 6/9/97 **Chemical:** ARSINE

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y		
Steven Barbee	Y		
Lynn Beasley	Y		
David Belluck	Y		
Robert Benson	Y		
Kyle Blackman	Y		
Jonathan Borak	Y		
William Bress	Y		
Luz Claudio	Y		
Guy Colonna	A		
George Cushmac	Y		
Marion F. Ehrich	Y		
Ernest Falke	Y		
Larry Gephart	Y		
Robert E. Hazen	Y		
John Hinz	**		
Jim Holler	Y		
Thomas C. Hornshaw	Y		
Nancy K. Kim	Y		

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	Y		
Glenn Leach	Y		
Mark A. McClanahan	Y		
John S. Morawetz	Y		
William Pepelko	* *		
Richard W. Niemeier	A		
Zarena Post	Y		
George Rodgers	A		
George Rusch, Chair	Y		
Bob Snyder	A		
Thomas J. Sobotka	Y		
Kenneth Still	Y		
Patricia Ann Talcott	Y		
Richard Thomas	Y		
Thomas Tuccinardi/ Doan Hansen *	A Y *		
TALLY	27/27		

* = Not a voting member; ** = Abstain; A = Absent

FNOT APPROPRIATE

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	FNA ,( )	NA ,( )	NA ,( )	NA ,( )
AEGL 2	0.24 ,(0.8)	0.17 ,(0.5)	0.1 ,(0.3)	0.1 ,(0.3)
AEGL 3	0.7 ,(2.2)	0.5 ,(1.6)	0.25 ,(0.8)	0.18 ,(0.6)

AEGL 1 Motion: D. Belluck **Second:** G. Alexeeff

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/9/97

Comments:

Date of AEGL NAC meeting: 6/9/97 **Chemical:** CYANOGEN CHLORIDE

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y		
Steven Barbee	Y		
Lynn Beasley	Y		
David Belluck	Y		
Robert Benson	Y		
Kyle Blackman	Y		
Jonathan Borak	Y		
William Bress	Y		
Luz Claudio	Y		
Guy Colonna	A		
George Cushmac	Y		
Marion F. Ehrich	Y		
Ernest Falke	Y		
Larry Gephart	Y		
Robert E. Hazen	Y		
John Hinz	Y		
Jim Holler	Y		
Thomas C. Hornshaw	Y		
Nancy K. Kim	Y		

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	Y		
Glenn Leach	Y		
Mark A. McClanahan	Y		
John S. Morawetz	Y		
William Pepelko	Y		
Richard W. Niemeier	A		
Zarena Post	Y		
George Rodgers	A		
George Rusch, Chair	Y		
Bob Snyder	A		
Thomas J. Sobotka	Y		
Kenneth Still	Y		
Patricia Ann Talcott	Y		
Richard Thomas	Y		
Thomas Tuccinardi/ Doan Hansen *	A Y *		
TALLY	29/29		

* = Not a voting member; ** = Abstain; A = Absent

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )

AEGL 1 Motion: Tom Hornshaw **Second:** Richard Thomas

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/9/97

Comments: INADEQUATE TOXICOLOGY INFORMATION AND NO SIGNIFICANT PRODUCTION IDENTIFIED, SO NO AEGLs WILL BE DEVELOPED, BUT A PARAGRAPH FOR FEDERAL REGISTER WILL BE WRITTEN BY M. McCLANAHAN

Date of AEGL NAC meeting: 6/9/97 **Chemical:** AMMONIA

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff		N	N	Loren Koller		Y	Y
Steven Barbee		Y	Y	Glenn Leach		Y	Y
Lynn Beasley		A	Y	Mark A. McClanahan		N	Y
David Belluck		N	N	John S. Morawetz		N	* *
Robert Benson		* *	* *	William Pepelko *		A	* *
Kyle Blackman		N	Y	Richard W. Niemeier		A	A
Jonathan Borak		Y	Y	Zarena Post		Y	N
William Bress		Y	Y	George Rodgers		A	A
Luz Claudio		* *	Y	George Rusch, Chair		Y	Y
Guy Colonna		A	A	Bob Snyder		A	A
George Cushmac		Y	Y	Thomas J. Sobotka		N	Y
Marion F. Ehrich		Y	Y	Kenneth Still		Y	Y
Ernest Falke		Y	Y	Patricia Ann Talcott		N	Y
Larry Gephart		Y	Y	Richard Thomas		Y	Y
Robert E. Hazen		Y	Y	Thomas Tuccinardi/ Doan Hansen *		A Y *	A Y *
John Hinz		* * A	Y				
Jim Holler		Y	Y				
Thomas C. Hornshaw		Y	* *				
Nancy K. Kim		Y	Y	TALLY		18/~~23~~ 25	23/26

* = Not a voting member; ** = Abstain; A = Absent

PPM, (mg/m³)	5MIN	30 Min	60 Min	4 Hr	8Hr
AEGL 1		,( )	,( )	,( )	,( )
AEGL 2	380	160 ,( )	110 ,( )	110 ,( )	110 ,( )
AEGL 3	3800 (2657)	1600 ,(1119)	1100 ,(769)	550 ,(385)	390 ,(273)

AEGL 1 Motion: S. Barbee PP **Second:** L. Koller

AEGL 2 Motion: ~~E. Falke~~ E. Falke PP **Second:** ~~J. Hinz~~ R. Thomas

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DEO:** Paul S. Tobin **Date:** 6/9/97

Comments:

Date of AEGL NAC meeting: 6/10/97 **Chemical:** TDI (2,4 and 2,6 ISOMERS)

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff	N	Y		Loren Koller	Y	Y	
Steven Barbee	Y	Y		Glenn Leach	Y	Y	
Lynn Beasley	Y	Y		Mark A. McClanahan	Y	Y	
David Belluck	Y	Y		John S. Morawetz	N	Y	
Robert Benson	Y	Y		William Pepelko *	**	**	
Kyle Blackman	Y	Y		Richard W. Niemeier	A	A	
Jonathan Borak	Y	Y		Zarena Post	Y	Y	
William Bress	Y	Y		George Rodgers	A	A	
Luz Claudio	Y	Y		George Rusch, Chair	Y	Y	
Guy Colonna	A	A		Bob Snyder	A	A	
George Cushmac	Y	Y		Thomas J. Sobotka	Y	Y	
Marion F. Ehrich	Y	Y		Kenneth Still	Y	Y	
Ernest Falke	Y	Y		Patricia Ann Talcott	Y	Y	
Larry Gephart	Y	Y		Richard Thomas	A	A	
Robert E. Hazen	Y	Y		Thomas Tuccinardi/ Doan Hansen	A Y	A Y	
John Hinz	Y	Y					
Jim Holler	Y	Y					
Thomas C. Hornshaw	Y	Y					
Nancy K. Kim	Y	Y		TALLY	26/28	28/28	

* = Not a voting member; ** = Abstain; A = Absent

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
~~AEGL 1~~	0.02 ,(0.14)	0.02 ,(0.14)	0.01 ,(0.07)	0.01 ,(0.07)
AEGL 2	0.17 ,(1.22)	0.12 ,(0.86)	0.06 ,(0.43)	0.06 ,(0.43)
AEGL 3	,( )	,( )	,( )	,( )

AEGL 1 Motion: Z. Post **Second:** L. Koller

AEGL 2 Motion: Z. Post **Second:** L. Koller

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 6/10/97

Comments:

Date of AEGL NAC meeting: 6/10/97 **Chemical:** CHLORINE TRIFLUORIDE

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	N	N	Y
Steven Barbee	Y	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	Y	Y	Y
Robert Benson	Y	Y	Y
Kyle Blackman	Y	Y	Y
Jonathan Borak	N	Y	Y
William Bress	Y	Y	Y
Luz Claudio	Y	Y	Y
Guy Colonna	A	A	A
George Cushmac	Y	Y	Y
Marion F. Ehrich	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
Robert E. Hazen	Y	Y	Y
John Hinz	Y	Y	Y
Jim Holler	Y	Y	Y
Thomas C. Hornshaw	Y	Y	Y
Nancy K. Kim	Y	Y	Y

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	Y	Y	Y
Glenn Leach	Y	Y	Y
Mark A. McClanahan	Y	Y	Y
John S. Morawetz	N	Y	N
William Pepelko	* *	* *	* *
Richard W. Niemeier	A	A	A
Zarena Post	N	N	N
George Rodgers	A	A	A
George Rusch, Chair	Y	Y	Y
Bob Snyder	A	A	A
Thomas J. Sobotka	Y	Y	Y
Kenneth Still	Y	Y	Y
Patricia Ann Talcott	Y	Y	Y
Richard Thomas	A	A	A
Thomas Tuccinardi/ Doan Hansen	A Y	A Y	A Y
TALLY	24/28	26/28	26/28

* = Not a voting member; ** = Abstain; A = Absent

PPM, (mg/m^3)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	0.70 ,(2.7)	0.35,(1.3)	0.09 ,(0.34)	0.04 ,(0.15)
AEGL 2	6.2 ,(24)	3.1 ,(12)	0.77 ,(2.9)	0.39 ,(1.5)
AEGL 3	27 ,(103)	14 ,(53)	3.4 ,(13)	1.7 ,(6.5)

AEGL 1 Motion: E FALKE **Second:** J. HINZ

" "

AEGL 2 Motion: _____ **Second:** _____

" "

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 6/10/97

Comments:

Date of AEGL NAC meeting: 6/10/97 **Chemical:** ETHYLENIMINE

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	N	N
Steven Barbee	Y	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	Y	N	N
Robert Benson	Y	Y	Y
Kyle Blackman	Y	Y	Y
Jonathan Borak	Y	Y	Y
William Bress	Y	Y	Y
Luz Claudio	Y	N	Y
Guy Colonna	A	A	A
George Cushmac	Y	Y	Y
Marion F. Ehrich	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
Robert E. Hazen	Y	Y	Y
John Hinz	* *	* *	* *
Jim Holler	Y	Y	Y
Thomas C. Hornshaw	Y	Y	Y
Nancy K. Kim	Y	N	N
Loren Koller	Y	Y	Y
Glenn Leach	Y	Y	Y
Mark A. McClanahan	Y	Y	Y
John S. Morawetz	Y	Y	Y
William Pepelko	* *	* *	* *
Richard W. Niemeier	A	A	A
Zarena Post	Y	Y	Y
George Rodgers	A	A	A
George Rusch, Chair	Y	Y	Y
Bob Snyder	A	A	A
Thomas J. Sobotka	N	Y	Y
Kenneth Still	Y	Y	Y
Patricia Ann Talcott	Y	Y	Y
Richard Thomas	A	A	A
Thomas Tuccinardi/ Doan Hansen	A Y	A Y	A Y
TALLY	26/27	23/27	24/27

* = Not a voting member; ** = Abstain; A = Absent

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	F ,( )	F ,( )	F ,( )	F ,( )
AEGL 2	9.8 ,(17.5)	4.6 ,(8.2)	1.0 ,(1.79)	0.47 ,(0.84)
AEGL 3	18 ,(32.2)	9.6 ,(17.2)	2.8 ,(5.0)	1.5 ,(2.7)

F VALUES NOT RECOMMENDED

AEGL 1 Motion: S. Barbee **Second:** M. McClanahan

AEGL 2 Motion: 〃 **Second:** 〃

AEGL 3 Motion: 〃 **Second:** 〃

Approved by Chair: George M. Rusch **DFO:** Paul S. Tobin **Date:** 6/10/97

Comments:

Date of AEGL NAC meeting: 6/10/97 **Chemical:** DIBORANE

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	Y	Y
Steven Barbee	Y	N	Y
Lynn Beasley	Y	Y	Y
David Belluck	Y	Y	Y
Robert Benson	Y	Y	Y
Kyle Blackman	Y	Y	Y
Jonathan Borak	Y	Y	Y
William Bress	Y	Y	Y
Luz Claudio	Y	N	Y
Guy Colonna	A	A	A
George Cushmac	Y	Y	Y
Marion F. Ehrich	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
Robert E. Hazen	Y	Y	Y
John Hinz	Y	Y	Y
Jim Holler	Y	Y	Y
Thomas C. Hornshaw	Y	N	Y
Nancy K. Kim	Y	Y	Y

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	N	N	Y
Glenn Leach	Y	Y	Y
Mark A. McClanahan	Y	Y	Y
John S. Morawetz	Y	Y	Y
William Pepelko	* *	* *	* *
Richard W. Niemeier	A	A	A
Zarena Post	Y	Y	Y
George Rodgers	A	A	A
George Rusch, Chair	Y	Y	Y
Bob Snyder	A	A	A
Thomas J. Sobotka	Y	N	Y
Kenneth Still	Y	Y	Y
Patricia Ann Talcott	N	N	N
Richard Thomas	A	A	A
Thomas Tuccinardi/ Doan Hansen	A Y	A Y	A Y
TALLY	26/28	22/28	27/28

* = Not a voting member; ** = Abstain; A = Absent

NOT APPLICABLE (VALUES NOT RECOMMENDED)

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	# ,( )	# ,( )	# ,( )	# ,( )
AEGL 2	2 ,( )	1 ,( )	0.25 ,( )	0.13 ,( )
AEGL 3	7.3 ,( )	3.7 ,( )	0.92 ,( )	0.46 ,( )

AEGL 1 Motion: D. Hansen **Second:** W. Bress

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 6/10/97

Comments:

Date of AEGL NAC meeting: 6/10/97 **Chemical:** ALLYL AMINE

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	N	Y	Y
Steven Barbee	Y	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	N	Y	Y
Robert Benson	N	N	Y
Kyle Blackman	N	Y	Y
Jonathan Borak	A	A	A
William Bress	Y	Y	Y
Luz Claudio	A	A	A
Guy Colonna	A	A	A
George Cushmac	Y	Y	Y
Marion F. Ehrich	A	A	A
Ernest Falke	Y	N	Y
Larry Gephart	Y	Y	Y
Robert E. Hazen	N	Y	Y
John Hinz	Y	Y	Y
Jim Holler	Y	Y	Y
Thomas C. Hornshaw	N	Y	Y
Nancy K. Kim	Y	Y	Y

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	Y	Y	Y
Glenn Leach	Y	Y	Y
Mark A. McClanahan	Y	Y	Y
John S. Morawetz	**	Y	Y
William Pepelko	**	**	**
Richard W. Niemeier	A	A	A
Zarena Post	Y	Y	Y
George Rodgers	A	A	A
George Rusch, Chair	Y	Y	Y
Bob Snyder	A	A	A
Thomas J. Sobotka	A	A	A
Kenneth Still	Y	Y	Y
Patricia Ann Talcott	N	Y	Y
Richard Thomas	Y	Y	Y
Thomas Tuccinardi/ Doan Hansen	A Y	A A	A Y
TALLY	17/24	22/24	25/25

* = Not a voting member; ** = Abstain; A = Absent

F NOT RECOMMENDED

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	F ,( )	F ,( )	F ,( )	F ,( )
AEGL 2	11 ,(25.30)	4.7 ,(10.95)	0.91 ,(2.12)	0.40 ,(0.93)
AEGL 3	40 ,(94)	18 ,(42)	3.5 ,(8.1)	2.3 ,(5.4)

AEGL 1 Motion: ~~Z. Post~~ E. Falke **Second:** ~~J. Hinz~~ R. Thomas

AEGL 2 Motion: Z. Post **Second:** J. Hinz

AEGL 3 Motion: L. Gephart **Second:** Z. Post

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/10/97

Comments: Odor threshold is at or above AEGL-2 level (or we don't have data

Date of AEGL NAC meeting: 6/11/97 **Chemical:** Hydrogen Chloride (HCl)

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff	Y	Y	N	Loren Koller	Y	Y	Y
Steven Barbee	Y	Y	Y	Glenn Leach	Y	Y	A
Lynn Beasley	Y	A	A	Mark A. McClanahan	Y	Y	A
David Belluck	Y	Y	Y	John S. Morawetz	Y	Y	N
Robert Benson	Y	Y	N	William Pepelko	—	—	—
Kyle Blackman	Y	Y	Y	Richard W. Niemeier	A	A	A
Jonathan Borak	A	A	A	Zarena Post	Y	Y	N
William Bress	Y	Y	Y	George Rodgers	A	A	A
Luz Claudio	A	A	A	George Rusch, Chair	Y	Y	Y
Guy Colonna	A	A	A	Bob Snyder	A	A	A
George Cushmac	Y	Y	Y	Thomas J. Sobotka	A	A	A
Marion F. Ehrich	A	A	A	Kenneth Still	Y	Y	Y
Ernest Falke	Y	Y	N	Patricia Ann Talcott	Y	Y	Y
Larry Gephart	Y	N	Y	Richard Thomas	Y	Y	Y
Robert E. Hazen	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A Y	A Y	A Y
John Hinz	Y	Y	Y				
Jim Holler	Y	Y	Y				
Thomas C. Hornshaw	Y	Y	Y				
Nancy K. Kim	Y	Y	N	TALLY	25/25	23/24	16/22

* = Not a voting member; ** = Abstain; A = Absent

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	1.8 ,(2.7)	1.8 ,(2.7)	1.8 ,(2.7)	1.8 ,(2.7)
AEGL 2	43 ,(64)	22 ,(33)	5.4 ,(8.1)	2.7 ,(4.0)
AEGL 3	210 ,(313)	104 ,(155)	26 ,(39)	13 ,(19)

AEGL 1 Motion: D. Hansen **Second:** S. Barbee

AEGL 2 Motion: W. Bress **Second:** R. Benson

AEGL 3 Motion: L. Koller **Second:** D. Hansen

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 6/11/97

Comments: