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

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-5 Agenda

Monday, March 17, 1997

10:00 - 10:15 AM	Introduction and approval of NAC-4 highlights
10:15 - 10:35	Project Director remarks (Roger Garrett)
10:35 - 10:50	DFO reports (Paul Tobin) • Chemical selection/prioritization • OSHA monitoring survey data • AEGL internet site development • Federal register announcement of proposed AEGL values • ACS AEGL symposium in September 1997
10:50 - 12:00	Technical discussions • Protocol of acute inhalation study (George Rusch) • Uncertainty Factor Subcommittee report (Richard Thomas) • "Living Document" (Ernie Falke) • 10-minute AEGL for compressed gases (George Rusch) • Status of cyanogen chloride (Mark McClanahan) • Compilation of associated adverse health effects of AEGL-2 & -3 (Larry Gephart) • How developmental toxicity effects are to be used for AEGL-2 & -3?
12:00 - 1:00 PM	**Lunch**
1:00 - 2:00	Technical discussions (continued, if necessary)
2:00 - 3:00	Phosgene (Bill Bress/Jim Norris)
3:00 - 3:15	**Break**
3:15 - 4:15	Phosgene (continued)
4:15 - 5:00	Ethylene oxide (Kyle Blackman/Kowetha Davidson)

Tuesday, March 18, 1997

8:30 - 10:30 AM	Ethylene oxide (continued)
10:30 - 10:45	**Break**
10:45 - 12:00	Isopropyl chloroformate (Doan Hansen/Cheryl Bast)
12:00 - 1:00 PM	**Lunch**
1:00 - 3:00	Toluene 2,4- & 2,6-diisocyanate (Steve Barbee/Carol Forsyth)
3:00 - 3:15	**Break**
3:15 - 5:00	Aniline (Bob Snyder/Sylvia Talmage)

Wednesday, March 19, 1997

8:30 - 9:00 AM	Aniline (continued, if necessary)
9:00 - 11:00	Hydrogen chloride (John Hinz/Cheryl Bast)
11:00 - 11:15	Administrative issues
11:15	Adjournment

ATTACHMENT 2

ATTENDANCE SHEET

SUBJECT: NAC/AEGL

DATE: 3/17/97
TIME: 10 AM

LOCATION: Ariel Rios - Green Room

Name	Signature	Organization	Phone Number
Gene Reeves		AlliedSignal	201-455-3672
Paul Tobin	Paul Tobin	EPA/OPPT	202 260-1736
Rick Niemeier		NIOSH	(513) 533-8388
Kyle W. Blackman	Kyle W. Blackman	FDMA	202/646-4676
Dave Bellin		MPCA	612/296/7874
Tom Hornshaw	Thomas C. Hornshaw	ILEPA/STAMS	217-785-0830
Robert Snyder		Rutgers Univ	908-445-3700
Nancy Kim	Nancy Kim	NYS Dept of Health	518-458-6435
Lynn Beasley	Lynn M. Beasley	USEPA/Superfund	703-603-9086
George Rodgers	George Rodgers	AIHA	502-852-8626
Julian P. Hintz		USAF-AL/OEM	(210) 536-6136
Kenneth R. Still		USN/NMRI-TI	937-255-6858
John S. Horowitz	John S. Horowitz	ICI Canada (USA)	313-621-8882
Jim HOLLER		ATSDR	404 639-6208
MARK A. MCCLANAHAN		CDC/NCEH	770-488-7297
GLENN LEACH		ARMY-CHPPM	410-671-3980
Kaveetha Davidson		ORNL	423/574-7749
Cheryl Bast	Cheryl Bast	ORNL	423-574-7581
Sylvia Talmage	Sylvia Talmage	ORNL	423-576-7758
BO-YUNG LEE		ORNL	423-574-7803
Robert Hazen		NJDEP	609-292-8294
Marion Ehrich		Virginia Tech	504-54-6143
Zaeema Perot		TNRCC	512-239-1332
BILL BRESS		ASTHO	202-863-7220
Bob BENSON		EPA Region 8	303-312-7070

ATTENDANCE SHEET

SUBJECT:

DATE:
TIME:

LOCATION: Ariel Rios - Green Room

Name	Signature	Organization	Phone Number
Liz Claudio		Mount Sinai	212 241 7625
Loren Koller		Oregon State Univ	541 737 5547
George Alexeeff		Cal/EPA	(510) 540-3324
Steven Barber		Olin + AIHA	203-495-8550 x 5435
Larry Gephart		Exxon Biomedical	908 873-6519 / 6009
Joan Hausen		BNL/DOE	516 344-7535
Jonathan Borak		ACOEM	203-777-6611
Richard Thomas		ICF-H	703-276-3000
Ernest V. Falke		USEPA	202 260-3933
Roger Kemmerer		USEPA	202-260-3302
Sara Thurin Rollin		BNA	202-452-4584
Nancy Nickell		Air Daily	(202) 775-0240 x329 572-5045 FAX
Andrew Jaques		API	202-682-8563
William M. Sadleir		Union Carbide	203-794-3588
Jim Darr		U.S. EPA	202-260-3441
Marcie Francis		Battelle	301 770 2290
Barry Hoberman		Environ Corp	703-841-1388
David Layland		U.S. EPA	703-308-0482
James C. Norris		ORNL	423-576-6237

AEGL CHEMICAL PRIORITY LIST

POTENTIAL STRATEGIES TO IDENTIFY PRIORITY CHEMICALS

- Prioritize ~80,000 commercial chemicals (tox, v.p., production)

or

- Combine organization lists
  - equitable return to organizations
  - organization lists are prioritized

Organization Lists

- AIHA
  - ERPG
- ATSDR
  - Medical Management Guideline
  - Toxicology Profiles
- DOD
  - Navy
  - Army Tox Summary
  - Air Force Installation Restoration
  - SERDP
- DOE
  - SCAPA
- DOT
  - ERG
- EPA
  - CAAA 112r
  - CAAA 112b
  - Superfund
  - SARA EHS
  - (Master Testing List)
- NIOSH
  - IDLH
- OSHA
  - STEL
- International
  - (Seveso Annex III)
- Other

OSHA MONITORING DATA

- One example of data available from one organization (NIOSH - R. Niemeier)
- Routine workplace inspection data
- Monitoring Data obtained for 24 /78 Priority Chemicals
- Ppm or mg/m^3 of chemical concentration for min to hrs of workplace monitoring
- exposure duration is surrogate for 8 hours exposure
- no fatalities

(Option 2) Combination of Organization Lists

- Identify organization chemical lists (AIHA, ATSDR, DOD, DOE, DOT, EPA, NIOSH, OSHA)
- Include some chemicals from each list
- Choose chemicals on multiple lists
- Select about 50 - 100 chemicals

CHEMICAL PRIORITY LIST

- 78 Priority Chemicals
- Selected from organization lists
- May be amended (additions/deletions)
- ORAL will certify production - almost all are on TSCA Inventory
- Similar chemicals will be reviewed together when possible
- Public notification routes (Federal Register/Internet/Press/Organizations)
- Stakeholder check on applications

INTERNET DEVELOPMENT

- LINKS TO EPA/OPPT HOME PAGE
- PROPOSED AEGL RESULTS
- INTERIM AEGL RESULTS
- TECHNICAL SUPPORT DOCUMENTS FOR PROPOSED AND INTERIM AEGLS
- HISTORIC AND OTHER INFORMATION
- WEB SITE SCHEDULED FOR SPRING 1997

Attachment 3

FEDERAL REGISTER NOTICE FOR PROPOSED AEGLS

- Announcement of AEGL Chemicals to be published in the Federal Register as "Proposed" values
- Seven hundred and fifty (750) chemicals may be needed for the 15 chemicals
- Availability of technical support documents for Proposed AEGLs will be via the Internet or EPA Docket
- Public comments will be solicited on the AEGL chemicals and proposed values (60 days)
- AEGLs will become "interim" following NAC/AEGL consideration of public comments
- AEGLs and supporting documentation is provided to NAS/COT for consideration and publishing of "Final" AEGL values

American Chemical Society Symposium

- Sponsored by: Committee on Chemical Health and Safety Division (Dr. Po-Yung Lu, Chairman)
- Full-Day Symposium, Three Sessions
  - Concept and structure of the NAC/AEGL
  - Methodologies to develop AEGLs
  - Panel Discussion - Program Approaches for AEGLs

FEDERAL AGENCIES

(1) Agency for Toxic Substances and Disease Registry
(2) Centers for Disease Control
(3-5) Department of Defense
(Army/Navy/Air Force)
(6) Department of Energy
(7) Department of Transportation
(8-10) Environmental Protection Agency
(OPPT/Superfund/Regional Risk Assessors/ORD*)
(11) Federal Emergency Management Agency
(12) Food and Drug Administration
National Aeronautic and Space Agency*
(13) National Institute for Occupational Safety and Health

INDUSTRY

(14) AlliedSignal

(15) Exxon Biomedicals

(16) Olin Corporation

ORGANIZATIONS

(17) AFL-CIO

(18) American Association of Poison Control Centers

(19) American Association of State and Territorial Health Officials (Vermont rep)

American Industrial Hygiene Association (represented by Olin Chemical Co. rep.)

(20) American College of Occupational and Environmental Medicine

Environmmental Group*

(21) ICEH (International Consulting)

(22) National Fire Protection Agency

(23) STAPPA/ALAPCO (State/Local air quality)

(24) Environmental Justice

National Advisory Committee for the Development of Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL)
*** = not yet a member**

STATES

(25) California

(26) Minnesota

(27) New Jersey

(28) New York

(29) Texas

ACADEMIA

(30) Oregon State

(31) Rutgers University

(32) University of Idaho

(33) Virginia Polytechnical Institute

Starting List of 85 Priority Chemicals for Acute Exposure Guideline Level (AEGL) Development*

Contact: Paul S. Tobin, Ph.D. (202) 260-1736 e-mail tobin.paul@epamail.epa.gov

ORGANIZATION LISTS

[1]ATSDR Medical Managment	Agency for Toxic Substances and Disease Registry M = Chemicals with an ATSDR Medical Management Guideline T = Chemicals with an ATSDR Toxicology Profile
[2]DOD	Department of Defense A = Army Toxicity Summary Chemical C = Chemical Weapons Convention Schedule 3.A Toxic Chemical Cs = Chemical Stockpile Emergency Preparedness Program (CSEPP) Chemical I = Air Force Installation Restoration Program Chemical N = Navy Chemical S = Strategic Environmental Research and Development Program (SERDP) Chemical
[3]DOE SCAPA	DOE Subcommittee for Consequence Assessment and Protective Action Chemical
[4]DOT ERP	Department of Transportation Emergency Response Guidebook P = Priority DOT ERG Chemical O = Other ERG Chemical
[5]EPA CAA 112b	Environmental Protection Agency Clean Air Act 112b Chemical
[6]EPA CAA 112r	Environmental Protection Agency Clean Air Act 112b Chemical (+ = SARA s.302 also)
[7]EPA Superfund	Environmental Protection Agency Superfund Chemical
[8]OSHA PSM	OSHA Process Safety Management Chemical
[9]OSHA STEL	OSHA Short-term Exposure Limit Chemical
[10]NIOSH IDLH	NIOSH Immediately Dangerous to Life or Health Chemical
[11]Seveso Annex III	International Seveso Convention List

* This starting list of 85 priority chemicals below has been created by merging priority hazardous chemical lists of various organizations. This list is a starting point for the selection of chemicals for AEGL development by the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Chemicals (NAC/AEGL). However, the list of chemicals is susceptible to modification, pending further input from the organizations that make up the NAC/AEGL. While it is anticipated that most of these chemicals will remain of high priority for AEGL development, changes to the list could occur. The NAC/AEGL hopes to select at least 30 chemicals per year to initiate through the AEGL development process and thus this list is planned for expansion as the NAC/AEGL continues to address chemicals of interest to its member organizations.

Any one organization list should not be interpreted as being of interest only to that organization in whose list the chemical appears. Certain lists, such as the EPA CAA 112r list, are considered important to organizations other than EPA, since any facility and site that possesses these chemicals are responsible for federal regulatory requirements triggered by the listed chemicals. In additioin, many of the hazardous chemicals listed below are commodity chemicals, the AEGLs for which are of potential importance to many organization programs.

ATTACHMENT 4

CAS NO.	CHEMICAL	[1]ATSDR	[2]DOD	[3]DOE SCAPA	[4]DOT ERG	[5]EPA CAA 112b	[6]EPA CAA 112r	[7]EPA Superfund	[8]OSHA PSM	Seveso Annex III	[9]OSHA STEL	[10]NIOSH IDLH
56-23-5	Carbon tetrachloride	T	AIS			X		X				X
57-14-7	Dimethyl hydrazine				P	X	X+		X			X
60-34-4	Methyl hydrazine				P	X	X+	X	X			X
62-53-3	Aniline	M			P	X	+	X				X
67-66-3	Chloroform	T	AIS			X	X+	X				X
68-12-2	Dimethylformamide			X		X						
71-43-2	Benzene	X	AIS	X		X		X				
74-90-8	Hydrogen cyanide	M	C		P	X	X+		X	X		X
74-93-1	Methyl mercaptan	T			P		X+		X			X
75-09-2	Methylene chloride	MT	AIS	X		X		X				
75-21-8	Ethylene oxide	MT			P	X	X+		X	X		X
75-44-5	Phosgene	M	C		P	X	X+		X	X		X
75-55-8	Propyleneimine					X	X+			X		X
75-56-9	Propylene oxide					X	X+			X		X
75-74-1	Tetramethyllead					X	X+		X	X		X
75-77-4	Trimethychlorosilane						X+					
75-78-5	Dimethyldichlorosilane			X			X+		X			
75-79-6	Methyltrichlorosilane						X+		X			
78-82-0	Isobutyronitrile						X+					
79-01-6	Trichloroethylene	MT	AIS	X		X		X				
79-21-0	Peracetic acid						X+		X	X		

CAS NO.	CHEMICAL	[1]ATSDR	[2]DOD	[3]DOE SCAPA	[4]DOT ERG	[5]EPA CAA 112b	[6]EPA CAA 112r	[7]EPA Superfund	[8]OSHA PSM	Seveso Annex III	[9]OSHA STEL	[10]NIOSH IDLH
79-22-1	Methy chloroformate						X+					
91-08-7	Toluene 2,6-diisocyanate	M					X+					
106-89-8	Epichlorohydrin					X	X+					X
107-02-8	Acrolein	T			P	X	X+	X	X	X	X	X
107-11-9	Allyl amine				P		X+		X	X		
107-12-0	Propionitrile						X+					
107-15-3	Ethylenediamine						X+					X
107-18-6	Allyl alcohol				P		X+			X	X	X
107-30-2	Chloromethyl methyl ether				O	X	X+		X	X		
108-23-6	Isopropyl chloroformate				P		X+					
108-88-3	Toluene	MT	AINS			X		X				
108-91-8	Cyclohexylamine						X+					
109-61-5	Propyl chloroformate				O		X+					
110-00-9	Furan						X+	X	X			
110-89-4	Piperidine						X+					
123-73-9	Crotonaldehyde, (E)						X+					X
126-98-7	Methacrylonitrile				O		X+		X			
127-18-4	Tetrachloroethylene	T	AIS	X		X		X				
151-56-4	Ethyleneimine				P	X	X+			X	X	X
302-01-2	Hydrazine	T	I	X		X	X+					X

CAS NO.	CHEMICAL	[1]ATSDR	[2]DOD	[3]DOE SCAPA	[4]DOT ERG	[5]EPA CAA 112b	[6]EPA CAA 112r	[7]EPA Superfund	[8]OSHA PSM	Seveso Annex III	[9]OSHA STEL	[10]NIOSH IDLH
353-42-4	Boron triflouride compound with methyl ether (1:1)						X+					X
506-77-7	Cyanogen chloride						X+		X			
509-14-8	Tetranitromethane						X+					X
540-59-0	1,2-Dichloroethylene	T		X								X
584-84-9	Toluene 2,4-diisocyanate	M				X	X+	X			X	X
594-42-3	Perchloromethylmercaptan						X+		X	X		X
624-83-9	Methyl isocyanate				P	X	X+		X	X		X
811-97-2	HFC 134A (1,1,1,2-Tetrafluoroethane)		N									
814-68-6	Acrylyl chloride						X+		X			
1330-20-7	Xylenes (mixed)	X	AIN			X		X				
1717-00-6	HCFC 141b (1,1-Dichloro-1-fluoroethane)		N									
4170-30-3	Crotonaldehyde				P		X+					X
6423-43-4	Otto Fuel II	T	Navy									
7446-09-5	Sulfur dioxide				P		X+		X	X	X	X
7446-11-9	Sulfur trioxide				P		X+		X	X		
7647-01-0	Hydrogen chloride				P	X	X+	X	X	X	X	X
7647-01-0	Hydrochloric acid				P	X	X+	X	X		X	X
7664-39-3	Hydrogen fluoride	M			P	X	X+		X	X	X	X
7664-41-7	Ammonia	MT					X+	X	X	X		X

CAS NO.	CHEMICAL	[1]ATSDR	[2]DOD	[3]DOE SCAPA	[4]DOT ERG	[5]EPA CAA 112b	[6]EPA CAA 112r	[7]EPA Superfund	[8]OSHA PSM	Seveso Annex III	[9]OSHA STEL	[10]NIOSH IDLH
7664-93-9	Sulfuric acid				P		+	X				X
7697-37-2	Nitric acid			X	P		X+		X		X	X
7719-12-2	Phosphorus trichloride				P		X+		X		X	X
7726-95-6	Bromine				P		X+		X	X	X	X
7782-41-4	Fluorine				P		X+		X			X
7782-50-5	Chlorine	M			P	X	X+	X	X	X	X	X
7783-06-4	Hydrogen sulfide	M				X	X+		X			
7783-60-0	Sulfur tetrafluoride				P		X+					
7783-81-5	Uranium hexafluoride			X								
7784-34-1	Arsenous trichloride				P		X+					
7784-42-1	Arsine	M		X	P	X	X+	X	X	X		X
7790-91-2	Chlorine trifluoride			X	O				X			X
7803-51-2	Phosphine	M		X	P	X	X+		X	X	X	X
8014-95-7	Oleum				P		X+		X			
10025-87-3	Phosphorus oxychloride				O		X+		X			
10049-04-4	Chlorine dioxide						X		X		X	X
10102-43-9	Nitric oxide				P		X+		X			X
10294-34-5	Boron trichloride				P		X+		X			
13463-39-3	Nickel carbonyl				P	X	X+		X	X	X	
13463-40-6	Iron, pentacarbonyl-				P		X+		X		X	
19287-45-7	Diborane			X	P		X+		X			X

CAS NO.	CHEMICAL	[1]ATSDR	[2]DOD	[3]DOE SCAPA	[4]DOT ERG	[5]EPA CAA 112b	[6]EPA CAA 112r	[7]EPA Superfund	[8]OSHA PSM	Seveso Annex III	[9]OSHA STEL	[10]NIOSH IDLH
25323-89-1	Trichloroethane	T	AS	X		X		X				
163702-07-6	Methyl nonafluorobutyl ether (HFE 7100 component)		N									
163702-08-7	Methyl nonafluorobutyl ether (HFE 7100 component)		N									
MIXTURE	Otto Fuel II (Propylene glycol dinitrate major component)	T	INS									

AEGL Chemical Progress				
Chemical	**Author**	**Go as is**	**Go with changes**	**Nogo**
Arsine	Young			
Chlorine	Talmage			
Cyanogen chloride	Forsyth			
1,2-Dichloroethylene	Bast			
Dimethyl hydrazine	Young			
Dimethyldichlorosilane	Bast			
Fluorine	Talmage			
Hydrazine	Young			
Hydrogen chloride	Bast/Hinz			
Hydrogen cyanide	Norris			
Hydrogen fluoride	Talmage			
Methyl mercaptan	Norris			
Methyl hydrazine	Young			
Nitric acid	Forsyth			
Phosphine	Bast			

1. GENERAL

   Where the author is unable to follow the guidance below, the chemical will be brought back to the next meeting for consideration.

2. ROUNDING OFF

   Authors will round off values as agreed.

3. MULTIPLICATION OF UNCERTAINTY FACTORS

   Authors will change instance where 3 * 3 = 9 to 10.

4. LEVELING OF AEGL-1 VALUES

   Leave a single value for hydrazine and nitric acid.
   Leave 2 levels with fluorine and hydrogen fluoride.
   Should chlorine and dimethldichlorosilane values be flattened or left alone with the current ten Berge derivation which gives different numbers for each time point.

5. INTRASPECIES VARABILITY

   Where the justification for a value of 3 is that we are not going to protect hypersusceptible individuals a chemical specific rationale will be written by the author.

6. ARSINE
   a. Delete AEGL-1 values.
   b. Justify the use of n=2.

7. DIMETHYLDICHLOROSILANE
   a. The AEGL-1 and AEGL-2 values were based upon the RD50 of HCl. However, in the HCl document being considered at this meeting the levels are based upon baboon data. After we vote on the current HCl

document we should change the dimethyldichlorosilane values to reflect the new HCl values.

8. HYDRAZINE
   a. Intraspecies uncertainty factor of 3 needs to be justified specifically for all AEGL levels.
   b. AEGL-1 values are the same for all times. This was done by using the ten Berge equation to extrapolate back (0.308, 0.218, 0.109., 0.077 respectively for 30 min & 1, 4, and 8 our levels. A single value of 0.1 was chosen for all times. If we flatten the values we are saying time is not a factor. In that case the use of the tenBerge equation is not valid. We should take the 24 hour value of 0.4 ppm and divide it by our uncertainty factor of 10 to give an AEGL-1 of 0.04 ppm and apply it to all times.
   c. The HEC RGDRr gives an HEC of 150 ppm but 173 ppm was used to derive the AEGL-2 values. Why?
   d. For pulmonary effects we have typically not used the EPA RfC methodology because it depends upon 100% deposition of the chemical in the pulmonary region. If less than 100% is deposited with each breath then the relationship breaks down.

9. HYDROGEN FLUORIDE
   a. For the AEGL-1 values the ten Berge equation is used on 6 hour data to derive the 4 hour value and the numbers are then flattened because of tolerance to irritants (this needs to be stated explicitly). If the numbers are going to be flattened then ten Berge is really not valid for the AEGL-1. In that event it seems appropriate to divide the 6 hour irritation value by the intraspecies UF and use that for the 4 and 8 hour AEGL-1 value. If ten Berge is not valid for mild irritating

effects what is the rationale for using one set of values for the 4 and 8 hour periods and another for the shorter time periods of 10 to 60 minutes?

b. Do we want to stay with 2 step values for the AEGL-1 (0.2 and 0.1) or go to one value across time?

c. Why is the midpoint between the 10 minute NOAEL and LOAEL used to compute the 10 minute AEGL-2 value and the NOAEL is used to compute the 30 minute and 1 hour AEGL-2 values?

d. In the derivation of the AEGL-2 values, why is an interspecies uncertainty factor of 3 used for the 10 minute AEGL value and 10 for the 30-minute and 1-hour AEGL value? The rationale used for the 30 minute and 1 hour UF seems valid for the 10 minute value. In this case the 10 minute interspecies UF should be 10, not 3. Perhaps the best rationale for what was done is the fact that when one looks at the entire gestalt of the AEGL-2 values for the different time periods, the numbers derived from the animal data are consistent with the numbers derived from human data. They should certainly be protective.

e. The base value for the derivation of the 10-minute AEGL-3 value was the dose that caused death in 1/20 animals. While this is an LC_{05} value, generally when working with data we chose a value in which there were no animal deaths. Do we want to do this or use a derived value? For example, back-extrapolating from the Wohlslagel et al. (1976) data for a one hour LC0 gives a 10 minute AEGL value of 107 ppm.

10. HYDROGEN CYANIDE

a. No mention is made in the HCN document about whether the NaCN was administered as a bolus dose or infused over a 1 hour period. This is important because

a 1 hour exposure time was used to calculate the airborne concentration needed to attain a dose of 0.06 mg/kg. Haber's Law must true for this methodology to be valid. If Haber's law is valid then n must = 1. However, the HCN document uses a value of n = 2 and the ten Berge paper uses a value of n = 2.7. Both of the values of n which could be applied to HCN are greater than 1, will substantially impact the calculation of the AEGL values, and are not consistent with Haber's Law.

b. The rationale for using no uncertainty factor for sensitive individuals "No protection of susceptible individuals was needed given the mechanism of action of cyanide" does not state why the mechanism of action would lead one to this conclusion. This justification should be more specific and precise.

c. The justification for the use of n = 2 in the $c^n t=k$ equation needs to be better justified. In fact ten Berge specifically discusses HCN and gives a value of n=2.7.

d. Appendix A. 0.06 * 70 = 4.2 not 4.3. This changes the 4 hour value from 4 to 3.

e. Why was the multiplier of 2 times the AEGL-2 value chosen to calculate the AEGL-3 levels? What is the rationale of 2 vs 3, or 5, or 10?

11. METHYL HYDRAZINE

a. A composite uncertainty factor of 10 is used for intra- and inter-species uncertainty. These should be separated out into 3 and 3 and the multiplied factor should be 10.

12. METHYL MERCAPTAN

a. There is no real justification for the selection of the AEGL-1 value of 0.5 ppm other than a statement that the value "... was chosen by the NAC AEGL

committee...". Presumably this value was selected because the ACGIH TLV and OSHA PEL values are 0.5 ppm. This is not scientifically based.

b. For the AEGL-2 the justification of the use of an uncertainty factor of 10 is "*U.S. EPA routinely uses uncertainty factors of 10 to account for this variable.*" This should be justified specifically for methyl mercaptan. For example some statement could be made about the potential for variability in metabolism/detoxification between and within species. Because this variability is unknown the uncertainty is great. For this reason the default factor of 10 is used.

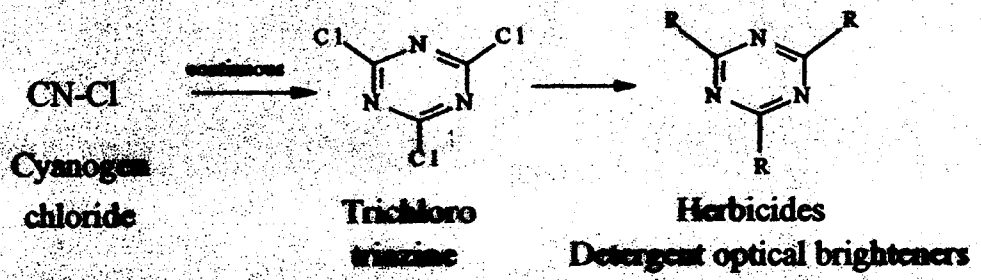
c. The justification for using an intraspecies uncertainty factor of 3 for the AEGL-3 derivation is a steep dose-response curve for the lethality of methyl mercaptan exposure. The same could probably be said for the derivation of the AEGL-2 value but in this case an uncertainty factor of 10 was used. This is inconsistent with the same chemical. However, if the value of 10 which was used in the AEGL-2 derivation is changed to 3, or the 3 used in the AEGL-3 derivation is changed to 10 to be consistent with one another, the AEGL-3 and AEGL-2 values will be almost identical. An approach analogous to that taken with nitric acid should be used here. In other words we should consistently use 3 or 10 for the intraspecies uncertainty factor to generate both values and then state that when we do it the AEGL-2 and AEGL-3 values overlap. Since there is an overlap, professional judgement will have to be used to select the most appropriate AEGL-2 value and the other number adjusted accordingly. While a somewhat pragmatic attempt to generate reasonable numbers it is an above board methodology.

13. NITRIC ACID

a. For most irritant gases we use an intraspecies uncertainty factor of 3 because they are considered to act by a simple chemical reaction mechanism and the sensitivity should not differ much between individuals. Here we say "Both human and animal data suggest that asthmatics may be especially sensitive to acidic atmospheres." This might imply increasing the uncertainty factor of 3 normally used for irritant gases because a defined population exists or stating we believe asthmatics will still fall within the range defined by an uncertainty factor of 3.

b. Justification of an intraspecies uncertainty factor of 3 for AEGL-2 and AEGL-3. No rationale given in the text. In the appendix the statement is made "3 for intraspecies variability (not protecting hypersusceptible individuals)"

Cyanogen Chloride



Manufacturers: Novartis (Gabriel, LA)
Degussa (Theodore, AL)

Production Volume: 100,000's lbs
TSCA Inventory: 500,000 lbs +
CAAA 112r Threshold Planning Quantity = 1,000 lb

Attachment 6

AEGL ENDPOINTS

Sensory Irritation and Organoleptic Effects

Examples of AEGL-1 effects include mild irritation of the eyes, nose, or throat, mild lacrimation, mucous secretions, and mild odor or taste. AEGL-2 effects include moderate to severe irritation of the eyes, nose, or throat, profuse lacrimation which could inhibit escape, labored breathing, and pulmonary congestion. The endpoints for AEGL-3 would include necrosis or destruction of tissue.

Respiratory System

Pulmonary Function

A wide variety of minor changes in pulmonary function parameters or maneuvers could be used to define AEGL-1, 2, and 3 level effects. For example, a low level (e.g., 5-20%) decrease in the Forced Expiratory Volume at 1-second (FEV_1), indicative of mild impairment of ventilation would be consistent with the defintion of AEGL-1. With a decrease in FEV_1 between 20-40%, there is a moderate impairment of ventilation. A severe impairment of ventilation occurs when the FEV_1 decreases by more than 40%.

Other pulmonary function parameters of potential use include forced vital capacity, inspiratory capacity, expiratory reserve volume, functional residual capacity, airway resistance, specific airway resistance, total lung capacity, and residual volume.

Pulmonary Edema

Pulmonary edema alters the ventilation-perfusion relationship by limiting the transfer of oxygen and carbon dioxide. This type of response is a sign of acute lung injury and even a mild evidence of pulmonary edema indicates a potentially serious (AEGL-2) effect.

Respiratory Rate Depression

In a respiratory irritation (Alarie) study in animals, according to ASTM-E961:

a decrease in respiratory rate of 12-20% is considered slight irritation
-a decrease in respiratory rate of 20-50% is considered moderate irritation
-a decrease in respiratory rate of 50-80% is considered extreme irritation

Nervous System

CNS Depression

Mild CNS effects include slight odor and headache. More serious CNS effects would include dizziness, confusion, tremors, ataxia, impaired psychomotor functions, and lethargy. Signs of severe CNS depression include coma and unconsciousness

Inhibition of RBC Cholinesterase

The RBC chloinesterase level is the preferred index of exposure to ogranophosphate poisioing since it is the same enzyme as found in nervous tissue and is less labile than the plasma chloinesterase level. Generally, acute exposures are classified as mild (20-50% of baseline), moderate (10-20% of baseline), and severe (10% of baseline).[2]

Blood

Methemoglobin

Under normal conditions, methemoglobin levels are around 1 to 2%. At 30% methemoglobin in a healthy individual, symptoms include fatigue, light headedness, and headache. At methemoglobin levels between 30 and 50%, there is a serious depression of the CNS including weakness, headache,, tachycardia, and mild labored breathing. When methemoglobin is between 50 and 70%, there are severe effects including stupor, bradycardia, respiratory depression, convulsions, dysrhythmias, and acidosis. Methemoglobin levels >70% are not compatible with life.[2]

Carboxyhemoglobin

The normal carboxyhemoglobin level is between 0.4 and 0.7%. In smokers, this level is between 5 and 6%. At 10% carboxyhemoglobin, there are no appreciable effects. At 20% carboxyhemoglobin, effects include shortness of breath and headache. Tachycardia and electrocardiographic changes suggestive of hypoxia are observed at around 30% carboxyhemoglobin. Some additional symptoms at this level include headache, weakness, dizziness, and dimness of vision. At 50 to 80% carboxyhemoglobin, the effects include unconsciousness, coma, convulsions, and death.[2]

Hemolytic Changes

Various disease states can contribute to increased hemolysis. The processes by which increased hemolysis occurs includes a decrease in red cell lifespan, and an increase in the destruction of red cells. Even a mild evidence of chemically induced hemolysis is indicative of a potentially serious event which could lead to kidney damage, and eventually death.

Target Organ Effects

A full listing of the target organ effects corresponding with AEGL 1, 2, and 3 definitions is outside the scope of this review. The following general scheme developed by Hartung and Durkin (1989) can be used as a guide for ranking the clinical severity of target organ effects according to the AEGL definitions.

AEGL-1

-Enzyme induction or other reversible biochemical changes without pathologic changes and no change in organ weights.
-Reversible enzyme induction and subcellular changes

AEGL-2

-Reversible hyperplasia, hypertrophy, or atrophy with changes in organ weights
-Reversible cloudy swelling, hydropic change, or fatty changes
-Degenerative or necrotic changes with no apparent decrement of organ functions
-Reversible slight changes in organ functions

AEGL-3

-Pathologic changes with definite organ dysfunction which are unlikely to be fully reversible
-Pronounced pathologic changes with severe organ dysfunction with long term sequelae
-Effects that are potentially life threatening or life-shortening

Developmental Effects

The following scheme can be used to classify developmental effects.

Common Variants

These effects are generally considered as normal occurrences in untreated fetuses. Examples include

-supernumerary 14th rib
-incomplete ossification of the sternum, vertebra, or thoracic center
-minor hydronephrosis (renal pelvic dilation)
-hydroureter

Minor Embryofetotoxicity

These effects are generally considered either innocuous or reversible. Examples include:

-growth retardations (i.e., birth weights) in which affected offspring differ from appropriate controls by ≤ 2 standard deviations
-small eyes (microphthalmia)
-limb flexures (rabbit only)
-minor hydrocephalus (i.e., substantial involvement of the organ is not observed)
-ossified digits
-ocular opacity
-isolated hemorrhages
-reduced skull ossification
-failure of testicles to descend
-bipartite sternebrae
-rib anomalies (extra 15th or 16th, fused, wavy, knobby, or branched ribs)
-distended urinary bladder
-minor anitfertililty effects

Major Embryofetotoxicity

These effects are usually irreversible and either extremely deleterious or lethal to affected offspring. Examples include:

-growth retardation (i.e., decreased fetal body weight) in which affected offspring differ from controls by ≥2 standard deviations
-major increase in embryofetolethality

Major Antifertility

-major decreases in fertility as measure by decreases in implantation sites, effects on sperm or ova, or serious pathological changes in the reproduction tract

Teratogenicity

Serious morphologic changes affecting vital organs and resulting in decreased functional abilities or decreased survival. Examples include:

-cleft palate
-missing or malformed organs
-malpositioned organs or blood vessels
-uncovered organs (i.e., brain or spinal cord)
-nonfunctional organs

References

Hartung, Rolf, and Durkin, Partick (1986). Ranking the Severity of Toxic Effects: Potential Applications to Risk Assessment. Comments Toxicology Vol. 1, No. 1, pp. 49-63.

Ellerhorn, M. and Barceloux, D. (1988). Medical Toxicology. Diagnosis and Treatment of Poisoning. Elsevier Press, NY.

Endpoint	AEGL - 1	AEGL - 2	AEGL - 3
Sensory Irritation, organoloptic	Mild irritation, odor, or taste	Strong irritation without necrosis	Severe irritation with necrosis
Respiratory System Pulmonary Function Pulmonary Edema Respiratory Rate (from Alarie study)	5-20% decrease in FEV_1 Not applicable 12-20% decrease	20-40% decrease in FEV_1 Mild Edema 20-50% decrease	>40% decrease in FEV_1 moderate edema with alveolar capillary surface denuded >50% decrease in
Nervous System CNS depression AChE Inhib. (RBC)	Mild, e.g., headache 50-80%	Serious e.g., tremors, dizziness, confusion, ataxia 80-90%	Severe, e.g., incapacitation, coma, unconsciousness >90%
Blood Methemoglobin Carboxyhemoglobin Hemolytic	Levels <30% Levels <20% Not applicable	Levels <30-50% Levels between 20 and 40% Mild hemolysis	Levels >50% Levels>40% Moderate to severe hemolysis with hemoglobinuria, renal failure
Kidney Effects	Minor effects, e.g. changes in clearance, secretory, transport, renal enzyme	impairment of renal function(reversible), e.g., nephritis	irreversible renal damage (e.g., necrosis) complete renal failure
Liver Effects	Minor effects, e.g., changes in liver enzymes	Lipid accumulation, cytotoxic effects, cholestatic effects (reversible)	irreversible liver damage (e.g., necrosis) complete liver failure -
Cancer	Not applicable	$1x10^{-4}$ risk level for Possible or Probable human carcinogen using NRC method	Not applicable
Developmental Effects	Not applicable	Evidence of developmental toxicity, e.g., minor or major embryofetotoxicity, major antifertility, teratogenicity	Not applicable

Key Findings from SOT Session on Uncertainty Analysis in Non-Cancer Risk Assessment (March 12, 1997) USEPA/Chem Risk

Based on theoretical and data-driven basis:

For uncertainty factors for interspecies, intraspecies and LOAEL to NOAEL

50th percentile is 2-4

95th percentile is 5-30

The 10-fold factor is 75th-99th percentile

ATTACHMENT B

Poster 1054, Table 2 on Multiplying UFs

Percentile	UF_1	UF_2	UF_3	UF_4	UF_5
50	3.16	11	37	127	433
95	10	51	234	1040	4440
99	17	104	544	2700	12700
Standard Approach	10	100	1000	3000	10000

ATTACHMENT 9

Phosgene

- WWI 85% of Chemical Warfare Deaths
- Pulmonary Edema
- HCL Formation (Nash 1925) (1971)
- Diamide Formation (Potts 1949)
- Biochemical Changes in Lung (Frosolono 1977)

ORIGINAL VALUES (UNCERTAINTY FACTOR = 100)

8. SUMMARY OF PROPOSED AEGLS

TABLE 20: Summary of Proposed AEGL Values for Phosgene				
Classification	30-min	1-hr	4-hr	8-hr
AEGL-1 (Nondisabling)	Not Determined	Not Determined	Not Determined	Not Determined
AEGL-2 (Disabling)	0.014 ppm (0.058 mg/m^3)	0.01 ppm (0.04 mg/m^3)	0.005 ppm (0.021 mg/m^3)	0.004 ppm (0.016 mg/m^3)
AEGL-3 (Lethality)	0.64 ppm (2.63 mg/m^3)	0.45 ppm (1.85 mg/m^3)	0.23 ppm (0.95 mg/m^3)	0.16 ppm (0.66 mg/m^3)

PROPOSED VALUES (UNCERTAINTY FACTOR = 30)

8. SUMMARY OF PROPOSED AEGLS

TABLE 20: Summary of Proposed AEGL Values for Phosgene				
Classification	30-min	1-hr	4-hr	8-hr
AEGL-1 (Nondisabling)	Not Determined	Not Determined	Not Determined	Not Determined
AEGL-2 (Disabling)	0.047 ppm (0.193 mg/m^3)	0.033 ppm (0.133 mg/m^3)	0.017 ppm (0.070 mg/m^3)	0.013 ppm (0.533 mg/m^3)
AEGL-3 (Lethality)	2.13 ppm (8.77 mg/m^3)	1.50 ppm (6.17 mg/m^3)	0.77 ppm (3.17 mg/m^3)	0.53 ppm (2.20 mg/m^3)

- **Blood Air Barrier Damage**
- Pulmonary Capillaries
- Tight Junction
- Clara Cells
- Type I Alveolar Cells
- Type II Alveolar Cells
- Alveolar Proteinosis

Summary of Animal Data for AEGL-2				
Species: Effect (ppm & time): Reference	**AEGL-2**			
	30 minutes	1 hour	4 hours	8 hours
Monkeys: illness and labored breathing (0.86 ppm & 5 hr exposure): Cameron et al., 1942	0.027	0.019	0.0096	0.007
Dogs: acute respiratory bronchiolitis (24 ppm & 30 min exposure): Clay and Rossing, 1964	0.24	0.17	0.09	0.06
Rats: decreased body wgt. & food consumption; increased wet lung weight (1 ppm & 4 hr exposure): Franch and Hatch, 1986	0.028	0.02	0.01	0.007
Rats: decreased body wgt. & increased lung wgt. (0.5 ppm & 4 hr exposure): Currie, 1987a	0.014	0.01	0.005	0.004

ATTACHMENT 10

Summary of Animal Data for AEGL-3				
Species: Effect (ppm & time): Reference	AEGL-3			
	30 minutes	1 hour	4 hours	8 hours
Monkeys: LC_{50} value (240 ppm for 1 min exposure): Chasis, 1944	0.15	0.10	0.05	0.03
Sheep: LC_{50} value (333 ppm for 10 min exposure): Keeler et al., 1990b	0.64	0.45	0.23	0.16
Dogs: lethality (80-100 ppm for 30 minutes): Meek and Eyster, 1920	0.80	0.57	0.28	0.20
Dogs: lethality (41-50 ppm for 30 min exposure): Underhill, 1920	0.41	0.29	0.15	0.10
Dogs: emphysema (108 ppm & 30 min exposure): Coman et al., 1947	1.08	0.76	0.38	0.27
Dogs: emphysema (71 ppm & 3 min exposure): Coman et al., 1947	0.23	0.16	0.08	0.06
Rats: LC_{50} value (34 ppm for 10 min exposure): Box and Cullumbine, 1947a	0.07	0.05	0.02	0.02

PHOSGENE Animal Tox

	PPM	HRS	ENDPOINT	REF
⇒	0.1	1	No edema, No histo	Diller et al. 1985
	0.05	4	↓ ATP	Currie et al. 1987b
	0.1	4	No LFP changes	Hatch et al. 1986
	0.1	4	↓ ATP, No LFP Changes	Currie et al. 1987b
	0.1	4	No PNKC activity changes	Burlson & Keyes 1989
	0.1	4	↑ LFP	Hatch et al. 1986
⇒	0.1	4	Lung histopath changes No edema	Diller et al. 1985
	0.125	4	No LFP changes No organ wt changes	Currie et al. 1987a
	0.2	4	↑ LFP	Hatch et al. 1986
	0.2	4	↑ LFP	Currie et al. 1987b
→	0.25	4	↑ LFP; ↑ PMN No Lung wt changes	Currie et al. 1987a
	0.5	4	↓ PNKC activity	Burlson & Keyes 1989
→	0.5	4	↓ BW ↑ LFP ↑ Lung wt	Currie et al. 1987a
	1	4	↓ PNKC activity	Burlson & Keyes 1989
→	1	4	↑ Lung wt (till Day 14) ↓ BW	Franchard & Hatch 1986
→	1	4	↑ Lung wt ↓ BW	
			↓ cytotoxic T-lymphocyte	Ehrlich et al 1989

LFP - lavage fluid protein
PNKC - pulmonary natural killer cell

Ethylene Oxide
AEGL/NAC #5

First Data Rich Chemical

- Multiple Endpoints
  - Cancer
  - Developmental
  - Acute
- May set precedence for following chemicals

Burning Issues

- Inter-species Uncertainty Factor
- Single exposure cancer risk
- Appropriateness of AEGL-1
- Chronic data used for AEGL-1 & AEGL-2
- "Laugh Test" against limited human exposure data

Ethylene Oxide
AEGL/NAC #4

Issues Raised

- Odor threshold validation
- Dermal absorption
- Blood gas coefficient
- Fetal lethality AEGL-2 or AEGL-3
- Anesthetic properties
- Single exposure cancer risk
- Defense of n=1
- Heritable translocation as AEGL-3 endpoint
- Evaluation of Salinas et al, 1981 report of ~5min accidental exposure
- Peripheral neuropathy as AEGL endpoint
- Mother or fetus as sensitive population

ACUTE EXPOSURE GUIDELINE LELELS (AEGLs) FOR ETHYLENE OXIDE

PRELIMINARY REPORT

PREPARED BY

KOWETHA A. DAVIDSON, Ph.D., D.A.B.T.
OAK RIDGE NATIONAL LABORATORY
OAK RIDGE, TENNESSEE

MARCH 1997

Managed by Lockheed Martin Energy Research Corporation, for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400

ATTACHMENT 13

DEVELOPMENTAL AND REPRODUCTIVE EFFECTS OF ETHYLENE OXIDE VAPOR

Species	Exposure	Effect	Reference
Rat	0, 10, 33, 100 ppm, 6 h/day, gd 6-15	33 ppm – NOEL 100 ppm – mild retarded growth of fetus	Snellings et al., 1982a
Rat	0, 50, 125, 250 ppm, 6 h/day, gd 6-15	50 ppm – NOEL 125 ppm – growth retardation of fetus 250 – more severe growth retardation	BRRC, 1993
Rat	0, 150 ppm, 7 h/day, 5 d/wk, premating, gd 7-16, or 1-16	growth retardation of fetus regardless of stage of exposure	Hackett, 1982
Rat	0, 400, 800, 1200 ppm, 0.5 h/day, gd 6-15	no effects on the fetus at any concentration	Saillenfait et al., 1996
Rat	0, 200, 400, 800, 1200 ppm, 0.5 h, 3 times per day, gd 6-15	800 ppm – fetal growth retardation 1200 ppm – maternal effects and fetal growth retardation	Saillenfait et al., 1996
Mouse	0, 1200 ppm, 1½ h, gd 1	fetal deaths, hydrops, and other malformations	Rutledge and Generoso, 1989
Mouse	0, 200, 400 ppm, 6 h/day, 5, 15, or 25 exposures	200 ppm: abnormal spermatozoa 400 ppm: abnormal spermatozoa	Ribeiro et al., 1987
Rat	0, 10, 33, 100 ppm, 6 h/day, 1-generation reproduction	33 ppm – NOEL 100 ppm – reproductive and fetal effects	Snellings et al., 1982b
Rat, males	0, 50, 100, 250 ppm, 6 h/day, subchronic	50 ppm – abnormal sperm, teratic type 100 ppm – abnormal sperm, teratic type 250 ppm – abnormal sperm, testicular degeneration	Mori et al., 1991
Rabbits	0, 150 ppm, 7 h/day, gd 7-19 or 1-19	no developmental effects	Hackett et al., 1982

AEGL-3 VALUES			
30 minutes	1 hour	4 hours	8 hours
704 ppm	352 ppm	88 ppm	44 ppm

Reference:	NTP, 1987
Comments:	This is a well-conducted study using adequate numbers of animals at each exposure level; probit analysis was used to extrapolate lethality data for males and females combined to LC_{01}; the mouse appear to be more sensitive than the rat, but the 95% confidence intervals showed the species not to be statistically different.
Uncertainty factors:	3 for intraspecies sensitivity based on potential polymorphism in the glutathione detoxification pathway for ethylene oxide, the need to protect individuals with respiratory and heart diseases, and the steepness of the concentration-response relationship No uncertainty factor applied for interspecies differences because systemic uptake, distribution, and modes of action are likely to be similar. Species differences in metabolism kinetics unlikely to affect responses to high acute exposures

AEGL-2 VALUES			
30 minutes	1 hour	4 hours	8 hours
204 ppm	102 ppm	26 ppm	13 ppm

Reference:	BRRC, 1993
Comments:	This is a well-conducted study using rats exposed during organogenesis; AEGL values were derived from the 50-ppm, which approximated the threshold for fetal growth retardation.
Uncertainty factors:	3 for intraspecies sensitivity based on potential polymorphism in the glutathione detoxification pathway for ethylene oxide and for protection of individuals with respiratory and heart diseases. No uncertainty factor applied for interspecies differences because systemic uptake, distribution, and modes of action are likely to be similar across species; metabolism kinetics may vary somewhat.

AEGL-1 VALUES			
30 minutes	1 hour	4 hours	8 hours
132 ppm	66ppm	17 ppm	8 ppm
Reference:	Snellings et al., 1982a		
Comments:	This is a well-conducted study using rats exposed during organogenesis; AEGL values were derived from the 33-ppm exposure level, which was a no-effect level for fetal growth retardation.		
Uncertainty factors:	3 for intraspecies sensitivity based on potential for polymorphism in the glutathione detoxification pathway for ethylene oxide and for protection of individuals with respiratory and heart diseases. No uncertainty factor applied for interspecies differences because systemic uptake, distribution, and modes of action are likely to be similar across species; metabolism kinetics may vary somewhat.		

based on head nurse recall of where they worked, not on IH data, and what chem they worked with (other agents)

30 years

Hemminki Study

Issues Related to Interpretation

- Disease/Exposure Misclassification
  - *Potential for Recall/Reporting Biases*
  - *Failure to Validate*

→ only validated 1/3 of the study → even controls forget this had miscar

- Representativeness of TWA8 Data
  - *0.1-0.5 ppm TWA8*
  - *Peaks Up to 250 ppm*

Saillenfait et al Report
Fetal Body Weight Effects Males

ppm-hour/day	1800	1200	600	600	0
exposure day	0.5hr x 3	0.5hr x 3	0.5hr x 3	0.5hr x 1	
concentration ppm	1200	800	400	1200	
body weight (g) per litter	5.22*	5.43*	5.84	5.70	5.75

* $p < 0.01$

Summary of Studies Reporting Fetal Body Effects From 10 Days of Repetitive Exposure to Ethylene Oxide

	Exposure (ppm-hour/day)	
	NOEL	**LOEL**
Snellings, 1982	200 (6hr x 33ppm)	600 (6hr x 100ppm)
BRRC Report 92N1045	300 (6hr x 50ppm) (threshold?)	750 (6hr x 125ppm)
Saillenfait, 1996	600 (1.5hr x 400ppm)	1200 (1.5hr x 800ppm)
Saillenfait, 1996	600 (0.5hr x 1200ppm)	

Gary et al, (1979)

- Subject exposed ~ 1500ppm for 5 minutes without symptoms.

- Others over a 2-month period reported nausea, dizziness, and incoordination.

Salinas

"...she accidentally dropped and broke an ethylene oxide ampul, while not wearing a mask. Feeling the fumes surrounding her, she immediately disposed of the broken ampul."

ACETONE

Boiling Point (760 mmHg)	132°F
Vapor Pressure (20°C)	184 mmHg

ETHYLENE OXIDE

Boiling Point (760 mmHg)	51°F
Vapor Pressure (20°C)	1095 mmHg

ISOCYANATES

ATTACHMENT 15

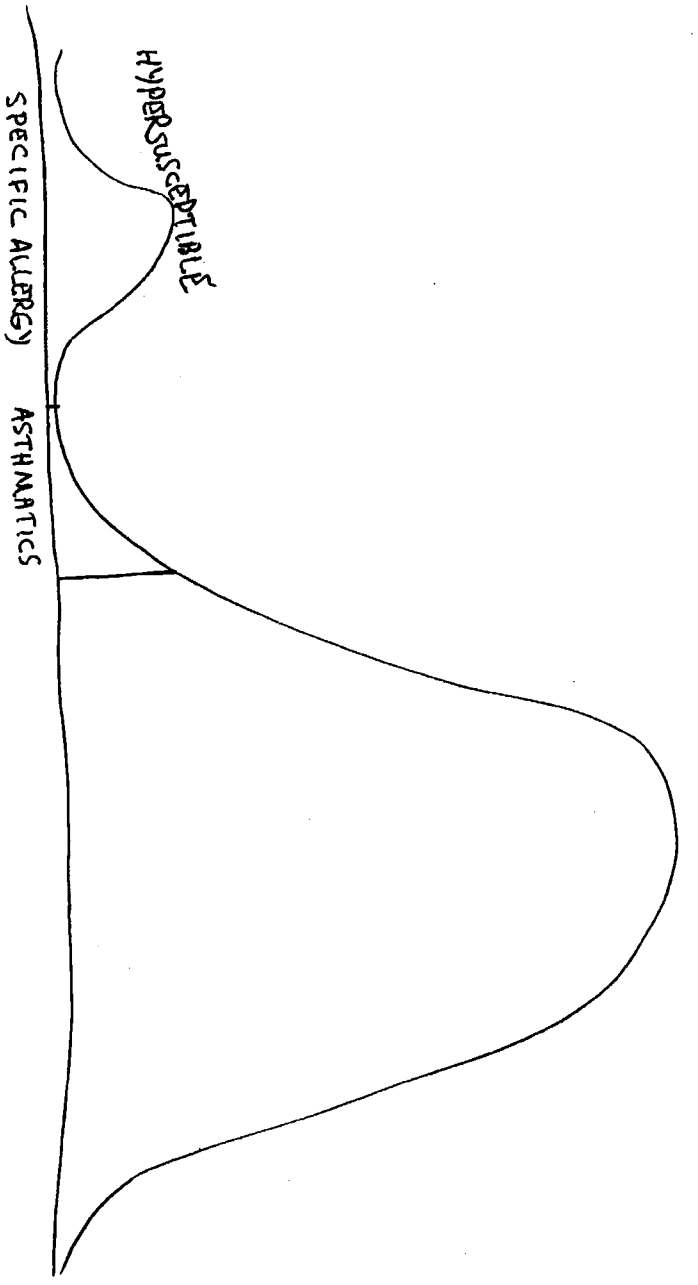
- COATINGS
- ADHESHIVES
- ELASTOMERS
- FOAM – RIGID AND FLEXIBLE
    - CUSHIONS
    - RIGID MOLDED PARTS
    - INSULATION

2,4- and 2,6-TOLUENE DIISOCYANATE

- PRIMARY RESPIRATORY IRRITANT
- HYPERSENSITIVITY PNEUMONITIS
- ASTHMA
- DECREMENTS IN LUNG FUNCTION FROM CHRONIC EXPOSURE
    - MOST SENSITIVE EFFECT
    - BASE FOR TLV OF 5 PPB

THRESHOLD FOR SENSITIZATION

GUINEA PIGS EXPOSED TO 120 PPB TDI FOR 3 HR/DAY FOR 5 CONSECUTIVE DAYS SHOWED NO ANTIBODIES SPECIFIC TO TDI AND SHOWED NO PULMONARY SENSITIVITY BY BRONCHIAL PROVOCATION CHALLENGE WITH TDI-PROTEIN ANTIGEN.



PROPOSED AEGL-1 VALUES FOR 2,4/2,6-TOLUENE DIISOCYANATE (ppm [mg/m^3])				
	30-min	1-hr	4-hr	8-hr
AEGL-1	0.02 (0.14)	0.02 (0.14)	0.01 (0.07)	0.01 (0.07)

UF = none

Scaling: none

Key Study: Baur, 1985

Protocol: Asthmatics exposed to 0.01 ppm for 1 hour, rested for 45 min., exposed to 0.02 ppm for 1 hour

Healthy controls exposed to 0.02 ppm for 2 hours

Endpoint: Respiratory irritation

Baur, 1985

Results:

Subjective Symptoms		
	Asthmatics	Controls
Chest tightness	3/15	
Cough	2/15	1/10
Irritation/Rhinitis	1/15	3/10
Dyspnea	1/15	
Headache	1/15	
Total Affected	**5/15**	**3/10**

Baur, 1985

Results (cont.):

Lung Function Parameters - Group Means		
	Asthmatics	Controls
R_{aw}	ns	0 and 30 min ($p \leq 0.05$)
IGV	ns	ns
SR_{aw}	ns	ns
VC	ns	ns
FEV_1	ns	ns

Individuals Considered Pathologically Significant		
	Asthmatics	Controls
R_{aw} (>50%)	8/15	0/10
SR_{aw} (>50%) Bronchial Obstruction	4/15	0/10

Baur, 1985

Population: 15 asthmatics, 10 healthy controls

Exposure: Asthmatics - 0.01 ppm for 1 hr, rested 45 min, 0.02 ppm for 1 hr

Controls - 0.02 ppm for 2 hours

Lung function parameters: R_{aw} (airway resistance)

IGV (intrathoracic gas volume)

SR_{aw} (specific airway resistance = $R_{aw} \times$ IGV)

VC (vital capacity)

FEV_1 (forced expiratory volume in 1 sec)

Bronchial obstruction = incr. in SR_{aw} >50%

ADDITIONAL HUMAN DATA IN SUPPORT OF AEGL-1 AND -2 VALUES

Study: Hama, 1957

Population: plant workers involved in manufacture of isocyanate foam

Concentration: 0.03 to 0.07 ppm (0.21-0.50 mg/m^3)

Effects: Respiratory irritation

Study: Moller et al., 1986

Population: individuals with positive methacholine challenge

Concentration: up to 0.02 ppm for 15 min

Effects: no change in FEV_1

WORKER EXPOSURE TO ISOCYANATE VAPOR		
Average Conc. (ppm [mg/m^3])	Duration (minutes)	Duration Above 0.02 ppm (minutes)[a]
0.043 (0.31)	442	300
0.031 (0.22)	165	75
0.041 (0.29)	120	105
0.045 (0.32)	115	75
0.020 (0.14)	240	90
0.021 (0.15)	198	n/a
0.026 (0.19)	105	n/a

Data from Hosein and Farkas, 1981.
[a]The OSHA and NIOSH ceiling for TDI is 0.02 ppm (0.14 mg/m^3).
n/a = not applicable; sampling was over periods of 40-60 minutes.

ANIMAL DATA IN SUPPORT OF AEGL-2 VALUES				
Species	Duration and Endpoint	Conc. (ppm)	Isomer	Reference
Rat	4 hour; lethargy	2	2,4-	Timchalk, 1992
Rat	3-hr RD_{50}	1.37	2,4-	Shiotsuka, 1987a
Rat	3-hr RD_{50}	2.12	2,4-/2,6- (80:20)	Shiotsuka, 1987b
Rat	6 hr; ocular and nasal irritation, labored breathing	2	mixed; not defined	Wazeter, 1964a
Mouse, Rat, GP, Rabbit	4 hour; clearing of inflammation by day 7	2 UF - inter 10	not defined	Duncan et al., 1962

intra - 3

AEGL-1

3 hr RD_{50} - 1370 ppb

~~x 0.001~~

The precursory int x 0.01 - 13.7 ppb

SUMMARY OF ANIMAL TOXICITY DATA WITH TDI				
Species	Duration and Endpoint	Concentration	Isomer	Reference
Rat	4-hr LC_{50}	13.9 ppm	unknown	Duncan et al., 1962
Male rat	4-hr LC_{50}	50.56	unknown	Kimmerle, 1976
Male and Female Rat	1-hr LC_{50}	66	2,4-/2,6- (80:20)	Horspool and Doe, 1977
Mouse	4-hr LC_{50}	9.7	unknown	Duncan et al., 1962
Guinea pig	4-hr LC_{50}	12.7	unknown	Duncan et al., 1962
Rabbit	4-hr LC_{50}	11	unknown	Duncan et al., 1962
Dog	30-120 min; coughing, lacrimation, restlessness	1.3	2,4-	Zapp, 1957
Rat	3-hr RD_{50}	1.37	2,4-	Shiotsuka, 1987a
Rat	3-hr RD_{50}	2.12	2,4-/2,6- (80:20)	Shiotsuka, 1987b
Rat	6 hr; ocular and nasal irritation, labored breathing	2	mixed; not defined	Wazeter, 1964a
Mouse	10-min RD_{50}	0.813	2,4-	Sangha and Alarie, 1979
Mouse	4-hr RD_{50}	0.199	2,4-	Sangha and Alarie, 1979

ANIMAL DATA IN SUPPORT OF AEGL-2 VALUES (continued)

Study: Shiotsuka, 1987a,b

Endpoint: 3-hour RD_{50} in the rat is approximately 2 ppm

Scaling: 30 min, 1, 4, and 8 hour time points

$C^n \times t = k$; n = 2 (ten Berge et al., 1986)

UF = 10 and 3

AEGL-2 Values from Animal Data	
30-min	0.16 ppm
1-hour	0.11 ppm
4-hour	0.06 ppm
8-hour	(0.04 ppm)

EFFECTS OF EXPOSURE TO TOLUENE DIISOCYANATE IN HUMANS[a]	
Concentration (ppm)	Effect
0.01 or 0.02	2,4/2,6-; 2,4-; 2,6-: no odor perception, no effects
0.05	2,4/2,6-: odor noted immediately upon entering the room; after about 5 minutes of exposure, 3/6 volunteers experienced a slight "tingling" sensation of the eyes described as lacrimation urge without tears
	2,4-: weak odor perception; no eye irritation
	2,6-: odor was stronger as compared to the 2,4-isomer
0.075	2,6/2,4-: odor became stronger; slight burning of the eyes occurred after 1-6 minutes, but there was no lacrimation; with deeper breaths, volunteers experienced tickling or a slight stabbing pain in the nose
0.08	2,4-: slight conjunctival irritation and tickling of nose
	2,6-: eye and nose irritation more severe as compared to same concentration of the 2,4-isomer; effects on throat were perceived as dryness, not scratching sensation
0.10	2,4/2,6-: eye and nose irritation became more severe described as resembling a cold (catarrh)
	2,4-: more pronounced conjunctival irritation and tickling of nose
	2,6-: eye and nose irritation more severe as compared to same concentration of the 2,4-isomer; effects on throat were perceived as dryness, not scratching sensation
0.20	2,4-: eye irritation was perceived by 2/5 as stinging and uncomfortable
	2,6-: eye and nose irritation more severe as compared to same concentration of the 2,4-isomer; effects on throat were perceived as dryness, not scratching sensation

0.50	2,4/2,6-: lacrimation, but eye irritation was still tolerable; one had copious nasal secretion that was associated with "stinging" nasal pain; all had scratchy and burning sensations in the throat, without cough
	2,4-: eye irritation was perceived by all as stinging and uncomfortable with lacrimation
	2,6-: effects similar to the 2,4-isomer
1.3	2,4/2,6-: two individuals were able to remain in the room for 10 minutes; irritation was intolerable; several hours later, cold-like symptoms with cough persisted

[a]Data from Henschler et al. (1962).

Concentrations Resulting in Irritation in Humans		
Concentration (ppm)	Population	Study
0.02	volunteers	Baur, 1985
≥0.08	volunteers	Henschler, 1962
0.02-0.045	spray foam applicators	Hosein and Farkas, 1981
0.03-0.07	foam manufacturing plant workers	Hama, 1957
0.08-0.10	sprayers, dippers, painters at furniture factory	Maxon, 1964
0.07	several manufacturing plants	Elkins, 1962
0.03-0.05	(irritation threshold - review article)	Karol, 1986

Review of Human Effects	
Concentration (ppm)	Effect
0.01/0.02	chest tightness, cough, irritation
0.5	lacrimation, but eye irritation was still tolerable; one had copious nasal secretion that was associated with "stinging" nasal pain; all had scratchy and burning sensations in the throat, without cough
1.3	two individuals were able to remain in the room for 10 minutes; irritation was intolerable; several hours later, cold-like symptoms with cough persisted

Methacholine Challenge Test

Methacholine = parasympathomimetic (cholinergic)

Asthmatic

Bronchoconstriction after inhalation of methacholine

decreased Forced Vital Capacity (FVC)

decreased Forced Expiratory Volume in 1 sec (FEV_1)

Normal

No effect

AEGL-3 - From LC_{01}

ALTERNATE AEGL-3 VALUES (ppm [mg/m³])				
	30-min	1-hr	4-hr	8-hr
AEGL-3	0.38 (2.69)	0.27 (1.90)	0.13 (0.95)	0.09 (0.67)

UF = 30

Scaling: 30 min, 1 and 8 hour time points

$C^n \times t = k$; n = 2 (ten Berge et al., 1986)

Key study: Duncan et al., 1962

Protocol: LC_{50} determination in several species

Endpoint: 4-hour LC_{01} extrapolation to 4 ppm from the mouse data

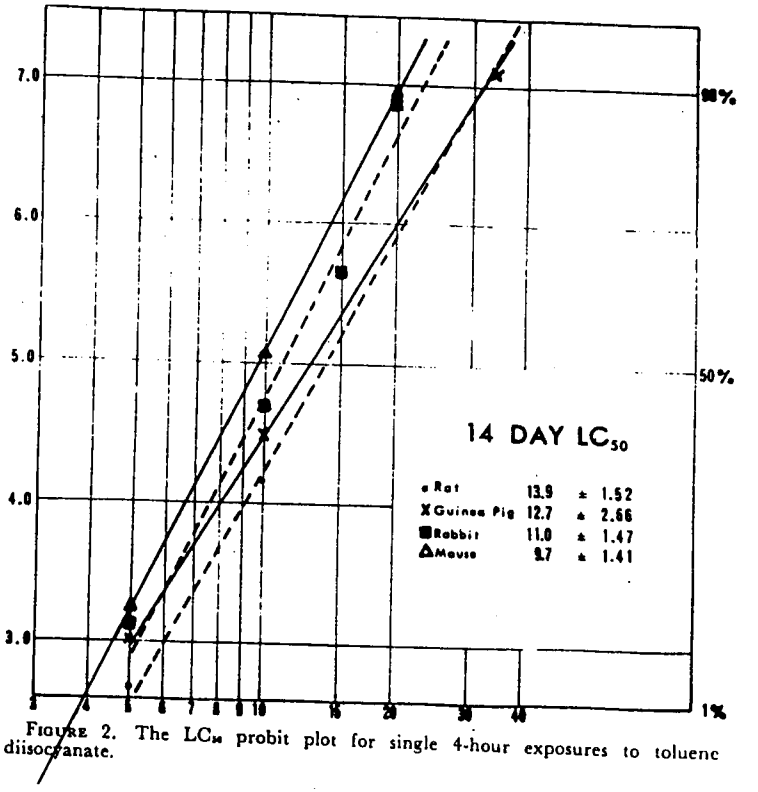


FIGURE 2. The LC_{50} probit plot for single 4-hour exposures to toluene diisocyanate.

PROPOSED AEGL-3 VALUES FOR 2,4/2,6-TOLUENE DIISOCYANATE (ppm [mg/m^3])				
	30-min	1-hr	4-hr	8-hr
AEGL-3	0.9 (6.4)	0.6 (4.3)	0.3 (2.1)	0.2 (1.4)

UF = 3

Scaling: 30 min, 1 and 8 hour time points

$C^n \times t = k$; n = 2 (ten Berge et al., 1986)

Key study: Duncan et al., 1962

Protocol: LC_{50} determination in several species

Endpoint: 4-hour LC_{50} in the mouse of 9.7 ppm

PROPOSED AEGL-2 VALUES FOR 2,4/2,6-TOLUENE DIISOCYANATE (ppm [mg/m^3])				
	30-min	1-hr	4-hr	8-hr
AEGL-2	0.20 (1.42)	0.10 (0.71)	0.06 (0.43)	0.06 (0.43)

UF = 3

Scaling: 1 and 4 hour time points

$C^n \times t = k$; n = 2 (ten Berge et al., 1986)

Key study: Henschler et al., 1962

Protocol: Six healthy men exposed for 30 min to various concentrations

Endpoint: Eye and throat irritation at 0.5 ppm

ADDITIONAL HUMAN DATA IN SUPPORT OF AEGL-1 AND -2 VALUES

Study: Hosein and Farkas, 1981

Population: polyurethane foam applicators

Effects: Eye irritation

WORKER EXPOSURE TO ISOCYANATE VAPOR	
Average Conc. (ppm [mg/m^3])	Duration (hours)
0.043 (0.31)	7.4
0.031 (0.22)	2.8
0.041 (0.29)	2
0.045 (0.32)	1.9
0.020 (0.14)	4
0.021 (0.15)	3.3
0.026 (0.19)	1.8

SUMMARY OF PROPOSED AEGL VALUES (ppm [mg/m^3])					
Level	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1	0.02 (0.14)	0.02 (0.14)	0.01 (0.07)	0.01 (0.07)	sensory irritation in asthmatics (Baur, 1985)
AEGL-2	0.20 (1.42)	0.10 (0.71)	0.06 (0.43)	0.06 (0.43)	eye, throat irritation and lacrimation (Henschler et al., 1962)
AEGL-3	0.9 (6.4)	0.6 (4.3)	0.3 (2.1)	0.2 (1.4)	4-hour LC_{50} in the mouse (Duncan et al., 1962)

Proposed AEGLs for ANILINE

March 1997

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Robert Snyder

Chemical Reviewer:
George Rodgers

ATTACHMENT 17

ANILINE

- STRUCTURE:

- PRODUCTION: 989 million pounds (1993)

- USES: Manufacture of dyes, dye intermediates rubber accelerators, antioxidants. Used as a solvent, in printing inks, many other processes.

- TOXICITY CONCERNS: Formation of methemoglobin

- AVAILABLE DATA: Citations in older literature involving human exposures
  Nonlethal and lethal inhalation studies with rats

SIGNS AND SYMPTOMS ASSOCIATED WITH METHEMOGLOBIN CONCENTRATIONS

Methemoglobin Concentration (%)	Signs and Symptoms
1.1	Normal
1-15	None
15-20	Clinical cyanosis (chocolate brown blood)
30	Recovery without treatment
20-45	Anxiety, exertional dyspnea, weakness, fatigue, dizziness, lethargy, headache, syncope, tachycardia
45-55	Decreased level of consciousness
55-70, ~60	Semistupor, lethargy, seizures, coma, bradycardia, cardiac arrhythmias
>70	Heart failure from hypoxia, High incidence of mortality
>85	Lethal

Sources: Kiese, 1974, Seger, 1992

ANIMAL DATA

- ACUTE LETHALITY DATA

SUMMARY OF ACUTE LETHAL INHALATION DATA IN LABORATORY ANIMALS[a]				
Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	839[b]	4 hours	LC_{50}	E.I. du Pont de Nemours 1982a
Rat	478[c]	4 hours	LC_{50}	E.I. du Pont de Nemours 1982a
Rat	250[d]	4 hours	approximate LC_{50}	Carpenter et al. 1949
Rat	550	8 hours	82% mortality	Comstock and Oberst 1952
Mouse	175	7 hours	LC_{50}	von Oettingen et al. 1947

[a] LC_{50} values were obtained 14 days post exposure (Carpenter et al. 1949, E.I. du Pont de Nemours 1982a)
[b] Head-only exposure.
[c] Whole-body exposure.
[d] Concentrations not measured.

- SUBLETHAL DATA

SUMMARY OF ACUTE SUBLETHAL INHALATION DATA IN LABORATORY ANIMALS[a]				
Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	15,302	10 minutes	no deaths	Kakkar et al., 1992
Rat	359	4 hours	no deaths	E.I. du Pont de Nemours, 1982a
Rat	150	8 hours	no deaths; 41% methemoglobin	Kim and Carlson, 1986

ANIMAL DATA (con't)

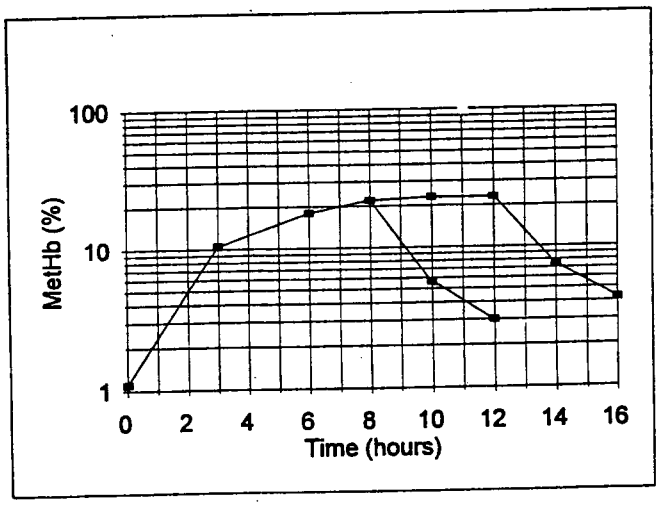
- SUBLETHAL EFFECTS

METHEMOGLOBIN FORMATION

METHEMOGLOBIN LEVELS IN RATS FOLLOWING 8 OR 12 HOURS OF EXPOSURE TO ANILINE		
Concentration (ppm)	Methemoglobin % at 8 Hours	Methemoglobin % at 12 Hours
0	1.1 (0.4-1.7)	1.1 (0.4-1.7)
10	0.4-1.7	0.4-1.7
30	1.6	3.3
50	4.7	6.5
100	22	23
150	41	46

Source: Kim and Carlson, 1986.

- METHEMOGLOBIN FORMATION



FORMATION AND DISAPPEARANCE OF METHEMOGLOBIN FROM BLOOD OF RATS EXPOSED TO 100 PPM FOR 8 OR 12 HOURS

RELATIVE SPECIES SENSITIVITY

Oral Data (Jenkins et al., 1972)
Oral dose resulting in ~16% methemoglobin: human, ~1 mg/kg; rat, 20 mg/kg

Methemoglobin reductase in red blood cells (Smith, 1966)
Activity in rat is 1.5 to 5 times that of human cells

Other Factors (not water soluble, not reactive with lung tissue, well absorbed)
Must be metabolized (phenylhydroxyamine)
Percent formation of active metabolite
Target remote from lungs
Recycling of phenylhydroxyamine
Rate of elimination

INTRASPECIES SENSITIVITY

Heart patients more sensitive than healthy adults
Infants more sensitive than adults (less reductase? fetal hemoglobin)

SCALING ACROSS TIME

Concentration x time is a constant among lethality studies ($C^1 \times t = k$)

AEGL DERIVATIONS

Used data of Kim and Carlson (1986)
Scaling across time: $C^1 \times t = k$ (k values were close for different studies)
Uncertainty factors:
10 for interspecies (Humans may be much more sensitive than laboratory animals)
3 for intraspecies (Infants and heart patients may be much more sensitive than healthy adults, but the endpoint were very conservative)

SUMMARY OF PROPOSED AEGL VALUES				
Classification	**Exposure Duration**			
	30-Minute	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1 (Nondisabling)	27 ppm (103 mg/m^3)	13 ppm (49 mg/m^3)	3.3 ppm (13 mg/m^3)	1.7 ppm (6 mg/m^3)
AEGL-2 (Disabling)	53 ppm (201 mg/m^3)	27 ppm (103 mg/m^3)	7 ppm (27 mg/m^3)	3 ppm (11 mg/m^3)
AEGL-3 (Lethal)	80 ppm (304 mg/m^3)	40 ppm (152 mg/m^3)	10 ppm (38 mg/m^3)	5 ppm (19 mg/m^3)

Use LC_{50} data to derive AEGL-3:

Rat (E.I. du Pont de Nemours 1982a)

4-hour LC_{50} of 478 ppm
Divide by 3 to reach LC_0, then by UFs of 10 and 3
Scale by $C^1 \times t = k$
30-minute AEGL-3 = 42 ppm

Mouse (von Oettingen et al. 1947)

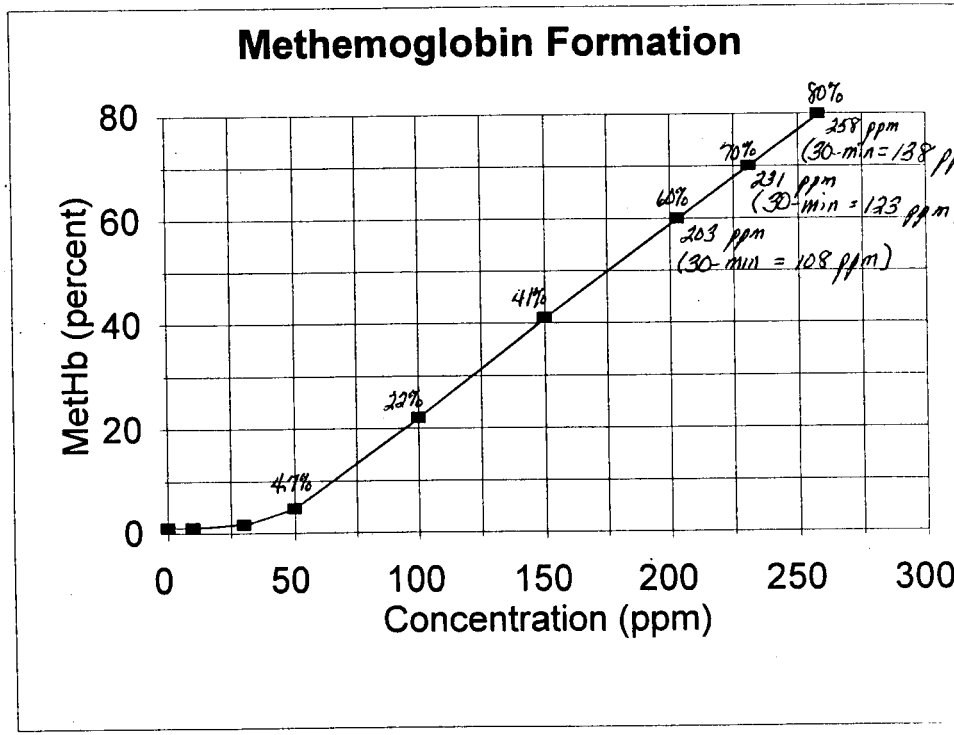
7-hour LC_{50} of 175 ppm
Divide by 3 to reach LC_0, then by UFs of 10 and 3
Scale by $C^1 \times t = k$
30-minute AEGL-3 = 27 ppm

Use LC_0 data to derive AEGL-3:

Rat (E.I. du Pont de Nemours 1982a)

4-hour LC_0 of 359 ppm
Use UFs of 10 and 3
Scale by $C^1 \times t = k$
30-minute AEGL-3 = 96 ppm

Rat (Kakkar et al. 1992
10-minute LC_0 of 15,302
Use UFs of 10 and 3
Scale by $C^1 \times t = k$
30-minute AEGL-3 = 170 ppm


Methemoglobin Formation
MetHb (percent)
Concentration (ppm)
0
20
40
60
80
0
50
100
150
200
250
300
4.7%
22%
41%
60%
70%
80%
203 ppm
(30-min = 108 ppm)
231 ppm
(30-min = 123 ppm
258 ppm
(30-min = 138 pp

Isopropyl chloroformate CAS # 108-23-6

Author: Cheryl Bast, PhD
Chemical Manager: Doan Hansen, PhD

- Paucity of Literature
- Identified Manufacturers, Requested Data
- Use RD_{50} to derive AEGLs
- Q1: Is Alarie/RD_{50} extrapolation appropriate for use when $RD_{50} \sim LC_{50}$?
- Q2: Compare Isopropyl chloroformate AEGLs with other chloroformates (Methyl chloroformate + Propyl chloroformate) in June '97 ?

PROPOSED AEGL VALUES FOR ISOPROPYL CHLOROFORMATE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (nondisabling)	0.5 ppm 2.5 mg/m^3	0.35 ppm 1.75 mg/m^3	0.18 ppm 0.88 mg/m^3	0.13 ppm 0.63 mg/m^3	RD_{50} for mice modified by 0.01 to estimate a no irritation level in humans (Key study: Anderson, 1984; Method: Alarie, 1981)
AEGL-2 (Disabling)	5 ppm 25 mg/m^3	3.5 ppm 17.5 mg/m^3	1.76 ppm 8.8 mg/m^3	1.25 ppm 6.25 mg/m^3	RD_{50} in mice modified by 0.1 to estimate an irritation level in humans (Key study: Anderson, 1984; Method: Alarie, 1981)
AEGL-3 (Lethality)	50 ppm 250 mg/m^3	35 ppm 175 mg/m^3	17.6 ppm 88 mg/m^3	12.5 ppm 62.5 mg/m^3	RD_{50} in mice modified by 1 to estimate an intolerable level in humans (Key study: Anderson, 1984; Method: Alarie, 1981)

ATTACHMENT 19

Table 3. Predictions of level and type of responses in humans at various multiples of RD_{50} value found in mice.

Multiples of RD_{50}	Response
10	Severe injury, possibly lethal
1	Intolerable to humans
0.1	Some sensory irritation
0.01	No sensory irritation
0.001	No effect of any kind on respiratory system

AEGL-1 FOR ISOPROPYL CHLOROFORMATE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-1	0.5 [2.5]	0.35 [1.75]	0.18 [0.88]	0.13 [0.63]

Species: Mouse
Concentration: 375 ppm
Time: 10 minutes
Endpoint: RD_{50}

RD_{50} x 0.01 = 8-hour human exposure level corresponding to no sensory irritation

n = 2

Uncertainty Factors:

3 for intraspecies variability
10 for limited database and convergence of LC_{50} and RD_{50} values

(No factor is used for mouse to human extrapolation. The multiplicative factor yields a human response level)

AEGL-2 FOR ISOPROPYL CHLOROFORMATE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-2	5 [25]	3.5 [17.5]	1.76 [8.8]	1.25 [6.25]

Species: Mouse
Concentration: 375 ppm
Time: 10 minutes
Endpoint: RD_{50}

RD_{50} x 0.1 = 8-hour human exposure level corresponding to some sensory irritation

n = 2

Uncertainty Factors:

3 for intraspecies variability
10 for limited database and convergence of LC_{50} and RD_{50} values

(No factor is used for mouse to human extrapolation. The multiplicative factor yields a human response level)

AEGL-3 FOR ISOPROPYL CHLOROFORMATE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-3	50 [250]	35 [175]	17.6 [88]	12.5 [62.5]

Species: Mouse
Concentration: 375 ppm
Time: 10 minutes
Endpoint: RD_{50}

RD_{50} x 1 = 8-hour human exposure level corresponding to intolerability

n = 2

Uncertainty Factors:

3 for intraspecies variability
10 for limited database and convergence of LC_{50} and RD_{50} values

(No factor is used for mouse to human extrapolation. The multiplicative factor yields a human response level)

Alertnative AEGL-2 Calculation

	30 min	1 hour	4 hour	8 hour
Collins and Proctor (1984): 22 ppm, 6 hr.; Weight loss, increased lung weight, alveolar edema, bronchiolitis, emphysema (actual exposure 6 hr/day, 5 days)	8.5	6	3	2
AEGL- 2 determined from Alarie methodology	5	3.5	1.76	1.25

n=2
Intra/interspecies combined UF of 10

Alertnative AEGL-3 Calculations

	30 min	1 hour	4 hour	8 hour
Carpenter 1982: LC_0 = 1/3 of the LC_{25}= 16.7 ppm for 30 minutes from the mouse RD_{50} experiment.	1.7	1.2	0.6	0.4
Anderson 1984: LC_0 = 141 ppm for 15 minute exposure in mouse RD_{50} study (2/4 mice died at 283 ppm for 15 minutes).	10	7	3.5	2.5
Gage 1970: LC_0 = 20 ppm in rats exposed for 360 minutes for 11 days.	6.9	4.8	2.4	1.7
Gage 1970: LC_0 = ½ of LC_{25} = 100 ppm for 300 minutes (LC_{25}= 200 ppm in rats exposed one day for 300 minutes).	32	22	11	7.9
AEGL- 3 determined from Alarie methodology	50	35	18	12

n=2

Intra/interspecies combined UF of 10

7

PROPYL CHLOROFORMATE

•MOUSE (SWISS-WEBSTER MALE): 10 MIN. RD_{50} = 83.5 PPM

NO EVIDENCE OF PULMONARY EFFECTS

PPM	MORTALITY
25	0/4
50	1/4
75	2/4
100	0/4

(reference: Carpenter, 1982)

•RAT (CHARLES RIVER MALE & FEMALE): 1-HR LC_{50} = 410 PPM

NOEL FOR ALL EFFECTS (INCLUDING DEATH): 249 PPM

(Reference, Bio-test, 1970)

•MOUSE: 1-HR LC_{50} = 319 PPM

(Reference, RTECS, 1996)

8

METHYL CHLOROFORMATE

- RAT (SPRAGUE-DAWLEY MALE): 1-HR LC_{50} = <728 PPM

(reference: Warf, 1971)

- RAT (CHARLES RIVER): 1-HR LC_{50} = 1625 PPM

(Reference: Bio-test, 1975)

- RAT: 1-HR LC_{50} (MALE)= 88 PPM
  1-HR LC_{50} (FEMALE) = 103 PPM

(reference: Vernot et al., 1977)

- RAT (SPRAGUE-DAWLEY MALE & FEMALE):

REPEATED EXPOSURE: 6 HR/DAY, 5 DAYS/WEEK, 4 WEEKS

NOEL:	0.38 PPM
UPPER RESPIRATORY HISTOPATHOLOGY:	1.0 PPM
NOEL FOR DEATH (INCLUDED HISTOPATH):	3.1 PPM
DEATH:	8.8 PPM

(Reference: BASF, 1993)

- MOUSE (SWISS-WEBSTER MALE): 10 MIN. RD_{50} = 52.4 PPM

LC_{25} = 50-75 PPM

HEMORRHAGIC LUNG TISSUE AT NECROPSY: 125 PPM

National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 4 Highlights
Green Room, 3rd Floor, Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, D.C.
December 16-18, 1996

INTRODUCTION

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

Dr. Roger Garrett welcomed the committee members and provided a brief overview of the NAC/AEGL program for new Committee members. He noted that the Committee should attempt to increase efficiency but not at the expense of quality.

The summary of meeting 3 (September 17-19, 1996) was reviewed and approved with minor changes (Appendix A). Dr. Steve Barbee noted that clarification was needed regarding the AEGL values for hydrogen cyanide. He stated that the Wexler et al. (1974) data should have been used to derive the AEGL-2 values instead of the AEGL-3 values. This change will not affect the selected concentrations and will be reflected in the final draft report to be circulated for public comments. It was noted that the 4-hr and 8-hr AEGL-2 values for arsine as proposed by the NAC/AEGL and listed in the meeting summary should be rounded to the nearest tenth to maintain relational consistency (the arsine values in question were amended accordingly the following day [12/17/96]) (Appendix B). Dr. Doan Hansen noted that for methyl mercaptan, the *n* exponent for temporal scaling was changed from 2.5 to 2.2 resulting in slightly altered values for the 30-minute and 1-hr AEGL-2 and AEGL-3 values.

Dr. Robert Snyder commented that it is the NAC/AEGL that recommends the AEGL values and that ORNL provides data analyses and submits draft documents to the NAC/AEGL.

REPORTS FROM SUBCOMMITTEES AND GENERAL INTEREST ITEMS

Uncertainty Factor Subcommittee
Dr. David Belluck indicated that requests were made to all 50 states regarding how they addressed uncertainty factor application and issues and that 20-25 states had responded thus far. An updated report will be provided at the next NAC/AEGL meeting. Mr. Larry Gephart noted that a report on the use and interspecies variability of the RD_{50} had been provided to Dr. Richard Thomas. Dr. Richard Thomas noted that an overview of uncertainty factor application will be an agenda item at the next (March) meeting.

Time-line for Document Review
A revised time-line for document review to facilitate the effectiveness of the review process and in the use of meeting time was briefly discussed by Dr. George Rusch, NAC/Chair (Attachment 3). It was noted that the Committees' role in document review had been expanded (chemical manager and two secondary reviewers) and that a list of priority chemicals would be made available to the NAC in January 1997 (Attachment 4). Dr. Po-Yung Lu (ORNL) noted that the chemicals and chemical managers for the March

meeting had mostly been identified and that the June meeting chemicals were also selected but that chemical managers had not yet been identified.

Acute Inhalation Toxicity Study Outline
Dr. George Rusch noted that no comments had been received to date regarding the study outline.

Literature Search/Acquisition Considerations
Dr. P.-Y. Lu provided an overview of the literature search/acquisition processes at ORNL for AEGL document preparation. The NAC/AEGL members were encouraged to continue assisting in identifying pertinent literature. Dr. Paul Tobin noted that the exact measured exposure levels are requested from OSHA and will be submitted in the near future. Dr. David Belluck also offered assistance in obtaining very old documents. Dr. Roger Garrett noted that non peer-reviewed data from the private sector is not always easily accessed and that a mechanism needs to be developed to obtain these reports.

Compilation of "Living Document"
Dr. Ernest Falke is in the process of compiling critical data used in deriving AEGL levels (e.g., species, critical effect, reference, scaling procedures, uncertainty factor application, etc.). He noted that special attention should be directed to justifying assumptions and methods used in the derivation of AEGL values. Essentially, we must capture what we have done and why it was done. This will be discussed at the next meeting.

AEGL Document Format
Dr. David Belluck noted that comments regarding document format will be deferred until the next meeting.

AEGL PRIORITY CHEMICALS

Nitric Acid, CAS Reg. No. 7697-37-2

Chemical Manager: Dr. Loren Koller, Orgeon State Univ.
Staff Scientist: Dr. Carol Forsyth, ORNL
Dr. Koller noted that the NO_2 data had been examined relative to revisiting the nitric acid AEGLs. He recommended that the nitric acid AEGLs not be revised and that the report should be considered as complete. The current AEGLs for nitric acid are shown in the table below.

SUMMARY OF PROPOSED AEGL VALUES FOR NITRIC ACID

Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	0.5 ppm 1.3 mg/m^3	0.5 ppm 1.3 mg/m^3	0.5 ppm 1.3 mg/m^3	0.5 ppm 1.3 mg/m^3	Minor irritation in humans
AEGL-2	5 ppm 12.9 mg/m^3	4 ppm 10.3 mg/m^3	3 ppm 7.7 mg/m^3	2 ppm 5.2 mg/m^3	Notable irritation, respiratory effects in humans
AEGL-3	15 ppm 38.7 mg/m^3	13 ppm 33.5 mg/m^3	8 ppm 20.6 mg/m^3	7 ppm 18.1 mg/m^3	Approximate LC_0 in rats

Hydrogen Fluoride, CAS Reg. No. 7664-39-3

Chemical Manager: Mr. Larry Gephart, Exxon Biomedical Sciences
Staff Scientist: Dr. Sylvia Talmage, ORNL

Data were presented and issues discussed regarding the derivation of 10-minute AEGLs for hydrogen fluoride (HF). Mr. Larry Gephart provided a brief overview of the AEGLs previously proposed for HF (August 1996 NAC meeting). These are shown in the table below.

SUMMARY OF PROPOSED AEGL VALUES FOR HYDROGEN FLUORIDE

Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	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	Slight eye and nose irritation in humans (Largent 1960; 1961)
AEGL-2	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	NOAEL for serious lung effects in rats (PERF 1966)[a], highest concentration for slight eye and nose irritation and reddening of facial skin in humans (Largent 1960; 1961)[b]
AEGL-3	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	Threshold for lethality in mice (Wohlslagel et al., 1976)

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

Mr. Larry Gephart and Dr. Walden Dalbey (Mobil Business Resources Corporation) provided data to support a 10-minute AEGL-2 for HF (Attachments 5&6). They provided the results of a study conducted by the Petroleum Environmental Research Forum that was designed to define the HF concentration causing serious effects and estimating the threshold for these effects. Exposure of mouth-breathing rats for 10 minutes to 1764 ppm HF resulted in serious effects including lethality (1/20 animals), 950 ppm caused local irritation but no serious effects, and 271 ppm HF was a NOAEL. The uncertainty factor application included 3 for interspecies variability (HF is a primary irritant, LC_{50} values are similar across species, and the irritation endpoint is appropriate for human health risk assessment), and 3 for intraspecies variability (mouth breathing by test species bypasses nasal scrubbing and maximizes the dose). The approximate arithmetic mean value of the concentrations causing serious effects (1764 ppm) and no serious effects (950 ppm), i.e., 1300 ppm was chosen as the threshold for serious effects for the 10-minute AEGL-2. Based upon this estimated threshold and a total UF of 10 (3 x 3), 130 ppm was proposed as the 10-minute AEGL-2 for HF. The proposed 10-minute AEGL-2 of 130 ppm was accepted by the Committee (Appendix C). A 10-minute AEGL-3 of 170 ppm (1764 ppm/10) and a 10-minute AEGL-1 of 2 ppm (the effect would not change between the 10- and 30-minute time frames) were proposed and accepted by the Committee (Appendix C).

Ammonia, CAS Reg. No. 7664-41-7

Chemical Manager: Mr. Larry Gephart, Exxon Biomedical Sciences
Staff Scientist: Dr. Kowetha Davidson, ORNL

Mr. Larry Gephart provided a brief overview of the AEGL derivation effort for ammonia. Although AEGL-1 levels have been accepted by the Committee, AEGL-2 and AEGL-3 levels are still in the derivation process. Dr. Kowetha Davidson provided an overview (Attachment 7) of the data sets

and previously proposed AEGL values, noting the variability in animal data and the uncertainty in accident reconstruction. Dr. Robert Michaels (RAM-TRAC Corp.) agreed that the animal data are variable and again stated that the conservative accident reconstruction was more appropriate for AEGL estimation (Attachment 8). Dr. Joseph Rodricks* (Environ Corp.) provided an overview of Environ's report addressing proposed AEGLs for ammonia (Attachment 9). He emphasized that the mouse is an especially sensitive species and that the ten Berge extrapolation is applicable to limited exposure durations, concentrations, and chemicals. Mr. Kent Andersen (International Institute of Ammonia Refrigeration) expressed reservations regarding the use of the RD_{50} for derivation of AEGLs (Attachment 10). Dr. Mazzola (DOE) provided an overview (Attachment 11) of the weaknesses and uncertainties of accident reconstruction. Dr. George Rusch recommended that the toxicity data as well as the accident reconstruction data be re-examined and also suggested consideration of the need for longer-term AEGLs for ammonia since lethality usually occurs at short-duration exposures. Dr. Borak noted that glottis closure may not be a valid endpoint for use in AEGL derivation. Discussion ensued regarding the use of human equivalent concentrations and the use of established risk assessment paradigms for AEGL derivations. It was the consensus of the Committee to defer ammonia to the next meeting and that the accident reconstruction modeling may require re-visitation by taking into account Dr. Mazzola's discussion. Additional action items for ammonia included: (1) defining appropriateness of using the RD_{50}; (2) consideration of Environ Corp. comments; (3) assessing the validity of 4-hr and 8-hr AEGLs for ammonia; and, (4) assessing the appropriateness of human equivalent concentrations, especially at high exposure levels.

(*1/28/97 Note: Responses to NAC issues by Dr. Rodricks were transmitted by Dr. James M. Skillen and received on 1/27/97.) (Attachment 21)

Methylhydrazine, CAS Reg. No. 60-34-4

Chemical Manager: Dr. Richard Thomas, ICEH
Chemical Reviewers: Dr. George Rogers, AAPCC; Dr. Kyle Blackman, FEMA
Staff Scientist: Dr. Robert A. Young, ORNL

Dr. Richard Thomas presented a brief overview of the properties and toxicity of methylhydrazine which was followed by a presentation by Dr. Young of the draft AEGL values and a summary of the data sets used for their derivation (Attachment 12). Of special concern was the steep exposure-response relationship indicated by animal data and the apparent low toxicity shown by 10-min exposure of human subjects. Following extensive discussion, it was decided by the Committee that the AEGL-3 be based upon a 1-hr LC_{50} in squirrel monkeys (the most sensitive species) and that the AEGL-2 be adjusted based upon a 3-fold reduction of the AEGL-3 values; a reduction considered adequate for estimating a threshold for serious, irreversible toxic effects. An AEGL-1 was considered to be inappropriate because notable toxicity may occur at concentrations below those that may result in serious toxic effects. A cancer risk assessment indicated that carcinogenic potential would be irrelevant compared to noncarcinogenic toxicity for acute exposures to methylhydrazine. Based upon the above discussion the following AEGL values were accepted by the Committee (Appendix D).

SUMMARY OF PROPOSED AEGL VALUES FOR METHYLHYDRAZINE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint

AEGL-1	NA	NA	NA	NA	
AEGL-2	2 ppm 3.8 mg/m^3	1 ppm 1.9 mg/m^3	0.2 ppm 0.4 mg/m^3	0.1 ppm 0.2 mg/m^3	Three-fold reduction of AEGL-3
AEGL-3	6 ppm 11.3 mg/m^3	3 ppm 5.6 mg/m^3	0.6 ppm 1.1 mg/m^3	0.3 ppm 0.6 mg/m^3	1-hr LC_{50} of 82 ppm reduced by 3-fold to estimate lethality threshold; UF=30[a]

[a] UF=3 for interspecies variability because mechanism of lethality appears to be similar across species, UF=10 for sensitive populations.

It was noted that in the practical application arena, if hydrazine is known to be present with methylhydrazine, the AEGL-1 for hydrazine (0.1 ppm for all time points) should be used.

Dimethylhydrazine, CAS Reg. No. 57-14-7 (1,1-DMH); 540-73-8 (1,2-DMH)

Chemical Manager: Dr. Richard Thomas, ICEH
Chemical Reviewers: Dr. George Rogers, AAPCC; Dr. Kyle Blackman, FEMA
Staff Scientist: Dr. Robert A. Young, ORNL

Dr. Richard Thomas provided a brief overview of the properties and toxicity of dimethylhydrazines (1,1-dimethylhydrazine and 1,2-dimethylhydrazine) which was followed by a presentation by Dr. Young of the draft AEGL values and a summary of the data sets used to derive draft AEGL values (Attachment 13). As for methylhydrazine, an AEGL-1 was considered to be inappropriate because the odor threshold was above concentrations that could produce effects. The data sets for deriving AEGL-2 and AEGL-3 levels were reviewed by Dr. Young and the draft AEGL-2 and AEGL-3 values were revised slightly. Similar to methylhydrazine, the AEGL values were not driven by excess cancer risk. Both Dr. Young and Dr. Thomas noted that the accepted AEGL-3 values for dimethylhydrazine, methylhydrazine, and hydrazine were relationally consistent with the reported relative toxicity of these chemicals. Additionally, it was noted that for emergency planning purposes, if hydrazine is known to be present, the hydrazine AEGL-1 of 0.1 ppm (for all time points) should be employed. Because of the paucity of toxicity data for 1,2-dimethylhydrazine, it was the consensus of the Committee (Appendix E&F) that the values for 1,1-dimethylhydrazine be used for 1,2-dimethylhydrazine.

SUMMARY OF PROPOSED AEGL VALUES FOR DIMETHYLHYDRAZINE

Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	NA	NA	NA	NA	
AEGL-2	6 ppm 15 mg/m^3	3 ppm 7 mg/m^3	0.8 ppm 2 mg/m^3	0.4 ppm 1 mg/m^3	Behavioral changes and muscle fasciculations in dogs exposed to 360 ppm for 15 minutes (Weeks et al., 1963)[a]
AEGL-3	22 ppm 54 mg/m^3	11 ppm 27 mg/m^3	3 ppm 7 mg/m^3	1.5 ppm 4 mg/m^3	Lethality threshold of 327 ppm estimated from 1-hr LC_{50} for dogs (Weeks et al., 1963)[a]

[a] Uncertainty factor of 30

Phosphine, CAS Reg. No. 7803-51-2

Chemical Manager: Dr. Ernest Falke, USEPA

Chemical Reviewers: Dr. George Alexeeff, Calif. EPA; Dr. Zarena Post, Texas
Staff Scientist: Dr. Cheryl Bast, ORNL

Dr. Falke provided an outline of issues pertaining to the phosphine AEGLs: critical effect, study selection, allometric scaling between laboratory species and humans, uncertainty factor application for inter- and intraspecies variability, temporal scaling, and interpretation of exposure-response curve data (Attachment 14). Dr. Cheryl Bast provided an overview of the draft AEGLs for phosphine (Attachment 15), noting the exceptionally steep exposure-response curve and lack of time and concentration data from human accidents. Following extensive discussion, the Committee decided to base the AEGL-3 on a no-effect-level for death in Sprague-Dawley rats exposed to phosphine for 6 hours. The Committee then decided to base the AEGL-2 on a no-effect-level for renal and pulmonary pathology in Fischer 344 rats exposed to phosphine 6 hours/day, 5 days/week for 13 weeks. Due to a lack of data, and the fact that lethality has been observed in animals exposed to phosphine concentrations below the odor threshold, the Committee decided that derivation of AEGL-1 values was not appropriate for phosphine (Appendix G).

SUMMARY OF PROPOSED AEGL VALUES FOR PHOSPHINE

Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	NA	NA	NA	NA	
AEGL-2	0.4 ppm 0.6 mg/m^3	0.2 ppm 0.3 mg/m^3	0.1 ppm 0.14 mg/m^3	0.1 ppm 0.14 mg/m^3	No-effect level for renal and pulmonary pathology on rats exposed to 3.1 ppm phosphine 6 hr/day, 5 days/week for 13 weeks (Newton et al., 1993). UF=30[a]
AEGL-3	2 ppm 2.8 mg/m^3	1.5 ppm 2.1 mg/m^3	0.7 ppm 0.99 mg/m^3	0.5 ppm 0.7 mg/m^3	No-effect level for lethality in rats exposed to 18 ppm phosphine for 6 hr (Newton, 1991). UF=30[a]

[a]UF=3 for interspecies variability because mechanism of toxicity appears to be similar across species, UF=10 for sensitive populations because children appear to be more sensitive than adults.

Chlorine, CAS Reg. No. 7782-50-5

Chemical Manager: Mr. Larry Gephart, Exxon Biomedical Sciences
Chemical Reviewers: Dr. George Alexeeff, Calif. EPA; Dr. Kyle Blackman, FEMA
Staff Scientist: Dr. Sylvia Talmage, ORNL

Following an introduction by Mr. Larry Gephart, the presentation on chlorine (Cl_2) continued with an overview of the studies (human and animal) and data selection for deriving AEGLs by Dr. Sylvia Talmage (Attachment 16). During the discussion of the human data, the seriousness of an asthmatic attack from exposure to an irritant gas was pointed out by Dr. Jonathan Borak. Therefore, the data from the sensitive individual who suffered the asthmatic attack, exposure to 1 ppm of Cl_2 for 4 hours, was used as the basis for the AEGL-2; the no-effect concentration for this individual, 0.5 ppm for 4 hours, was used as the basis for the AEGL-1. Since human data were used and a sensitive individual was involved, no UFs were applied. The data were scaled across time using the relationship $C^2 \times t = k$.

During discussion of the animal data for the AEGL-3, it was noted that the endpoint was selected based upon study and data quality and not necessarily the most sensitive species; mouse data appeared to provide an overly conservative estimate of lethality that was not consistent with the

overall preponderance of the data. Mice suffered delayed deaths attributed to bronchopneumonia. One-hour LC_0 values for the rat were >200 ppm as was the 30-minute LC_0 for the rabbit. Therefore 200 ppm for one hour, which corresponds to an LC_{20} for the mouse, was chosen as the basis for the AEGL-3. Uncertainty factors of 3 for interspecies (Cl_2 is a direct-acting primary irritant with little difference among species in the response of biological tissue and the irritation endpoint is appropriate for human health risk assessment) and 3 for intraspecies (the mechanism of toxicity is the same for individuals of the same species) differences were applied. The data were scaled across time using the relationship $C^2 \times t = k$. The resulting AEGLs for chlorine were approved by the NCA (Appendix H) and are shown in the table below.

SUMMARY OF PROPOSED AEGL VALUES FOR CHLORINE

Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	1 ppm 3 mg/m^3	1 ppm 3 mg/m^3	0.5 ppm 1.5 mg/m^3	0.5 ppm 1.5 mg/m^3	No-effect level in humans including sensitive individual (Rotman et al., 1983)
AEGL-2	3 ppm 9 mg/m^3	2 ppm 6 mg/m^3	1 ppm 3 mg/m^3	1 ppm 3 mg/m^3	Asthmatic attack in sensitive individual (Rotman et al., 1983)
AEGL-3	31 ppm 90 mg/m^3	22 ppm 64 mg/m^3	11 ppm 32 mg/m^3	8 ppm 23 mg/m^3	LC_0 for rat (MacEwen and Vernot 1972; Zwart and Woultersen 1988), LC_{20} for mouse (O'Neill 1991)

Phosgene, CAS Reg. No. 75-44-5

Chemical Manager: Dr. William C. Bress, ASTHO
Chemical Reviewers: Dr. David Belluck, Minnesota; Mr. Larry Gephart, EXXON
Staff Scientist: Dr. Jim Norris, ORNL

This document will be reviewed in March due to the recently uncovered, key references.

Ethylene Oxide, CAS Reg. No. 75-21-8

Chemical Manager: Dr. Kyle Blackman, FEMA
Chemical Reviewers: Dr. George Alexeeff, Calif. EPA; Dr. Jonathan Borak, ACOEM/ACEP
Staff Scientist: Dr. Kowetha Davidson, ORNL

Dr. Davidson provided an overview of the extensive database for ethylene oxide (EO) (Attachment 17). Several issues were identified regarding EO and included: (1) evaluating toxic vs anesthetic effects and obtaining information on blood:gas partition coefficients; (2) the need for the NAC/AEGL to determine if reproductive/developmental effects are AEGL-2 or AEGL-3 effects; (3) cancer risk issues: data from long-term bioassays may not be appropriate for a direct alkylating agent; and, (4) investigate details of the ampoule exposure case report.

Dr. Bill Snellings (Product Safety, Union Carbide) provided information on the toxicity of EO (Attachment 18) and noted that the only know fatalities from ethylene oxide accidents were associated with the chemical's explosivity. He noted that the TLV has been sequentially lowered over the years, that vomiting may be an important critical effect, that EO may induce dominant lethal effects in female rodents, and that no developmental effects have been shown at <1200 ppm but that exposure to 450 ppm caused hindleg paresis in rodents. Dr. Snellings noted that it is important to

evaluate effects relative to their biological relevance. The Committee requested that Dr. Snellings review the ORNL draft document and Dr. Snellings noted that he would attempt to provide odor threshold data.

Agenda Items

1. Determine if the fetus or pregnant woman should be considered the sensitive population and obtain information on what percent of the population is represented by pregnant women.

2. Dr. Belluck will discuss document formatting.

3. A request from Dr. Eugene Ngai (Solkatronic Chemicals) has been made to consider development of 10-minute AEGLs for compressed gases (Attachment 19). This topic will be discussed by the NAC.

4. A compiltaion of adverse health effect endpoints upon which to base AEGL-2 and AEGL-3 values will be discussed.

5. "Uncertainty" subcommittee report by Dr. Thomas.

6. The "living document" being developed by Dr. Falke regarding rationales for AEGL derivations will be discussed.

7. Consideration of all public comments that convey new and significant information pertinent to the development of AEGLs for ammonia, including any new and significant findings submitted by Ram Trac Corp.

Wrap-Up Comments from all participants:

- good discussions regarding relevant technical issues
- presentation of calculations in documents very helpful
- handouts of overheads very helpful
- document distribution was timely; preferred sequential receipt of documents rather than one large overwhelming package
- timely comments on documents appreciated; as document distribution improves, receipt of comments will hopefully improve as well
- need data on production, use, storage, etc. for chemicals
- because of the dynamics and diversity of the NAC, consistency in methodology application (e.g., uncertainty factor application) is important
- may want 10-minute AEGL routinely
- must make sure to provide rationale for assumptions and adjustments to methodologies
- compile summary of currently derived AEGL "living document"
- quality and good science are critical, productivity and efficiency also important
- include chemical manager on draft document; include exposure-response graphs if possible

Dr. Tobin distributed a chart on the various agencies interactions on the NAC/AEGL project (Attachment 20).

Dr. Garrett provided closing comments regarding the overall effectiveness of the NAC/AEGL and ORNL activities to date. He reiterated the objective and function of the Committee to develop AEGLs for 30 to 40 chemicals per year that are solidly based on good science. He emphasized the point that to attain this level of production together with scientifically defensible values, most of the work must be done in iterative fashion outside of the formal meetings.

To accomplish this, Roger emphasized that it is critical for each chemical manager to accept the "ownership" of the chemicals assigned to them and to serve aggressively as the catalyst and monitor of productive work, the liaison between the Oak Ridge staff scientist and the Committee members, and the key individual for resolving as many of the scientific and technical issues as possible prior to the formal meeting.

Based on his observations of the first four meetings, Roger believes that we have seen examples of very good, average and poor performances of Chemical Managers. He added that if we are to reach our goals, all chemical managers must perform at the upper end of the scale. He speculated that many Committee members may not fully understand the role of the chemical manager and committed himself to providing more definitive guidance. Roger concluded his remarks by emphasizing that the Chemical Manager function represents the "engine" that will drive an efficient and effective process.

Next meeting: March 17-19, 1997, Washington, D.C.

(Minutes were prepared by Drs. Robert Young and Po-Yung Lu, ORNL, and were approved on March 17, 1997.)

List of Attachments

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

1. NAC meeting 4 agenda
2. NAC meeting 4 attendees
3. Time-line for document review - revised from Dr. Rusch
4. Future chemicals for NAC review
5. Data analysis for 10-minute AEGL of HF from Gephart
6. Data analysis for 10-minute AEGL of HF from Dalbey
7. Data analysis of ammonia from Davidson
8. Residual issues of Ammonia Emergency Planning from Michaels
9. Review and technical critique of AEGLs proposed for ammonia from Rodricks
10. Ammonia for RD_{50} documents from Andersen
11. Overview of accident reconstruction from Mazzola
12. Data analysis of methylhydrazine AEGLs from Young
13. Data analysis of dimethylhydrazine AEGLs from Young
14. Data analysis of phosphine from Falke
15. Data analysis of phosphine from Bast
16. Data analysis of chlorine from Talmage
17. Preliminary data analysis of ethylene oxide from Davidson
18. Ethylene oxide LC_{50} values from Snellings
19. Correspondence to Dr. Rusch on compressed gases from Ngai
20. Agencies interactions on the NAC/AEGL from Tobin
21. Skillen/Rodricks response to NAC comments

List of Appendices

A. Final NAC meeting 3 highlights
B. Ballot of arsine modification
C. Ballot of hydrogenfluoride 10-minute AEGLs
D. Ballot of methylhydrazine AEGLs
E. Ballot of 1,2-dimethylhydrazine AEGLs
F. Ballot of 1,1-dimethylhydrazine AEGLs
G. Ballot of phosphine AEGLs
H. Ballot of chlorine AEGLs

Society of Toxicology Meeting
March 1997 - Cincinnati, Ohio

George V. Alexeeff, Ph.D., D.A.B.T

California Environmental Protection Agency
Office of Environmental Health Hazard Assessment
Air Toxicology and Epidemiology Section
2151 Berkeley Way, Annex 11
Berkeley, California 94704

(510) 540-3324
(510) 540-2923

e-mail: berkeley.galexeef@hw1.cahwnet.gov

STOCHASTIC EVALUATION OF ACUTE INHALATION THRESHOLDS FROM REPORTED LOAELS.

GV Alexeeff, JR Fowles, M Hill;* and D Dodge*
Office of Environmental Health Hazard Assessment,
California Environmental Protection Agency, Berkeley, CA.
* under contract.

To estimate threshold doses for acute inhalation exposures, No Observed Adverse Effect Levels (NOAELs) are generally used. However, since NOAELs are often not available, Lowest Observed Adverse Effect Levels (LOAELs) divided by an uncertainty factor (UF) are often substituted. US EPA has recommended that a UF between 1 and 10 be used, and that it reflect the scientific judgment of the LOAEL to NOAEL difference. In practice, 10 has generally been used as the UF for standard setting. The purpose of this paper is to evaluate the distribution of the LOAEL to NOAEL ratios and to consider the importance of severity of the adverse effect in the evaluation. Data (quantal and continuous) from a number of different chemicals, and a variety of acute inhalation toxicity endpoints, were utilized in the analysis. LOAELs and NOAELs from reported studies were used to evaluate the lower range of the ratio. Other adverse effect levels in the reported studies were compared with the NOAEL to evaluate the upper range of the of the ratio. The ratio was also evaluated for lethal and non-lethal endpoints. The results indicate that a UF of approximately 3 to 5 would encompass the 95th percentile of results when calculating the LOAEL to NOAEL ratio within a severity category (e.g., discomforting, disabling and lethal categories), or when calculating the NOAEL for the least severe endpoint. However, an UF of 10 would encompass the 95th percentile when extrapolating from a lethal effect level to the lowest NOAEL. This relationship did not consider the effects of the intraspecies or intraspecies UFs, nor were the UFs to be used by other exposure routes or durations evaluated.

Introduction

In 1995, OEHHA released a draft document for assessing the non-cancer risks of acute 1-hour exposures to airborne toxicants. This document identified 1-hour exposure levels for the general public at which no adverse health effects would be anticipated. Many of the exposure levels are based on no observed adverse effect levels (NOAELs) for appropriate endpoints in key studies.

NOAELs have been defined by U.S. EPA as the exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its control (U.S. EPA, 1990).

However, due to the absence of a NOAEL in some key studies, some of the exposure levels are based on a lowest observed adverse effect level (LOAEL). The threshold is defined as the dose or exposure below which a significant adverse effect is not reported; thus, it is thought to be between the NOAEL and the LOAEL. To estimate a NOAEL when one is not available, the LOAEL is commonly divided by an uncertainty factor (UF) between 1 and 10, based on the severity of the adverse effect of the LOAEL (Dourson and Stara, 1983). In practice, 10 has generally been used as the UF for standard setting and is considered a health-protective value for adjusting a LOAEL to a NOAEL. An uncertainty factor of 3 has on occasion been used to arrive at the NOAEL, particularly for less severe non-lethal endpoints such as mild irritation. The justification for use of a UF between 1 and 10 is generally based on chronic or subchronic LOAEL to NOAEL ratios (Dourson and Stara, 1983); guidance specifically for acute toxicity is unavailable. Specific justification for the use of a UF for the LOAEL to NOAEL extrapolation is lacking for acute toxicity.

The purpose of this paper is to evaluate the distribution of the LOAEL to NOAEL ratios for acute inhalation studies and to consider the importance of severity of the adverse effect in the evaluation. This may provide a more objective scientific basis for the determination of UFs in LOAEL to NOAEL extrapolations.

Results

Within Severity Level Comparisons:

- At the 90th percentile, the results indicate a UF of 3.5 to 6 when calculating a NOAEL from a LOAEL within each severity category.

- At the 95th percentile, the results indicate a UF of 6 to 10 when calculating a NOAEL from a LOAEL within each severity category.

- The lethal NOAEL/LOAEL ratio (Level III) was smaller than the NOAEL/LOAEL ratio for severe disability (Level II) or the NOAEL/LOAEL ratio for mild adverse effects (Level I).

Across Severity Level Comparisons:

- At the 90th percentile, the results indicate a UF of 10 to 12 when calculating a NOAEL for severe disability (Level II) from a lethal LOAEL (Level III), or a NOAEL for mild discomfort (Level I) from a LOAEL for severe disability (Level II).

- At the 95th percentile, the results indicate a UF of 10 when calculating a NOAEL for severe disability (Level II) from a lethal LOAEL (Level III). When calculating a NOAEL for mild discomfort (Level I) from a LOAEL for severe disability (Level II), the UF increases to 40.

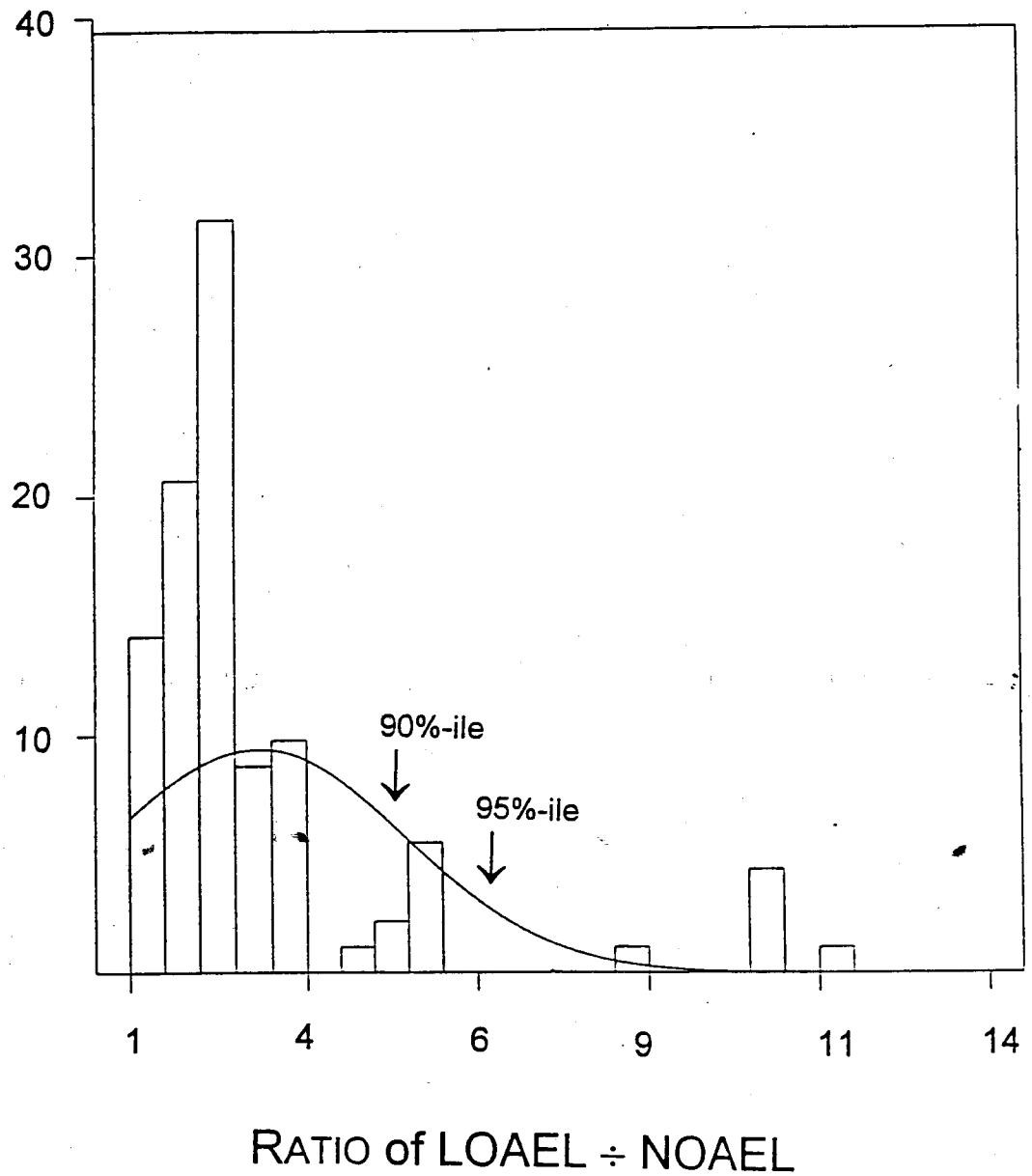
Table 1. Comparison of LOAEL to NOAEL Ratios for Discomforting or Mild Adverse Effects (Level I Effects).

	n	50th percentile	90th percentile	95th percentile	99th percentile
Lowest LOAEL/NOAEL	112	2.2	5.0	6.2	10.0
All LOAELs/NOAEL	130	2.7	6.0	10.0	10.0
LOAELS (w/out 100% responses)/NOAEL	122	2.3	5.0	7.3	10.0

Table 3. Comparison of LOAEL to NOAEL Ratios for Lethality.

	n	50th percentile	90th percentile	95th percentile	99th percentile
Lowest LOAEL / NOAEL	260	1.5	3.5	6.6	10.0
All LOAELs / NOAEL	631	1.9	4.0	6.6	10.5
LOAELs (w/out 100% responses) / NOAEL	493	1.7	3.4	6.0	10.0
LC_{50} / NOAEL	88	1.7	2.9	3.5	6.4

Figure 1. Distribution of LOAEL to NOAEL Ratios for Mild Adverse Effects (Level I); n=112



Conclusions

- The UF ratios of LOAELs to NOAELs across all adverse effects range from 2.2 within Level I effects (50^{th} percentile) to 117 for Level III effects (99^{th} percentile).

- Choice of a UF of 10 to estimate a NOAEL from a LOAEL of a specified severity represents a 99^{th} percentile.

- To estimate a NOAEL from a LOAEL within the same severity level, the UF value appears to be independent of severity level. The notion that extrapolation to NOAELs for mild effects (i.e., irritation) requires a UF substantially less than extrapolations to NOAELs for lethality is not supported by the data reported here.

- For each of the three acute toxicity levels, there was little difference in the LOAEL/NOAEL ratio for different estimates of the LOAEL. Thus, the results are robust and statistically sound.

- At the 90th percentile, the results indicate that the LOAEL to NOAEL UF is between the most common UFs used currently, 3 and 10. At the 95th percentile, 10 is the most appropriate value.

- The small LC_{50}/NOAEL ratios relative to other NOAEL/LOAEL ratios for lethality appeared to result from the higher quality study design of this subset of studies.

- In estimating a NOAEL for all acute inhalation adverse effects from a lethal LOAEL, a UF of 40 would be needed to avoid overestimating the NOAEL 95 % of the time.

Date of AEGL NAC meeting: 3/18/97 **Chemical:** ETHYLENE OXIDE

NAC Member	AEGL1	AEGL2	AEGL3	NAC Member	AEGL1	AEGL2	AEGL3
George Alexeeff	Y	N	Y≠	Thomas C. Hornshaw	Y	Y	Y
Steven Barbee	Y	Y	Y	Nancy K. Kim	Y	P	Y
Lynn Beasley	Y	Y	Y	Loren Koller	Y	Y	Y
David Belluck	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
Robert Benson	Y	Y	Y	John S. Morawetz	Y	N	Y
Kyle Blackman	Y	Y	Y	Richard W. Niemeier	Y	Y	Y
Jonathan Borak	A	A	A	Zarena Post	Y	N	Y
William Bress	A	A	Y	George Rodgers	Y	Y	Y
Luz Claudio	P	P	P	George Rusch, Chair	Y	Y	Y
Guy Colonna	A	A	A	Bob Snyder	Y	Y	Y
George Cushmac	Y	Y	Y	Thomas J. Sobotka	Y	Y	Y
Marion F. Ehrich	A	A	A	Kenneth Still	Y	Y	Y
Ernest Falke	Y	Y	Y	Patricia Ann Talcott	A	A	A
Larry Gephart	Y	Y≠	Y	Richard Thomas	A	A	A
Robert E. Hazen	Y	Y	Y	Thomas Tuccinardi/	A	A	
John Hinz	Y	P	Y	Doan Hansen *	Y	Y	Y
Jim Holler	Y	Y	Y	TALLY		19/22	

≠ Revise document to capture minutes A = Absent

* Not a member P = Pass

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	**N/A ,( )	**N/A ,( )	**N/A ,( )	**N/A ,( )
AEGL 2	190 ,( )	110 ,( )	33 ,( )	19 ,( )
AEGL 3	360 ,( )	200 ,( )	63 ,( )	35 ,( )

** No supporting data for mild irritating effects

AEGL 1 Motion: K. Blackman **Second:** R. Belluck

AEGL 2 Motion: S. Barbee **Second:** L. Koller

AEGL 3 Motion: L. Gephart **Second:** D. Belluck

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 3/18/97

Comments:

Date of AEGL NAC meeting: 3/18/97 **Chemical:** TDI

NAC Member	AEGL1	AEGL2	AEGL3	NAC Member	AEGL1	AEGL2	AEGL3
George Alexeeff			A	Thomas C. Hornshaw			Y
Steven Barbee			Y	Nancy K. Kim			Y
Lynn Beasley			A	Loren Koller			A
David Belluck			Y	Mark A. McClanahan			Y
Robert Benson			Y	John S. Morawetz			Y
Kyle Blackman			Y	Richard W. Niemeier			Y
Jonathan Borak			A	Zarena Post			Y
William Bress			A	George Rodgers			A
Luz Claudio			A	George Rusch, Chair			Y
Guy Colonna			A	Bob Snyder			Y
George Cushmac			Y	Thomas J. Sobotka			Y
Marion F. Ehrich			A	Kenneth Still			Y
Ernest Falke			Y	Patricia Ann Talcott			A
Larry Gephart			Y	Richard Thomas			A
Robert E. Hazen			Y	Thomas Tuccinardi/ Doan Hansen			A N
John Hinz			Y				
Jim Holler			Y	TALLY			20/21

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )
AEGL 3	0.92,( )	0.65,( )	0.32,( )	0.23,( )

AEGL 1 Motion: _____ **Second:** _____

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

AEGL 3 Motion: J. Hinz **Second:** J. Morawetz

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 3/18/97

Comments:

Date of AEGL NAC meeting: 3/19/97 **Chemical:** ANILINE 

NAC Member	AEGL1	AEGL2	AEGL3
George Alexeeff	A	A	A
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	A	A	A
William Bress	A	A	A
Luz Claudio	P	P	P
Guy Colonna	A	A	A
George Cushmac	A	A	A
Marion F. Ehrich	A	A	A
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

NAC Member	AEGL1	AEGL2	AEGL3
Thomas C. Hornshaw	N	N	N
Nancy K. Kim	Y	Y	Y
Loren Koller	A	A	A
Mark A. McClanahan	N	N	N
John S. Morawetz	Y	Y	Y
Richard W. Niemeier	Y	Y	Y
Zarena Post	Y	Y	Y
George Rodgers	A	A	A
George Rusch, Chair	N	N	N
Bob Snyder	N	N	N
Thomas J. Sobotka	P	P	P
Kenneth Still	Y	Y	Y
Patricia Ann Talcott	A	A	A
Richard Thomas	Y	Y	Y
Thomas Tuccinardi/ Doan Hansen	A Y	A Y	A Y
TALLY	17/21	17/21	17/21

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	16 ,( )	8 ,( )	2 ,( )	1 ,( )
AEGL 2	24 ,( )	12 ,( )	3 ,( )	1.5 ,( )
AEGL 3	40 ,( )	20 ,( )	5 ,( )	2.5 ,( )

AEGL 1 Motion: R. Benson **Second:** R. Niemeier

AEGL 2 Motion: R. Benson **Second:** R. Niemeier

AEGL 3 Motion: R. Benson **Second:** R. Niemeier

Approved by Chair: [signature] **DFO:** Paul S. [signature] **Date:** 3/17/97

Comments: