National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 18 Highlights
U.S. Department of Transportation
DOT Headquarters/Nassif Building, Rooms 8236-40
400 7th Street, S.W., Washington, D.C.
July 26-28, 2000

INTRODUCTION

Welcoming remarks were conveyed by Roger Garrett, AEGL Program Director. There was a brief discussion regarding the inclusion in the meeting highlights of *Federal Register* comments and their disposition. It was emphasized that the summaries should reflect important highlights but not become voluminous. If extensive statements are required by a NAC/AEGL member, that individual should prepare the statement and submit it to ORNL for inclusion in the NAC/AEGL meeting highlights.

The meeting highlights for the NAC/AEGL meeting no. 17 were discussed. Following discussions on some technical points and editorial adjustments, the highlights were approved (Appendix A).

The highlights of meeting no. 18 are presented below, and the meeting agenda (Attachment 1) and attendee list (Attachment 2) are attached.

GENERAL INTEREST ITEMS

Standing Operating Procedures (SOP) and Final AEGL Technical Support Documents (TSDs)
The final versions of the SOP and TSDs for six chemicals have been prepared and submitted to the National Academy of Sciences (NAS) Committee on Toxicology (COT) Subcommittee on AEGLs. The TSDs include: aniline, arsine, hydrazine, methyl hydrazine and dimethyl hydrazine (1,1- and 1,2-dimethyl hydrazine isomers). These are tentatively scheduled to be published by the NAS in two volumes (SOP and TSDs) in late October. The publication will be in hardcopy form as well as on the National Academy Sciences website. Additionally, there were comments indicating concern that published SOPs will exist but that they may also change as needed. A statement will be in place to note that the SOPs can, in fact, be revised if necessary as future experience might suggest. Additionally, the SOPs and TSDs will be published in the journal, *Inhalation Toxicology*.

Margaret Whittaker (Weinberg Group, representing the Fertilizer Institute) presented comments (Attachments 3 and 4) on the SOPs. Most of the comments addressed issues/concerns previously addressed by the NAS/COT subcommittee or by the NAC/AEGL.

Paul Tobin provided information regarding the forthcoming AEGL internet site (Attachment 5) and solicited comments for the chemical priority list. It was requested that NAC members submit any comments/suggestions to Paul Tobin in a timely fashion.

The fact that "ceiling" was a troublesome term for the NAS/COT was briefly discussed. It was noted that Ernest Falke had provided alternate phrasing in the SOPs in response to comments that were submitted to him.

CHEMICAL-SPECIFIC STATUS UPDATES

Hydrogen cyanide

Discussions regarding the AEGL-1 for HCN focused on the need for AEGL-1 values and the most appropriate method for obtaining these values was presented by Sylvia Talmage (Attachment 6). It was the consensus of the NAC/AEGL to develop AEGL-1 values and to scale the values from an 8-hr TWA of 1 ppm. Because exponential extrapolation using an n=3 (as opposed to scaling from 30 minutes to 10 minutes) was consistent with the SOPs and because HCN is a cumulative toxicant, the following AEGL-1 values were accepted by a motion made by Richard Neimeier and second by Steven Barbee: (YES: 15; NO: 4; ABSTAIN: 0) (Appendix B). These were based upon a 3-ppm NOAEL (8 hours duration) and a total uncertainty factor adjustment of 3 for sensitive individuals.

INTERIM AEGL-1 VALUES FOR HYDROGEN CYANIDE					
AEGL Tier	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm

However, there was a concern from the NAC/AEGL regarding the absence of the human exposure data in the TSD which reported on the Leeser et al. 1990 study. Following a brief discussion, it was decided to make the human exposure data available and revisit this issue at the NAC/AEGL-20 meeting (January 2001).

Hydrogen fluoride

Larry Gephart and Sylvia Talmage opened the discussion by revisiting the AEGL values for hydrogen fluoride (Attachments 7 and 8). Larry Gephart stated that data from the Dalbey study could serve as the basis for the 10- and 30-minute AEGL-2 and -3 values and the Rosenholtz study could be used for longer durations. Sylvia Talmage noted that there was no actual pulmonary irritation noted in the Lund et al. (1999) study; and, therefore, the human data are indicative of a NOAEL. Richard Thomas stated that the bronchoalveolar lavage fluid is a sensitive biomarker of inflammation but it would be subclinical. Following additional discussion, the AEGL-1 values of 1 ppm for 10 minutes, 30 minutes, and 1 hour, and 0.5 ppm for 4- and 8-hours were accepted (motion made by Richard Thomas; seconded by Richard Niemier. Vote: YES: 14; NO: 4; ABSTAIN: 1) (Appendix C). For AEGL-2 and AEGL-3, Larry Gephart stated that data from the Dalbey study could serve as the basis for the 10- and 30-minute values, and the Rosenholtz study could be used for longer durations. However, the NAC decided not to update the 30-minute values with the Dalbey data. All of the previously accepted AEGL-2 and AEGL-3 values were moved to interim status. A motion was made by George Alexeeff (seconded by Bob Benson) to accept the values shown in the following table passed (YES: 15; NO: 5; ABSTAIN: 0) (Appendix C). The revised TSD will be resubmitted to the NAS/COT for review.

INTERIM AEGL VALUES FOR HYDROGEN FLUORIDE					
AEGL Tier	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	1 ppm	1 ppm	1 ppm	0.5 ppm	0.5 ppm
AEGL-2	95 ppm	34 ppm	24 ppm	12 ppm	8.6 ppm
AEGL-3	170 ppm	62 ppm	44 ppm	22 ppm	13 ppm

DEVELOPMENT OF 10-MINUTE AEGLS

In response to the need for 10-minute AEGLs, TSDs were revised to incorporate the development of 10-minute AEGLs. These values were developed by assessing data available for time periods less than 30 minutes, by temporal extrapolation from exposure with durations of 4 hours or less, or by equating to previously established 30-minute AEGLs. The 10-minute AEGLs and their rationales were presented by ORNL staff scientists or the chemical managers. Discussions were focused primarily on the newly derived 10-minute values and their relational consistency with the previously derived AEGLs.

Acrolein

Cheryl Bast and Ernest Falke presented the 10-minute AEGLs and their respective rationales. For the 10-minute values, the exposure concentrations were held constant to reflect the straight-line extrapolation (from a 1-hour exposure duration) and applied to the other time periods. There was discussion regarding the key study endpoint of ocular irritation and its applicability to an AEGL-2. The resulting 10-minute AEGLs were 0.030 ppm, 0.44 ppm, and 6.2 ppm for AEGL-1, -2, and -3, respectively. A motion was made by John Hinz (seconded by Mark McClanahan) to accept these values passed (YES: 12; NO: 5; ABSTAIN: 0). (Appendix D)

Chlorine trifluoride

Sylvia Talmage provided rationales for proposed 10-minute AEGLs derived by time scaling from the 30-minute values (Attachment 9). Several different approaches for development of the 10-minute values were discussed: (1) time scale for all AEGL levels, (2) time scale AEGL-3 but set the AEGL-1 values equal to that of AEGL-2; (3) time scale AEGL-2 and AEGL-3, but set the AEGL 10- and 30-minute values the same. A motion was made by Ernest Falke (seconded by John Hinz) to adopt 10-minute AEGL-1, -2, and -3 values using approach # 2 of 0.70 ppm, 6.2 ppm, and 81 ppm, respectively. This is because the data was not sufficient to allow extrapolation from a longer time period. The motion passed (YES: 14; NO: 3; ABSTAIN: 2). (Appendix E)

Epichlorohydrin

Nancy Kim provided the rationale for development of 10-minute AEGLs for epichlorohydrin. For the AEGL-1 and AEGL-2 tiers, the 10-minute values were set equal to the 30-minute values. Due to concerns regarding the magnitude of the difference between the 30-minute and resulting 10-minute value for AEGL-3, an exponential extrapolation using the derived *n* value of 0.87 was applied for the 10-minute AEGL-3. Although a motion was made to accept all of the 10-minute values, concerns regarding the relationship between some the proposed values and the existing TLV, and the fact that AEGL-1 was based on odor threshold, necessitated withdrawal of the motion. Following discussion, a motion was made by Tom Hornshaw (seconded by Ernest Falke) to accept the values (5 ppm, 53 ppm and 570 ppm, respectively, for AEGL-1, -2, and -3; voting on each tier separately). The motion passed separately (AEGL-1: YES: 19; NO: 1; ABSTAIN: 0; AEGL-2: YES: 17; NO: 2; ABSTAIN: 0; AEGL-3: YES: 17; NO: 2; ABSTAIN: 0). (Appendix F)

Ethyleneimine

Mark McClanahan provided the rationale for development of 10-minute AEGLs for ethyleneimine (Attachment 10). No AEGL-1 values were developed due to lack of data for this chemical; and, therefore, there was no basis with which to develop a 10-minute AEGL-1. For AEGL-2 and AEGL-3, the 10-minute values of 33 ppm and 48 ppm, respectively were based on predominately using the ethylenemine comparative mortality data that demonstrates that propylenemine appears to be one-fifth as toxic with a modifying factor of 2 recognizing the data deficiency. The motion was made by Larry Gephart and second by John Hinz. The motion passed unanimously (YES: 25; NO: 0; ABSTAIN: 0). (Appendix G)

Ethylene oxide

No AEGL-1 values were developed for ethylene oxide because the odor threshold and concentrations causing mild sensory irritation would be above the AEGL-2 levels. For AEGL-2 and -3, the 10-minute values were set equal to the respective 30-minute values because the key studies (Snelling et al., 1982a and Jacobson et al., 1956) used to derive a time scaling exponent (*n*) were of 4- and 6-hour durations. The proposed 10-minute values for AEGL-2 and -3 were 80 ppm and 360 ppm, respectively. A motion to accept these values was made by John Hinz (seconded by Mark McClanahan). The motion passed separately (vote: AEGL-1: YES: 18; NO: 0; ABSTAIN: 0; AEGL-2: YES: 16; NO: 1; ABSTAIN: 1; AEGL-3: YES: 11; NO: 6; ABSTAIN: 0). (Appendix H)

Isobutyronitrile

Cheryl Bast provided an overview of the AEGL values for this chemical. No AEGL-1 values were developed for isobutyronitirile due to insufficient data. Because the key study used in the development of the AEGL-2 and -3 values was a repeated dose protocol, the 10-minute values for both of these AEGL tiers was time scaled from the respective 30-minute values. The resulting 10-minute AEGL-2 and -3 values were 13 ppm and 40 ppm, respectively. A motion to accept these values was made by Bob Benson (seconded by Richard Thomas). The motion passed unanimously (YES: 19; NO: 0; ABSTAIN 0). (Appendix I)

Methacrylonitrile

Cheryl Bast provided an overview of the AEGL values for this chemical. No AEGL-1 values were developed for methacrylonitirile due to insufficient data. Because the key study used in the development of the AEGL-2 and -3 values was of 4-hour duration, the 10-minute values for both of these AEGL tiers was set equal to the respective 30-minute values: 10-minute AEGL-2 = 1.5 ppm, 10-minute AEGL-3 = 4.5 ppm. A motion to accept these values was made by Richard Niemeier (seconded by John Hinz). The motion passed (YES: 16; NO: 1; ABSTAIN 0). (Appendix J)

Peracetic acid

Mark McClanahan provided an overview of the proposal for 10-minute AEGL values for peracetic acid. The AEGL-1 and -2 values were collinear; and, therefore, the 10-minute values were developed similarly at 0.17 ppm and 0.50 ppm, respectively. The 10-minute AEGL-3 values were developed by exponential extrapolation using an empirically derived *n* of 1.6. The resulting 10-minute AEGL-3 of 19 ppm was proposed. A motion to adopt these values was made by Larry Gephart (seconded by Bob Benson). The motion passed (Vote: AEGL-1: YES: 15; NO: 1; ABSTAIN: 0; AEGL-2: YES: 16; NO: 0; ABSTAIN: 0; AEGL-3: YES: 13; NO: 3; ABSTAIN: 0). (Appendix K)

Phosgene

No AEGL-1values were developed for phosgene because the odor threshold is above the toxicity level. The proposed 10-minute value for AEGL-2 (0.60 ppm) was collinear with the 0.60 ppm 30-minute value

The key study (Gross et al. 1965) utilized a 90-minute exposure duration because the same exposure concentration produced similar toxic effects at both 10- and 30 minutes. For AEGL-3 the 10-minute value of 3.6 ppm was developed by exponential extrapolation. A motion to adopt these values was made by John Hinz (seconded by Larry Gephart). The motion passed (AEGL-1: YES: 18; NO: 0; ABSTAIN: 0; AEGL-2: YES: 17; NO: 1; ABSTAIN: 0; AEGL-3: YES: 17; NO: 0; ABSTAIN: 1). (Appendix L)

Proprionitrile

Cheryl Bast reviewed the AEGL values for this chemical. No AEGL-1 values were developed for proprionitrile due to insufficient data. For AEGL-2 and -3, 9.6 ppm and 51 ppm (equal to respective 30-minute values) were proposed for 10-minute values. A motion to accept these values was made by John Hinz (seconded by Richard Niemeier). The motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix M).

Propyleneimine

Mark McClanahan provided the rationale for development of 10-minute AEGLs for propyleneimine (Attachment 11). No AEGL-1 values were developed for this chemical because of the lack of available data . The 10-minute AEGL-2 and -3 values were based upon a relative toxicity comparison with ethyleneimine (propyleneimine considered to be approximately 5-fold less toxic but modifying factor of 2 applied for deficient data). A motion was made by John Hinz (second by Richard Niemeier) to accept 83 ppm and 167 ppm, respectively, for the 10-minute AEGL-2 and -3. The motion passed (AEGL-1: YES: 17; NO: 1; ABSTAIN: 0; AEGL-3: YES: 16; NO: 2; ABSTAIN: 0). (Appendix N)

RESPONSE TO COMMENTS ON THE *FEDERAL REGISTER* NOTICE

Discussions were held regarding comments (Attachment 12) on the *Federal Register* notice of June 23, 2000, for allylamine, cyclohexylamine, crotonaldehyde, dimethyldichlorosilane, ethylendiamine, hydrogen chloride, methyl isocyanate, iron pentacarbonyl, nickel carbonyl, methyltrichlorosilane, phosphine, and 2,4 and 2,6-toluene diisocyanate. Cheryl Bast collated comments from the submitted letters and the comment dispositions are summarized in the following sections.

Allylamine

There were no comments received for this chemical. Allylamine was elevated to Interim status. (Appendix O)

Crotonaldehyde (*cis*- and *trans*-)

No comments were received for this chemical. The AEGLs for this chemical were elevated to Interim status. (Appendix O)

Cyclohexylamine
There were no comments received for this chemical. Cyclohexylamine was also elevated to Interim status. (Appendix O)

Dimethyldichlorosilane
The Air Quality Division, Michigan Department of Environmental Quality, noted concerns about the interspecies uncertainty factor used for developing the AEGLs for hydrogen chloride upon which was based the AEGLs for dimethyldichlorosilane (issue addressed under hydrogen chloride discussion). A similar concern was expressed by John Morawetz of the International Chemical Workers Union (ICWU) with respect to data for guinea pigs. The NAC indicated these data were given consideration but that the rationale for the uncertainty factor will be enhanced in the TSD. A motion was made by John Hinz (seconded by Mark McClanahan) to re-affirm the AEGLs for dimethyldichlorosilane. (Appendix P)

Ethylenediamine
A comment was received by the Air Quality Division, Michigan Department of Environmental Quality, regarding the sensitization potential associated with this chemical. This is an issue that the NAC/AEGL had previously considered, noting that it is difficult to incorporate the potential for this effect into a single exposure situation. Furthermore, the NAC considered that previously sensitized individuals as hypersensitive responders (that the AEGLs may not protect these individuals will be incorporated into the Executive Summary of the TSD). The AEGLs were re-affirmed and elevated to interim status. (Appendix Q)

Hydrogen chloride
The Air Quality Division, Michigan Department of Environmental Quality, expressed concern regarding the appropriateness of the interspecies uncertainty factor of 3 for the rat data used in the development of the AEGLs. In the course of development of the AEGLs, this was given consideration by the NAC. As required, the TSD will be modified to reflect such consideration. The NAC voted (motion was made by John Hinz and second by Mark McClanahan) to re-affirm the AEGLs. (Appendix R)

Iron pentacarbonyl
No comments were received for this chemical. The AEGLs for this chemical were elevated to interim status. (Appendix O)

Methyl isocyanate
In response to a comment by the Air Quality Division, Michigan Department of Environmental Quality, suggesting derivation of the AEGL-1 value by reduction in AEGL-2 values, the NAC responded by noting that this is an not a accepted procedure. Additionally, concerns expressed by the Metam-Sodium Task Force regarding body weight changes and cardiac effects had been previously considered by the NAC during deliberations on this chemical. This would be clarified in the TSD and Loren Koller would draft a letter to the Task Force with respect to these issues. A motion was made by John Hinz (seconded by Mark McClanahan) to re-affirm the AEGLs for methyl isocyanate and elevated them to interim status. (Appendix S)

Methyltrichlorosilane
As for dimethyldichlorosilane, representatives from the Air Quality Division, Michigan Department of Environmental Quality and the ICWU noted concerns about the interspecies uncertainty factor used for developing the AEGLs for hydrogen chloride upon which was based the AEGLs for dimethyldichlorosilane (issue addressed under hydrogen chloride and dimethyldichlorosilane discussions). (Appendix T)

Nickel carbonyl
No comments were received for this chemical. The AEGLs for this chemical were elevated to interim status. (Appendix O)

Phosphine
A significant number of *Federal Register* comments similar to those previously made by the COT were received for phosphine. These included selection of the appropriate key study for AEGL-2 values, the appropriate exponent '*n*' for time scaling, and the selection of the interspecies uncertainty factor. The AEGL Development Team (Falke, Bast, Benson, McClanahan, and Morawetz) will come to the NAC/AEGL meeting 20 (January 2001) with two options: one will be to keep the number as proposed in the *Federal Register*. Another option will be to change it as proposed by the AEGL Development Team prior to the meeting. ORNL will send the original TSD as published in the *Federal Register* along with the proposed version. In a cover letter the AEGL Development Team should state what they propose to do to respond to the public and committee comments.

2,4- and 2,6-Toluene diisocyanate
Comments from the Air Quality Division, Michigan Department of Environmental Quality, focused on the potential for sensitization and the validity of the time scaling exponent. As discussed for ethylenediamine, the sensitized individual is considered a hypersensitive responder; this will be noted in the revised TSD with a more thorough justification for the time scaling exponent. A motion was made by Mark McClanahan (seconded by John Hinz) to re-affirm the AEGL values and make the noted modifications in the TSD. (Appendix U)

AEGL PRIORITY CHEMICALS

Several additional priority chemicals were also addressed including acetone cyanohydrin, acrylic acid, methanol, and several chemical warfare agents (the nerve agents GA, GB, GD, GF and VX).

Acetone cyanohydrin
CAS Reg. No. 75-86-5

Chemical Manager: Larry Gephart, ExxonMobil Biomedical Sciences, Inc.
Staff Scientist: Peter Griem, Forschungs- und Beratungsinstitut Gefahrstoffe GmbH

Peter Griem presented an overview of the data analysis pertinent to AEGL development for acetone cyanohydrin (Attachment 13). There was some concern expressed regarding the relationship between exposure, the rate of acetone cyanohydrin decomposition, and the red nasal discharge observed in the experimental and control groups of the test species. The AEGL-3 values were based on analogy to hydrogen cyanide but their development also involved consideration of lethality data from studies in rats using acetone cyanohydrin (Monsanto, 1986a), hydrogen cyanide (Blank, 1983) as well as data from human occupational exposure to cyanide (Blanc et al., 1985) The resulting AEGL-3 values (same as

those for HCN) were proposed by Nancy Kim (seconded by Richard Thomas) and approved by NAC/AEGL (YES: 14; NO: 2; ABSTAIN: 0) (Appendix Y). For AEGL-2, there was some discussion regarding the application of a database modifying factor but it was the consensus of the NAC/AEGL that this was not required. It was noted that the draft AEGL-2 values for HCN were set the same as AEGL-1 which are based on an endpoint that is of minimal severity for an AEGL-2 definition. Opposition to this contention indicated that the use of such an endpoint when chemical-specific data were available (respiratory distress; Monsanto, 1986a) was inappropriate. An alternate set of AEGL-2 values was proposed with a motion made by Bob Benson (second by Steven Barbee) based on a 6-hour exposure to 29.9 ppm that produced no respiratory distress in the test species. The motion passed (YES: 17; NO: 1; ABSTAIN: 0) (Appendix V). There was additional validation for the AEGL-2 values because on a molar basis they are similar to those for HCN. For AEGL-1, there was discussion regarding determination of a NOAEL, uncertainty factor application, and time scaling in reference to the observed red nasal discharge in rats (Monsanto, 1986 a,b). Following discussion and evaluation of several proposals, a motion was made by Ernie Falke (seconded by Richard Niemeier) to use 9.2 ppm for 6 hours as a NOAEL (Monsanto, 1986a), total uncertainty factor of 10 (3x3), a modifying factor of 2 for the data set, and time scaling using an *n* of 3 and 1. The motion passed (YES: 19; NO: 0; ABSTAIN: 0) (Appendix V). The proposed AEGLs for acetone cyanohydrin are shown in the following table:

SUMMARY OF PROPOSED AEGL VALUES FOR ACETONE CYANOHYDRIN					
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	1.1 ppm	1.1 ppm	0.84 ppm	0.53 ppm	0.35 ppm
AEGL-2	6.8 ppm*	6.8 ppm*	5.4 ppm	3.4 ppm	2.2 ppm
AEGL-3	27 ppm	21 ppm	15 ppm	8.6 ppm	6.6 ppm

*Correction: Due to minor calculation error in the Appendix A, the values are 6.8 ppm for the 10-minute and 30-minute period.

Acrylic acid
CAS Reg. No. 79-10-7

Chemical Manager: Ernest Falke, U.S. EPA
Staff Scientist: Peter Griem, Forschungs- und Beratungsinstitut Gefahrstoffe GmbH

Peter Griem presented the data summary and development of the draft AEGL values (Attachment 14). For the AEGL-1, discussion focused on the use of odor or ocular irritation as a critical endpoint. It was the consensus of the NAC/AEGL that odor recognition with potential for slight ocular irritation were appropriate endpoints for AEGL-1. A motion was made by Richard Thomas (seconded by Richard Neimeier) to accept the 1 ppm as the AEGL-1 for all time periods passed (YES: 12; NO: 6; ABSTAIN: 2) (Appendix W). Following discussions, the NAC/AEGL considered AEGL-2 values based on a 75-ppm minimum irritation level in a single 6-hour exposure study in rats (Frederick et al., 1998), a total uncertainty factor of 10 (3 for intraspecies and 3 for interspecies) and use of an empirically derived time scaling factor of 1.8 from lethality data. A motion was made by Richard Thomas and seconded by Bill Bress to adopt the resulting AEGL-2 values (YES: 16; NO: 3; ABSTAIN: 0)

SUMMARY OF PROPOSED AEGL VALUES FOR ACRYLIC ACID

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm
AEGL-2	30 ppm	30 ppm	20 ppm	9.4 ppm	6.4 ppm
AEGL-3	480 ppm	260 ppm	180 ppm	85 ppm	58 ppm

For AEGL-3, an animal lethality study (Hagan and Emmons, 1998) in which exposure of rats to acrylic acid aerosol resulted in death caused by lung damage, was discussed. The results of the aerosol study are supported by vapor studies in animals. Proposed AEGL-3 values were derived with a time scaling exponent of $n = 1.8$ calculated from the data of the key study and a total uncertainty factor of 10 (3 for intraspecies and 3 for interspecies) as 480- 260-, 85-, and 58 ppm to 10 minute, 30 minutes, and 1-, 4-, and 8-hours, respectively. A motion was made by Bob Benson (seconded by Thomas Sobotka) to adopt the proposed AEGL-3 values. The motion passed (YES: 18; NO: 1; ABSTAIN: 0) (Appendix W).

Methanol, CAS Reg. No. 67-56-1

Chemical Manager: Ernest Falke, U.S. EPA
Staff Scientist: Peter Griem, Forschungs- und Beratungsinstitut Gefahrstoffe GmbH

Peter Griem presented an overview of the data analysis pertinent to AEGL development for methanol (Attachment 15). An extensive discussion was held focusing on concern over developmental toxicity in laboratory animals, the relevance of electroencephalogram alterations in humans, and the suitability of occupational exposure studies for AEGL derivation. A motion was made by Loren Koller (seconded by Richard Niemeier) to accept the AEGL-1 values as proposed in the draft TSD using the NOAEL in humans of 800 ppm for 8 hours (Batterman et al., 1998). A total uncertainty factor of 3 for intraspecies variability was utilized, and time extrapolation was done with $n = 3$ (default value) for the 30-minute 1-, and 4-hour time points. The 30-minute value was adopted as the 10-minute value. The motion passed (YES: 15; NO: 0; ABSTAIN: 0) (Appendix X). Since for lethality large species difference exist, the use of human oral data was discussed. On the basis of a measured blood-methanol concentration of 730 mg/L, 10 hours after intoxication (Naraqi et al., 1979), the lowest lethal peak blood concentration of 1109 mg/L was calculated using Michaelis-Menten kinetics. To this blood-methanol concentration a LOEL-NOEL extrapolation factor of 2 and an intraspecies uncertainty factor of 3 were applied because of the steep dose-response relationship reported for rhesus monkeys, and, because conservative assumptions were made in the calculation of peak (human) blood concentrations. Application of the total adjustment factor of 6 resulted in a blood concentration of 185 mg/L. This blood concentration was transformed into exposure concentrations for relevant time periods using pharmacokinetic modeling. Exposure concentrations of 15,000-, 7,900-, 2,500-, and 1,600 ppm were calculated for periods of 30 minutes, 1-, 4-, and 8 hours. The 30-minute value was adopted as the 10-minute value, because at the 10-minute concentration calculated using the pharmacokinetic model additional effects by other mechanisms of action could not be excluded and the value was close to the explosive limit in air. Loren Koller made a motion (seconded by Steve Barbee) to accept AEGL-3 values as proposed in the draft TSD. The motion passed (YES: 14; NO: 0; ABSTAIN: 3) (Appendix X). A motion was made by Bob Benson (seconded by Mark McClanahan) to accept AEGL-2 values based on a NOEL for mouse fetal malformations after a 7-hour exposure resulting in a blood-methanol concentration of 487 mg/L (Rogers et al., 1983; 1995; 1999).

An intraspecies UF of 10 was applied and an interspecies uncertainty factor of 1 was applied based on pharmacokinetic modeling. The resulting blood concentration of 48.7 mg/L was transformed into exposure concentrations for relevant time periods using pharmacokinetic modeling. The motion passed for the 30-minute, 1-, 4-, and 8-hour values (YES: 17; NO: 0; ABSTAIN: 0) (Appendix X). The motion did not pass for the 10-minute values (YES: 10; NO: 7; ABSTAIN: 0) (Appendix X). Zarena Post then made a motion (seconded by John Hinz) to adopt the 30-minute AEGL-2 value as the 10-minute value. This motion passed (YES: 11; NO: 6; ABSTAIN: 0) (Appendix X).

SUMMARY OF PROPOSED AEGL VALUES FOR METHANOL					
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	670 ppm	670 ppm	530 ppm	340 ppm	270 ppm
AEGL-2	4000 ppm	4000 ppm	2100 ppm	720 ppm	510 ppm
AEGL-3	15,000 ppm	15,000 ppm	7900 ppm	2500 ppm	1600 ppm

Nerve Agents
Agent GA CAS Reg. No. 77-81-6
Agent GB CAS Reg. No. 107-44-8
Agent GD CAS Reg. No. 96-64-0
Agent GF CAS Reg. No. 329-99-7

Chemical Manager: John Hinz, U.S. Air Force
Staff Scientist: Annetta Watson, ORNL

Introductory remarks by Veronique Hauschild, U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM), delineated the need and urgency for AEGLs for these agents (Attachment 16). The U.S. Army Office of the Surgeon General (OTSG), of which the USACHPPM is a part, wishes to facilitate the incorporation of agent AEGLs into emergency preparedness planning for communities hosting domestic stockpiles of obsolete chemical munitions. Annetta Watson presented general information on the G agents as well as an overview of the pertinent data and logic used in developing AEGL values for these agents (Attachment 17). Information was provided on the physico-chemical characteristics of the G agents, mechanism of toxicity, and the signs/symptoms associated with exposures to these agents. An overall summary of lethal and nonlethal toxicity was presented (Attachment 18). Discussions ensued regarding monitoring of cholinesterases and various toxicity endpoints. Dr. Ursula Gundert-Remy, Head of the Chemical Risk Assessment Department of the German Federal Institute for Consumers Health Protection and Veterinary Medicine, pointed out that signs such as miosis and rhinorrhea were a more stable toxicological effect than ChE depression, which is highly variable in humans. This observation was based on Dr. Gundert-Remy's experience regarding organophosphate pesticide poisonings and cholinesterase monitoring in agricultural areas of Germany. Annetta Watson presented the approach used to develop the draft AEGL values for these agents, but the NAC did not deliberate regarding adoption of values due to concerns that there was insufficient review time and a request by the chemical manager to allow time for a more extensive service-wide review. Further deliberations on the nerve agent AEGLs were tabled until the next NAC meeting.

Action Item: The NAC/AEGL Chairperson instructed NAC/AEGL members to have their review comments on the G-Agent TSD to the chemical manager and Annetta Watson by September 1, 2000.

So that nerve agent AEGLs could continue to be developed and adopted in a timely manner, the USACHPPM offered to sponsor and host a fall meeting of the NAC/AEGL. This invitation was accepted by the NAC/AEGL, and planning for dates in October and convenient meeting locations began.

Nerve Agent VX CAS Reg. No. 50782-69-9

Chemical Manager: Glenn Leach, U.S. Army, CHPPM
Staff Scientist: Annetta Watson, ORNL

Annetta Watson presented general information on Agent VX as well as an overview of the pertinent data and logic used in developing AEGLs for this chemical (Attachment 19). As for the G-agents, deliberations were tabled until the next meeting.

Action Item: The NAC/AEGL Chairperson instructed NAC/AEGL members to submit comments on the Agent VX TSD to the chemical manager and Annetta Watson by September 1, 2000.

Meeting highlights prepared by Bob Young and Po-Yung Lu, Oak Ridge National Laboratory.

LIST OF ATTACHMENTS

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

1. NAC/AEGL Meeting No. 18 Agenda
2. NAC/AEGL Meeting No. 18 Attendee List
3. Comments on the National Advisory Committee's Draft AEGL SOP
4. Evaluation of the NAC Draft AEGL SOP
5. Draft of AEGL Program Website
6. HCN: Consideration of AEGL-1 Values
7. Response to comments/summary of deliberations on HF AEGLs
8. HF: Response to Comments to *Federal Register*
9. Data analysis for Chlorine Trifluoride
10. Data analysis for Ethyleneimine
11. Data analysis for Propyleneimine
12. *Federal Register* Comments
13. Data analysis for Acetone Cyanohydrin
14. Data analysis for Acrylic Acid
15. Data analysis for Methanol
16. AEGLs for Chemical Warfare Agents
17. Issues for NAC/AEGL in Developing AEGLs for Nerve Agents
18. Data analysis for Nerve Agents (GA, GB, GD, and GF)
19. Data analysis for Nerve Agent VX

LIST OF APPENDICES

A. Approved NAC/AEGL-17 Meeting Highlights
B. Ballot for HCN
C. Ballot for HF
D. Ballot for Acrolein
E. Ballot for Chlorine trifluoride
F. Ballot for Epichlorohydrin
G. Ballot for Ethyleneimine
H. Ballot for Ethylene oxide
I. Ballot for Isobutyronitrile
J. Ballot for Methacrylonitrile
K. Ballot for Peracetic acid
L. Ballot for Phosgene
M. Ballot for Propionitrile
N. Ballot for Propylenimine
O. Ballot for Allylamine, Cyclohexamine, cis- & trans-Crotonaldehyde
P. Ballot for Dimethyldichlorosilane
Q. Ballot for Ethylendiamine
R. Ballot for HCl

S. Ballot for Methyl isocyanate
T. Ballot for Methyltrichlorosilane
U. Ballot for 2,4- & 2,6-Toluene diisocyanate
V. Ballot for Acetone cyanohydrin
W. Ballot for Acrylic acid
X. Ballot for Methanol

Attachment 1

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-18
July 26-28, 2000

U.S. Department of Transportation
DOT Headquarters/Nassif Building, Rooms 8236-40
400 7th Street, S.W., Washington, D. C.

AGENDA

Wednesday, July 26, 2000

10:00 AM	Introductory remarks and approval of NAC/AEGL-17 Highlights (George Rusch, Roger Garrett, and Paul Tobin)
10:15	Status of SOP manual and final TSDs (Roger Garrett and Ernie Falke)
10:30	Status of Internet site and chemical priority list (Paul Tobin)
10:40	Status of HCN-AEGL 1 (George Rodgers/Sylvia Talmage)
11:15	Acetone cyanohydrin (Larry Gephart/Peter Griem)
12:30 PM	Lunch
1:30	Acetone cyanohydrin (continued)
2:30	Status of Hydrogen fluoride–AEGL 2 & 3 (Larry Gephart/Sylvia Talmage)
3:00	Break
3:15	Review of 10-minute AEGLs ✦ Acrolein (Falke/Bast); Chlorine trifluoride (Benson/Talmage); Epichlorohydrin (Kim/Davidson); Ethylenimine (McClanahan/Davidson); Ethylene oxide (Alexeeff/Davidson); *i*-Butyronitrile (Falke/Bast); Methacrylonitrile (Falke/Bast); Peracetic acid (McClanahan/Davidson); Phosgene (Bress/Bast); Propionitrile (Falke/Bast); and Propyleneamine (McClanahan/Davidson).
5:15	Administrative matters
5:30	Adjourn for the day

Thursday, July 27, 2000

8:00 AM	Acrylic acid (Ernie Falke/Peter Griem)
10:15	Break
10:30	Overview of Nerve Agent G: GA, GB, GD, and GF (Annetta Watson)
11:30	Lunch
12:30 PM	Overview of Nerve Agent VX (Annetta Watson)
1:30	Methanol (Ernie Falke/Peter Griem)
3:00	Break
3:15	Methanol (continued)
4:30	Review and Discussions of Proposed AEGLs from *Federal Register* Notice (George Rusch, Ernest Falke) ✦ Allylamine (Koller/Milanez); Cyclohexamine (McClanahan/Milanez); Crotonaldehyde (Hansen/Milanez); Dimethyldichlorosilane (Falke/Bast); Ethylendiamine (McClanahan/Milanez); Hydrogen chloride (Hinz/Bast); Iron pentacarbonyl (Blackman/Young); Methyl isocyante (Koller/Forsyth); Methyltrichlorosilane (Falke/Bast); Nickel carbonyl (Blackman/Young); Phosphine (Falke/Bast); and 2,4 &2,6-Toluene diisocynate (Barbee/Forsyth).
5:30	Adjourn for the day

Friday, July 28, 2000

8:30 AM	Review and Discussions of Proposed AEGLs from *Federal Register* Notice (continued)
9:30	Uranium hexafluoride (George Rusch/Cheryl Bast)
10:30	Break
10:45	Uranium hexafluoride (continued)
12:00 PM	Adjourn meeting

NAC/AEGL-18 (C)

Attachment 2

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THE WEINBERG GROUP INC.

July 24, 2000

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Re: Comments on the National Advisory Committee's Draft AEGL SOP

Dear Drs. Rusch and Falke:

On behalf of The Fertilizer Institute, THE WEINBERG GROUP INC. has reviewed the National Advisory Committee's November 2, 1999 Draft Standard Operating Procedures (SOP) of the Acute Exposure Guideline Levels for Hazardous Substances (AEGLs). It is our understanding that AEGLs have been, and will continue to be developed, for approximately 400 chemicals that pose acute health hazards to most individuals in the general population, including sensitive individuals. Furthermore, it is our understanding that AEGLs are intended to be used for both regulatory and non-regulatory purposes, and will assist emergency responders in the development of emergency response plans, as well as the safe and adequate execution of emergency response actions.

THE WEINBERG GROUP critically evaluated the following aspects of the draft SOP:

1. The adequacy of the AEGL development and peer review process
2. The use of the benchmark concentration (BMC) approach over the traditional no observed adverse effect level (NOAEL) approach
3. Guidelines for the selection of health effects endpoints
4. Methodologies used to collect and interpret health effects and toxicological data

5. Rationale for not applying a dosimetry correction factor when extrapolating from animals to humans
6. Appropriateness of the selection of uncertainty and modifying factors
7. Appropriateness of the use of time-scaling factors.

We would like to communicate to the NAS AEGL Committee the conclusions of our review, and suggest revisions that could be made to improve the AEGL SOP. Our analysis of the draft SOP indicates that this document is in need of revision. Although the methodology proposed in the draft SOP is generally based on acceptable scientific principles and practices, the draft SOP falls short in terms of prescribing strict adherence to these principles and practices. The comment numbers listed below correspond to the seven key aspects of our review. Each comment section of this letter provides a brief introduction to the draft SOP section, and then elaborates upon our comments and/or suggested revisions.

COMMENTS

1. ADEQUACY OF THE AEGL DEVELOPMENT AND PEER REVIEW PROCESS (DRAFT SOP SECTION 1)

The AEGL development process prescribes four basic stages (i.e., Stage 1 - draft AEGLs, Stage 2 - proposed AEGLs, Stage 3 - interim AEGLs, and Stage 4 - final AEGLs). Public comment is solicited on an AEGL through publication in the *Federal Register* (Stage 2-proposed AEGLs), and consensus is reached, first by the NAC/AEGL Committee (Stage-1 and Stage-2), then by the NAS Expert Committee (Stage-3 and Stage-4). Although this process ensures that AEGLs are developed by consensus, and allows submission of comments by private industry, it is somewhat tedious, appears to inhibit speedy development of AEGLs, and is not a particularly open and transparent process.

Based on our review of this section of the draft SOP, we recommend three revisions:

- The exact proportion of the Expert Committee of the National Academy of Sciences (NAS Committee) required for consensus (e.g., 2/3 majority) should be specifically identified in the description of Stage-3: Interim AEGLs.

- The National Academy of Sciences should improve access to AEGL toxicity support documents (TSD), in addition to detailed AEGL committee meeting minutes (currently, meeting minutes are very short and contain few details). Ideally, all TSDs and AEGL committee meeting minutes should be available on the WWW as pdf files. Each stage of the process needs to be fully described and documented for each chemical under consideration.

- The draft SOP should be revised to require a regular review process for established AEGLs. In addition to determining whether new toxicity data have been generated for a specific chemical, the methods used to derive an AEGL should be evaluated on a regular basis (e.g., every three years).

2. COMMENTS ON THE USE OF THE BENCHMARK CONCENTRATION (BMC) APPROACH OVER THE TRADITIONAL NO OBSERVED ADVERSE EFFECT LEVEL (NOAEL) APPROACH (DRAFT SOP SECTION 2.2)

As defined by the U.S. EPA, a benchmark concentration (BMC) is the statistical lower confidence limit on a concentration that produces a predetermined change in response rate of an adverse effect compared to background (U.S. EPA 2000). A BMC is calculated by fitting a mathematical dose-response model to data using appropriate statistical procedures (U.S. EPA 1995). An AEGL is derived from a BMC through the incorporation of appropriate uncertainty factors, modifying factors, and time scaling factors.[1] The draft SOP states that the preferred approach to calculating a BMC will involve use of the BMC_{05}. For an acute lethality endpoint, a BMC_{05} would represent the 95% lower confidence limit at a specific chemical concentration that produces a 5% excess proportion of death.

Although used primarily by the regulatory community to derive chronic reference values, THE WEINBERG GROUP INC. agrees that the BMC approach is a valid method to derive acceptable acute exposure levels. In 1998, the U.S. EPA proposed using the BMC approach to develop 24-hour acute reference exposures (AREs).[2] Members of the U.S. EPA Science Advisory Board's Environmental Health Committee stated that use of the BMC approach, in addition to the traditional NOAEL approach, appeared to be appropriate for developing AREs (U.S. EPA 1998b). Alexeeff et al. (1993) employed a log-probit extrapolation of hydrogen fluoride dose-response data to calculate a BMC_{01}, which was used to derive a 1-hour reference exposure level. Fowles et al. (1999) estimated BMCs (at the 1, 5, and 10% response level) for 47 chemicals using data from 120 acute tests performed on rats, mice, guinea pigs, hamsters, rabbits, and dogs.

The draft SOP correctly states that the probit and Weibull models are the recommended BMC models for AEGL derivation. According to Fowles (1996), these models are the dominant models used in the evaluation of acute toxicity studies. The draft SOP does demonstrate

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[1] According to the draft SOP, the BMC approach will primarily be used to establish AEGL-3 levels, although its use to establish AEGL-1 and AEGL-2 levels will be considered on a chemical-by-chemical basis.

[2] An ARE is a chemical-specific acute exposure level estimate for noncancer effects (with uncertainty spanning an order of magnitude) that is not likely to cause adverse effects in a human population after exposure for up to 24 hours. The EPA developed the ARE methodology to support the needs of health risk assessments as specifically required by the Clean Air Act Amendments (U.S. EPA 1998a).

flexibility by allowing the use of other models to estimate BMCs, provided that the models adequately fit the experimental data.

The BMC approach is generally more conservative than the NOAEL approach (U.S. EPA 1995). As such, use of the BMC approach will likely result in lower AEGLs. Indeed, this was confirmed by Fowles et al. (1999), who determined that mean NOAEL/BMC_{05} ratios were 1.16 (using the probit model) and 1.59 (using the Weibull model). This means that Fowles et al.'s BMC_{05} estimates were, on average, 1.16-fold lower (using the probit model) and 1.59-fold lower (using the Weibull model) than their respective NOAELs.[3] In other words, if AEGLs were derived from BMC_{05} estimates in the Fowles et al. dataset, they would be lower than AEGLs derived using corresponding NOAELs. To date, the overwhelming majority of comparisons of the traditional NOAEL approach vs. the BMC approach have been performed on developmental toxicity datasets (*e.g.*, Allen et al. 1994, Barnes et al. 1995). These comparisons have identified greater differences in BMC/NOAEL ratios than the Fowles et al. dataset. Because these comparisons have examined developmental toxicity endpoints, as opposed to acute toxicity endpoints, they are not considered appropriate for determining whether the BMC approach should be used to derive AEGLs.

The Fowles et al. dataset indicates that BMC_{05} estimates are generally within an order of magnitude of NOAELs. The Fowles et al. dataset is somewhat limited in that the dataset comprised only 47 chemicals. However, many of the chemicals in Fowles et al.'s dataset (including ammonia) are on the NAC/AEGL list of chemicals for guideline development. An on-line database search identified no other comprehensive comparisons of BMCs and NOAELs derived from acute datasets.

Based on our review of this section of the draft SOP, the following revisions are recommended:

- It is recommended that the draft SOP be revised to require that AEGL-3s be derived using both the traditional NOAEL approach and the BMC approach. Results from each approach should be compared and contrasted, which would serve to generate more comparative data on the use of the BMC approach for acute health effects modeling. The scientific basis for a decision to set an AEGL for a specific chemical by one or the other method should be detailed in the AEGL documentation.

- The draft SOP should also be revised to reference more detailed guidance on the proper application and interpretation of BMC data to ensure that all members of the NAC/AEGL

[3] Fowles et al. also estimated BMC_{01} and BMC_{10} levels. Since the draft AEGL SOP specified that the BMC_{05} level be used to derive AEGLs (in the absence of other estimates, such as the estimate of the maximum likelihood estimate at the 1% response level), only results relating to the BMC_{05} are being discussed in this letter.

Review Committee are knowledgeable of the BMC approach and are not merely "rubber-stamping" AEGL derivations. For example, the following references should be cited in the draft SOP: U.S. EPA 1995, U.S. EPA 1996a, U.S. EPA 1996b, U.S. EPA 1997.

3. COMMENTS ON GUIDELINES FOR THE SELECTION OF HEALTH EFFECTS ENDPOINTS (DRAFT SECTION 2.3)

The draft SOP adequately establishes that AEGLs are clearly toxic levels, and are distinct from nontoxic exposure levels established from NOAELs. The AEGL SOP adequately communicates that derivation of AEGL-1, 2, and 3 values are demarcated by increasingly toxic effects (e.g., irritation→impaired pulmonary function→near (but not complete) lethality). The rationale used to select specific AEGLs was consistent with the increasing severity of effect AEGL-1, 2, and 3 paradigm established by the NRC (1993).

Based on our review of this section of the draft SOP, the following revisions are recommended:

- The AEGL SOP should be revised to require that AEGLs are established at an exposure level where an adverse health effect is expected, in contrast to an exposure level where no adverse health effect is expected.

- The AEGL SOP should be revised to require a discussion and justification demonstrating that the health effect endpoint chosen as the basis for an AEGL is appropriate, reasonable, and biologically significant.

4. COMMENTS ON METHODOLOGIES USED TO COLLECT AND INTERPRET HEALTH EFFECTS AND TOXICOLOGICAL DATA (DRAFT SOP SECTION 2.4)

This is one of the weakest sections of the draft SOP, and does not adequately stress that data collection must be exhaustive and complete in order to identify critical health effects endpoint(s) and study(ies). The draft SOP only mandates searching for relevant data in three on-line databases: Toxline, Toxline65, and NTIS. Such limited searching could result in key studies being overlooked.

The draft SOP specifically mentions that searching should be performed by Chemical Abstracts Service (CAS) registry number. Although searching by CAS number is extremely effective in on-line bibliographic databases (such as Toxline), it is not effective when searching in NTIS using the NTIS search engine (e.g., not all manufacturers provide CAS numbers with their TSCA submissions or voluntary EPA submissions).

The toxicity test evaluation guidelines (e.g., EPA Health Effects Testing Guidelines) specified in the draft SOP for evaluation and selection of key and supporting data are adequate. The draft SOP clearly indicates that older studies, although not meeting current regulatory guidelines, may be valuable in the derivation of AEGL values. Furthermore, this section of the draft SOP prescribes three important rules:

1. Only primary reference sources should be relied upon for key toxicity data
2. Bioassay guidelines used for study evaluation should be widely accepted (e.g., EPA Health Effects Testing Guidelines)
3. Toxicity data involving routes other than inhalation should only be used to derive an AEGL value when adequate data exist to perform a scientifically credible route-to-route extrapolation (see 2nd bullet/recommendation for Comment 3 above).

Based on our review of this section of the draft SOP, the following revisions are recommended:

- While it is recognized that time and resources are limited, the draft SOP should be revised to require an expanded database search, in order to include databases such as:

  RTECS, Toxlit, SciSearch, Occupational Safety and Health (NIOSHTIC), and OldMedline (In particular, OldMedline covers scientific literature from 1957-1965, and may identify older studies not indexed in newer databases. It can be accessed at http://igm.nlm.nih.gov/).

- The draft SOP should be revised to require mandatory tree-searching of bibliographies from all relevant primary and secondary references. "Tree-searching" involves reading an article's bibliography, and then identifying relevant publications cited in the bibliography based on the title or author. For purposes of identifying relevant toxicity data for derivation of an AEGL, tree-searching would be very important because it would likely identify some of the early published studies that would not be recorded in on-line databases.

- The draft SOP should be revised to state that NTIS searching should incorporate the use of CAS numbers as well as chemical names.

- The draft SOP should be revised to require use of the keyword LC_{50} when database searching.

- Finally, the draft SOP should be revised to provide specific guidance or criteria to be fulfilled as part of assigning confidence levels to key and supporting toxicity data and AEGL values. The draft SOP does not clearly explain how "high", "medium", or "low"

confidence levels should be assigned. Because each AEGL and TSD will be authored by different AEGL development teams, the assignment of confidence levels will likely be subjective. Therefore, it is important to provide as much direction as possible in order to minimize subjective assignment of confidence levels.

5. RATIONALE FOR NOT APPLYING DOSIMETRY CORRECTION FACTOR WHEN EXTRAPOLATING FROM ANIMAL TO HUMAN (DRAFT SOP SECTION 2.5)

Dosimetry corrections take into account the physiological differences between animals and humans, and adjust animal doses to predict human doses. Because dosimetric corrections for gases have not been validated with experimental data, the draft SOP does not require the use of dosimetric corrections across species. The draft SOP does allow for the use of dosimetric corrections in the event that "scientifically supportable" data are available for review. The draft SOP is correct in deciding not to prescribe the use of the U.S. EPA's RfC methodology for dosimetry correction. This methodology is not supported by empirical data, and can either overestimate or underestimate human health risk. Other potential dosimetric corrections, such as adjusting for minute volume to body weight ratios or using a cross species scaling factor ($mg/kg^{3/4}/day$), are either not appropriate for acute high exposure concentrations, or are cancelled out by other factors. We agree that dosimetry corrections are unjustified until experimental data specific to acute inhalation exposures exist to support empirically-derived dosimetric correction factors.

We have no recommendations to revise this section of the draft SOP.

6. COMMENTS ON THE APPROPRIATENESS OF THE PROPOSED GUIDELINES FOR THE SELECTION OF UNCERTAINTY AND MODIFYING FACTORS (DRAFT SOP SECTIONS 2.6 AND 2.7)

The uncertainty factors for interspecies and intraspecies extrapolation that are specified in the draft SOP are acceptable and based on standard risk assessment methodology. For example, the draft SOP requires use of an uncertainty factor of 10 for interspecies or intraspecies extrapolation in the absence of data. The use of such factors accounts for physiological and pharmacokinetic differences between animals and humans, as well as differences among individuals within the human population. The draft SOP clearly states that hypersusceptible people are not necessarily protected by these factors, which is in agreement with NRC (1993).

Based on our review of these two sections of the draft SOP, the following addition is recommended:

- Dourson et al. (1996) should be added as a reference in Section 2.7. This reference provides additional guidance on the selection of uncertainty and modifying factors.

7. APPROPRIATENESS OF THE INTERIM GUIDELINES CONCERNING THE USE OF TIME-SCALING FACTORS (DRAFT SOP SECTION 2.8)

Because AEGLs are derived for different exposure durations, extrapolation from an experimental exposure period to an equivalent concentration for an AEGL timeperiod is usually required. Historically, Haber's Rule has been used to relate exposure concentration and duration to a toxic effect: $C \times t = k$. This rule states that exposure concentration ("C") and duration ("t") may be reciprocally adjusted to maintain a cumulative constant (k) and that this constant will always reflect a toxic response. However, ten Berge et al. (1986) analyzed the results of acute inhalation toxicity experiments in animals and demonstrated that Haber's Rule does not apply to acutely toxic chemicals. Instead, the relationship was observed to be: $C^n \times t = k$, where n is an exponent that is often chemical-specific (e.g., for ammonia, the value of n was determined to be 2.0). In the absence of toxicological data for AEGL-specified exposure periods (*e.g.*, 10 minutes, 1 hour, 4 hours, or 8 hours), the draft SOP prescribes the use of empirically-derived values of n, or in the absence of empirically-derived n values, prescribes n values of 1 (when extrapolating from shorter to longer exposure periods) or 3 (when extrapolating from longer to shorter exposure periods) to extrapolate AEGL-2 and AEGL-3 values.[4] The use of time-scaling factors assumes that the value of n calculated from animal experiments is applicable to humans. This is a major assumption, but is somewhat akin to the assumption that animal models themselves are relevant for human health risk assessment. It appears that the regulatory community has embraced the use of time-scaling factors, and that it is an accepted means to adjust for different exposure timeperiods. For example, NIOSH now uses the $C^n \times t = k$ time-scaling factor in derivation of their immediately dangerous to life and health (IDLH) values (NIOSH 2000).

The draft SOP provides adequate guidance on the derivation of n values through the use of probit analysis. One problem that may arise in the future is that AEGL-2 values may be derived with n values that were based on lethality data. In fact, the AEGL SOP states that the value of n derived from lethality experiments has been typically applied to both the AEGL-2 and AEGL-3 exposure period extrapolations (pg. 60).

Based on our review of this section of the draft SOP, we recommend the following revisions:

- The NAC/AEGL Committee should make publicly available the probit analysis software provided to them by Dr. Wil ten Berge (described on page 61 of the draft SOP). With the

[4] The AEGL SOP does not recommend the derivation of AEGL-1 values using time-scaling factors.

probit analysis software, experimental data can be used to solve the equation: $Y = b_0 + b_2 \ln[C^n t]$, and identify the value of n (where $n = b_1/b_2$).

- Appendix F of the draft SOP should be revised to require complete justification for the selection and use of n values. For example, AEGL-2 levels derived with n values calculated from lethality data (*e.g.*, LC_{50} data) must address whether use of the n value is scientifically defensible. Such AEGLs would need to provide empirical data to justify that the mechanism of toxicity causing the health effect of concern at the AEGL-2 level is the same as that causing lethality.

We hope that these comments and suggestions serve to strengthen and improve the draft SOP. Thank you for the opportunity to provide comments to the NAS AEGL Committee.

Sincerely,

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DMW/ees

Attachment

CITED REFERENCES

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Evaluation of the NAC Draft AEGL SOP

July 26, 2000

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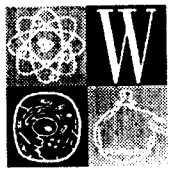
Senior Consultant
The Weinberg Group, Inc.



THE WEINBERG GROUP INC.

Attachment 4

At the request of The Fertilizer Institute, Dr. Dan Woltering and I critically evaluated seven aspects of the Draft AEGL SOP:

- The adequacy of the AEGL development and peer review process
- The use of the BMC approach over the NOAEL approach
- The SOP's guidelines for the selection of health effects endpoints
- The methods used to collect/interpret health effects data
- The SOP's rationale for not applying a dosimetry correction factor
- The appropriateness of the selection of UF and MF
- The appropriateness of use of time-scaling factors.

Critical Evaluation Letter

- The results of our critical evaluation were presented in a letter to Drs. Rusch and Falke on July 24, 2000.

Bottom Line of Our Critical Evaluation

- The methodology proposed in the draft SOP is generally based upon acceptable scientific principles and practices
- However, the draft SOP fails to prescribe strict adherence to these principles and practices
- On July 24, Dr. Dan Woltering and I sent a letter to Drs. Rusch and Falke that suggested numerous SOP revisions
- Today, I will briefly describe these revisions
  - Detailed explanations can be found in our 7/24 letter.

First Aspect: The Adequacy of the AEGL Development and Peer Review Process (SOP Section 1)

- We recommend three revisions to this SOP section:
  - The exact proportion of the NAS Expert Committee required for consensus should be specifically identified in the description of Stage-3: interim AEGLs
  - Access to AEGLs, TSDs, and committee meeting minutes should be improved
    - These documents should all be accessible on the WWW
  - A regular review process for AEGLs should be specified in the SOP in order to determine whether toxicity data and/or methodological data are still appropriate

Second Aspect: The BMC Approach over the NOAEL Approach (Section 2.2)

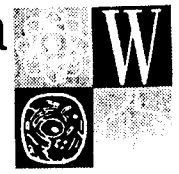
- We recommend two revisions this SOP section:
  - AEGL-3s should be derived using both the traditional NOAEL approach and the BMC approach
    - Results should be compared and contrasted
    - This would serve to provide comparative data on the use of the BMC approach for acute health effects modeling
  - The draft SOP should reference more detailed guidance on application and interpretation of BMC data
    - We cite four particularly useful U.S. EPA reports in our letter

Third Aspect: Guidelines for Selection of Health Effects Endpoints (Section 2.3)

- We recommend two revisions to this SOP section:
  - The draft SOP should require that AEGLs be established at an exposure level where an adverse health effect is expected (in contrast to a level where no adverse health effect is expected)
  - The draft SOP should require a discussion and justification demonstrating that the health effect endpoint is appropriate, reasonable, and biologically significant.

Fourth Aspect: Methodologies Used to Collect/Interpret Health Effect Data (Section 2.4)

- Five revisions are recommended to this SOP section:
  - An expanded database search must be required
    - RTECS, Toxlit, SciSearch, Occupational Safety and Health, and OldMedline must be searched
  - "Tree-searching" must be mandated
  - NTIS searching should require use of both CAS number and chemical name
  - The keyword "LC50" should be used when database searching
  - Better guidance/criteria should be provided as part of assigning confidence levels to key and supporting data
    - "High", "medium", or "low" confidence level assignments must be adequately explained.



Fifth Aspect: Rationale for Not Applying a Dosimetry Correction Factor (Section 2.5)

- We have no recommended revisions on this section of the draft SOP.

Sixth Aspect: Appropriateness of UF and MF Selection (Sections 2.6 and 2.7)

- We recommend that additional references be cited in this section of the SOP to provide additional guidance: Dourson et al. (1996).

Seventh Aspect: Appropriateness of Time-Scaling Factors (Section 2.8)

- We recommend two revisions to this SOP section:
  - The probit analysis software provided to the NAC AEGL Committee by Dr. Wil ten Berge should be made publicly available and downloadable via the WWW
    - This software would allow members of the public to derive "n" values and calculate their own time-scaling factors
  - Appendix F of the draft SOP should provide complete justification for the use and selection of "n" values
    - For example, are AEGL-2 values derived with "n" values calculated from lethality data scientifically defensible?

Conclusions

- Dr. Dan Woltering and I believe that our suggested revisions will improve risk assessment of acute health effects endpoints
- Dr. Dan Woltering and I would be happy to provide the Committee with additional explanations on any of our suggested revisions
  - Dawo@weinberggroup.com
  - Mewh@weinberggroup.com

Attachment 5

EPA United States Environmental Protection Agency

AEGL Program

Home
History
Stakeholders

AEGL Committee

Charter
Membership
AEGL Process
Meetings
AEGL Chemicals
SOP

AEGL Program

The Development of Acute Exposure Guideline Levels (AEGLs)

A collaborative effort of the public and private sectors worldwide

Acute Exposure Guideline Levels, or AEGLs, describe the dangers to humans resulting from short-term exposure to chemicals. The National Advisory Committee for AEGLs is developing these guidelines to help both federal and local authorities, as well as private companies, deal with emergencies involving spills, explosions or other accidental exposures.

[Metadata Record | AEGL Home]
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Last Revision: June 29, 2000
URL: http://www.epa.gov/opptintr/aegl/index.htm

EPA United States Environmental Protection Agency

AEGL Program

Home
History
Stakeholders

AEGL Committee

Charter
Membership
AEGL Process
Meetings
AEGL Chemicals
SOP

AEGL Program

History of Acute Exposure Guideline Levels (AEGLs)

This is the template for the history page.

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EPA United States Environmental Protection Agency

AEGL Program

Home
History
Stakeholders

AEGL Committee

Charter
Membership
AEGL Process
Meetings
AEGL Chemicals
SOP

AEGL Program

Stakeholders of Acute Exposure Guideline Levels (AEGLs)

The following organizations support the AEGL Program through one of more activities: funding, member representation, AEGL chemical nominations, and information resources.

Federal Government
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention
Department of Transportation
Mine Safety and Health Administration
National Institute for Occupational Safety and Health
U.S. Air Force
U.S. of Army
U. S. Navy

States
American Association of State and Territorial Health Officials
California
Illinois
Minnesota
New York
Texas Vermont

Industry
Arch Chemicals, Inc.
Exxon Biomedical Sciences, Inc.
Honeywell

Organizatgions
American Association of Poison Control Centers
American College of Emergency Physicians
American College of Occupational and Environmental Medicine
International Chemical Workers Union

[Metadata Record | AEGL Home]
[OPPT Home | EPA Home | Search | Comments]

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EPA United States Environmental Protection Agency

AEGL Program

Home
History
Stakeholders

AEGL Committee

Charter
Membership
AEGL Process
Meetings
AEGL Chemicals
SOP

AEGL Program

Charter of the National Advisory Committee for Acute Exposure Guidance Levels (AEGLs) for Hazardous Substances

1. Committee's Official Designation (Title):

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

2. Authority:

This charter renews the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL) in accordance with the provisions of the Federal Advisory Committee Act (FACA), 5 U.S.C. App § 9 (c). NAC/AEGL is in the public interest and supports EPA in performing its duties and responsibilities.

3. Objectives and Scope of Activities: Return to Top

The NAC/AEGL will provide advice, data, information and recommendations on the Acute Exposure Guideline Levels which can be used by federal, state and local agencies, the private sector and the international community for purposes of emergency planning, response and prevention activities related to the accidental release of hazardous substances. NAC/AEGL's recommended values will represent standardized national exposure guideline levels developed by a cross-section of the U.S. scientific community and international experts and based on the use of consistent methodology developed by the National Academy of Sciences.

The major objectives are to provide advice and recommendations to EPA on:

- Toxicology data presented in technical support documents prepared by contractors
- Technical scientific issues related to acute exposures to hazardous substances
- Development of Interim Acute Exposure Guideline Levels for chemical emergency planning, response and prevention programs related to chemical manufacture, processing, storage, and transportation and the remediation of governmental and industrial waste sites
- Identifying critical gaps in toxicological data and recommending that relevant acute toxicity studies be conducted through appropriate means to eliminate such data gaps
- Avoiding duplication of effort and cost by various federal and state regulatory agencies with the establishment of one standard, uniform set of short-term acute exposure limits

EPA United States Environmental Protection Agency

AEGL Program

Home
History
Stakeholders

AEGL Committee

Charter
Membership
AEGL Process
Meetings
AEGL Chemicals
SOP

AEGL Program

Membership

AEGL Program Director:
Roger Garrett, Ph.D.
U.S. EPA

AEGL Designated Federal Officer:
Paul S. Tobin, Ph.D.
U.S. EPA

AEGL Commiittee Members:
George Alexeeff, Ph.D.
California EPA

Steven Barbee, Ph.D.
Arch Chemicals, Inc.

Lynn Beasley, J.D.
U.S. EPA/Superfund

David Belluck, Ph.D.
Minnesota Department of Transportation

Robert Benson, Ph. D.
U.S. EPA Region VIII

Jonathan Borak, M.D.
American College of Occupational & Environmental Medicine

William Bress, Ph.D.
Vermont Department of Health

George Cushmac, Ph. D.
Department of Transportation

Ernest Falke, Ph.D.
U.S. EPA/Office of Pollution Prevention & Toxics

Larry Gephart
Exxon Mobil Biomedical Sciences, Inc.

John P. Hinz
U. S. Air Force

Jim Holler, Ph.D.
Agency for Toxic Substances & Disease Registry

Thomas C. Hornshaw, Ph.D.
Illinois Environmental Protection Agency

Nancy K. Kim, Ph.D.
New York State Department of Health

EPA United States Environmental Protection Agency

AEGL Program

Home
History
Stakeholders

AEGL Committee

Charter
Membership
AEGL Process
Meetings
AEGL Chemicals
SOP

AEGL Program

AEGL Development Process

AEGL Development Process (pdf -- 9K) - The development of AEGL values through the Federal Advisory Committee and stakeholder concept strives to accomplish the following process objectives:

1. Development of scientifically valid AEGL values for use in chemical emergency planning, prevention and response programs.
2. Comprehensive indentification of published and unpublished information sources used to set AEGLs.
3. Sharing resource burdens by stakeholder members.
4. Adoption of consistent emergency planning both domestically and internationally.
5. Transparency of program methods (Standard Operating Procedures) and information through public participation at meetings and by commenting on Federal Register notices.
6. Inclusion of National Academly of Sciences peer review and final arbitration of AEGL values and methods.

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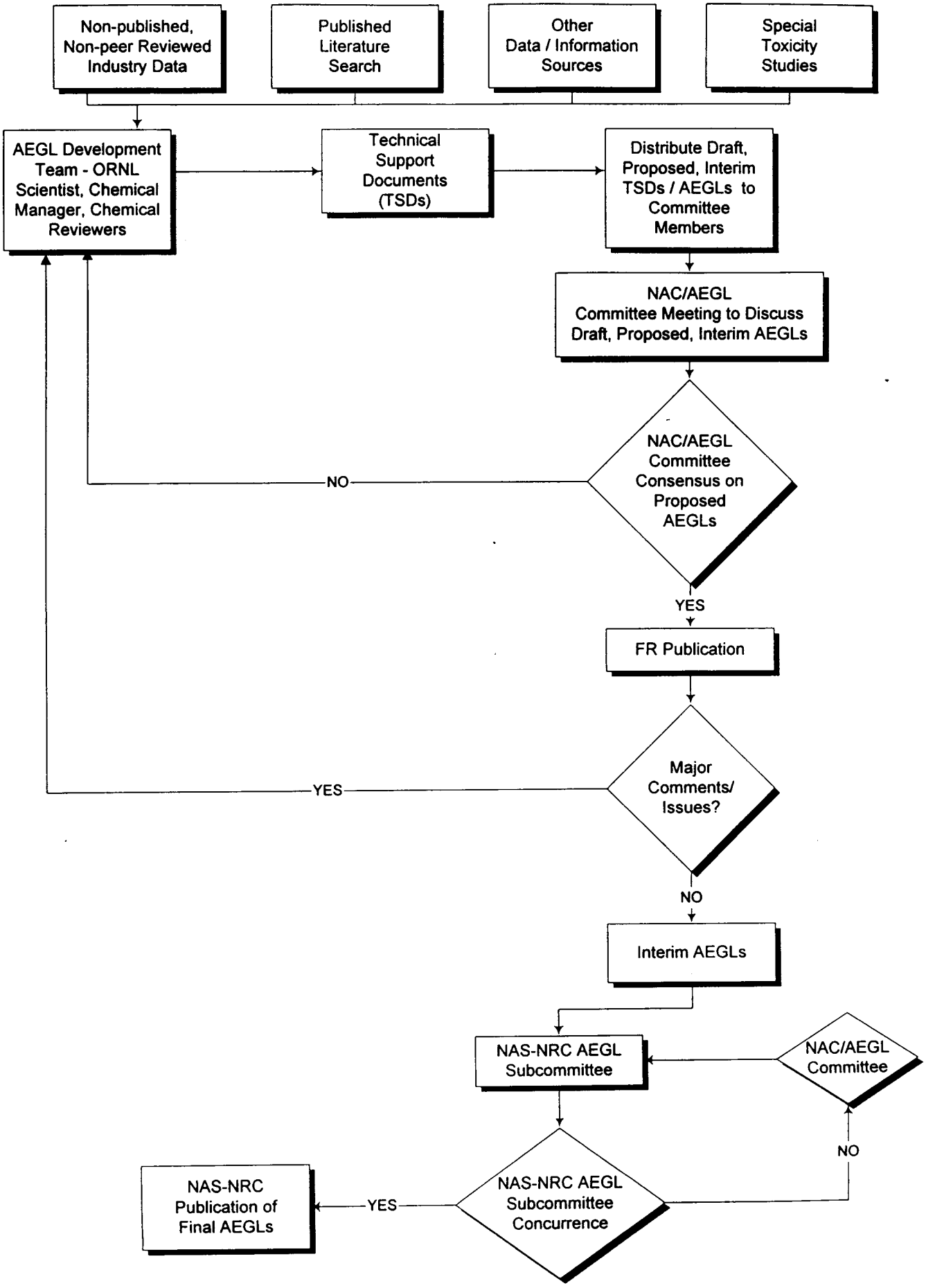
URL: http://www.epa.gov/opptintr/aegl/docs/process.htm

AEGL Development Process



EPA United States Environmental Protection Agency

AEGL Program

Home
History
Stakeholders

AEGL Committee

Charter
Membership
AEGL Process
Meetings
AEGL Chemicals
SOP

AEGL Program

Upcoming National Advisory Committee for Acute Exposure Guideline Levels (AEGLs) Meetings

Scheduled Meetings:

- July 26 - 28, 2000 (Washington, D.C.)
- October 18 - 20, 2000 (Washington, D.C.)
- December 04 - 06, 2000 (San Antonio, Texas)

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EPA United States Environmental Protection Agency

AEGL Program

Home
History
Stakeholders

AEGL Committee

Charter
Membership
AEGL Process
Meetings
AEGL Chemicals
SOP

AEGL Program

AEGL Chemicals

AEGL chemicals are listed alphabeticaly in the table below. A cross-reference by CAS number is also provided. CAS numbers for synonyms of AEGL chemicals can be identified at www.chemfinder.com from other sources.

The following fields are provided in the AEGL Chemical table:

D (Draft): Draft AEGLs have been proposed in draft AEGL Technical Support Documents, but have not yet been accepted by the National Advisory Committee for Acute Exposure Guideline Levels (NAC/AEGL Committee).

P (Proposed): Proposed AEGLs have been adopted by the NAC/AEGL Committee by a 23 majority ballot. Proposed AEGLs are not recommended for use in chemical emergency programs, since public comment has not yet been formally received via Federal Register announcement.

I (Interim): Interim AEGLs have been adopted by the NAC/AEGL Committee, following receipt and review of public comment on Proposed AEGLs that have been published in the Federal Register.

F (Final): Final AEGLs have been accepted by the Natonal Academy of Sciences, National Research Council, Committee on Toxicology, AEGL Subcommittee and published by the National Academy Press.

H (Holding): Holding AEGL chemicals are those for which the NAC/AEGL Committee has determined that insufficient information exists for setting AEGL values.

R (Remaining): Remaining AEGL chemicals are those on an AEGL Chemical Priority List that have yet been initiated through the AEGL Chmical Development Process

CAS NO.	CHEMICAL	Status	Results	FR Notice	TSD	NAS
107-02-8	Acrolein	P	L	L	L	
814-68-6	Acrylyl chloride	H				
107-18-6	Allyl alcohol	P	L	L	L	
107-11-9	Allyl amine	P	L	L	L	

EPA United States Environmental Protection Agency

AEGL Program

Home
History
Stakeholders

AEGL Committee

Charter
Membership
AEGL Process
Meetings
AEGL Chemicals
SOP

AEGL Program

Standard Operating Procedures of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances

Standard Operating Procedures (SOP) of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (pdf -- 734K) - The initial guidance for use by the AEGL Committee to develop AEGL values was the National Academy of Sciences/Committee on Toxicology publication, "Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances." This publication provided broad guidance that could be used by a committee to develop AEGL values. As recommended in this guidance, the AEGL Committee has adopted a chemical approach and proceeded to develop and record more chemical specific and detailed methodology and specific procedures for setting AEGL values. These "Standard Operating Procedures".are provided below in order to meet the goal of making the AEGL Committee's efforts systematic, consistent, documented and transparent to the public.

As the AEGL Committee encounters new toxicological information and decision needs, it plans to continue to revise and document its methods, and thus term "Standard" Operating Procedures has been adopted.

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URL: http://www.epa.gov/opptintr/aegl/docs/sop.htm

HCN: Consideration of AEGL-1 values

The Committee on Toxicology, Subcommittee for AEGLs of the National Research Council, has suggested that where possible, the NAC derive AEGL-1 values.

Two monitoring studies discussed in the HCN technical support document, El Ghawabi et al. (1975) and Grabois (1954), are relevant to the derivation of AEGL-1 values. Grabois (1954) reported that workers in plants processing apricot kernels reported no ill effects when exposed to HCN at air concentrations of ~10 ppm. Workers in three plants monitored by El Ghawabi reported a range of symptoms, the most common of which were headache, weakness, and changes in taste and smell. There were also a few reports of effort dyspnea and vomiting. Average HCN concentrations in the three plants were 6, 8, and 10 ppm (range, 4.2-12.4 ppm). The NRC/COT Subcommittee on Spacecraft Maximum Allowable Concentrations (SMACs) used the monitoring data of El Ghawabi et al. (1975) to develop SMACs. They suggested that the average concentration of "8.0 ppm in the three plants would likely produce no more than mild CNS effects (e.g., mild headache) which would be acceptable for 1-hour exposures in a spacecraft. The Subcommittee said that it is was likely that the more serious symptoms, such as vomiting, were the result of brief exposures to high HCN concentrations. Therefore, 8 ppm is set as the 1-hour allowable concentration of HCN." The 24-hour SMAC is 4 ppm and the 7-day SMAC is 1 ppm.

At the last NAC meeting, another monitoring study was recommended for inclusion in the TSD. This study is also incorporated into the acetone cyanohydrin TSD supplied by Peter Griem. "Leeser et al. (1990) reported a cross-sectional study of the health of cyanide salt production workers. Sixty three cyanide workers were compared with one hundred control workers from a diphenyl oxide plant. All workers had full medical examinations, routine blood tests and blood samples taken for blood cyanide and carboxyhemoglobin. In addition blood levels of vitamin B_{12} and thyroxin (T4) were measured. Concentration measurements for the workplace were between 1 and 3 ppm hydrogen cyanide. Blood cyanide levels in exposed workers whilst still low were higher than in control workers. Results of clinical and physical examinations and evaluation of medical histories did not reveal any exposure-related health effects." In addition, during part of the year, production problems in part of the plant caused the hydrogen cyanide level to be 6 ppm instead of the usual 1-3 ppm.

Suggestion: divide the 8 ppm chronic exposure concentration which produces mild headaches in healthy adults in the El Ghawabi et al. (1975) study by 3 to protect sensitive individuals (an intraspecies UF of 3 was used for the AEGL-2 and AEGL-3). Unfortunately, the resulting 2.7 ppm is above the 8-hour AEGL-2 of 2.5 ppm.

Another suggestion: set the AEGL-1 equal to the 1 ppm no-effect level from the Leeser et al. (1990) study and flatline this concentration across all exposure durations. Do not apply an intraspecies UF as this concentration is well below the 8 ppm that meets the definition of an AEGL-1.

SUMMARY TABLE OF AEGL VALUES FOR HYDROGEN CYANIDE						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	1 ppm (1.1 mg/m^3)	1 ppm (1.1 mg/m^3)	1 ppm (1.1 mg/m^3)	1 ppm (1.1 mg/m^3)	1 ppm (1.1 mg/m^3)	No-effect level in humans - Leeser et al., 1990
AEGL-2 (Disabling)	17 ppm (19 mg/m^3)	10 ppm (11 mg/m^3)	7.1 ppm (7.8 mg/m^3)	3.5 ppm (3.9 mg/m^3)	2.5 ppm (2.8 mg/m^3)	Slight central nervous system depression - monkey (Purser, 1984)
AEGL-3 (Lethal)	27 ppm (30 mg/m^3)	21 ppm (23 mg/m^3)	15 ppm (17 mg/m^3)	8.6 ppm (9.7 mg/m^3)	6.6 ppm (7.3 mg/m^3)	Lethality (LC_{01}) - rat (E.I. du Pont de Nemours, 1981

RESPONSE TO COMMENTS / SUMMARY OF DELIBERATIONS ON HF AEGLs

APRIL 2000 NAC MEETING

- Use Study by Dalbey to the Extent Possible to Derive AEGL 2 and 3 Values
  - Agreement that this is the highest quality data set
- Do Not Extrapolate Too Far Across Timeframes
  - Will likely need to use another study (e.g. Rosenholtz) at some point
  - Check to see if other data can be used (e.g. 1-hour exposure in Dalbey study)
  - If use Rosenholtz study, should use for 1-hour AEGLs since exposures were 1-hour
- There is a Limit to How Much the AEGL Scheme Should be Altered in Order to Provide Consistency, Re: Dispersion Modeling
- Need to Consider Latest Studies Before Sending TSD to the NAS
  - Consider study by Lund 1999 for AEGL-1 values
- Uncertainty Factors Used in Current TSD Are Appropriate
  - Some comments indicated certain Ufs too large, some indicated too small
  - NAC considers Ufs to be appropriate; may need to enhance rationale

Attachment 7

HYDROGEN FLUORIDE:
RESPONSE TO COMMENTS TO FEDERAL REGISTER
From: The State of Michigan, ExxonMobil, and The American Petroleum Institute

Suggestion: For AEGL-2 and -3, replace study of Rosenholtz et al. (1963) with the more recent study by Dalbey (1996; Dalbey et al., 1998a,b). (The AEGL-2 and AEGL-3 10-minute values are already based on Dalbey, 1996).

AEGL-2

The Rosenholtz et al. (1963) study with the dog showed sensory irritation (blinking, sneezing, and coughing) during a 1-hour exposure to 243 ppm. The one-hour exposure was used as the basis for the AEGL-2 values with the exception of the 10-minute value. For time-scaling to the 30-minute and 4- and 8-hour exposures, the concentration-exposure duration relationship of $C^2 \times t = k$ was used. UF = 10 (3 x 3)

The 10-minute AEGL-2 is on based irritation but an absence of serious effects during a 10-minute exposure of cannulated rats (a conservative model as HF was delivered directly to the trachea) to 950 ppm. UF = 10 (3 x 3).

It has been suggested that the Dalbey (1996) study be used for the 30-minute and 1-hour AEGL-2 values. However, the Rosenholtz et al. (1963) was a 1-hour study and perhaps should be used for the 1 hour and longer term values. Using the Dalbey value of 950 ppm and scaling to the 30-minute value results in a 30-minute AEGL-2 of 55 ppm (See table below). There are no 1-hour or longer exposure durations in the Dalbey (1996) study that addressed irritation at the AEGL-2 definition. (Exposures of orally-cannulated rats to 48 or 74 ppm for 1 hour were without effects on the respiratory tract). The Dalbey (1996) 10-minute value time scaled to 30 minutes is 55 ppm.

Suggestion: change 30-minute AEGL-2 from 34 to 55 ppm.

AEGL-2

	10-minute	30-minute	1-hour	4-hour	8-hour
Rosenholtz et al. (1963)		**34 ppm**	**24 ppm**	**12 ppm**	**8.6 ppm**
Dalbey et al. (1996)	**95 ppm**	55 ppm	??		

Values previously accepted by the NAC are in bold.

The State of Michigan questions the use of interspecies and intraspecies Uncertainty Factors of less than 10 each.

AEGL-3

The 10-minute AEGL-3 was based on the death of 1 of 20 rats during a 10-minute exposure of orally-cannulated rats to 1764 ppm (Dalbey, 1996). This value was rounded down to 1700 and adjusted by UFs of 10 (3 x 3).

The longer-term values were based on no deaths in the mouse (the most sensitive of 7 tested species) during a 1-hour exposure to 243 ppm (Wohlslagel et al. (1976). This value was adjusted by interspecies (1) and intraspecies (3) UFs and a modifying factor of 2 (= 6).

Base the 30-minute value on the Dalbey (1996) study with UFs of 3 and 3? The 10-minute 170 ppm value time scaled to 30 minutes is 98 ppm.

Suggestion: change the 30-minute AEGL from 62 to 98 ppm. (See table below)

Support for the change: Dalbey also exposed groups of 10 nose-breathing rats to 1224 or 2039 ppm for 1 hour. There was 1 death at 2039 ppm and no deaths but severe irritant effects at 1224 ppm (respiratory distress, mucosal necosis, alveolitis, ocular damage). Use this study for all time periods with UFs of 3 and 3? Time-scaled values are 298, 172, 122, 61, and 43 ppm. (See table below)

AEGL-3

	10-minute	30-minute	1-hour	4-hour	8-hour
Wohlslagel et al. (1976)		**62 ppm**	**44 ppm**	**22 ppm**	**15 ppm**
Dalbey 10-minute study	**170 ppm**	98 ppm	??		
Dalbey 1 hour study	298 ppm	172 ppm	122 ppm	61 ppm	43 ppm

Values previously accepted by the NAC are in bold.

Higher values for the AEGL-3 are supported by a study showing no deaths in groups of 4 monkeys during 1-hour exposures to 690, 1575, or 1600 ppm; one death occurred at 1035 ppm (MacEwen and Vernot, 1970). Also, there was respiratory tract inflammation and necrosis but no deaths in rats exposed to 1630 ppm for 1 hour (Haskell Labs., 1990).

The State of Michigan questions the use of interspecies and intraspecies Uncertainty Factors of less than 10 each.

AEGL-1

The present AEGL-1 values are based on slight irritation in healthy human subjects exposed to ≤2 ppm for 6 hours (Largent, 1969; 1961). Exposures ranged up to 8.1 ppm with only slightly greater irritation.

It has been suggested by a NAC member that a new study by Lund et al. (1999) be incorporated into the TSD for HF and perhaps be reflected in the AEGL-1 values. Previous studies by Lund et al. (1995, 1997) are already incorporated into the TSD. The 1995 study was an abstract. In the 1997 study, healthy male volunteers were exposed to concentrations of 0.24 to 6.3 ppm for one hour. There were 3 exposure groups: 0.2-0.7 ppm, 0.9-2.9 ppm, and 3.0-6.3 ppm. The subjects exercised for 15 minutes of the 1-hour exposure. There was no dose-related change in spirometry measurements (FVC, FEV_1, etc) during or after exposure. None of the subjects had signs reflecting bronchial constriction. Three of nine subjects in the highest exposure group (3.0-6.3 ppm) reported some upper airway irritation (itching or soreness of the nose or throat) and one subject in this group had lower airway irritation (not clearly described). Some of the subjects had itching and irritation of the respiratory tract before the exposures began!

In the Lund et al. (1999) study, the authors reported on changes in components of the bronchoalveloar lavage fluid (BAL) 24 hours after the one-hour exposure to the above concentrations. In particular, they looked at an inflammatory response as indicated by changes in types of white blood cells and several noncellular components compared with preexposure numbers taken three weeks before the exposures. The aspirated BAL was divided into bronchial and alvelolar portions, the latter reflecting the more distal air spaces of the lung. The percentage of CD3 positive cells (a marker of T-lymphocytes) was significantly increased in the bronchial portion of the BAL in the two higher exposure groups and in the bronchoalveloar portion of the BAL in the highest exposure group (3.0-6.3 ppm). Myeloperoxidase and interleukin-6 were also increased significantly in the bronchial portion in the highest exposure group. There were no dose-response related differences in percentages of lymphocytes, eosinophils, neutrophils, and macrophages among the groups, for either portion of the BAL, although for the exposure groups combined, the percentages of lymphocytes and macrophages were slightly but significantly increased and decreased, respectively, over preexposure values. Methyl histamine and intercellular adhesion molecule-1 in the bronchial portion were unchanged and, several protein components including albumin and total protein were decreased in the bronchoalveolar portion. Although the authors characterized this as an inflammatory reponse, they noted the effects were confined to the upper respiratory tract. Upper respiratory tract irritation with minor clinical changes falls within or below the AEGL-1 definition of notable discomfort. This study appears to support the present AEGL-1 values (6 ppm/UF of 3 = 2 ppm).

AEGL-1

	10-minute	30-minute	1-hour	4-hour	8-hour
Largent, 1960, 1961	**2 ppm**	**2 ppm**	**2 ppm**	**1 ppm**	**1 ppm**

Values previously accepted by the NAC are in bold.

CHLORINE TRIFLUORIDE
DERIVATION OF 10-MINUTE VALUES

NAC 18, JULY 26-28, 2000
ORNL STAFF SCIENTIST: Sylvia Talmage
CHEMICAL MANAGER: Robert Benson

Attachment 9

DATA BASE FOR CHLORINE TRIFLUORIDE

1. 1-hour exposures of monkeys, rats, and mice to determine LC_{50} values (MacEwen and Vernot, 1970). Also determination of LC_{01} or highest concentrations resulting in no deaths.

2. Exposures of rats to 400 ppm for 20-40 minutes or 800 ppm for 10-30 minutes for determination of Lt_{50} values (Dost et al., 1974). Animals that survived for 4 hours "survived indefinitely."

3. Exposure of rats to 96 ppm for ~1.5-4.8 hours or 480 ppm for ~25-60 minutes to determine lethality (Horn and Weir, 1955).

4. Exposure of dogs to 21 ppm for 6 hours (Horn and Weir, 1955). Severe, nonlethal effects described during exposure.

5. Exposure of dogs and rats to 5.15 ppm for 6 hours (Horn and Weir, 1955). Effects described at 6 hours.

6. Exposure of dogs and rats to 1.17 ppm for 6 hours (Horn and Weir, 1956). Effects described at various times during exposure.

Calculation of n

1. Horn and Weir, 1955
   50% mortality at concentration of 96 ppm for 3.7 hours
   50% mortality at concentration of 480 ppm for 40 minutes
   $n = \sim 1$

2. Dost et al., 1974
   Approximate LC_{50} (Lt_{50}) values of 400 ppm for 26-30 minutes and 800 ppm for 13-14 minutes
   $n = 1$

Proposed 10-minute AEGL-3 of 81 ppm

Based on 1-hour LC_{01} of 135 ppm in mice (MacEwen and Vernot, 1970)
Interspecies and intraspecies UFs of 3 each for an irritant
Time-scaling based on an n value of 1

Support for AEGL-3:

1. No deaths during 1-hour exposure of monkeys to 127 ppm and rats to 200 ppm (MacEwen and Vernot, 1970). Using interspecies and intraspecies UFs of 3 each, the resulting 10-minute values would be 76 and 120 ppm, respectively. The data set for the mouse was used because the mouse was the most sensitive species as determined by LC_{50} values and the dose-response curve for the mouse was better than for the other species.

3. No deaths during 10-minute exposure of rats to 800 ppm (Dost et al., 1974). Using interspecies and intraspecies UFs of 3 each, the resulting 10-minute values would be 80 ppm.

4. No deaths during 25-minute exposure of rats to 400 ppm (Dost et al., 1974). Using interspecies and intraspecies UFs of 3 each, the resulting 10-minute values would be 100 ppm.

5. No deaths during 6-hour exposure of dogs or rats to 21 ppm (Horn and Weir, 1955). Using interspecies and intraspecies UFs of 3 each, the resulting 10-minute values would be 76 ppm.

Proposed 10-minute AEGL-2 of 19 ppm

Based on 6-hour exposure of dogs to 5.15 ppm (Horn and Weir, 1955)
Interspecies and intraspecies UFs of 3 each for an irritant

Support for AEGL-2
At 21 ppm, rhinorrhea and lacrimation were observed in dogs after 10 minutes (Horn and Weir, 1955).

Alternative suggestion: Consider flatlining the 10-minute value to the 30-minute value (6.2 ppm) because the exposure duration of the study was longer than 4 hours.

Proposed 10-minute AEGL-1 of 2.1 ppm

Based on observation of lacrimation at 3 hours in dogs exposed to 1.17 ppm for 6 hours (Horn and Weir, 1956). Rats appeared unaffected during exposure but may have huddled in corners of exposure chamber.

Interspecies and intraspecies UFs of 3 each for an irritant

Support for AEGL-1

No supporting studies

Irritancy of ClF_3 may be due to hydrogen fluoride (HF) breakdown product

3 moles of HF from each mole of ClF_3

HF 30-minute value is 1/3 of ClF_3 30-minute value

HF 10-minute value was flatlined to 30-minute value

Alternative suggestion: Consider flatlining 10-minute AEGL-1 to 30-minute AEGL-1 of 0.70 ppm

PREVIOUSLY PROPOSED CHLORINE TRIFLUORIDE AEGLS

Classification	Exposure Duration				
	10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1 (Nondisabling)	**2.1 ppm** 8.0 mg/m^3	0.70 ppm 2.7 mg/m^3	0.35 ppm 1.3 mg/m^3	0.09 ppm 0.34 mg/m^3	0.04 ppm 0.15 mg/m^3
AEGL-2 (Disabling)	**19 ppm** 72 mg/m^3	6.2 ppm 24 mg/m^3	3.1 ppm 12 mg/m^3	0.77 ppm 2.9 mg/m^3	0.39 ppm 1.5 mg/m^3
AEGL-3 (Lethal)	**81 ppm** 308 mg/m^3	27 ppm 103 mg/m^3	14 ppm 53 mg/m^3	3.4 ppm 13 mg/m^3	1.7 ppm 6.5 mg/m^3

The proposed 10-minute values are in bold. The 30-minute and 1-, 4-, and 8-hour values were previously passed by the NAC. Using the time-scaled values for the AEGL-1 and AEGL-2 is supported by the clear exposure duration-dose-response relationship for lethality (AEGL-3). The mechanism of action - irritation - is the same for all AEGL levels.

FLATLINED PROPOSED CHLORINE TRIFLUORIDE AEGLS

Classification	Exposure Duration				
	10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1 (Nondisabling)	**0.70 ppm** 2.7 mg/m^3	0.70 ppm 2.7 mg/m^3	0.35 ppm 1.3 mg/m^3	0.09 ppm 0.34 mg/m^3	0.04 ppm 0.15 mg/m^3
AEGL-2 (Disabling)	**6.2 ppm** 24 mg/m^3	6.2 ppm 24 mg/m^3	3.1 ppm 12 mg/m^3	0.77 ppm 2.9 mg/m^3	0.39 ppm 1.5 mg/m^3
AEGL-3 (Lethal)	**81 ppm** 308 mg/m^3	27 ppm 103 mg/m^3	14 ppm 53 mg/m^3	3.4 ppm 13 mg/m^3	1.7 ppm 6.5 mg/m^3

The AEGL-3 values are not flatlined because exposure durations ranged from 10 minutes to 6 hours.

ACUTE EXPOSURE GUIDELINE LEVELS FOR

ETHYLENIMINE

(10-MINUTE VALUES)

PRESENTED BY
MARK MCCLANAHAN, CHEMICAL MANAGER

NAC/AEGL MEETING, WASHINGTON, DC
JULY 26-28, 2000

Attachment 10

ETHYLENIMINE – AEGL -2 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
33 ppm	9.8 ppm	4.6 ppm	1.0 ppm	0.47 ppm

Reference: Carpenter, C.P.; Smyth, H.F., Jr.; Shaffer, C.B. 1948. The acute toxicity of ethylene imine to small animals. J. Ind. Hyg. Toxicol. 30:2-6.

Test Species/Strain/Number: male guinea pigs, 6 per group

Exposure Route/Concentration/Durations: Inhalation; 10, 25, 50, 100, or 250 ppm for 240 minutes

Effects: Guinea pigs were exposed for 240 minutes.
Clinical signs: eye and respiratory irritation, and extreme respiratory difficulty at 25-250 ppm; prostration at 250 ppm; no effects at 10 ppm
Gross pathologic effects: congestion and hemorrhage in the lungs, congestion in all internal organs at 25-250 ppm; no effects at 10 ppm
Microscopic effects: lung congestion leakage of fluid and red blood cells into bronchioles, tubular necrosis and cloudy swelling in the kidneys at 25-250 ppm; no effects at 10 ppm
Mortality: 10 ppm, (0/6), 25 ppm (2/6), 50 ppm (2/6), 100 ppm (6/6), and 250 ppm (6/6)

Endpoint/Concentration/Rationale: No-effect-level for lethality in the guinea pig, 10 ppm exposure for 4 hours; effects at 25 ppm and higher were above the definition for AEGL 2.

ACUTE EXPOSURE GUIDELINES FOR ETHYLENIMINE (CAS No. 151-56-4)

AEGL -3 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
48 ppm	18 ppm	9.6 ppm	2.8 ppm	1.5 ppm

Reference: Carpenter, C.P.; Smyth, H.F., Jr.; Shaffer, C.B. 1948. The acute toxicity of ethylene imine to small animals. J. Ind. Hyg. Toxicol. 30:2-6.

Test Species/Strain/Number: Male Wistar rats, 6 per group

Exposure Route/Concentration/Durations: Inhalation, 25 or 50 ppm for 480 minutes.

Effects: Exposure was for 480 minutes.
Clinical signs: eye and respiratory irritation, and extreme respiratory difficulty
Gross pathologic effects: congestion and hemorrhage in the lungs, congestion in all internal organs
Microscopic effects: lung congestion leakage of fluid and red blood cells into bronchioles, tubular necrosis and cloudy swelling in the kidneys
Mortality: 25 ppm (1/6) and 50 ppm (5/6)

Endpoint/Concentration/Rationale: Lethality in rats for 480 minute exposure; LC_{01} = 15 ppm, the estimated threshold for lethality derived by probit analysis of the data. The LC_{01} for 480 minutes was selected because it had the smallest standard error.

ETHYLENIMINE – AEGL-3 Values Continued

Uncertainty Factors/Rationale:

Total uncertainty factor: 10

Interspecies: 3 - Ethylenimine is a very reactive direct-acting alkylating agent, and the mechanism of action is expected to be the same for different species. In addition, the rat and guinea pig LC_{50} values differ by a factor of approximately 2 for exposures ranging from 5 minutes to 480 minutes.

Intraspecies: 3 - Ethylenimine is a very reactive direct-acting alkylating agent, and the mechanism of action is expected to be the same for different species. In addition, 5 humans accidentally exposed to the same concentration of ethylenimine responded at similar times after exposure and with a similar progression through time. Since ethylenimine is an insidious agent and effects may be delayed until after exposure; individuals in the population may respond similarly to exposure.

Modifying Factor: 1

Animal to Human Dosimetric Adjustment: 1

Time Scaling: $C^n \times k = t$, where $n = 1.12$ derived empirically from rat LC_{50} data for exposures from 5 minutes to 480 minutes. Log LC_{50} vs log time showed a linear trend over the entire time range. The 480 minute value gave the LC_{01} with the smallest standard error. AEGL values for 10, 30, 60, and 240 minutes were calculated from 480 minutes.

Confidence and Support of AEGL-Values: Scaling from 480 minutes to 10 minutes is valid for ethylenimine, because the log concentration vs log time was linear from 5 minutes to 480 minutes. Any effects caused by ethylenimine exposure at these concentrations may be delayed until after exposure. Ethylenimine has carcinogenic activity; these values do not take into consideration the potential excess lifetime cancer risk due to a single exposure.

ETHYLENIMINE – AEGL-2 Values Continued

Uncertainty Factors/Rationale:

Total uncertainty factor: 10

Interspecies: 3 - Ethylenimine is a very reactive direct-acting alkylating agent, and the mechanism of action is expected to be the same for different species.

Intraspecies: 3 - Ethylenimine is a very reactive direct-acting alkylating agent, and the mechanism of action is expected to be the same for different species. In addition, 5 humans accidentally exposed to the same concentration of ethylenimine responded at similar times after exposure and with a similar progression through time. Since ethylenimine is an insidious agent and effects may be delayed until after exposure; individuals in the population may respond similarly to exposure.

Modifying Factor: 1

Animal to Human Dosimetric Adjustment: 1

Time Scaling: $C^n \times k = t$, where $n = 0.91$ derived empirically from guinea pig LC_{50} data with exposure times ranging from 5 minutes to 480 minutes. Log LC_{50} vs log time showed a linear trend over the entire time range.

Confidence and Support of AEGL Values: Scaling from 240 minutes to 10 minutes is valid for ethylenimine, because the log concentration vs log time was linear from 5 minutes to 480 minutes. Any effects caused by ethylenimine exposure at these concentrations may be delayed until after exposure. Ethylenimine has carcinogenic activity; these values do not take into consideration the potential excess lifetime cancer risk due to a single exposure.

ETHYLENIMINE – AEGL -1 VALUES			
30 minutes	1 hour	4 hours	8 hours
no values derived			

Reference: not applicable

Test Species/Strain/Number: not applicable

Exposure Route/Concentration/Durations: not applicable

Effects: not applicable

Endpoint/Concentration/Rationale: not applicable

Uncertainty Factors/Rationale: not applicable

Total uncertainty factor:

Interspecies: NA

Intraspecies: NA

Modifying Factor: not applicable

Animal to Human Dosimetric Adjustment: not applicable

Time Scaling: not applicable

Comments: AEGL-1 values were not derived, because ethylenimine is an insidious agent (effects are delayed) with an odor similar to that of ammonia and an odor detection level of 2 ppm; consequently, ethylenimine has no specific warning properties (sensory irritation or odor). The odor detection level is higher than the AEGL-2 values for 4 and 8 hour exposures; therefore, it is not be valid nor would it be a benefit to the public to propose AEGL-1 values. In addition, data are not available to assess the concentration of ethylenimine associated with effects consistent with AEGL-1 endpoints.

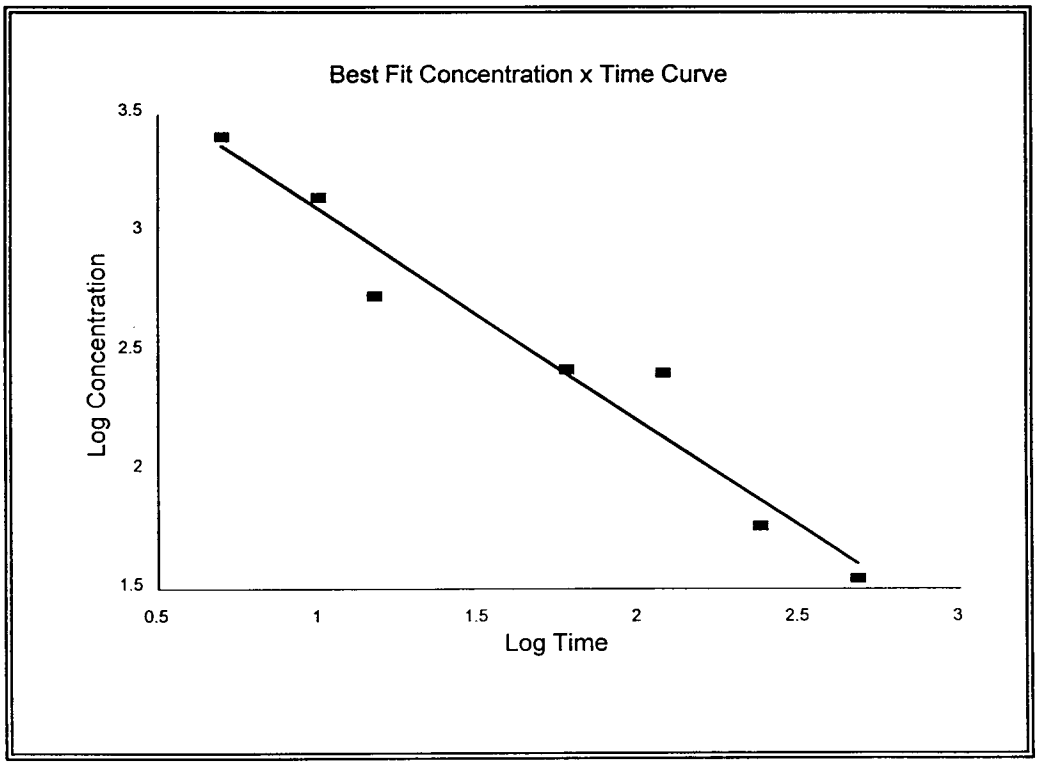
PROPOSED AEGL VALUES FOR ETHYLENIMINE[a,b]						
Class.	ppm (mg/m^3)					Endpoint (Reference)
	10 min.	30 min.	1 h	4 h	8 h	
AEGL-1	No values derived for AEGL-1					
AEGL-2	33 (18)	9.8 (5.5)	4.6 (2.6)	1.0 ppm (0.56)	0.47 (0.26)	No effect for respiratory difficulty Carpenter et al., 1948
AEGL-3	48 (27)	18 (10)	9.6 (5.4)	2.8 (1.6)	1.5 (0.84)	Lethality Carpenter et al., 1948

[a]AEGL-2 and -3 values do not take into consideration the potential cancer risk due to exposure to ethylenimine.
[b]Effects at these concentrations may be delayed until sometime after exposure.

ETHYLENEMINE

Rat Data: Carpenter et al., 1948)

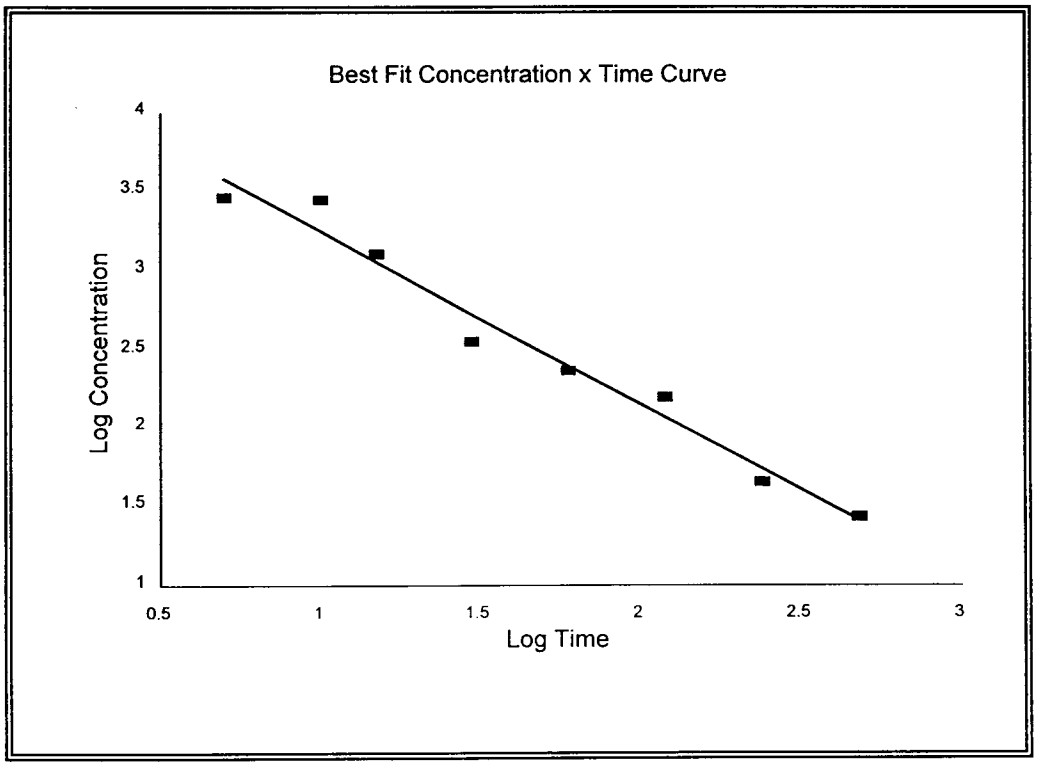
Time (min)	LC_{50} Concentration (ppm)
5	2558
10	1407
15	545
60	268
120	259
240	58
480	35



ETHYLENEMINE

Guinea Pig Data: Carpenter et al., 1948)

Time (min)	LC_{50} Concentration (ppm)
5	2906
10	2824
15	1283
30	364
60	235
120	158
240	45
480	27



ACUTE EXPOSURE GUIDELINE LEVELS FOR

PROPYLENIMINE

(10-MINUTE VALUES)

PRESENTED BY
MARK MCCLANAHAN, CHEMICAL MANAGER

NAC/AEGL MEETING, WASHINGTON, DC
JULY 26-28, 2000

Attachment 11

PROPYLENIMINE – AEGL -1 VALUES			
30 minutes	1 hour	4 hours	8 hours
No AEGL-1 values were derived			
Reference: not applicable			
Test Species/Strain/Number: not applicable			
Exposure Route/Concentration/Durations: not applicable			
Effects: not applicable			
Endpoint/Concentration/Rationale: not applicable			
Uncertainty Factors/Rationale: not applicable Total uncertainty factor: Interspecies: not applicable Intraspecies: not applicable			
Modifying Factor: not applicable			
Animal to Human Dosimetric Adjustment: not applicable			
Time Scaling: not applicable			
Comments: No AEGL-1 values are proposed for propylenimine. Propylenimine has an odor similar to that of ammonia, the odor detection and irritation thresholds are not known, and propylenimine is probably an insidious agent similar to ethylenimine. No AEGL-1 values were proposed for ethylenimine. It would not be valid nor beneficial to propose AEGL-1 values for propylenimine. In addition, data are not available to assess the concentration of ethylenimine associated with effects consistent with AEGL-1 endpoints.			

PROPYLENIMINE – AEGL -2 VALUES CONTINUED

Uncertainty Factors/Rationale: Based on ethylenimine

Total uncertainty factor:10

Interspecies: 3 - Ethylenimine is a very reactive direct-acting alkylating agent, and the mechanism of action is expected to be the same for different species.

Intraspecies: 3 - Ethylenimine is a very reactive direct-acting alkylating agent, and the mechanism of action is expected to be the same for all individuals in the population. In addition, 5 humans accidentally exposed to the same concentration of ethylenimine responded at similar times after exposure and with a similar progression with time. Since ethylenimine is an insidious agent and effects may be delayed until after exposure, individuals in the population may respond similarly to exposure.

Modifying Factor: 2 because of a deficient database.

Animal to Human Dosimetric Adjustment: 1

Time Scaling: Based on ethylenimine: $C^n \times k = t$, where $n = 0.91$ derived empirically from guinea pig LC50 data with exposure times ranging from 5 minutes to 480 minutes. Log LC_{50} vs log time showed a linear rend over the entire time range.

Confidence and Support of AEGL-2 Values: The AEGL-2 values for propylenimine were derived by the relative potency method; a relative potency of 5 was selected for propylenimine (based on lethality data, propylenimine was considered to be 5 times less potent than ethylenimine). The AEGL 2 values for ethylenimine were 33, 9.8, 4.6, 1.0, and 0.47 for 30 minutes, 1 hour, 4 hours, and 8 hours, respectively. The resulting values were reduced by a factor of 2 because of a deficient database.

PROPYLENIMINE – AEGL -2 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
83 ppm	25 ppm	11 ppm	2.5 ppm	1.2 ppm

Reference:
ORNL (Oak Ridge National Laboratory). 1997. Acute Exposure Guideline Levels for Ethylenimine. Draft.
Carpenter, C.P.; Smyth, H.F., Jr. Shaffer, C.B. 1948. The acute toxicity of ethylene imine to small animals. J. Ind. Toxicol. 30:2-6.

Test Species/Strain/Number: Ethylenimine: male guinea pigs, 6 per gorup

Exposure Route/Concentration/Durations: Ethylenimine: inhalation; 10, 25, 50, 100, or 250 ppm for 240 minutes

Effects: Ethylenimine: Guinea pigs were exposed for 240 minutes.
Clinical signs: eye and respiratory irritation, and extreme respiratory difficulty at 25-250 ppm; prostration at 250 ppm; no effects at 10 ppm
Gross pathologic effects: congestion and hemorrhage in the lungs, congestion in all internal organs at 25-250 ppm; no effects at 10 ppm
Microscopic effects: lung congestion leakage of fluid and red blood cells into bronchioles, tubular necrosis and cloudy swelling in the kidneys at 25-250 ppm; no effects at 10 ppm
Mortality: 10 ppm, (0/6), 25 ppm (2/6), 50 ppm (2/6), 100 ppm (6/6), and 250 ppm (6/6)

Endpoint/Concentration/Rationale: Ethylenimine: No-effect-level for lethality in the guinea pig, 10 ppm exposure for 4 hours; effects at 25 ppm and higher were above the definition for AEGL 2.

ACUTE EXPOSURE GUIDELINES FOR
PROPYLENIMINE (CAS No. 75-55-8)

PROPYLENIMINE – AEGL -3 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
167 ppm	50 ppm	23 ppm	5.1 ppm	2.4 ppm

Reference: Carpenter, C.P.; Smyth, H.F., Jr. Shaffer, C.B. 1948. The acute toxicity of ethylene imine to small animals. J. Ind. Toxicol. 30:2-6.

Test Species/Strain/Number: guinea pig/6 per group — Ethylenimine

Exposure Route/Concentration/Durations: inhalation/500 ppm for 5, 10, 30, 60, 120, or 240 minutes

Effects: lethality, 1/6, 3/5, 6/6 at 60, 120, and 240 minutes, respectively; no deaths at ≤30 min

Endpoint/Concentration/Rationale: no effect level for lethality

Uncertainty Factors/Rationale:

Total uncertainty factor: 10

Interspecies: 3 - Propylenimine is a very reactive direct-acting alkylating agent, and the mechanism of action is expected to be the same for different species.

Intraspecies: 3 - Propylenimine is a very reactive direct-acting alkylating agent, and the mechanism of action is expected to be the same for different species. In addition, 5 humans accidentally exposed to the same concentration of ethylenimine (similar chemical) responded at similar times after exposure and with a similar progression through time. Since propylenimine is an insidious agent and effects may be delayed until after exposure, individuals in the population may respond similarly to exposure

PROPYLENIMINE – AEGL -3 VALUES
Modifying Factor: 1
Animal to Human Dosimetric Adjustment: none applied
Time Scaling: $C^n \times k = t$, where n = 0.91 derived empirically from LC50 data in which guinea pigs were exposed to ethylenimine for times ranging from 5 minutes to 480 minutes.
Confidence and Support of AEGL Values: The confidence in the AEGL-3 values for propylenimine is low because the values were derived from a time-response study; a dose-response study was not available for either rats or guinea pigs. Guinea pigs were more sensitive than rats; lethality occurred after exposure of guinea pigs to 500 ppm for 60 minutes and after exposure of rats to 500 ppm for 240 minutes.

Proposed AEGL Values for propylenimine[a,b]						
Class.	ppm (mg/m^3)					Endpoint (Reference)
	10 min.	30 min.	1 h	4 h	8 h	
AEGL-1	No values derived for AEGL-1					
AEGL-2	83 (36)	25 (10.7)	11 (4.7)	2.5 (1.1)	1.2 (0.51)	Respiratory difficulty (Carpenter et al., 1948)
AEGL-3	167 (71)	50 (21.4)	23 (9.8)	5.1 (2.2)	2.4 (1.0)	Lethality threshold, Carpenter et al., 1948

[a]AEGL-2 and -3 values do not take into consideration the potential cancer risk due to inhalation exposure to propylenimine.
[b]Effects including lethality, irritation to eyes, and irritation to the respiratory tract may be delayed until after exposure; toxic levels of propylenimine may be absorbed through the skin.

Carpenter, C.P.; Smyth, H.F., Jr.; Shaffer, C.B. 1948. The acute toxicity of ethylene imine to small animals. J. Ind. Hyg. Toxicol. 30:2-6.

Phosphine - postpone? (significant comments

Attachment 12

sunzon@bbnp.com on 07/24/2000 03:06:38 PM

RECEIVED
OPPT CBIC

2000 JUL 26 AM 7:05

To: NCIC OPPT/DC/USEPA/US@EPA
cc:

Subject: Fw: Undeliverable: Fw: Docket Control Number OPPTS-00293

----- Original Message -----
From: System Administrator <postmaster@bbnp.com>
To: Pestcon Systems, Inc. <sunzon@bbnp.com>
Sent: Monday, July 24, 2000 3:09 PM
Subject: Undeliverable: Fw: Docket Control Number OPPTS-00293

> Your message
>
> To: hhoppt.ncic@epamail.epa.gov
> Subject: Fw: Docket Control Number OPPTS-00293
> Sent: Mon, 24 Jul 2000 14:56:20 -0400
>
> did not reach the following recipient(s):
>
> hhoppt.ncic@epamail.epa.gov on Mon, 24 Jul 2000 15:09:53 -0400
> The recipient name is not recognized
> The MTS-ID of the original message is: c=US;a= ;p=Bits, Bytes
> and ;I=DESTINY20007241907PLMKLR9X
>
>
>

Date: Mon, 24 Jul 2000 14:56:20 -0400
From: Sunzon <sunzon@bbnp.com>
Subject: Fw: Docket Control Number OPPTS-00293
To: hhoppt.ncic@epamail.epa.gov
Message-id: <002701bff5a0$dff7e180$0500a8c0@betty>
MIME-version: 1.0
Content-type: multipart/mixed; boundary="Boundary_(ID_7Px2cyq/DGnNqOFSDRY3sQ)"

----- Original Message -----
From: Sunzon <mailto:sunzon@bbnp.com>
To: www.oppt.ncic@epamail.epa.gov <http://www.oppt.ncic@epamail.epa.gov>

Sent: Monday, July 24, 2000 2:43 PM
Subject: Docket Control Number OPPTS-00293

Attached are comments relative to the proposed AEGLS for phosphine

Regards
D & D Holdings, Inc.
Casa Bernardo Ltda
Cytec Industries
Inventa Corporation
Midland Fumigation Inc.

 - COVERLET.doc

 - FINALAEG.doc

July 24, 2000

OPPT Document Control Center (7407)
Office of Prevention, Pesticides & Toxic Substances
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Docket Control Number OPPTS-00293

Dear Sir/Madam:

As technical manufactures of all the currently registered phosphine products that are used as pesticides in the United States, we are submitting the attached comments relative to the proposed AEGLs for phosphine. These proposals are contained in Federal Register Notice dated June 23, 2000, Volume 65, and Number 122.

We are convinced that EPA and the States rigorously regulate these products and believe the current ambient thresholds adequately protect users and bystanders.

We ask that we become listed as parties of interest in this matter so that we receive all future relevant communications.

Sincerely,

Casa BernardoLtda.
c/o Piper, Marbury, Rudnick & Wolfe
1200 Nineteenth Street, NW
Washington, DC 20036-2430

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Leavenworth, KS 66048

Review of EPA's AEGLs for Phosphine

ABSTRACT

This report provides comments on the recent U.S. Environmental Protection Agency 's (EPA) support document entitled "PHOSPHINE (CAS Reg. No. 7803-51-2) PROPOSED ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) 'PUBLIC DRAFT' Federal Register - May 2000." This review focuses on the approach that EPA took in deriving phosphine AEGLs. The derivation of the 6-hour AEGL-2 for phosphine was reviewed and considered flawed for several reasons. First, the study selected for the calculation of the AEGL-2 value (i.e., Morgan et al. 1995) did not involve a single 6-hour exposure, but rather a total of 24 hours of exposure. In contrast, the study reported by Newton et al. (1993) is considered appropriate for the calculation of an AEGL-2. Newton et al. (1993) established a no-observable-adverse-effect-level (NOAEL) for toxicity in rats, the most sensitive species, following a single 6-hour exposure. The AEGL-2 was also flawed in that a variation of Haber's rule, $c^n \times t = k$ (with n=3), was utilized for temporal scaling to extrapolate to durations shorter than 6 hours. Analysis of data reveal that the concentration-response relationship for phosphine is best described by $c^1 \times t^1 = k$. Finally, evaluation of pharmacokinetic and pharmacodynamic factors for phosphine yields an uncertainty factor (UF) of 10 instead of 30. Revised AEGL-2 values were derived when Newton et al. (1993), an UF = 10, and a $c^1 \times t^1 = k$ relationship were considered. Although the AEGL-3 was calculated from a suitable study, this value also was flawed in that an UF of 30 and the equation $c^n \times t = k$ (with n=3), were inappropriately utilized for temporal scaling to extrapolate to durations shorter than 6 hours. A revised AEGL-3 is proposed taking into account an UF = 10 and a $c^1 \times t^1 = k$ relationship.

INTRODUCTION

The EPA document derived an AEGL-2 based on a no-effect-level (NOEL) for renal, cardiac, and liver histopathology in mice exposed to 5 ppm phosphine 6 hours/day for 4 days (Morgan et al. 1995). Values were derived assuming a single 6-hour exposure. An uncertainty factor of 3 (rather than the typical value of 10) was applied to account for interspecies variability since lethality data from rats, mice, rabbits, and guinea pigs suggest little species variability. EPA also applied an uncertainty factor of 10 to account for intraspecies variability since the human data suggest that children may be more sensitive than adults when exposed to presumably similar phosphine concentrations (total UF = 30). To obtain conservative and protective AEGL-2 values for the 30-minute, 1-, 4-, and 8-hour time points in the absence of an empirically derived chemical-specific scaling exponent, EPA used a version of Haber's rule $c^n \times t = k$. EPA applied temporal scaling using n = 3 when extrapolating to time points shorter than 6 hours and n = 1 when extrapolating to the 8-hour time point. The 30-min AEGL-2 value was also adopted as the 10-minute value because it was considered inappropriate to extrapolate back to 10 minutes. AEGL-2 values presented in the EPA support document are shown in Table 1.

The AEGL-3 was based on a no-effect-level for lethality (18 ppm phosphine) in Sprague Dawley rats exposed to phosphine for 6 hours (Newton, 1991). An uncertainty factor of 3 was applied as for the AEGL-2 calculation to account for interspecies variability since lethality data from rats, mice, rabbits, and guinea pigs suggest little species variability. An uncertainty factor of 10 was applied to account for intraspecies variability based on the assumed greater sensitivity of children (total UF =30). Temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $c^n \times t = k$ equation in the same manner as these values were used for the AEGL-2 calculations. The 30-min AEGL-3 value was also adopted as the 10 minute value since EPA considers it inappropriate to extrapolate back to 10 minutes. AEGL-3 values presented in the EPA support document are summarized in Table 1.

Table 1. Summary of Proposed AEGL Values For Phosphine [ppm (mg/m^3)]

Classification	10-min.	30-min.	1-hr.	4-hr.	8-hr.	Endpoint (Reference)
AEGL-1 (Nondisabling)	–	–	–	–	–	Appropriate data not available
AEGL-2 (Disabling)	0.38 (0.54)	0.38 (0.54)	0.30 (0.42)	0.19 (0.27)	0.13 (0.18)	NOEL for histopathology in mice exposed to 5 ppm phosphine 6 hr/day for 4 days. Values were calculated assuming a single 6 hr exposure (Morgan et al., 1995)
AEGL-3 (Lethality)	1.4 (1.9)	1.4 (1.9)	1.1 (1.6)	0.69 (0.97)	0.45 (0.63)	No-effect-level for lethality in rats exposed to 18 ppm phosphine for 6 hr. (Newton, 1991)

SPECIFIC REVIEW COMMENTS

1. Derivation of the AEGL-2

Selection of the study used for AEGL-2

EPA selected the Morgan et al. (1995) study for the derivation of the AEGL-2 value. Although the animals were dosed 6 hours per day for 4 days (a total of 24 hours), a 6-hour

exposure was assumed. There is no explanation for the use of a 24 total hour study as a substitute for an acute 6-hour study in the EPA support document. The misuse of the Morgan et al. (1995) study for the calculation of acute exposure guideline levels is especially puzzling in light of the existence of a valid single 6-hour study. The study by Newton et al. (1993) is appropriate for the derivation of the 6-hour AEGL-2 value. In the Newton et al. (1993) study, male and female Fischer 344 rats received a single 6-hour inhalation exposure to 0, 2.5, 5, and 10 ppm phosphine. All animals survived these exposures. During the exposures, the authors reported that a few animals showed red or mucoidal nasal discharge, which abated during the 14-day recovery period. There was no effect on body weight. Gross postmortem and microscopic examinations revealed no treatment-related findings. These findings indicate that 10 ppm is a 6-hour NOEL. The use of the 24-hour 5 ppm value from the Morgan et al. (1995) results in an error of a factor of 2 in the AEGL-2 value.

Choice of exponent value "n" in the C x T relationship

As described above, temporal scaling was performed using n = 3 when extrapolating to time points shorter than 6 hours and n = 1 when extrapolating to longer time points using the $c^n \times t = k$ equation. The choice of n = 3 for durations shorter than 6 hours when studies using shorter dose durations clearly demonstrate that the true concentration exponent is 1, not 3, is not discussed in the support document. C x T response data have been reported for phosphine studies that exposed animals less than 6 hours, e.g., Omae et al. (1996), Muthu et al. (1980), Klimmer (1969). These studies clearly demonstrate that the C x T product for sublethal effects and lethality at exposure durations less than 6 hours are essentially equivalent to those involving 6-hour exposure durations. Moreover, the animal studies demonstrate that the critical effect associated with phosphine exposure is lethality. Studies in a number of species demonstrate that lethality is dependent on the product of concentration and duration of exposure (C x T). For rats, the lethality threshold is 5-7 ppm, and a C x T product of approximately 180 ppm-hour as a median lethal dose has been reported (Newton et al. 1999). As shown in Table 2 , a summary of 15 studies in rats indicates a similar average C x T value (204 ppm-hrs), and a similar C x T product is obtained for the median lethal dose in other species. The studies using exposure durations shorter than 6 hours yield C x T products of 134-280 in mice (Omae et al. 1996) and 160-240 in rats (Muthu et al. 1980). These values are essentially equivalent to the C x T products shown in Table 2.

Table 2. Concentration (C) x Time of Dosing (T) Values for Lethality

Species (# of studies)	Average C x T (ppm-hrs)	Median C x T (ppm-hrs)	Range (ppm-hrs)
Mice (5)	204.6 52.0	199	134-268
Rats (15)	204.3 31.8	203	150-250
Guinea Pigs (3)	171.7 52.9	150	133-232
Cats (6)	222.6 43.7	210.3	178-306
Rabbits (4)	201 53.8	201	150-262
Turkeys (1)	186 0	186	NA
Hens (1)	157 0	157	NA
All species	202.4 40.7	203	133-306

Klimmer, 1969; Morgan et al, 1995; Muthu et al, 1980; Newton et al, 1993; and Omae et al, 1996. (All exposures were 5 ppm and greater.)

Application of UF = 30

In the derivation of the AEGL-2, EPA has applied an uncertainty factor of 3 to account for interspecies variability since lethality data from rats, mice, rabbits, and guinea pigs suggest little species variability. In addition, an uncertainty factor of 10 was applied to account for intraspecies variability since the EPA document states that human data suggest that children may be more sensitive than adults.

A more realistic uncertainty factor for interspecies variability can be obtained if one considers pharmacokinetic and pharmacodynamic factors for phosphine. The default interspecies UF is 10 and is comprised of one factor of 3 for pharmacokinetic uncertainty and one factor of 3 for pharmacodynamic uncertainty. The pharmacokinetic uncertainty factor is typically reduced to 1 in the case of an animal study for an inhaled toxicant if it can be shown that dosimetric adjustments between animals and humans are small.

To support a conclusion that the dosimetric adjustment is small, the dosimetric adjustment factor (DAF) must be shown to be close to one. A finding that animals are dosimetrically more sensitive than humans (DAF > 1) also supports a reduction of the pharmacokinetic UF to 1.

The primary toxic effect of phosphine exposure is extrarespiratory. Therefore, the DAF is computed here as the regional gas dose ratio (RGDR) of systemic dose of phosphine in the

F344 rat (the rat used in Newton et al. 1999) to the systemic dose in humans, assuming identical inhaled concentrations of the gas.

Phosphine is slightly soluble in water at 368 mg/L (EPA, 1989), but is not known to be highly reactive with tissue. We therefore consider phosphine as a category 2 gas in the categorization scheme identified in the EPA Inhaled Reference Concentration (RfC) document (EPA, 1994). Therefore, some scrubbing of the gas from the airstream by the upper respiratory tract may be expected; we assume that this scrubbing is dependent only on the solubility of the gas in the mucous lining of the respiratory tract.

The following notations and subscripts have been employed:

ER = Extra respiratory
Syst = Systemic
TB = Tracheobronchial
A = Animal
H = Human
E = Extraction efficiency
V_e = Minute ventilation
BW = Body Weight
SA = Surface area
Q_T = Cardiac output
C_i = Inhaled gas concentration
C_{bg} = Gas concentration in equilibrium with blood concentration
H_{bg} = Blood: gas partition coefficient
H_{tg} = Tissue: gas partition coefficient
k_g = Mass transport coefficient in the gas phase
k_l = Mass transport coefficient in the liquid-tissue phase
K_g = Overall mass transport coefficient
E_T = Liver extraction efficiency
V_{lg} = Volume of active lung compartment
k_{lg} = Elimination rate in lung compartment
f_p = Fractional penetration to the alveolar region

The regional gas dose ratio for extrarespiratory effects is given by

$$RGDR_{ER} = \frac{(\text{Systemic Dose})_{Animal}}{(\text{Systemic Dose})_{Human}} \quad (1)$$

In the expression for $RGDR_{ER}$, as given by equation 4-45 of the EPA RfC document (EPA, 1994), the systemic dose for category 2 gases is considered proportional to the product of the minute volume, V_e, and the systemic extraction efficiency, E_{syst}. Thus, the RGDR prescribed

by equation 4-45 of the EPA RfC document is

$$RGDR_{ER}^{RfC\,doc} = \frac{(V_e \times E_{Syst})_A}{(V_e \times E_{Syst})_H}. \quad (2)$$

Ignoring desorption or further absorption that may occur during expiration, under steady-state conditions, E_{Syst} is given by

$$E_{Syst} = 1 - \frac{C_{bg}}{C_i}. \quad (3)$$

The $RGDR_{ER}$ so derived ignores the scrubbing that takes place in the head and TB regions prior to delivery of the toxicant to the alveolar region. This scrubbing may be significant for category 2 gases, and furthermore, will differ significantly across species. Secondly, we believe that a more appropriate metric of extrarespiratory dose is the amount of gas absorbed systemically normalized by body-weight. We incorporate such normalization in our calculation.

We calculate $RGDR_{ER}$ with the scrubbing turned off. The animal: human ratio of the fractional penetration of the gas to the alveolar region in each species is developed separately later.

Dividing by the body weight of each species in equation 2, we have for the RGDR,

$$RGDR_{ER} = \frac{\left(\frac{V_e}{BW}\right)_A \times (E_{Syst})_A}{\left(\frac{V_e}{BW}\right)_H \times (E_{Syst})_H}. \quad (4)$$

E_{Syst} as given by equation I-77 in the EPA RfC document (EPA, 1994) is then,

$$E_{Syst} = 1 - \frac{C_{bg}}{C_i} = \frac{Q_T E_T H_{bg} + V_{lg} k_{lg} H_{tg}}{Q_T E_T H_{bg} + V_{lg} k_{lg} H_{tg} + V_e}. \quad (5)$$

In the above expression, we have incorporated a decomposition of the partition coefficient,

$$H_{tg} = H_{tb} \times H_{bg}. \quad (6)$$

Now, if systemic elimination is significantly greater than metabolism in the respiratory tract, then $V_{lg}k_{lg}H_{tg} << Q_T E_T H_{bg}$ and equation 5 may then be approximated to

$$E_{Syst} = 1 - \frac{C_{bg}}{C_i} = \left(1 + \frac{V_e}{Q_T E_T H_{bg}}\right)^{-1}. \quad (7)$$

Equation 7 is a corrected version of equation I-79 in the EPA RfC document, and furthermore, does not make the approximation that cardiac output is equal to the minute volume. Values of relevant parameters and numerical details of the calculation are presented in Table 5. The ratio $(V_e/BW)_A(V_e/BW)_H$ is the dominant term of the DAF.

Values for the variables were obtained from EPA (1994). This ratio for the F344 rat:human is equal to 6.0. Note that if this term were to be comprised of only the unnormalized animal to human ventilatory ratio, as is the case in the EPA RfC document, one would obtain a value of 0.03.

Next, we determine the animal:human ratio of systemic extraction efficiencies in equation 4. The liver extraction efficiency, E_T in equation 5 is set to the maximum value of 0.25 for both species (Andersen 1981), and values for the cardiac output were obtained from ILSI (1994). The blood-gas partition coefficient for phosphine, H_{bg}, is an unknown in this calculation. However, this quantity is likely to be similar in both species. In Table 5, we examine the sensitivity of $RGDR_{ER}$ to variations in H_{bg}, and find that the outcome varies little over a very large range of values. We have used a value for H_{bg} that is significantly greater than the Henry's Law constant for phosphine (EPA 1985). The values of other parameters used are given in Table 5. Then, the animal:human ratio of systemic extraction efficiencies is nearly equal to 1.0. Thus, ignoring the scrubbing effect of the Head and TB regions, the RGDR calculated by equation 4 indicates that, in the steady-state, the rat receives a six-fold higher systemic dose than the human.

Interspecies differences in the amount of gas scrubbed off in the head and TB regions are likely to arise on account of differences in airphase resistance between the species (because of very different airway geometries), and the surface areas presented. The fractional penetration to the alveolar region may be written in terms of the mass transfer coefficients (Cussler 1997) as (EPA 1994),

$$f_p = 1 - E_{(Head+TB)} = (1 - E_{Head}) \bullet (1 - E_{TB}) \quad (8)$$

$$= \exp\left(\frac{-K_g^{Head} SA^{Head}}{V_e}\right) \bullet \exp\left(\frac{-K_g^{TB} SA^{TB}}{V_e}\right). \quad (9)$$

Presuming negligible penetration to the blood compartment in the head and TB regions we may write

$$\frac{1}{K_g^{Head}} = \frac{1}{k_g^{Head}} + \frac{1}{H_{tg} k_l} \quad \text{and} \quad \frac{1}{K_g^{TB}} = \frac{1}{k_g^{TB}} + \frac{1}{H_{tg} k_l}. \quad (10)$$

Calculation of the above expressions and the ratio of the animal: human fractional penetration are presented in Table 3. The mass transfer coefficient for the TB region is not known; therefore, the animal: human ratio of the TB term in equation 9 is set equal to 1.0. For the Head region, the expressions in equations 9 and 10 involves:

(1) Calculating the air-phase mass transfer coefficient, k_g, for each species. This is obtained from the computational fluid dynamics (CFD) simulations of Subramaniam et al. (1998) for the human and Kimbell et al. (1997) for the rat. The mass transfer coefficients obtained from these simulations are being reported in manuscripts currently in preparation (Subramaniam et al. 2000; Kimbell et al. 2000). In the CFD computations, a boundary condition of zero concentration of the gas at the air-mucus interface was established. A mass transfer coefficient calculation from such a simulation corresponds to calculating only k_g, the air-phase contribution to the overall K_g. From the ratio of the concentrations of the gas C_{in} at the nostrils to C_{out}, the concentration at the nasopharynx; k_g is given by (EPA, 1994),

$$k_g = \frac{V_e}{SA} \ln\left(\frac{C_{in}}{C_{out}}\right) \quad (11)$$

This was originally calculated for formaldehyde gas. Since the diffusivity in air of formaldehyde gas is nearly the same as that of phosphine gas, calculated using Chapman-Enskog theory (Cussler 1997), no further scaling of the above k_g is needed. k_g is equal to 1.09 cm/s for the rat and 1.66 cm/s for the human.

(2) Estimating the product of the tissue-gas partition coefficient and the tissue phase mass transfer coefficient. Since there is no mention in the toxicological literature of phosphine gas reacting with nasal tissue, we consider only the effect of its solubility in the mucus lining. Then H_{tg} is set equal to the Henry's law constant for phosphine in non-dimensional form. The value for H_{tg} obtained from the literature (EPA, 1985) in dimensional form was divided by R.T to convert to the non-dimensional form in accordance with the ideal gas law. Here, R = 0.082 atm/(mole ^{o}K) and T is the temperature in ^{o}K.

The tissue-phase mass transfer coefficient, k_l, is given by

$$k_l = \frac{D_l}{l}$$

where D_l is the diffusivity of phosphine in mucus (water) and l is the thickness of the mucus layer (considered equal to 10 μm for both humans and 8 μm for rats (Miller et al., 1985). D_l is calculated using the Stokes Einstein equation (Cussler 1997).

Table 3. RGDR Calculation Worksheet

Physiological Parameters			
	Units	Rat (F344)	Human[a]
V_e	cm^3/s	4.17	125.00
BW	kg	0.38	70.00
E_t		0.25	0.25
Q_T	cm^3/s	1.90	85.73
H_{bg}	non-dim	100.00	100.00
H_{tg}		7.73	7.73
SA_{ET}	cm^2	15.00	200.00
SA_{TB}	cm^2	22.50	3200.00
D_l	cm^2/s	1.10E-05	1.10E-05
L	cm	8.00E-06	1.00E-05
Age of humans = 50 years			
Air phase mass transfer coefficient (k_g)			
	Rat	Human	
V_e/SA_{ET}	0.28	0.63	
C_{in}/C_{out}	50.00	14.29	
K_g	1.09	1.66	
Overall mass transfer coefficient (K_g)			
	Units	Rat	Human
k_g	cm/s	1.09	1.66
k_l	cm/s	1.37	1.10
K_g	cm/s	0.99	1.39
RGDR calculation			
	Rat	Human	Ratio A:H
Term1: V_e/BW	10.96	1.79	6.14
Term2: E_{syst}	0.92	0.95	0.97
RGDR			5.97
f_p: $1-E_{(head+TB)}$	0.03	0.11	0.27
Sensitivity of RGDR to H_{bg}			
H_{bg}	RGDR		
10.00	5.17		
20.00	5.51		
200.00	6.05		
1000.00	6.12		
5000.00	6.13		

The overall mass transfer coefficient, Kg is determined to be 0.99 cm/s for the rat and 1.39 cm/s for the human, resulting in an alveolar fractional penetration of 0.03 for the rat and 0.11 for the human. These results indicate the rat head to be a more efficient scrubber of phosphine gas than the human head. The net effect of this on the dosimetric adjustment factor would therefore be to reduce the large value of 6.0 obtained for the RGDR from equation 4.

These results indicate that the F344 rat receives a higher systemic dose of phosphine gas than an adult human. An important assumption made in deriving the RGDR is that the concentration levels of the gas in the blood have achieved a periodic steady-state. This is likely not to be the case for some of the acute exposures considered in this report. The results presented here must therefore be considered to be a rough estimate of the actual dosimetric adjustment factor.

The DAF is estimated to be somewhat greater than one. Because the calculated dosimetric adjustment factors indicate that rats are at least as sensitive and maybe more sensitive than humans based on dosimetric factors, the pharmacokinetic subfactor is set to one.

The remaining component of the interspecies uncertainty factor is the pharmacodynamic subfactor. This subfactor is intended to account for differences between experimental animal and human host susceptibility based on considerations other than pharmacokinetics (differences in tissue sensitivity). Mode of action data provide evidence of oxidative damage resulting from inhaled phosphine exposure for both humans and experimental animals (Chugh et al. 1996; 1997). Also, the reported findings of the human epidemiological studies provide evidence that humans can be exposed to maximum concentrations in the range of 2-7 ppm without effect (Misra et al. 1988; Barbosa and Bonin 1994; Shenyang Occupational Disease Prevention and Treatment Hospital 1986). This range is consistent with the reported no effect levels of the multiple animal studies shown above. Taken together, these findings indicate that it is reasonable to use data from animal studies of phosphine toxicity to extrapolate to safe levels of human exposure without the application a separate pharmacodynamic uncertainty factor. The product of the pharmacokinetic and pharmacodynamic factors, each of which is 1, results in a total interspecies uncertainty factor of 1.

For the intraspecies variability UF, EPA applied a value of 10 on the basis that data suggest that children may be more susceptible than adults. This conclusion was based on incidences of deaths in fumigated boxcars (MMWR 1994) and aboard a grain freighter (Wilson et al. 1980). However, none of these studies can be used to establish a dose-response relationship since concentrations were briefly variable. For instance, the concentrations of phosphine on the grain freighter ranged from 0.5 ppm to 30 ppm depending on the location. Men on the boxcars had periodically opened the hatch for fresh air as needed, and consequently may have received less exposure than the child. However, retaining an UF of 10 as the default appears prudent.

Revised AEGL-2 Values

Based on the above-mentioned issues on selection of the most appropriate study, an UF of 10 (1 for interspecies differences and 10 for intraspecies variability) and C x T relationship with n = 1, a revised AEGL-2 value using the Newton et al. (1993) study is proposed.
A C x T product of 60 ppm-hr is obtained from the NOEL of 10 ppm x 6-hour duration. Applying an UF of 10, results in a 6-hour AEGL-2 value of 1 ppm. Using n =1, time scaling

calculations result in the following AEGL-2 values for 30-minute, 1-hour, 4-hour and 8-hour durations (Table 4). The 30-minute AEGL-2 is adopted for the 10-minute duration.

Table 4. Revised AEGL-2 Values for Phosphine [ppm(mg/m³)].

Classification	10-min.	30-min.	1-hr.	4-hr.	8-hr.	Endpoint (Reference)
AEGL-2 (Disabling)	12.0 (17.1)	12.0 (17.1)	6.0 (8.53)	1.5 (2.13)	0.75 (1.07)	NOEL for rats exposed to 10 ppm phosphine for 6 hours. (Newton et al., 1993)

2. Derivation of the AEGL-3

EPA derived an AEGL-3 on the basis of a NOEL in rats exposed to 18 ppm phosphine for 6 hours (Newton, 1991). The selection of the study is appropriate. However, the time scaling with n = 3 for shorter exposure periods, and the UF of 30 are inappropriate for the derivation of this value. Applying an UF of 10 (1 for interspecies differences and 10 as a conservative default for intraspecies variability) and a C x T relationship with n = 1, a revised AEGL-3 value using the Newton (1991) study is obtained. A C x T product of 108 ppm-hr is obtained from the NOEL of 18 ppm x 6-hour duration. Applying an UF of 10 results in a 6-hour AEGL-3 value of 1.8 ppm. Using n =1, time scaling calculations result in the following AEGL-3 values for 30-minute, 1-hour, 4-hour and 8-hour durations (Table 5). The 30-minute AEGL-3 is adopted for the 10-minute duration.

Table 5. Revised AEGL-3 Values for Phosphine [ppm(mg/m³)].

Classification	10-min.	30-min.	1-hr.	4-hr.	8-hr.	Endpoint (Reference)
AEGL-3 (Lethality)	21.6 (30.7)	21.6 (30.7)	10.8 (15.3)	2.7 (3.84)	1.35 (1.92)	No-effect-level for lethality in rats exposed to 18 ppm phosphine for 6 hr. (Newton, 1991)

The AEGL-2 and AEGL-3 values derived for short-term exposures are supported by the results of phosphine monitoring exposure data. A risk assessment of exposure to fumigators using metal phosphides revealed that some workers were exposed to phosphine concentrations greater than 10 ppm for at least 17-minute durations (Mansdorf et al. 1988). Many of the workers did not wear respirators. In another study designed to assess worker exposures to phosphine during the treatment of grain with aluminum phosphide fumigant products, short-term measurements were made to evaluate very brief (2-5 minute) peak exposures during specific job tasks and peak concentrations (Zaebst et al. 1988). Zaebst et al. (1988) reported that employees were observed working without concern at concentrations up to and in excess of 50 ppm during

the peak exposures. The authors also report that the presence of high concentrations of phosphine "did not make working conditions unacceptable to the employee such that the employee was compelled to leave the area or don an appropriate respirator." Respirators were not seen in regular use by applicators or other exposed personnel at any of the elevators in the study.

CONCLUSION

- The 6-hour AEGL-2 should be based on the Newton et al. (1993) study rather than Morgan et al. (1995) . Unlike Morgan et al. (1995), Newton et al. (1993) reported the results of a single 6-hour exposure of rats to phosphine, and identified a NOAEL for toxicity.

- Application of $c^n \times t = k$ (with n=3) is not consistent with phosphine exposure and toxicity data. Instead, a $c \times t = k$ (n=1) fits the data well.

- Consideration of pharmacokinetic and pharmacodynamic factors supports a UF of 10.

- Revised AEGL-2 and AEGL-3 values, which take into consideration the conclusions above, are proposed.

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Subject: AEGL Values for MIC; Docket No. OPPTS-00293

Attached (in Wordperfect format and ASCII format) are comments re: OPPTS-00293 for submission. If you are unable to open any of the documents, please let us know and we will have a hard copy hand-delivered July 25, 2000. Thank you.
<<02LT005A.WPD>> <<02LT005B>>

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Metam-Sodium Task Force

Metam-Sodium
Task Force
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Metam-Sodium Task Force

Metam-Sodium Task Force

Metam-SodiumTask Force

July 24, 2000

Via E-Mail

Mr. Paul S. Tobin, Designated Federal Officer
OPPT Document Control Office (7407)
Office of Pollution Prevention and Toxics
United States Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Re: Proposed AEGL Values for MIC; Docket No. OPPTS-00293

Dear Mr. Tobin:

The Metam-Sodium Task Force (Task Force) submits these comments on the U.S. Environmental Protection Agency's (EPA) proposed Acute Exposure Guideline Levels (AEGLs) for methyl isocyanate (MIC). 65 Fed. Reg. 39264 (June 23, 2000). The Task Force includes the domestic producers of metam-sodium.1/

These comments address only issues specific to the proposed AEGL values for MIC. The Task Force opposes the AEGL values proposed, and urges EPA to withdraw them. EPA at the least should withdraw the AEGL-2 values because they are scientifically indefensible, as discussed below. EPA should also consider the additional references noted below in reconsidering AEGL values for MIC. The Task Force may submit additional information in this regard should more information become available.

Comments on AEGL-2

One of the toxicity endpoints EPA used to calculate an AEGL-2 is the occurrence of cardiac arrhythmias observed in rats exposed by inhalation to 3 or 10 ppm MIC for 2 hours (Tepper, et al. 1987). These rats were also exposed to a 4 or 8% carbon dioxide challenge 4 months after exposure to MIC. The Task Force questions whether this finding can be attributed solely to MIC. Exposure of rats to carbon dioxide at concentrations ranging from 5 to 70% for 20 minutes is known to cause cardiac arrhythmias (Petty and Sulkowski, 1971). There is no basis in the record to conclude that the cardiac arrhythmias observed in this study could be attributed to carbon dioxide exposure and not solely to MIC exposure as EPA suggests in the proposal. Based on the above, the Task Force does not believe that this endpoint should be used for calculation of the AEGL-2 for MIC, and urges EPA to withdraw these values.

1/ Metam-Sodium Task Force members are: Amvac Chemical Corporation, Tessenderlo Kerley, Inc., and UCB Chemicals Corporation.

Metam-Sodium
Task Force
Members:

Amvac Chemical
Corporation

Tessenderlo
Kerley, Inc.

UCB Chemicals
Corporation

RC

c/o Mr. Ian S. Chart, Amvac Chemical Corporation 4695 MacArthur Court Suite 1250
Newport Beach, California 92660
Metam-Sodium Task Force

The second endpoint that was used to calculate an AEGL-2 was reduced body weight gain observed in the fetuses of mice treated with MIC through inhalation exposure for 3 hours at concentrations of 2, 6, 9, and 15 ppm on gestation day 8 (Varma, 1987). The EPA document states that fetal body weights were statistically reduced to 73 to 93% of the control values. Assuming that the 93% value is attributed to the low dose group and the effects are dose-related, the Task Force questions the significance of a 7% decrease in fetal body weight in mice at 2 ppm. The fetal body weights observed at 2 ppm should be compared to historical control data and to intra-group variation within the study, itself, to determine the biological significance of the decrease. Thus, the Task Force questions the use of an extra factor of 3 in the calculation of the AEGL-2 to account for the lack of a NOEL for the effects of MIC on mouse fetal body weights. Depending upon the outcome of comparison to historical control data and intra-group variation, an extra uncertainty factor of 3 or any extra factor might not be justified for calculating the AEGL-2 if 2 ppm can be justified as a NOEL or very close to a NOEL.

Additional References

The Task Force offers additional references for the Committee's review. The Task Force believes that an additional reference on genotoxicity should be added to the EPA document. According to the abstract of this work, male BDF1-mice were exposed by inhalation to 2, 15, and 30 ppm of MIC for 3 hours (Conner, et al. 1987). SCE levels and cell cycle kinetics were determined in bone marrow and alveolar macrophages labeled with bromodeoxyuridine (BrdUrd) in vivo and in splenic and peripheral blood lymphocytes exposed to BrdUrd in vitro. From the results of the studies, the authors concluded that MIC is cytotoxic, but does not appear to be genotoxic under the conditions of this study.

Although a repeated exposure study, work by Fowler and Dodd (1987) indicates that the respiratory tract lesions (inflammation and squamous metaplasia of the respiratory epithelia in the nasal cavity, trachea, and bronchi and inflammation and submucosal fibroplasia of the bronchioles) in rats exposed to 3 ppm MIC for 6 hours/day for 4 consecutive days are almost completely reversible within 85 days of exposure. The Task Force believes that this study should be included in the EPA document to indicate the reversibility of MIC toxicity in the respiratory tract of the rat. References of interest include:

Conner, MK et al. (1987). "Evaluation of sister chromatid exchange and cytotoxicity in murine

tissues in vivo and lymphocytes in vitro following methyl isocyanate exposure." Envtl. Health Persp. 72:177-182.

Fowler, EH and Dodd, DE (1987). "Eighty-five day postexposure follow-up study in Fischer 344 rats after repeated exposures to methyl isocyanate vapor." Envtl. Health Persp. 72:125-132.

Petty, WB and Sulkowski, TS (1971). "CO2 narcosis in the Rat: Effects on the ECG." Aerospace Medicine 42:553-558.

Schwetz, BA, et al. (1987). "Methyl isocyanate: Reproductive and developmental toxicology studies in Swiss mice." Envtl. Health Persp. 72:149-152.

Tepper, JS, et al. (1987). "Cardiopulmonary effects in awake rats four and six months after exposure to methyl isocyanate." Envtl. Health Persp. 72:95-103.

Varma, DR (1987). "Epidemiological and experimental studies on the effects of methyl isocyanate on the course of pregnancy." Envtl. Health Persp. 72:153-157.

Varma, DR, et al. (1990). "Dissociation between maternal and fetal toxicity of methyl isocyanate

in mice and rats." J. Toxicol. Envtl. Health 30:1-14.

The Metam-Sodium Task Force appreciates the opportunity to comment on the proposed AEGLs.

Sincerely,

David A. Sullivan

Mr. David A. Sullivan,
Executive Director for The Metam-Sodium Task Force

cc: The Metam-Sodium Task Force (via e-mail)

Phosphine

gburin@tsgusa.com on 07/21/2000 02:17:26 PM

To: Paul Tobin/DC/USEPA/US
cc:

Subject: OPPTS-00293

Dear Mr. Tobin,

I am pleased to submit the following comments on the Proposed AEGL values for Phosphine (FR June 23,

2000, Volume 65, Number 122, pp. 39263-39277). These comments are submitted on behalf of the Midland

Fumigant Company, Inc.

The calculation of the AEGL-2 and AEGL-3 should be revised to be consistent with the available data showing

the relationship of toxicity to the duration of exposure. Existing toxicology data shows that the concentration-

time relationship ($c^n \times t = k$) used to derive the AEGL should use n=1 for all timepoints. This linear relationship

of toxicity plotted against time and concentration is shown in Figure 1 of Section 4.4.1. The caution of EPA in

assuming that Haber's Law requires an exponent of 3 rather than 1 is not supported by available toxicity

information. It should also be noted that EPA has assumed that the 4 day study of Morgan et al., (1995) was a

single day of exposure rather than the four days that was in fact used in this study. The application of the

previously described concentration-time relationship would result in an 8 hour AEGL-2 that is 4-fold greater

than that currently proposed.

Sincerely,

Gary J. Burin, Ph.D., M.P.H., DABT

Director, Toxicology, Ecotoxicology and Risk Assessment

Technology Sciences Group, Inc.

Washington, D.C.

20036

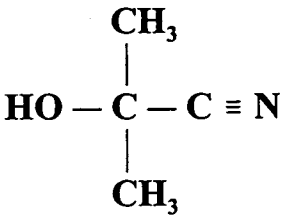
 - att1.htm

Acute Exposure Guideline Levels (AEGLs)

for

Acetone Cyanohydrin

(CAS No. 75-86-5)



NAC/AEGL Meeting 18, July 26-28, 2000

FoBiG Staff Scientist:

Peter Griem

Chemical Manager in German Expert Group:

Rüdiger Bartsch

Industry Reviewer for German Expert Group:

Harald Müllerschön

Chemical Manager:

Larry Gephart

ACETONE CYANOHYDRIN

PROPERTIES

- liquid, colorless to yellowish, bitter almond odor
- moderate vapor pressure at room temperature (1 hPa)
- soluble in water, alcohol and ether

PRODUCTION

- capacity about 1 million tons worldwide

USES

- industrial prodution of α-methacrylic acid esters and plexiglass
- industrial synthesis of several insecticides, pharmaceuticals and fragances

TOXICITY CONCERNS

- fast decomposition upon contact with water releasing HCN and acetone
- central nervous system and systemic toxicity (including CNS depression, convulsions, coma and death) due to inhibition of mitochondrial ATP generation by cyanide
- very steep dose-response relationship
- skin resorption

DATA RELEVANT TO AEGL-1

HUMAN

- ACH: no data for available in the literature
- (cyanide!) Leeser et al. (1993)

  occupational exposure to cyanide concentrations of 1-3 ppm caused no adverse effects

ANIMALS

- ACH: irritative effects in rats

  red nasal discharge, perioral wetness/red stain and inflammation around the eyes

Irritation effects in rats during first week of exposure for 6 h/d			
Exposure conc. (ppm)	No. of affected animals (controls)	Reference	study type and length
10.0 28.5 57.2	10/15 (10/15) 12/15 14/15	Monsanto, 1982b	fertility study in male rats, 5 d/w, 10 w
10.7 30.4 58.6	9/24 (6/24) 10/24 21/24	Monsanto, 1982c	fertility study in female rats, 7 d/w, 3w
9.2 29.9 59.6	0/20 (0/20) 4/20 2/20	Monsanto, 1986a	subacute study in male and female rats, 5 d/w, 4 w
10.1 28.6 57.7	20/30 (6/30) 21/30 22/30	Monsanto, 1986b	subchronic study in male and female rats, 5 d/w, 14 w

* after first exposure, death in 3 animals and severe symptoms in another

AEGL-1

Keystudy: Monsanto (1986b)

Endpoint: LOEL for red nasal discharge in rats after repeated exposure to 10.1 ppm ACH for 6 hours/day

LOEL-NOEL extrapolation factor: 3
10.1 ppm / 3 = 3.37 ppm

Time scaling: no time scaling was used,

but it was considered safe to use the value derived from the experimental 6-hour exposure for time periods of 8 h, 4 h, 1 h, 30 min and 10 min

Total uncertainty factor: 3

Interspecies: **1**

because rats were considered more sensitive for red nasal discharge than humans.

Intraspecies: **3**

because the interindividual differences are expected to be limited since decomposition of acetone cyanohydrin does not involve enzyme-catalyzed steps and the local effect on blood vessel epithelium is unlikely to differ substantially between individuals

AEGL-1 Values for Acetone Cyanohydrin				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
1.1ppm 3.9 mg/m^3	1.1ppm 3.9 mg/m^3	1.1ppm 3.9 mg/m^3	1.1ppm 3.9 mg/m^3	1.1ppm 3.9 mg/m^3

DATA RELEVANT TO AEGL-2

HUMAN

- ACH: no relevant data available
- (cyanide!) El Gawabi et al., 1975; Blanc et al., 1985

  occupational exposure to cyanide concentrations of 6-10 or 15 ppm caused eye irritation, headache, weakness, changes in taste and smell, irritation of the throat, vomiting and effort dyspnea

ANIMAL

- ACH: irritative effects in rats

  red nasal discharge, perioral wetness/red stain and inflammation around the eyes

Consideration:

- acetone cyanohydrin decomposes to HCN
- decomposition accelerated by heat and water
- systemic toxic effects are caused by free cyanide
- HCN has higher vapor pressure than acetone cyanohydrin (mixed exposure always will occur)

Conclusion: Apply AEGL-2 values derived for HCN

AEGL-2 Values for Acetone Cyanohydrin				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
17 ppm 60 mg/m^3	10 ppm 35 mg/m^3	7.1 ppm 25 mg/m^3	3.5 ppm 12 mg/m^3	2.5 ppm 8.8 mg/m^3

DATA RELEVANT TO AEGL-3

HUMAN

- ACH: fatal exposures after inhalation, skin contact and oral uptake have been documented
- ACH: no data relevant for AEGL derivation available
- (cyanide!) El Gawabi et al., 1975; Blanc et al., 1985

  occupational exposure to HCN concentrations of 6-10 or 15 ppm caused no lethal or irreversible effects

ANIMAL

- ACH: lethal effects in rats

Exposure	Effects	Reference
62.5 ppm x 4 h	death in 2/6	Smyth et al. (1962)
59.6 ppm x 6 h/d, 5 d/w, 4 w	death in 3/20	Monsanto, 1986a
58.6 ppm x 6 h/d, 7 d/w, 3 w	no death in 24	Monsanto, 1982c
57.7 ppm x 6 h/d, 5 d/w, 30 w	no death in 30	Monsanto, 1986b
57.2 ppm x 6 h/d, 5d/w, 14 w	no death in 15	Monsanto, 1982b

nominal conc. exp. 1: 64.8 ppm other exp.s: 60.4 ± 1.8 ppm
analytical conc. exp. 1: 55.5, 60.5, 63.5, 63.5 other exp.s: 59.5 ± 1.4 (max. 61.5) ppm

Consideration:

- acetone cyanohydrin decomposes to HCN
- decomposition accelerated by heat and water
- toxic effects are caused by free cyanide
- HCN has higher vapor pressure than acetone cyanohydrin (mixed exposure always will occur)

Conclusion: Apply AEGL-3 values derived for HCN

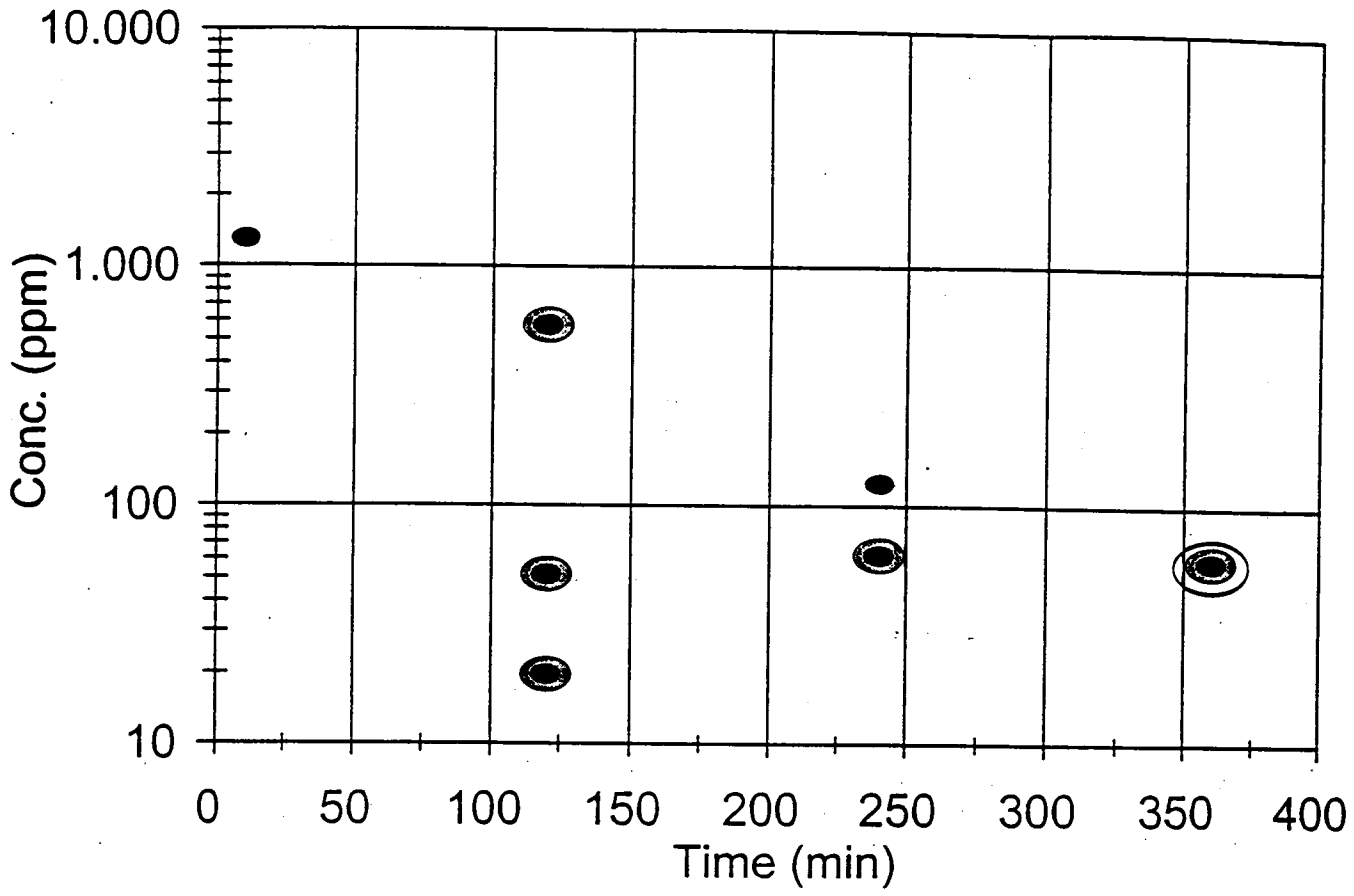
AEGL-3 Values for Acetone Cyanohydrin				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
27 ppm	21 ppm	15 ppm	8.8 ppm	6.6 ppm
95 mg/m^3	74 mg/m^3	53 mg/m^3	31 mg/m^3	23 mg/m^3

DATA RELEVANT TO AEGL-3

ANIMAL

SUMMARY OF ACUTE LETHAL INHALATION DATA IN LABORATORY ANIMALS				
Species	**Conc. (ppm)**	**Time**	**Effect**	**Reference**
Rat	sat. vapor ~ 1300 ppm	1.5 min	6/6 animals died in exposure; using commercial ACH	Sunderman and Kincaid, 1953
Rat	sat. vapor ~ 1300 ppm	10 min	6/6 animals died in exposure ; ACH with HCN removed	Sunderman and Kincaid, 1953
Rat	125	4 h	6/6 animals died	Smyth et al., 1962
Rat	62.5	4 h	2/6 animals died	Smyth et al., 1962
Rat	59.6	6 h/d, 5 d/w, 4 w	3/20 animals died after first exposure	Monsanto, 1986a
Rat	58.6	6 h/d, 7 d/w, 21 d	no deaths in 24 animals	Monsanto, 1982c
Rat	57.7	6 h/d, 5 d/w, 14 w	no deaths in 30 animals	Monsanto, 1986b
Rat	57.2	6 h/d, 5 d/w, 48 d	no deaths in 15 animals	Monsanto, 1982b
Rat	51.8	2 h	LC_{40}	Izmerov et al., 1982
Mouse	574	2 h	LC_{50}	Gabor et al., 1962
Mouse	19.6	2 h	LC_{30}	Izmerov et al., 1982

Lethal effects of acetone cyanohydrin



DATA RELEVANT TO AEGL-3

ANIMAL

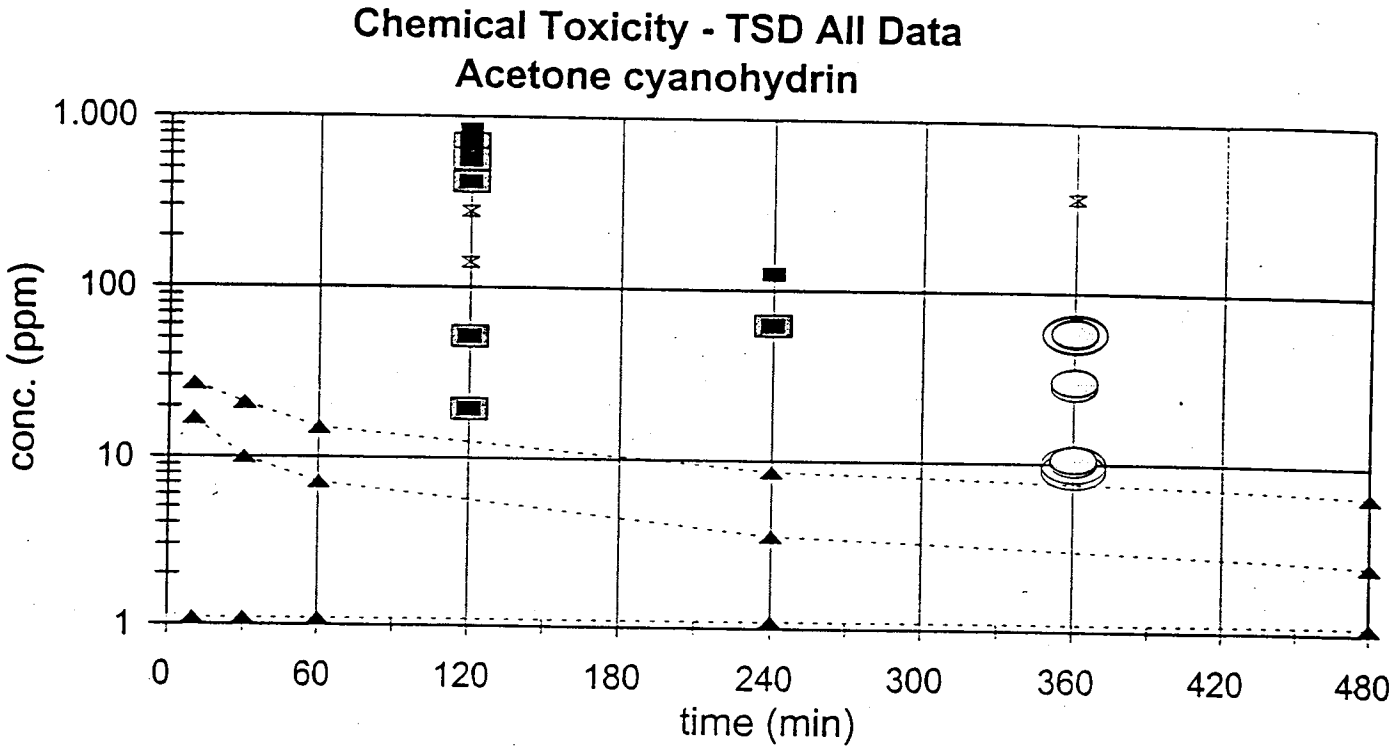
– oral lethality studies

ORAL LD_{50} DATA FOR ACETONE CYANOHYDRIN		
Species	**LD_{50} (mg/kg)**	**References**
Rat	17	Smyth et al., 1962
Rat	13,3	Shkodich, 1966
Rat	17,8	Marhold, 1972
Mouse	14	Marhold, 1972
Mouse	15	Hamblin, 1953
Mouse	2,9	Shkodich, 1966
Guinea pig	9	Shkodich, 1966
Rabbit	13,5	Shkodich, 1966

AEGL Values for Acetone Cyanohydrin [a]					
	10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
AEGL-1	1.1ppm 3.9 mg/m^3	1.1ppm 3.9 mg/m^3	1.1ppm 3.9 mg/m^3	1.1ppm 3.9 mg/m^3	1.1ppm 3.9 mg/m^3
AEGL-2	17 ppm 60 mg/m^3	10 ppm 35 mg/m^3	7.1 ppm 25 mg/m^3	3.5 ppm 12 mg/m^3	2.5 ppm 8.8 mg/m^3
AEGL-3	27 ppm 95 mg/m^3	21 ppm 74 mg/m^3	15 ppm 53 mg/m^3	8.8 ppm 31 mg/m^3	6.6 ppm 23 mg/m^3

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

Alternative AEGL Values for Acetone Cyanohydrin					
	10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
AEGL-2	#	6.9 ppm 24 mg/m^3	5.4 ppm 19 mg/m^3	3.4 ppm 12 mg/m^3	2.2 ppm 7.7 mg/m^3
AEGL-3	#	13 ppm 46 mg/m^3	10 ppm 35 mg/m^3	6.6 ppm 23 mg/m^3	4.3 ppm 15 mg/m^3


Chemical Toxicity - TSD All Data
Acetone cyanohydrin
1.000
100
10
1
conc. (ppm)
0
60
120
180
240
300
360
420
480
time (min)
no or minimal effect
discomfort
disabling
did not die @ lethal conc
lethal

AEGL-2 ALTERNATIVE DERIVATION

Keystudy: Monsanto (1986a)

Endpoint: Irritation, but no irreversible effects, after repeated exposure to 29.9 ppm ACH for 6 hours/day

Time Scaling: $C^n \times t = k$

due to lack of specific data default value of n = 3 for shorter exposure periods and n = 1 for longer periods

Total uncertainty factor: 10

Interspecies: 3

because repeated exposure of humans at the workplace to cyanide concentrations only about 2-3-fold lower than the estimated threshold for irreversible effects of acetone cyanohydrin in rats of 29.9 ppm did not lead to severe adverse health effects (El Ghawabi et al., 1975, Blanc et al., 1985)

Intraspecies: 3

because decomposition of acetone cyanohydrin does not involve enzyme-catalyzed steps and the binding to evolutionary conservative iron-containing proteins/ enzymes, i.e., the target protein cytochrome c oxidase, is unlikely to differ substantially between individuals

AEGL-2 Values for Acetone Cyanohydrin				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
#	6.9 ppm 24 mg/m^3	5.4 ppm 19 mg/m^3	3.4 ppm 12 mg/m^3	2.2 ppm 7.7 mg/m^3

AEGL-3 ALTERNATIVE DERIVATION

Keystudy: Monsanto (1986b)

Endpoint: No death in rats after repeated exposure to 57.7 ppm ACH for 6 hours/day

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

due to lack of specific data default value of n = 3 for shorter exposure periods and n = 1 for longer periods

Total uncertainty factor: 10

Interspecies: 3

because repeated exposure of humans at the workplace to cyanide concentrations only about 3-fold lower than the lethality threshold of acetone cyanohydrin in rats of 57.7 ppm did not lead to life-threatening or irreversible health effects (Blanc et al., 1985)

Intraspecies: 3

because decomposition of acetone cyanohydrin does not involve enzyme-catalyzed steps and the binding to evolutionary conservative iron-containing proteins/enzymes, i.e., the target protein cytochrome c oxidase, is unlikely to differ substantially between individuals

AEGL-3 Values for Acetone Cyanohydrin				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
#	13 ppm 46 mg/m^3	10 ppm 35 mg/m^3	6.6 ppm 23 mg/m^3	4.3 ppm 15 mg/m^3

Acute Exposure Guideline Levels (AEGLs)

for

Acrylic Acid

(CAS No. 79-10-7)

$CH_2 = CH - COOH$

NAC/AEGL Meeting 18, July 26-28, 2000

FoBiG Staff Scientist:

Peter Griem

Chemical Manager in German Expert Group:

Ursula Gundert-Remy

Industry Reviewer for German Expert Group:

Rudolf Jäckh

Chemical Manager:

Ernest Falke

ACRYLIC ACID

PROPERTIES

- liquid, colorless, pungent odor
- medium vapor pressure at room temperature (10 hPa)
- soluble in water, alcohol and ethers

PRODUCTION

- capacity about 2 million tons worldwide

USES

- industrial prodution of acrylic esters and resins

TOXICITY CONCERNS

- causes strong local irritation
- mechanism involves induction of mitochondrial permeability transition in causing breakdown of ATP synthesis and resulting in necrotic and apoptotic cell death

HUMAN DATA RELEVANT TO AEGL-1

ODOR

- Hellman and Small (1974)

  odor detection level: 0.094 ppm
  odor recognition level: 1.04 ppm

IRRITATION

- Renshaw, personal communication, cited in AIHA (1991)

REPORTED INDUSTRIAL EXPERIENCE FROM OCCUPATIONAL EXPOSURE TO ACRYLIC ACID (Rohm and Haas Co.) *				
Time (min)	**Conc. (ppm)**	**Sampling type**	**No. samples / individuals**	**Effects / operation**
10	63	personal	1 / 1	slight throat irritation / pumping from drums to mix tank
16 - 20	5.0 - 17.2	personal, area	3 / ≥3	eye irritation, sharp but intermittant / cleaning basket stainer
30	4.5 - 23.0	personal	2 / 2	eye irritation / loading tank truck
36 - 152	0.3 - 1.6	area	3 / ≥3	oder very noticeable, slight eye irritation / drums in hot room
78 - 93	5.8 - 11.6	personal	2 / 2	no sign of symptom among veteran chemical workers / filling drums

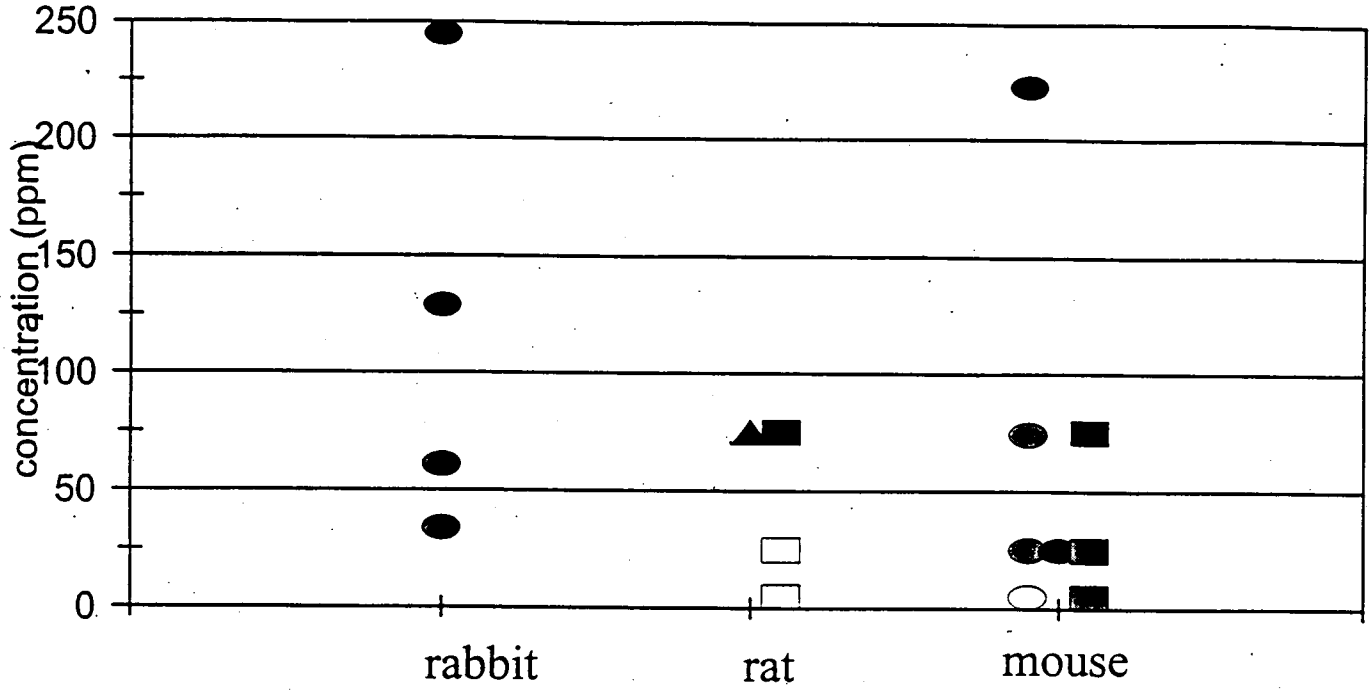
* Dr. Frank Renshaw, author of Rohm and Haas Company's ERPG report and former Director of Corporate Industrial Hygiene, suggested to assume each sample represents feedback from a single individual, as in "personal" sampling. While it is likely that more than one enployee was monitored in "area" sampling, the historical records do not support exactly how many were monitored. Thus, it is reasonable and conservative to conclude that this table represents at least 11 exposed individuals.

ANIMAL DATA RELEVANT TO AEGL-1

IRRITATION

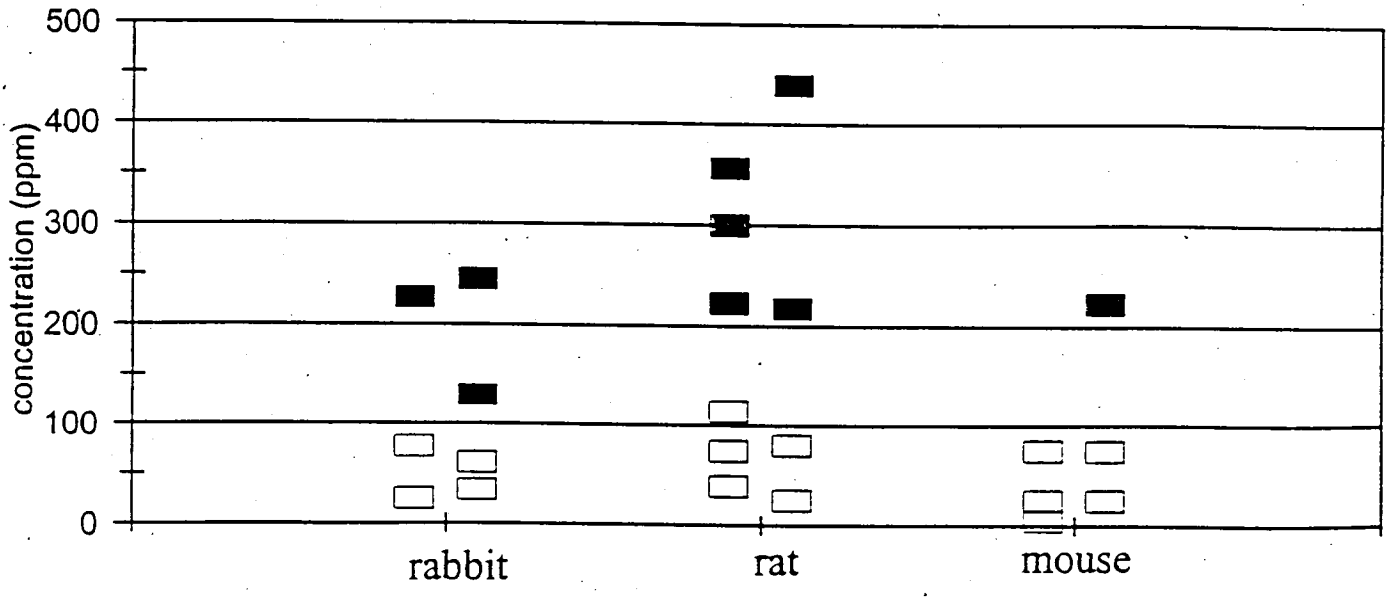
Species	NOEL / LOEL for signs of irritation	NOEL / LOEL for histopathologic effects	Reference
Rabbit	77 / 129 ppm (6 h/d)	n.d. / 34 ppm (6 h/d)	Neeper-Bradley et al., 1997
	0, 25, *34*, *61*, 77, *129*, 227, *245* ppm for 6 h/d, 13 d (8 pregnant rabbits/group)		
	perinasal and perioral wetness (2/7, 4/7 only 1st day), blepharospasm	mild metaplasia (2/3), mild erosion of epithelium (1/3)	
Rat	114 / 218 ppm (6 h/d) (a)	25 / 74 ppm (6 h/d) (b)	(a) Klimisch and Hellwig, 1991; (b) Miller et al., 1981;
	0, 39, 114, *218*, 356, *439* ppm for 6 h/d, 10 d (30 pregnant/group)	0, 5, 25, 75 ppm for 6 h/d, 5 d/w, 13 w (15f+15m/group)	
	eyelid closure, discharge from eyes, reddish discharge from nose (on 1st and subsequent exposures)	slight focal degeneration of olfactory epithelium	
		n.d. / 75 ppm (3 h)	Frederick et al., 1998
		0, 75 ppm for 3, 6 h (5f/group)	
		olfactory epithelial cell degeneration and sustentaculare cell necrosis	
Mouse	75 / 223 ppm (6 h/d) (a)	5 / 25 ppm (6 h/d) (b) - / 5 ppm (22 h/d) - / 25 ppm (4.4 h/d)	(a) Miller et al., 1981; (b) Lomax et al., 1994
	0, 5, *25*, 25, *74*, 75, *223* ppm for 6 h/d, 5 d/w, *2*, 13 w (*5m+5f*, 15m+15f/group)	0, 5 ppm x 6 h/d, 25 ppm x 4.4 h/d, 25 ppm x 22 h/d, 2 w (10f/group)	
	scratching at the nose	disorganization, atrophy, desquamation and necrosis of olfactory epithelium, basal cell hypertrophy	

Histopathologic effects on olfactory epithelium after 6-hour exposures



- moderate/marked effects, single
- very slight/slight/mild effects, 2 w
- no effects, 13 w
- moderate/marked effects, 13 w
- no effects, 2 w
- moderate/marked effects, 2 w
- very slight/slight/mild effects, 13 w

Observed irritative effects



- no irritation
- slight irritation
- severe irritation

AEGL-1

Keystudy: Hellman and Small (1974)

Endpoint: odor recognition threshold: 1.04 ppm

Time scaling: flat line

because the odor threshold is considered to depend primarily on exposure concentration and not much on exposure time

Total uncertainty factor: 1

Interspecies: not applicable

Intraspecies: 1

because this factor was considered adequate for an odor threshold.

AEGL-1 Values for Acrylic Acid				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
1.0 ppm 3.0 mg/m^3	1.0 ppm 3.0 mg/m^3	1.0 ppm 3.0 mg/m^3	1.0 ppm 3.0 mg/m^3	1.0 ppm 3.0 mg/m^3

DATA RELEVANT TO AEGL-2

HUMAN

- no relevant data available

ANIMAL

- severe irritative effects in rabbits, rats and mice, such as erosion and ulceration of the olfactory epithelium which might lead to permanent functional deficit; a threshold cannot be established for these effects
- blepharospasm in rabbits (at 129 ppm) or eye lid closure in rats (at 218 ppm) during 6-hour exposures can be interpreted as an irritation severity level high enough to impair ability to escape

Blepharospasm

Blepharo means "eyelid" and spasm means "uncontrolled muscle contraction"

- involuntary tight closure of the eyelids caused by chemical irritation (probably through irritation of the corneal nerves) or physical irritation (e.g. dust, sand)
- in medicine applied to any abnormal blinking or eyelid tic or twitch, very often developing spontaneously in susceptible people (thought to be due to abnormal functioning of the basal ganglia)

"Personal defense sprays: effects and management of exposure"

J. Am. Optometric Assoc. 67 (1996) 548-560

- CN (ω-chloroacetophenone) , CS (o-chlorobenzylidene malonitrile)

  "... cause extreme irritation of the eyes, burning pain, conjuctival hyperemia, lacrimation, and possibly blepharospasm."

- OC (oleoresin capsicum)

  "In the eye, it produces blepharospasm,..., extreme buring pain, lacrimation, conjunctival edema and hyperemia."

  After being sprayed with OC, all (n=22) police officers experienced immediate and intense blepharospasm, conjuntival injection, burning pain, mild respiratory difficulties, excessive mucous secretion and incapacitation. The incapacitating effects were transient and lasted between 5 and 10 minutes.

AEGL-2

Keystudy: Neeper-Bradley et al. (1997)

Endpoint: Blepharospasm in rabbits at 129 ppm (LOEL), but not at 77 ppm (NOEL)

Time scaling: flat line
because the increase of this effect with time was assumed to be small and observations form 6-hour exposure periods were available, use of a flat line was considered an appropriate approach

Total uncertainty factor: 3

Interspecies: 1

because the rabbit was considered a species especially sensitive for blepharospasm/eyelid closure: 129 ppm was the LOEL in rabbits while 218 ppm was the LOEL in rats and no effect was seen in mice at 223 ppm.

Intraspecies: 3

because it was assumed that only toxicodynamic, but not toxicokinetic differences contribute to variability of this local effect.

AEGL-2 Values for Acrylic Acid				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
26 ppm 78 mg/m^3	26 ppm 78 mg/m^3	26 ppm 78 mg/m^3	26 ppm 78 mg/m^3	26 ppm 78 mg/m^3

DATA RELEVANT TO AEGL-3

HUMAN

- no relevant data available

ANIMAL

- Hagan and Emmons (1988)

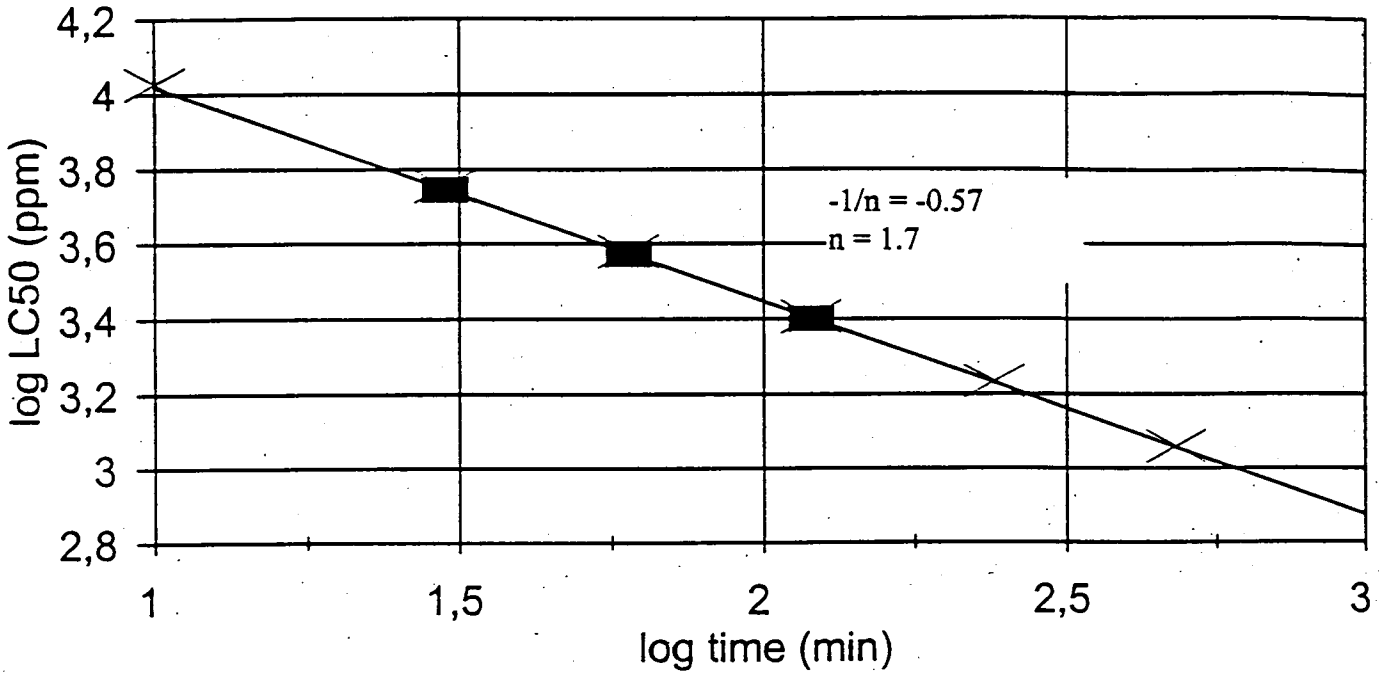
  Whole-body inhalation exposure to acrylic acid **aerosol**
  (mean mass median diameter 2.4 ± 0.5 µm)
  30 min: 10 concentrations, 2925 - 4715 ppm
  60 min: 7 concentrations, 2713 - 4208 ppm
  120 min: 7 concentrations, 1223 - 3413 ppm

  Nose-only exposure of restrained rats to acrylic acid **aerosol**
  30 min: 8 concentrations, 757 - 3850 ppm
  60 min: 6 concentrations, 1088 - 3882 ppm
  120 min: 5 concentrations, 1223 - 3922 ppm

  Whole-body exposure to acrylic acid **vapor**
  60 minutes: 5 concentrations between 928 and 2142 ppm
  (no deaths were observed).

PROBIT ANALYSIS OF LETHALITY DATA FOR SINGLE EXPOSURE TO ACRYLIC ACID AEROSOLS IN RATS			
Time	**Calculated exposure concentration (ppm)**		
	LC_{50} (MLE)	**LC_{01} (MLE)**	**LC_{05} (95% C.I.)**
10 min	10690	4772	5105
30 min	5676	2533	2767
1 h	3806	1139	1722
4 h	1712	767	620
8 h	1148	512	369

Graphical Determination of Exponent n

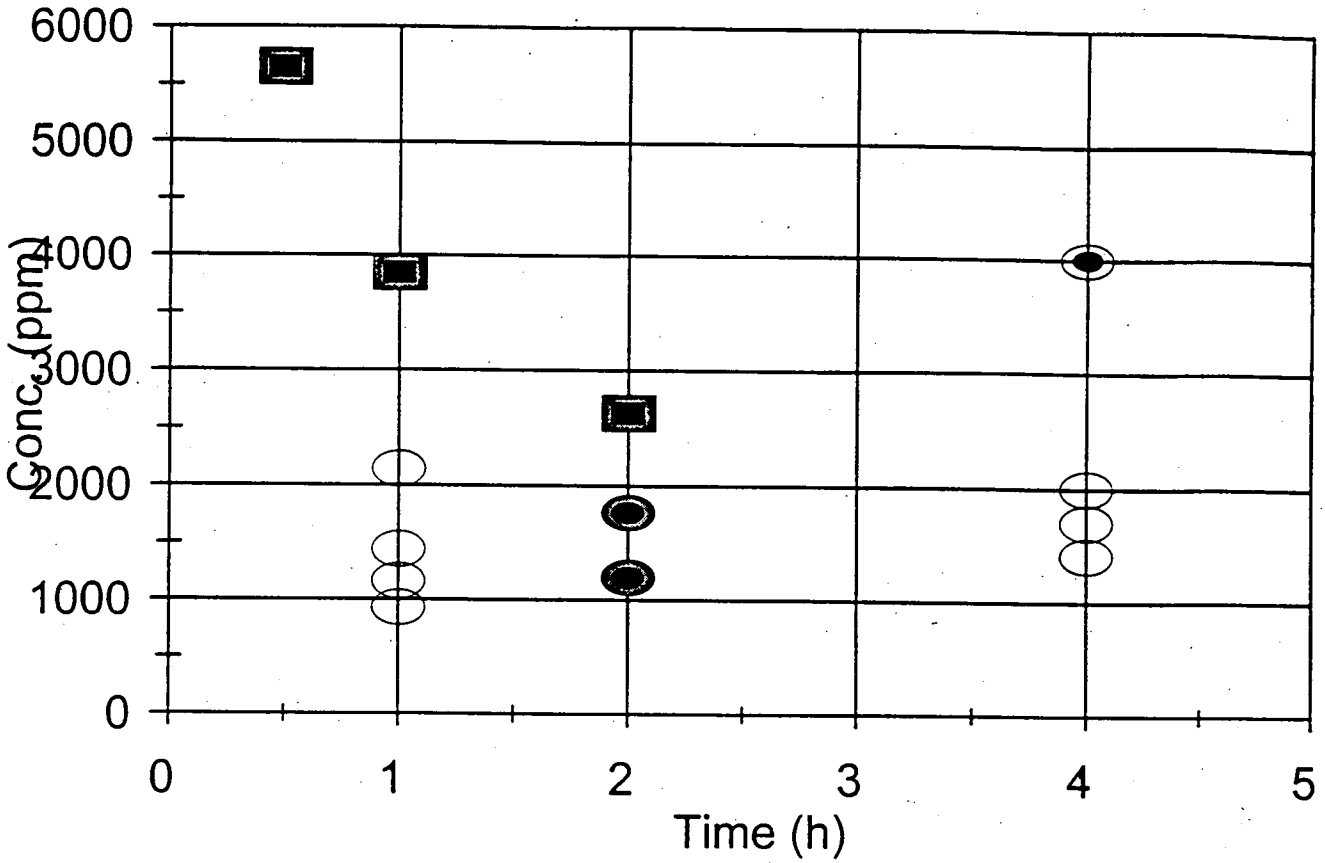


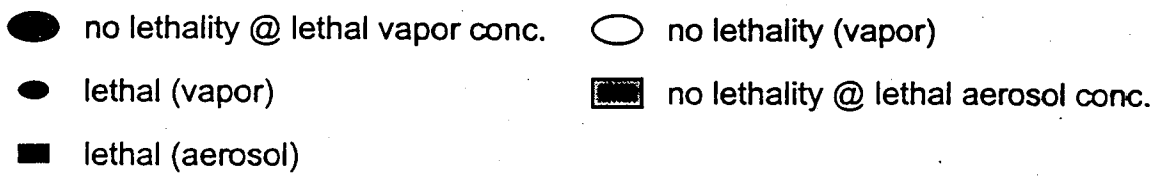
ANIMAL DATA RELEVANT TO AEGL-3

- comparison of aerosol and vapor studies

SUMMARY OF ACUTE LETHAL INHALATION DATA IN LABORATORY ANIMALS					
Species	**Time (h)**	**Conc. (ppm)**	**No. of animals used**	**Effect**	**Reference**
rat	5	sat. vapor	4	1/4 died	Gage (1970)
rat	4	4000 (vapor)	6	6/6 died	Carpenter et al. (1974)
rat	4	3996 (vapor)	6	no deaths	Union Carbide Co., 1977
rat	4	2000 (vapor)	6	0/6 died	Carpenter et al. (1974)
rat	4	1705 (vapor)	20	0/20 died	BASF, 1980
rat	2	2552 (aerosol)	70 (var. conc.)	LC_{50}	Hagan and Emmons, 1988
mouse	2	1765 (not stated)	?	LC_{50}	Izmerov et al. (1982)
rat	2	1200 (vapor)	?	LC_{50}	Majka et al. (1974)
rat	1	3806 (aerosol)	72 (var. conc.)	LC_{50} for aerosol	Hagan and Emmons, 1988
rat	1	2142 (vapor)	10	no deaths	Hagan and Emmons, 1988
rat	0,5	5676 (aerosol)	100 (var. conc.)	LC_{50} for aerosol	Hagan and Emmons, 1988

Lethal effects of acrylic acid





AEGL-3

Keystudy: Hagan and Emmons (1988)

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

Time scaling: $C^{1.7} \times t = k$ (n = 1.7) for shorter and longer exposure periods; n was derived by Probit analysis from the data by Hagan and Emmons (1988)

Total uncertainty factor: 10

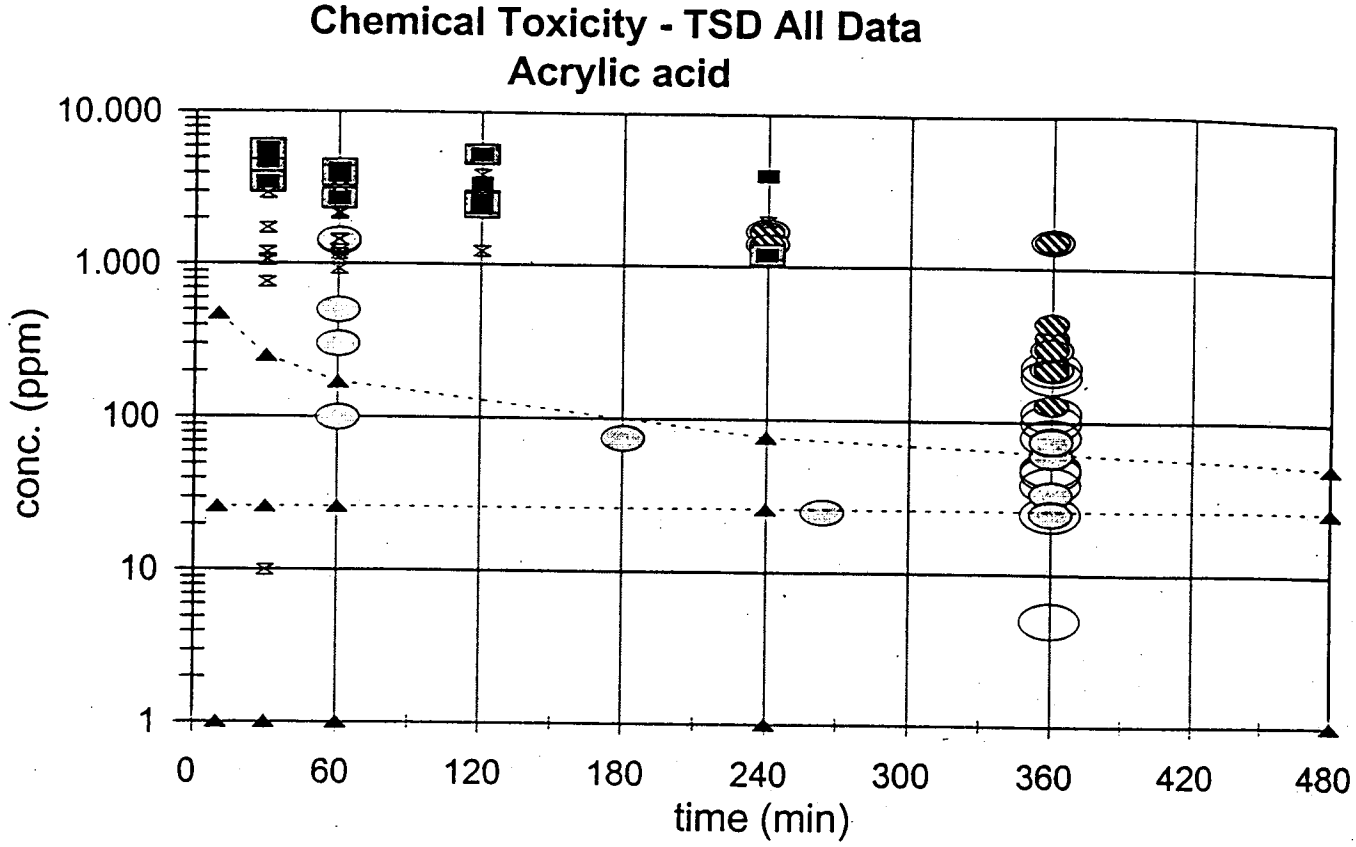
Interspecies: 3

because the interspecies variability was assumed to be small due to the facts that acrylic acid is a contact-site, direct-acting toxicant, the mechanism of action is unlikely to differ between species and the influence of metabolism, detoxification and elimination on lethal effects after inhalation is estimated to be small.

Intraspecies: 3

because a small interindividual variability can be assumed considering that acrylic acid is a contact-site, direct-acting toxicant not requiring metabolic conversion.

AEGL-3 Values for Acrylic Acid				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
480 ppm 1400 mg/m^3	250 ppm 750 mg/m^3	170 ppm 510 mg/m^3	77 ppm 230 mg/m^3	51 ppm 150 mg/m^3


Chemical Toxicity - TSD All Data
Acrylic acid
10.000
1.000
100
10
1
conc. (ppm)
0
60
120
180
240
300
360
420
480
time (min)
no or minimal effect
discomfort
disabling
did not die @ lethal conc
lethal

AEGL VALUES FOR ACRYLIC ACID					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1 (Nondisabling)	1.0 ppm 3.0 mg/m^3	1.0 ppm 3.0 mg/m^3	1.0 ppm 3.0 mg/m^3	1.0 ppm 3.0 mg/m^3	1.0 ppm 3.0 mg/m^3
AEGL-2 (Disabling)	26 ppm 78 mg/m^3	26 ppm 78 mg/m^3	26 ppm 78 mg/m^3	26 ppm 78 mg/m^3	26 ppm 78 mg/m^3
AEGL-3 (Lethal)	480 ppm 1400 mg/m^3	250 ppm 750 mg/m^3	170 ppm 510 mg/m^3	77 ppm 230 mg/m^3	51 ppm 150 mg/m^3

Attachment 15

Acute Exposure Guideline Levels (AEGLs)

for

Methanol

(CAS No. 67-56-1)

CH_3OH

NAC/AEGL Meeting 18, July 26-28, 2000

FoBiG Staff Scientist:

Peter Griem

Chemical Manager in German Expert Group:

Henning Heberer

Industry Reviewer for German Expert Group:

Rudolf Jäckh

Chemical Manager:

Ernest Falke

METHANOL

PROPERTIES

- liquid, colorless, pungent odor, flammable
- high vapor pressure at room temperature (125 hPa)
- soluble in water and wide range of organic solvents

PRODUCTION

- capacity about 30 million tons worldwide in 1995

USES

- industrial solvent and raw material for prodution of many organic compounds
- solvents in consumer products, such as paints, paint thinners, cleasing and antifreeze solutions
- potentially large use as motor vehicle fuel

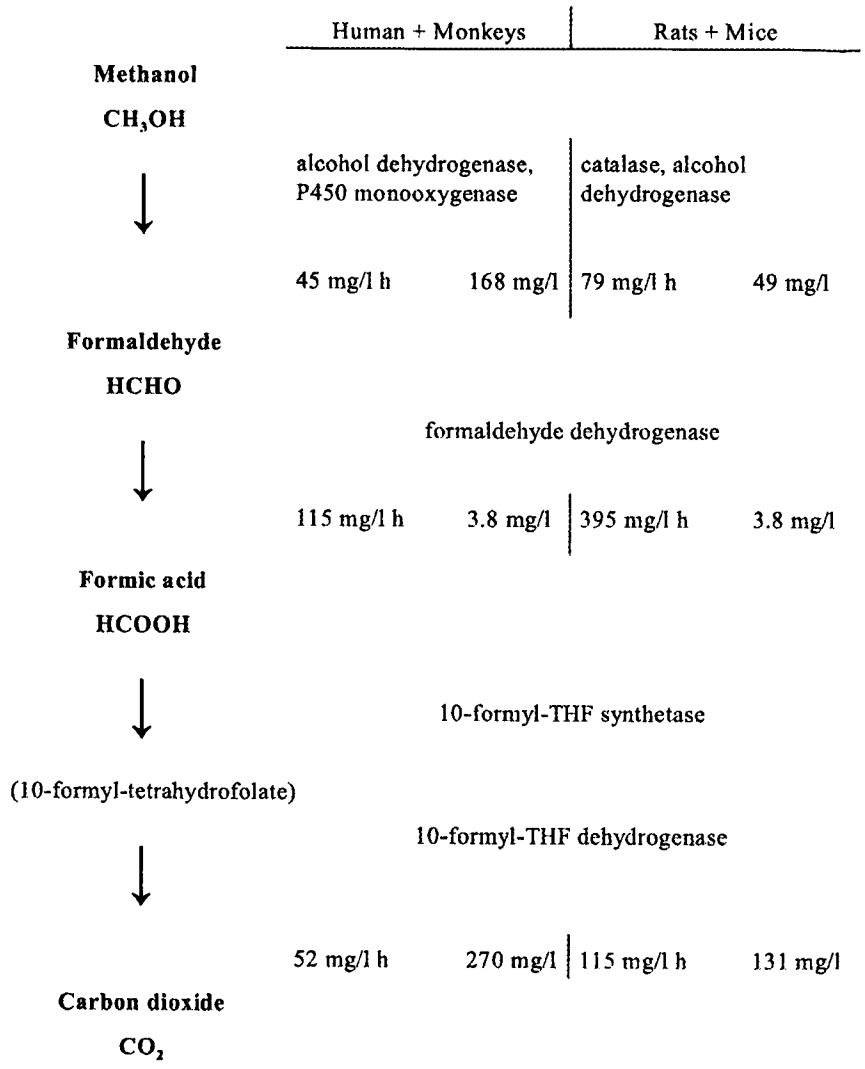
TOXICITY CONCERNS

- metabolic differences between rodents and primates leading to accumulation of formate in the latter, but not in the former species
- effects on central nervous system and vision in humans
- delayed deaths in humans
- developmental toxicity in animals
- skin resorption

METHANOL - OVERVIEW

Effect level	Humans and monkeys	Rats and mice
	Effects Data type, quality	**Effects** Data type, quality
AEGL-1	odor experimental, wide range of thresholds	irritation only in 1 rat study, effect uncertain
	irritation occupational, uncertain C-T	
	neurotoxicity: headache, dizziness, blurred vision occupational, uncertain C-T	
	non-adverse CNS effects experimental, high	
AEGL-2	irritation occupational, uncertain C-T	developmental toxicity: cervical rib, exencephaly, cleft palate single and repeated exposure, high
	neurotoxicity: headache, dizziness, blurred vision occupational, uncertain C-T	
AEGL-3	symptom-free latent period, then headache, nausea, visual disturbances, blindness, coma, death after 2-4 d oral poisoning case studies, oral dose uncertain, measured methanol blood conc., pharmacokinetic model	quickly developing drowsiness, ataxia, narcosis, coma, death experimental inhalation studies, high
		fetal death single and repeated inhalation exposure, high

Methanol metabolism



HUMAN DATA RELEVANT TO AEGL-1

ODOR

- Ruth (1986), Verschueren (1983), O'Neill and Phillips (1992) (reviews)

  range of reported thresholds: 3 - 20500 ppm

- **Hellman and Small (1974)** (trained odor panel)

  detection threshold: 4.26 ppm

  recognition threshold: 53.5 ppm

- **Leornardos et al. (1969)** (trained panel)

  threshold: 100 ppm

- **Chuwers et al. (1995)**

  no odor recognition at 200 ppm

- **Flury and Wirth (1933)**

  weak odor perception at 760 ppm

- **Batterman et al. (1998)**

  no odor perception at 800 ppm

HUMAN DATA RELEVANT TO AEGL-1

IRRITATION

- **Kawai et al. (1991)** (occupational exposure study)

  nasal irritation in 7/22 workers ("high") 459 ppm (g. mean) 8-h TWA

  no irritation in 11 workers ("low") 31 ppm (g. mean) 8-h TWA

  samples: 5 3000 - 5500 ppm
  10 1000 - 2000 ppm
  4 500 - 1000 ppm
  19 <500 ppm

  (grouping unclear, concentration-effect relationship not analyzed)

- **NIOSH (1981)** (occupational exposure from duplicating machines)

  45 % of operators experiences symptoms

  including eye irritation 1916 ppm (mean)

  (no information on individual exposure concentrations and duration)

- **Flury and Wirth (1933)** (experimental study)

  very weak nasal irritation at 7600 ppm for 5 min

  no irritation at 760 ppm for 5 min

- **Batterman et al. (1998)** (experimental study)

  no irritation at 800 ppm for 8 h

HUMAN DATA RELEVANT TO AEGL-1

NEUROTOXICITY

- **Frederick et al. (1984)** (occupational exposure form duplicating machines)

  headache, dizziness, blurred vision, nausea/upset stomach in 35-18 % of exposed subjects (n=66, 66 controls) 1060 ppm (mean)
  365-3080 ppm (range)
  (15/21 samples >800 ppm; 1/21 >1500 ppm)

  (variable duration (1-8 hours/day, 1-5 days/week)

- **NIOSH (1981)** (occupational exposure from duplicating machines)

  45 % of operators experiences symptoms including headache, blurred vision, nausea, dizziness 1016 ppm (mean)

  (no information on individual exposure concentrations and duration)

- **Kawai et al. (1991)** (occupational exposure in factory)

  dimmed vision in 11/22 workers ("high") 459 ppm (mean) 8-h TWA

  no irritation in 11 workers ("low") 31 ppm (mean) 8-h TWA

  samples: 5 3000 - 5500 ppm
  10 1000 - 2000 ppm
  4 500 - 1000 ppm
  19 <500 ppm

  (fog?, grouping unclear, concentration-effect relationship not analyzed)

- **Kingsley and Hirsch (1955)** (occupational exposure form duplicating machines)

  headaches generally 200 - 375 ppm
  15 - 375 ppm (range)

  (no information on number of subjects and exposure duration)

HUMAN DATA RELEVANT TO AEGL-1

NON-ADVERSE CNS EFFECTS

- **Batterman et al. (1998)** (Pharmacokinetic study)

Inhalation exposure	Subjects	Effects (Franzblau, pers. commun., 1999)
800 ppm x 8 hours	3 f, 12 m	none of the subjects reported odor, irritation, headache, alteration of vision or other non-specific symptoms
800 ppm x 2 hours 800 ppm x 1 hour 800 ppm x 0,5 hours	4 f	

- **Chuwers et al. (1995)**

Exposure conditions	Subjects	Effects
200 ppm x 4 hours	11 f, 15 m	no significant effect on neuro-behavioral, neurophysiological and visual performance

- **Muttray et al. (1999, abstract)**, Muttray (pers. commun., 1999)

Exposure conditions	Subjects	Effects
200 ppm x 4 hours	12 m	significant effect on electro-encephalograms (authors: subclinical, excitatory effect)

- **Cook et al. (1991)**

Exposure conditions	Subjects	Effects
190 ppm x 75 min	12 m	no significant effect in neurobehavioral and neurophysiological tests

MONKEYS

- **NEDO (1987)** (Macaca fascicularis)

Exposure conditions	Animals	Irritative effects during exposure	Other effects
21 h/d for 20 d		in all groups:	
10000 ppm	2	animals were	death on d 3, 6
7000 ppm	1	restless, moving	death on d 6
5000 ppm	3	around the cage,	death on d 5, 5, 14
3000 ppm	4	frequent	mild cerebral histol. alterations
0 ppm	6	yawning and blinking	none
21 h/d for 7 m		in all groups:	
3000 ppm	4	frequent yawning and	necrotic changes of basal ganglia (rev.), optic nerve atrophy
2000 ppm	3	runny noses	both groups: slight peripheral nerve degeneration
1000 ppm	5		all groups: round cell infiltration and fibrotic alterations in liver
21 h/d for 7, 19, 29 m			
1000 ppm	2	runny noses	round cell infiltration in liver, fibrosis after 29 m only
100 ppm	3	runny noses	none
10 ppm	3	none	none

- **Andrews et al. (1987)** (Macaca fascicularis)

Exposure conditions	Animals	Irritative effects during exposure	Other effects
6 h/d, 5 d/w for 4 w			
5000 ppm	3 f, 3 m	all groups: no upper	all groups: no
2000 ppm	3 f, 3 m	respiratory tract	histological alterations
500 ppm	3 f, 3 m	irritation	
0 ppm	3 f, 3 m		

MONKEY DATA RELEVANT TO AEGL-1, -2 AND -3

- **McCord et al. (1931)** (Rhesus)

  animals from wildlife, group of 31imported animals, two died from infections (health status ?)

Exposure conditions	Animals	Irritative effects during exposure	Other effects
40000 ppm x 4 h	2 (?)	not reported	prompt death
40000 ppm x 1 h	1		death on d 3
20000 ppm x ? h	?		?
10000 ppm x ? h	?		?
5000 ppm x ? h	1 (?)		"long survived" (?)
1000 ppm x 18 h/d for ? d	4		1 died after total 41 h

- **Gilger and Potts** (1955) (Rhesus)

Oral exposure (gavage) (g/kg)	Animals	Effects
1	1	no symptoms observed
2	1	no symptoms observed
3	1	death after 32 - 38 h
4	1	death after 29 - 36 h
6	1	death after 29 h
8	1	death after 6 - 23 h
		after lethal doses signs of inebriation, semicoma shortly before death

AEGL-1

Keystudy: Batterman et al. (1998); Franzblau, pers. commun. (1999)

Endpoint: No odor, irritation, headache, alteration of vision or other non-specific symptoms in humans after exposure to 800 ppm for 8 hours

Scaling: $C^3 \times t = k$

default value of n = 3 for shorter exposure periods due to lack of specific data

10 min = 30 min, because no studies were available that investigated effects after short exposure durations and because also for longer exposure periods characterization of the dose-response relationship for slight effects on the central nervous system is lacking.

Total uncertainty factor: 3

Interspecies: not applicable

Intraspecies: 3

because no effects were reported at the exposure concentration used and thus the effect level was less severe than defined for the AEGL level. However, interindividual variability with regard to slight neurotoxic effects (e.g. headache) is likely to exist (although it cannot be quantified exactly from the existing experimental and epidemiological studies) and, thus, it cannot be ruled out that a fraction of the general population might experience slight effects under the exposure conditions of the experimental study of Batterman et al. (1998), which used healthy individuals.

AEGL-1 Values for Methanol				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
670 ppm 880 mg/m^3	670 ppm 880 mg/m^3	530 ppm 690 mg/m^3	340 ppm 450 mg/m^3	270 ppm 350 mg/m^3

HUMAN DATA RELEVANT TO AEGL-2

HUMAN

- threshold for irreversible effects (blindness) cannot be derived from available data; oral doses leading to blindness are in the range of live-threatening doses

- **Frederick et al. (1984)** (occupational exposure form duplicating machines)

  headache, dizziness, blurred vision, nausea/upset stomach in 35-18 % of exposed subjects (n=66, 66 controls) 1060 ppm (mean)
  365-3080 ppm (range)
  (15/21 samples >800 ppm; 1/21 >1500 ppm)
  (variable duration (1-8 hours/day, 1-5 days/week)

- **NIOSH (1981)** (occupational exposure from duplicating machines)

  45 % of operators experiences symptoms including headache, blurred vision, nausea, dizziness 1016 ppm (mean)

  (no information on individual exposure concentrations and duration)

- **Kawai et al. (1991)** (occupational exposure study)

  dimmed vision in 11/22 workers ("high") 459 ppm (mean) 8-h TWA

  no irritation in 11 workers ("low") 31 ppm (mean) 8-h TWA

  samples: 5 3000 - 5500 ppm
  10 1000 - 2000 ppm
  4 500 - 1000 ppm
  19 <500 ppm

  (fog?, grouping unclear, concentration-effect relationship not analyzed)

ANIMAL DATA RELEVANT TO AEGL-2

DEVELOPMENTAL TOXICITY

Species	LOEL	NOEL	Reference
	single exposure		
Mouse CD-1	≥ CxT 15000 ppm h on gd 7 (5000 ppm x 3/5/7 h; 10000 ppm x 2/3/5 h; 15000 ppm x 1/2/3 h); cervical rib ≥ CxT 70000 ppm h on gd 7 (10000 ppm x 7 h; 15000 ppm x 5/7 h); fetal death, cleft palate, mulitple skeletal defects	< CxT 15000 ppm h on gd 7 (2000 ppm x 5/7 h; 5000 ppm x 2 h)	Rogers et al. (abstract, 1995); (pers. commun., 1999)
Mouse CD-1	10000 ppm x 7 h on 1or 2 d between gd 6 - 13 fetal death, cleft palate, skeletal malformations	not determined	Rogers et al. (1997)
	repeated exposure		
Mouse CD-1	7 h/d on gd 6 - 15 ≥ 2000 ppm; cervical rib ≥ 5000 ppm, cleft palate, exencephaly ≥ 7500 ppm, fetal death	7 h/d on gd 6 - 15 1000 ppm	Rogers et al. (1993)
Mouse CD-1	6 h/d on gd 7-9 (+other) ≥ 5000 ppm; renal pelvic cavitation ≥ 10000 ppm; ocular defects, cleft palate, hydronephrosis, deformed tails ≥ 15000 ppm; neural tube defects	not determined	Bolon et al. (1993)
Rat Sprague Dawley	7 h/d on gd 1 - 19 10000 ppm; not significant: cervical rib, urinary or cardiovascular defects 20000 ppm on gd 7 - 15; significant effects as above; unsteady gaint in dams	7 h/d on gd 1 - 19 5000 ppm	Nelson et al. (1985)
Rat Long Evans	neurobehavioral tests	4500 ppm x 6 h/d on gd 6 - pnd 21	Stern et al. (1996; 1997)
Monkey M. fasc.	1800 / 600 / 200 ppm x 2 h/d, 7d/w, 4 m and whole pregnancy decreased (by 8 d) pregnancy duration (but within literature range); no effects on early reflex responses, gross motor development, spatial and concept learning, memory, social behavior; delay (14 / 14 / 9 d) in senorimotor development (Visually Directed Reaching Test) of male, but not female infants; effects in 1/2 visual memory tests (all groups)		Burbacher et al. (1999a; 1999b)

AEGL-2

Keystudy: - derived as fraction of AEGL-3

Endpoint: -

Scaling: -

Total uncertainty factor: -

Divisor: 3

because AEGL-2 values are supported by

1) Kawai et al. (1991): nasal irritation and dimmed vision (?) after 3000 - 5500 ppm (n=5) and 1000 - 2000 ppm (n=5) during 8-h workshift;

2) Batterman et al. (1998): no effects after 800 ppm for 8 hours (n=15);

3) Frederick et al. (1984): headache, dizziness, blurred vision, nausea/upset stomach in 35-18 % of subjects repeatedly exposed to 365 - 3080 ppm at workplace.

A factor of 10 was considered overly conservative because exposure to 1/10 of AEGL-3 CxT would result in blood methanol concentration of about 18 - 24 mg/l and thus would be below 30.7 mg/l (800 ppm for 8 hours), which did not result in any effects (Batterman et al., 1998)

AEGL-2 Values for Methanol				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
5000 ppm 6600 mg/m^3	5000 ppm 6600 mg/m^3	2600 ppm 3400 mg/m^3	830 ppm 1100 mg/m^3	530 ppm 700 mg/m^3

HUMAN DATA RELEVANT TO AEGL-3

- no relevant inhalation data available
- **Kawai et al. (1991)**

  no severe effects after exposure to 3000-5500 ppm (n=5) or 1000-2000 ppm (n=10)

- **Buller and Wood (1904), Röe (1982)** (reviews)

  minimal lethal oral dose: about 1.0 g/kg

- **ATSDR (1993), Becker (1983), Meyer et al. (2000)**

  therapy of oral methanol intoxications:

  - sodium bicarbonate infusion against metabolic acidosis
  - ethanol therapy at 130 - 200 mg/l (measured after hospital admission)
  - + hemodialysis at 500 - 1000 mg/l

- **Naraqi et al. (1979), Erlanson et al. (1965), Bennett et al. (1953), Gonda et al. (1978)**

  case reports on lethal oral intoxications with

  - measured blood methanol concentrations
  - time reported between intoxication and measurement
  - no concomittant ethanol exposure

  Using oral lethality data for AEGL-3 derivation:

  - calculation of (theoretical) peak blood methanol concentrations using Michaelis-Menten kinetics
  - derivation of NOEL for lethality
  - calculation of concentration in air that would lead to NOEL blood concentration at the end of relevant exposure periods using pharmacokinetic model

HUMAN DATA RELEVANT TO AEGL-3

ACUTE ORAL METHANOL INTOXICATIONS IN HUMANS				
Time to death	**Sex, age**	**Blood methanol conc. (mg/l) at time (h)**	**Latent period, symptoms, remarks**	**Reference**
48 h	m, 27	730 (< 48 h)	8 h coma (admission)	Naraqi et al., 1979
36 h	m, 19	1110 (< 48 h)	36 h coma (admission)	
36 h	m, 20	3260 (< 48 h)	12 h coma (admission)	
136 h	m, 49	275 (52 h)	15 h failing vision, 24 h vomiting, hearing disturbances, 28 h restlessness, 29 h coma, 48 h (admission and ethanol therapy)	Erlanson et al., 1965
79 h	m, 65	277 (53 h)	15 h nausea, vomiting, headache, 19 h failing eye sight, 30 h severe visual disturbances, cyanosis, 42 h coma, 48 h (admission and ethanol therapy)	
110 h	f, 49	860 (53 h)	42 h unconsciousness, 43 h respiratory standstill, 44 h (admission and ethanol therapy)	
relapse, not stated	m, 41	4000 (18 h)	blind, headache; estimated oral dose about 50 ml	Bennett et al., 1953
4 d	m, 48	1300 (24 h)	blind, headache, abdominal pain, blind, stupor; estimated oral dose about 500 ml	
relapse, not stated	m, 26	2500 (48 h)	cloudy vision, headache, nausea, abdominal pain, vomiting	
died	m, 30	5600 (12 h)	comatose	Gonda et al., 1978
died	m, 48	3700 (24 h)	confusion, progressing coma	

Calculation of Peak Blood Methanol Concentrations in Humans I

Model: Michaelis-Menten kinetics

Equation:

$$\frac{dC}{dt} = \frac{V_{max} \bullet C}{K_m + C}$$

Parameters:
- C blood methanol concentration [mg/l]
- t time [h]
- V_{max} maximum rate of enzymatic methanol oxidation [mg/l h]
- K_m Michaelis-Menten constant of enzymatic methanol oxidation [mg/l]

Procedure: The simulations were performed on a spreadsheet program by converting the differentials to finite differences with a time step of 0.25 hours. For calculation of peak blood concentrations, 0.25-hour calculation steps were carried until reaching the time period between intoxication and blood methanol measurement.

Equation:

$$C_t = \frac{V_{max} \bullet C_{t-1}}{K_m + C_{t-1}} \bullet 0.25h + C_{t-1}$$

Parameter values:
- C_0 measured blood methanol concentration [mg/l]
- C_t blood methanol concentration [mg/l] at time t
- C_{t-1} blood methanol concentration [mg/l] at time t - 0.25 h
- t time [h]
- V_{max} 45 mg/l h (see Appendix C)
- K_m 168 mg/l (see Appendix C)

Calculation of Peak Blood Methanol Concentrations in Humans II

Calculations: For the cases reported by Naraqi et al. (1979) it was assumed that blood for methanol measurements was drawn 2 hours after the reported latent period; from the article it can be concluded that this assumption is leads to conservative concentration values.

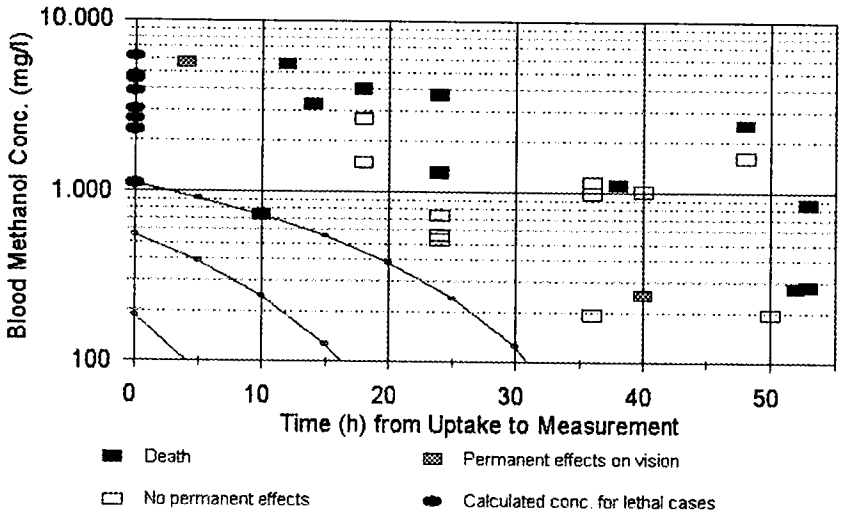
CALCULATED PEAK BLOOD METHANOL CONCENTRATIONS FROM ORAL LETHALITY DATA

measured methanol conc. (mg/l)	time between intoxication and measurement (h)	calculated peak methanol conc. (mg/l)	Reference
730	10 (estimated)	1109	Naraqi et al., 1979
1110	38 (estimated)	2672	
3260	14 (estimated)	3862	
275	52	2259	Erlanson et al., 1965
277	53	2304	
860	53	3033	
4000	18	4780	Bennett et al., 1953
1300	24	2285	
2500	48	4559	
5600	12	6125	Gonda et al., 1978
3700	24	4738	

mean	3430
standard deviation	1424
minimum	1109

HUMAN DATA RELEVANT TO AEGL-3

MEASURED BLOOD METHANOL CONCENTRATIONS IN HUMANS AND CALCULATED PEAK CONCENTRATIONS



Concentrations-time curves for peak concentrations of 1109 mg/l (LOEL)
555 mg/l (NOEL)
185 mg/l (AEGL-3)

ANIMAL DATA RELEVANT TO AEGL-3

- see separate monkey data

ACUTE LETHAL INHALATION DATA IN LABORATORY ANIMALS

Species	Conc. (ppm)	Exposure Time	Effect	Reference
Cat	33400	6 h	1of 2 animals died	Flury and Wirth, 1933
Rat	145000	1 h	LC_{50}	DuPont, 1974
Rat	97400	4 h	LC_{50}	BASF, 1980a
Rat	64000	4 h	LC_{50}	NPIRI, 1974
Rat	66500	6 h	LC_{50}	BASF, 1980b
Rat	50000 31600 22500	2,5 h 18-20 h 8 h	no mortality, narcosis lethal narcosis	Loewy and Von der Heide, 1914
Rat	5000	24 h/d, gd 7-17	fetal death in late pregnancy	NEDO, 1986
Rat	5000	7 h/d, gd 1-19	no fetal death	Nelson et al., 1985
Mouse	71800 71800 53500 48000	54 h 28 h 54 h 24 h	narcosis, death narcosis, death narcosis, death narcosis, survived	Weese, 1928
Mouse	54000	3.5-4 h/d, total 24 h	comatose, survived	Pavlenko, 1972
Mouse	30560-152800	≤ 4 h	narcosis after 190-94 min, overall mortality 45%	Marshbitz et al., 1936
Mouse	42000	7 h	narcosis	Lehmann und Flury, 1943
Mouse	41000	6 h	LC_{50}	Scott et al., 1979
Mouse	37594	2 h	LC_{lo}	Izmerov et al., 1982
Mouse	10000	7 h, gd 7	fetal death	Rogers et al., 1995
Mouse	7500	7 h/d, gd 6-15	fetal death; NOEL 5000 ppm	Rogers et al., 1993

AEGL-3

Keystudy: Naraqi et al. (1979) Erlanson et al. (1965), Bennett et al. (1953), Gonda et al. (1978)

Endpoint: Lethality in humans after oral intoxication. Lowest calculated peak blood methanol concentration of lethal cases without significant blood ethanol concentrations

peak blood methanol concentration: 1109 mg/l

LOEL-NOEL extrapolation factor: 2

because of the very steep dose-response relationship reported by Gilger and Potts (1955) for rhesus monkeys (no signs of toxicity after 2 g/kg or lower, but death at 3 g/kg or higher) and because conservative assumptions were made in the calculation of peak blood concentrations from the Naraqi et al. (1979) study.

peak blood methanol concentration: 1109 mg/l / 2 = 555 mg/l

Total uncertainty factor: 3

Interspecies: not applicable

Intraspecies: 3

because of the very steep dose response-relationship for lethality after oral exposure seen in rhesus monkeys and because a factor 10 would have resulted in blood methanol concentrations of about 55 mg/l which would be far below a level of 130 - 200 mg/l, at which ethanol therapy is recommended.

peak blood methanol concentration: 555 mg/l / 3 = 185 mg/l

Scaling: Exposure concentrations were calculated using a pharmacokinetic model

10 min = 30 min because 1) additional toxic effects, such as respiratory shock, cannot be excluded at the calculated concentration of 44000 ppm and 2) the value is close to the lower explosive limit in air

AEGL-3 Values for Methanol (ppm [mg/m³])				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
15000 ppm 20000 mg/m³	15000 ppm 20000 mg/m³	7900 ppm 10000 mg/m³	2500 ppm 3300 mg/m³	1600 ppm 2100 mg/m³

AEGL VALUES FOR METHANOL [a]					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1 (Nondisabling)	670 ppm 880 mg/m³	670 ppm 880 mg/m³	530 ppm 690 mg/m³	340 ppm 450 mg/m³	270 ppm 350 mg/m³
AEGL-2 (Disabling)	5000 ppm 6600 mg/m³	5000 ppm 6600 mg/m³	2600 ppm 3400 mg/m³	830 ppm 1100 mg/m³	530 ppm 700 mg/m³
AEGL-3 (Lethal)	15000 ppm 20000 mg/m³	15000 ppm 20000 mg/m³	7900 ppm 10000 mg/m³	2500 ppm 3300 mg/m³	1600 ppm 2100 mg/m³

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

AEGL-1 VALUES FOR METHANOL					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1 (Nondisabling)	670 ppm 880 mg/m³	670 ppm 880 mg/m³	530 ppm 690 mg/m³	340 ppm 450 mg/m³	270 ppm 350 mg/m³

AEGL-2 VALUES FOR METHANOL					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-2 (Disabling)	5000 ppm 6600 mg/m³	5000 ppm 6600 mg/m³	2600 ppm 3400 mg/m³	830 ppm 1100 mg/m³	530 ppm 700 mg/m³

AEGL-3 VALUES FOR METHANOL					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-3 (Lethal)	15000 ppm 20000 mg/m³	15000 ppm 20000 mg/m³	7900 ppm 10000 mg/m³	2500 ppm 3300 mg/m³	1600 ppm 2100 mg/m³

SUPPORTING DATA FOR AEGLs

- Blood concentrations at **AEGL-3**: **185 mg/l**

  15000 ppm x 10 & 30 min, 7900 ppm x 1 h, 2500 ppm x 4 h, 1600 ppm x 8 h

- **Kawai et al. (1991)**

  Nasal irritation, 8-h workplace exp. to 3000-5500 ppm (n=5): **442 mg/l**

- **Andrews et al. (1987)**

  No effects in rhesus monkeys after 5000 ppm x 6 h/d, 5 d/w, 4 w

- **Rogers et al. (1993; 1995; 1999)**

  NOEL for fetal death in mice (5000 ppm for 7 h): **2126 mg/l**

- Blood concentrations at **AEGL-2**: **22 - 61 mg/l**

  5000 ppm x 10 & 30 min, 2600 ppm x 1 h, 830 ppm x 4 h, 530 ppm x 8 h

- **Kawai et al. (1991)**

  Nasal irritation, 8-h workplace exp. at 500-5500 ppm (n=19): **≤442 mg/l**

- **Batterman et al. (1998)**

  No effects after 800 ppm for 8 h (n=15) **31 mg/l**

- **Rogers et al. (1993; 1995; 1999)**

  NOEL for malformations in mice (2000 ppm for 7 h): **487 mg/l**

- Blood concentrations at **AEGL-1**: **4 - 24 mg/l**

  670.ppm x 10 & 30 min, 530 ppm x 1 h, 340 ppm x 4 h, 270 ppm x 8 h

- **Batterman et al. (1998)**

  No effects after 800 ppm for 8 h (n=15) **31 mg/l**

Calculation of Exposure Concentrations for Humans I

Study: Perkins et al. (1995a)

Pharmacokinetic model for blood methanol concentrations after inhalation exposure.

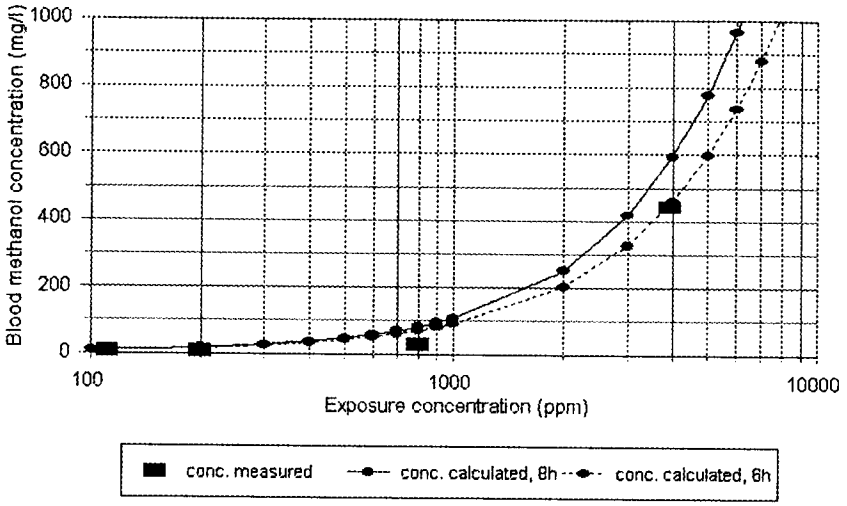
Equation:

$$\frac{dC}{dt} = \frac{\Phi \bullet V_h \bullet C_{inh}}{V_d} - \frac{V_{max} \bullet C}{K_m + C}$$

PARAMETERS OF PHARMACOKINETIC MODEL	
Parameter	**Value used for calculations**
C blood methanol conc. [mg/l]	
t time [h]	
C_{inh} methanol conc. in air [mg/l]	
Φ fraction of inhaled methanol absorbed	0.7 mean value of the range (0.53 - 0.85) reported by Leaf and Zatman (1952) and Sedivec et al. (1981) (Perkins model: 0.75)
V_h (l/kg h) ventilation rate	17.8 (body weight 70 kg and ventilation rate of 10 m³/8 h for occupational situations) (Perkins model: 10.3)
V_d (l/kg) volume of distribution	0.65 mean value of the range (0.6 - 0.7) reported by Yant and Schrenk (1937)(Perkins model: 0.7)
V_{max} (mg/l h) maximum rate of enzymatic methanol oxidation	45 mean of values derived from data from Jacobsen et al. (1988), Kane et al. (1968) and Leaf and Zatman (1952) (Perkins model: 115)
K_m (mg/l) Michaelis-Menten constant	168 mean value from data from Leaf and Zatman (1952) (Perkins model: 460)

Model compatibility with measured blood methanol concentrations

For exposure concentrations between 100 and 10000 ppm, blood methanol concentrations for exposure periods of 6 and 8 hours were calculated. The calculated concentrations are in good agreement with measured values after 6 - 8 hours exposure



Calculation of Exposure Concentrations for Humans II

Procedure: using a spreadsheet program, differentials were converted to finite differences with a time step of 0.1 hours. For the continuous, instantaneous values for the blood concentration of methanol (C), the value from the previous time step (C_{t-1}) was used. Background blood methanol in humans is approximately 1.0 mg/l from both endogenous and exogenous sources and this level was used for the initial time step (C_0).

Equation:

$$C_t = \frac{\Phi \bullet V_h \bullet C_{inh}}{V_d} \bullet 0.1\,h - \frac{V_{max} \bullet C_{t-1}}{K_m + C_{t-1}} \bullet 0.1\,h$$

CALCULATION OF METHANOL CONCENTRATIONS IN AIR RESULTING IN 185 mg/l		
Exposure time	**Calculated exposure concentration (ppm)**	**Rounded value (ppm)**
8 h	1560	1600
4 h	2450	2500
1 h	7880	7900
30 min	15200	15000
10 min	44000	44000

Calculation of Exposure Concentrations for Humans III

CALCULATION OF BLOOD METHANOL CONCENTRATIONS AFTER EXPOSURE TO AEGL-2 CONCENTRATIONS		
Exposure time	**Exposure concentration (ppm)**	**Blood methanol concentration (mg/l)**
8 h	530	51
4 h	830	57
1 h	2600	60
30 min	5000	61
10 min	5000	22

CALCULATION OF BLOOD METHANOL CONCENTRATIONS AFTER EXPOSURE TO 1/10 x AEGL-3 CONCENTRATIONS		
Exposure time	**Exposure concentration (ppm)**	**Blood methanol concentration (mg/l)**
8 h	160	14
4 h	250	16
1 h	790	19
30 min	1500	19
10 min	1500	7

Derivation of Michaelis-Menten Parameters

Example: Erlanson et al. (1965) reported the two following cases (numbers 3 and 4 in the article):

Case 3: female, 49 years old, dose: 40 g methanol + 50 g (29 hours)
measured concentration after 53 hours: 860 mg/l.

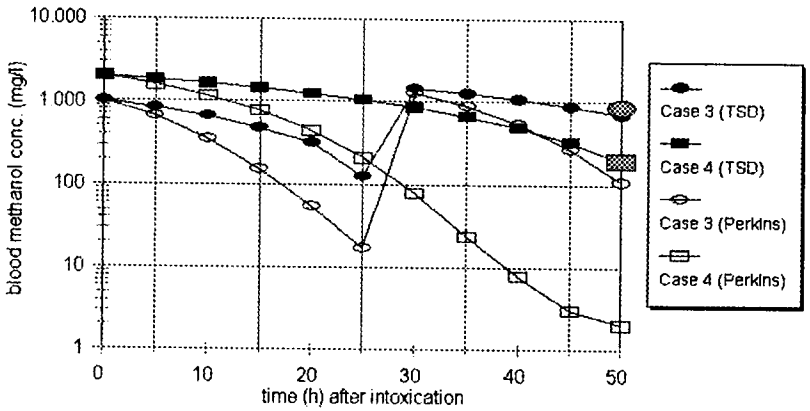
Parameters: volume of distribution: 0,65 l/kg (Yant and Schrenk, 1937)
body weight: 60 kg

maximum blood concentration: 40 g x 1/60 kg x 1/ 0.65 l/kg = 1025 mg/l

contribution of the second intake: 50 g x 1/60 kg x 1/ 0.65 l/kg = 1280 mg/l

Case 4: female, 39 years old, dose: 80 g of methanol
measured concentration after 50 hours: 194 mg/l.

maximum blood concentration: 80 g x 1/60 kg x 1/ 0.65 l/kg = 2050 mg/l



Derivation of Michaelis-Menten parameters

Values for v_{max} were calculated directly from the slope of blood-methanol-concentration vs. time plots when elimination occurred at the maximal rate (straight line, zero order kinetics). Otherwise, values for v_{max} and K_m were calculated by linear regression after transformation of data and graphical display in Lineweaver-Burke plots.

For this purpose, the Michaelis-Menten equation

$$V = \frac{V_{max} \bullet [S]}{K_m + [S]}$$

where [S] is the substrate concentration

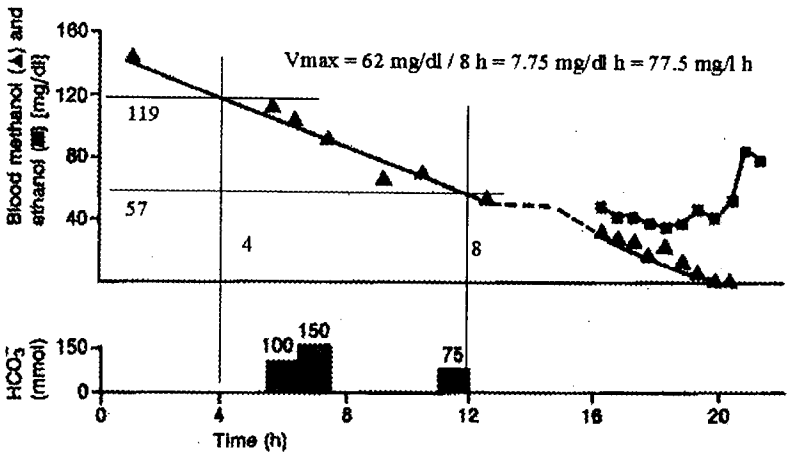
was transformed by taking the reciprocal of the equation, obtaining

$$\frac{1}{V} = \frac{K_m}{V_{max}} \bullet \frac{1}{[S]} + \frac{1}{V_{max}}$$

A plot of 1/v vs. 1/[S] (Lineweaver-Burke plot) yields a straight line with slope K_m/v_{max} and ordinate intercept $1/v_{max}$. The slope and ordinate intercept were calculated by linear regression using a spread sheet computer program.

Derivation of v_{max} from Jacobsen et al. (1988) data

One value for v_{max} was derived from Jacobsen et al. (1988) as shown in the next figure; the data were not suitable for derivation of K_m because data were available only for high methanol concentrations (before hemodialysis began), at which elimination rate was maximal.



Derivation of v_{max} from Kane et al. (1968) data

Two values for v_{max} were derived from Kane et al. (1968) as shown in the next figure; the data were not suitable for derivation of K_m because the number of data points at low methanol concentrations was too small. Values were derived for the two patients without ethanol additionally present in the blood.

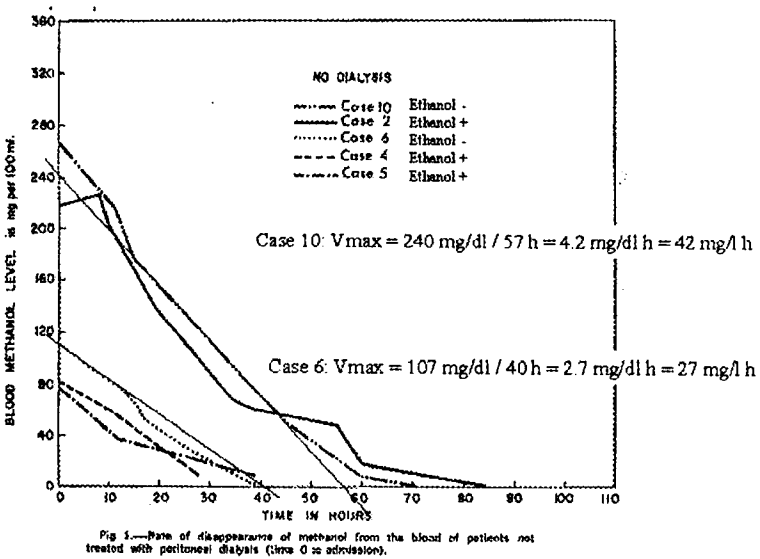


Fig 1.—Rate of disappearance of methanol from the blood of patients not treated with peritoneal dialysis (time 0 is admission).

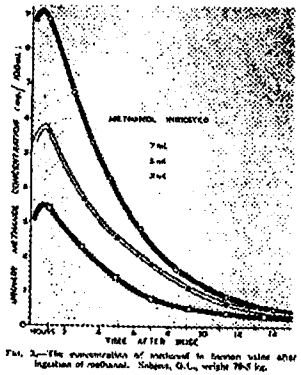
Derivation of v_{max} and K_m from Leaf and Zatman (1952) data I

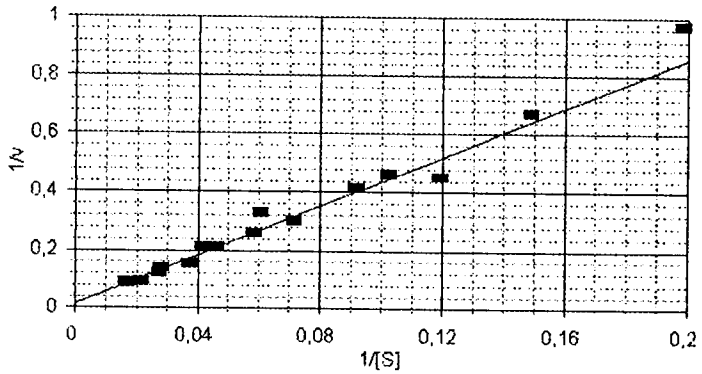
Values for v_{max} and K_m were derived for three subjects from Leaf and Zatman (1952) as shown in the next figures; the numerical values were read from the graphs and are given in the respective tables. For the relation between methanol concentrations in blood and urine the value of urine/blood = 1.3 determined by the authors was used.

Subject G.L.

v_{max}: 61 mg/l h

K_m: 259 mg/l



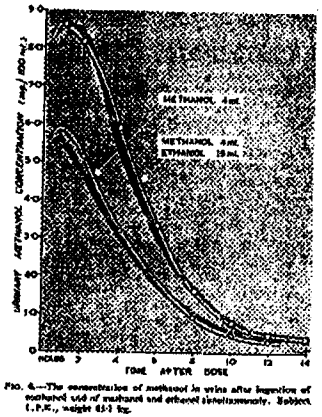


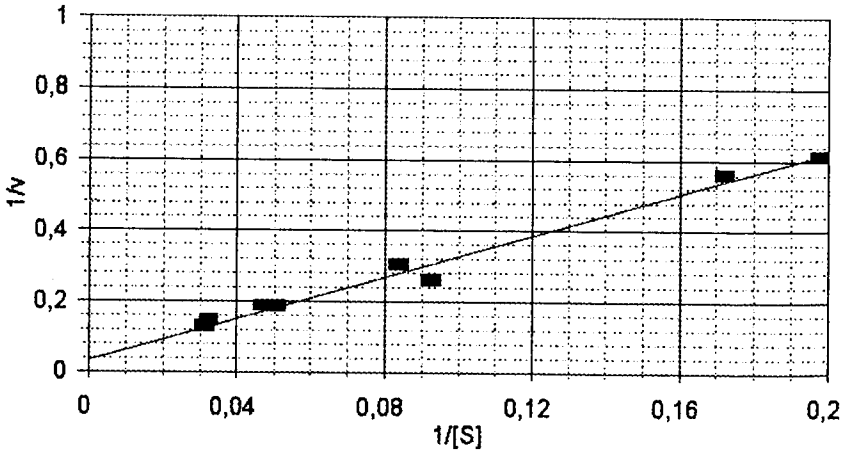
Derivation of v_{max} and K_m from Leaf and Zatman (1952) data II

Subject L.P.K.

v_{max}: 23 mg/l h

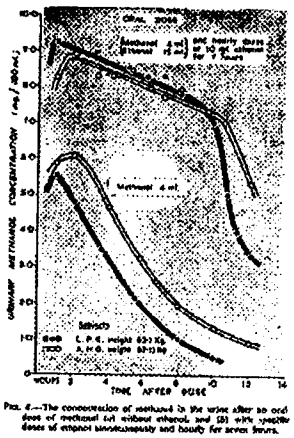
K_m: 67 mg/l

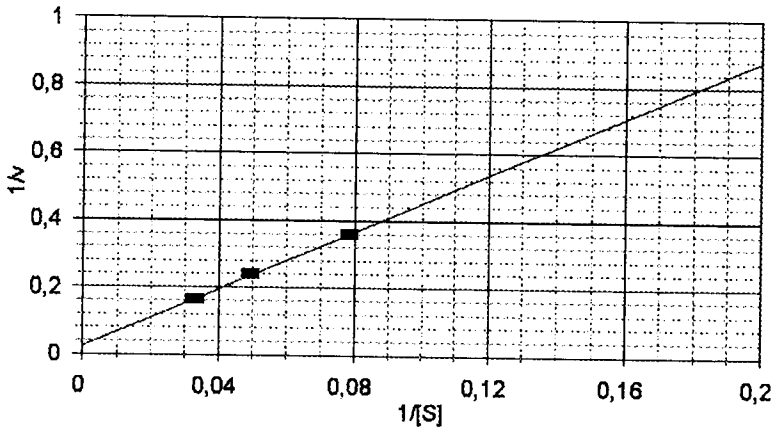




Derivation of v_{max} and K_m from Leaf and Zatman (1952) data III

Subject A.H.G.
v_{max}: 41 mg/l h
K_m: 176 mg/l





Derivation of v_{max} and K_m from Leaf and Zatman (1952) data IV

CALCULATION OF MEAN Vmax AND Km VALUES			
v_{max} (mg/l h)	**K_m (mg/l)**	**Subject**	**Data from Reference**
78	-	-	Jacobsen et al., 1988
42	-	Case 6	Kane et al., 1968
27	-	Case 10	Kane et al., 1968
61	259	G.L.	Leaf and Zatman, 1952
23	67	L.P.K.	Leaf and Zatman, 1952
41	178	A.H.G.	Leaf and Zatman, 1952

45	168	mean values

AEGLs for Chemical Warfare Agents

WHY:

Although the 1990 Bilateral Destruction Agreement and more recent Chemical Weapons Convention have effectively ended production of all chemical warfare munitions (CWM) in the U.S., the potential for a chemical agent incident at Army storage installations, non-stockpile cleanup sites, or from terrorist events, continues to exist.

1

Chemical Warfare Agents in the US

- Nerve Agents
  - G-agents (GA, GB, GD, GF)
  - VX
- Vesicants/Blister Agents
  - ✓***Sulfur Mustard (H, HD)***
  - Lewisite
  - Mixtures (HT, HL)

2

Potential Chemical Warfare Agent Release Scenarios

❑STOCKPILE (8 States + Johnston Island)

❑NON- STOCKPILE SITES

- Installations (ex: Ft. Polk, Raritan Army Ammunition Plant)
- Formerly Used Defense Sites (FUDS) (Spring Valley-American University, Wash D.C.)

❑ACTS OF TERRORISM

- EX: Tokyo subway incident
- Atlanta Olympics

3

"Incidents" May involve Accidental or Deliberate Releases of Agent

- Spill
  - Onto ground or other surface
  - Exposures may result from direct contact or from evaporation and drift of vapor
- Explosion
  - Example – from unstable munition
  - May cause formation of airborne droplets
  - Smaller droplets (aerosols) and vapors may travel far
- Fire
  - Aerosols and vapors formed
  - Agent lofted by heated air, increased capacity to travel

4

Current "Emergency" Levels

- Referred to by Army as "No effect levels" or "No significant effect levels"
- "Endorsed" by CDC ('1994 Thacker letter') as "Acute Threshold Effects Levels"

Recommended Acute Threshold Effects Levels for Determining Emergency Evacuation Distances in the CSEPP Program (CDC, 94)	
Chemical Agent	Level (mg-min/m^3)
Mustard (H, HT, HD)	2.0
Lewisite (L)	2.0
Sarin (GB)	0.5
VX	0.4

5

Anticipated "Uses" of CWA AEGLs

- Update existing acute toxicity values used in emergency planning;
- Provide scientifically and legally defensible values
- Assess requirements for new modeling/re-vamping emergency plans for fixed Stockpile sites

6

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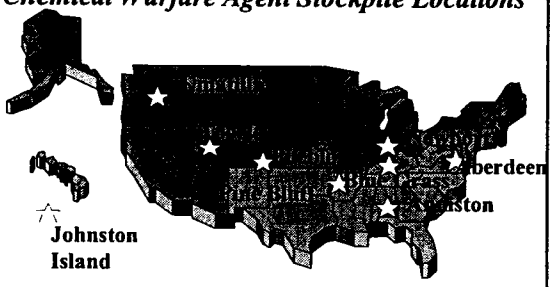
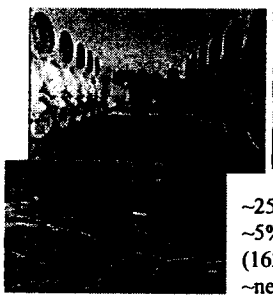
Chemical Warfare Agent Stockpile Locations



Aberdeen Proving Ground (Edgewood), Maryland



~25 miles north of Baltimore
~5% US Stockpile
(1623 tons bulk HD)
~neutralization to destroy

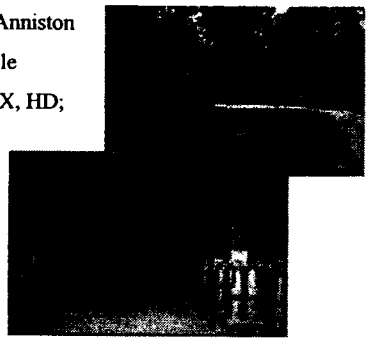
Anniston, Alabama

~8 miles west of Anniston

~7.4% US Stockpile

(2254 tons: GB, VX, HD; mines/cartridges, projectiles)

~incineration to destroy



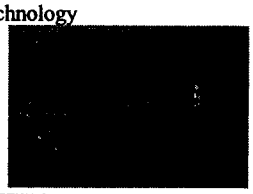
Pueblo, Colorado

~14 miles east of Pueblo

~storage since the 50's

~8.5% (2611 tons:HD projectiles, mortar rounds)

~destruction technology undetermined



Pine Bluff, Arkansas

~35 miles SE of Little Rock

~12.3% (3850 tons: HD,VX,GB; bulk, rockets)

~incineration

Newport, Indiana

~2 miles south of Newport/western Indiana

~4 % stockpile (1269 ton VX bulk)

~Neutralization technology to destroy

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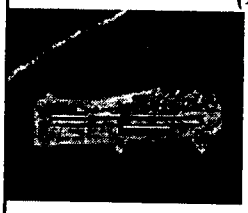
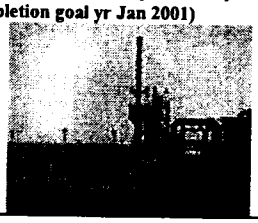
Johnston Island, Johnston Atoll (Pacific)



~Built 1985, 825 mi south Hawaii

~ all agents/items, stored since 70s (shipped from Germany, Solomon Islds)

~85% of original stockpile destroyed (completion goal yr Jan 2001)

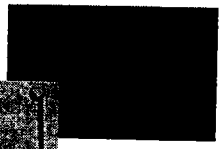


Lexington-Blue Grass (Richmond), Kentucky

~250 acres in central Kentucky

~1.7% (523 tons:GB, VX, HD; rockets, projectiles)

~destruction technology undetermined



Deseret (Tooele), Utah

- 22 miles south of Tooele
- 44.5% (13,616 tons – GA,GB, VX, HD, Lewisite)
- ~32% of original stockpile destroyed (incineration)

Umatilla, Oregon

~7 miles west Hermiston

~11.6% (3717 tons: GB, VX projectiles, mines, bombs and bulk HD)

~destruction to be incineration

Non-Stockpile

NonStockpile Sites: A Growing Problem

- Numerous sites, many still unknown
  - 96 locations (224 sites) [1996 survey]
    - Army – 37
    - Navy – 5
    - Air Force –6
    - Defense Logistics Agency - 3
    - Formerly Used Defense Sites (FUDS)- 45
  - 38 States plus Virgin Islands and District of Columbia
    - 1996 Survey added 5 States to 1993 survey
- No controlled destruction technology yet available (pilot tests ongoing)
- Potential for human exposures and environmental releases

18

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AEGLs for Nerve Agents: Issues for the NAC

- Use of unclassified 'limited distribution' documents from military literature
- Use of human (military volunteer) data
- Availability of these same data in other publicly available documents and data use to propose/establish related chemical agent health criteria

Related Chemical Agent Health Criteria and References

- CDC "Recommended Acute Threshold Effects Levels for Determining Emergency Evacuation Distances", policy letter (June 1994)
- CDC Federal Register notice for chronic worker and occupational air exposure limits (March 1988)
- Final Programmatic Environmental Impact Statement for the Chemical Stockpile Disposal Program (1988)

Key Publicly Available Technical Documents:

- *Review of Acute Human-Toxicity Estimates for Selected Chemical Warfare Agents*, COT –NRC (1997)
  - Is a review of a classified report but....
  - Includes references to classified material
  - Includes reference and use of human data for mild effects and SEVERE effects
  - Provides recommendations for military acute exposure threshold levels for mild, severe, and lethal effects
- *Textbook of Medical Aspects of Chemical and Biological Warfare*, 1997

Key Publicly Available Documents, cont'd:

Evaluation of Airborne Exposure Limits for G-Agents: Worker and General Population Exposure Criteria, Mioduszewski et al April 1998

and

Evaluation of Airborne Exposure Limits for VX: Worker and General Population Exposure Criteria, Reutter et al February 2000

- **Provide standards for the CDC to consider/endorse and publish in the Federal Register**
- **Makes use of most of the same "limited distribution" documents used for AEGL source documents (example: Harvey, 1952)**
- **Are available on website: http://chppm-www.apgea.army.mil/hrarcp/pages/caw/index.html**

V. Hauschild USACHPPM 410-436-5213

NERVE AGENTS (GA, GB, GD, GF) AEGLs
(CAS Nos. 77-81-6, 107-44-8, 96-64-0, and 329-99-7)

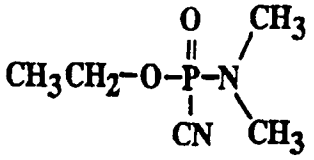
NAC/AEGL-18
U.S. Dept. of Transportation
DOT Headquarters/Nassif Bldg., Rms 8236-8240
400 7th Street, SW
Washington, D.C.

July 26-28, 2000

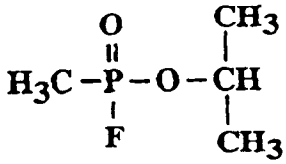
G-series Nerve Agents: Identification

- Organophosphate ester derivatives of phosphonic acid, containing either cyanide or fluoride substituent group

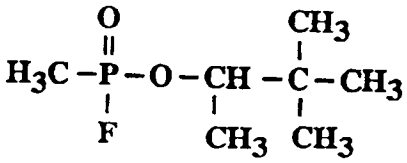
- Agent GA; tabun; Dimethylamidocyanophosphate; $C_3H_{11}N_2O_2P$; CAS. No. 77-81-6; contains cyanide group



- Agent GB; sarin; Isopropyl methylphosphono-fluoridate; $C_4H_{10}FO_2P$; CAS No. 107-44-8; contains fluoride group

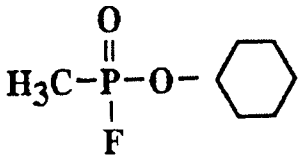


- Agent GD; soman; Pinacolyl methylphosphonofluoridate; $C_7H_{16}FO_2P$; CAS No. 96-64-0; contains fluoride group



G-series Nerve Agents: Identification (cont'd)

- Agent GF; *O*-cyclohexylmethylfluorophosphonate; $C_7H_{14}FO_2P$; CAS No. 329-99-7; contains fluoride group



- Agent GF currently considered of little strategic interest (thought to have been manufactured in Iraq during Persian Gulf War). Included for completeness.

G-series Nerve Agents: Characterization

- No commercial application
- Warfare agents; developed in WWII-era Germany; GA and GB part of U.S. unitary stockpile undergoing Congressionally mandated destruction; GA, GB, GD thought to be at non-stockpile sites undergoing installation restoration
- Agents GA, GB, GD considered potential military or terrorist threats
- Agent GB released during March, 1995, chemical terrorist attack on commuters in Tokyo subway system (passive volatilization); deliberate release of lethal concentrations
- Usually liquid in normal state
- Volatilization if heated
- Potential for release if in vapor or aerosol
- GB is single major G-agent in U.S. unitary stockpile

G-series Nerve Agents: Toxicity

- Cholinesterase inhibitors; acetylcholine accumulation results in continuous post-synaptic action potentials leading to adverse cholinergic effects in PNS and CNS + end organ stimulation

- no chronic neurological disorders following asymptomatic exposures

- limited data for possible neurophysiological deficits following recovery from chemical terrorist release in Japan (psychomotor performance, "postural sway," event-related and visual evoked potentials in asymptomatic persons) or cases of accidental occupational exposure (increased brain β activity and REM; no clinical significance); no dose-response information.

- small, measurable, non-clinical changes in single fibre electromyography (SFEMG) of forearm months after controlled vapor exposure to human volunteers experiencing minimal clinical signs/symptoms

- no data suggesting reproductive or developmental toxicity; no carcinogenicity evidence; GB not genotoxic in bioassay

- Agent GA considered weakly mutagenic (+8/11 Ames *Salmonella* assays with revertant strains and S-9 activation; + mutagen on mouse lymphoma cells w/o activation; ↑SCE in CHO cells exposed *in vitro*)

Gradation of Signs/Symptoms with ↑Cumulative Exposure

MILD Effects

EYES:	miosis, pain ("deep in eye" or head), dim or blurred vision
NOSE:	runny (rhinorrhea)
RESP:	"Tightness in chest," bronchoconstriction, secretions in airways, cough, breathing difficulty

Pupillary muscles v. sensitive to vapor contact; miosis early sign of nerve agent vapor exposure

MODERATE Effects

EYES:	increased degree of miosis, pain, and dim or blurred vision
NOSE:	severe rhinorrhea, nasal congestion
RESP:	increasing bronchoconstriction and breathing difficulty, secretions more copious
MUSCLES:	feeling of generalized weakness, twitching of large muscle groups
GI:	nausea, vomiting, diarrhea, cramps

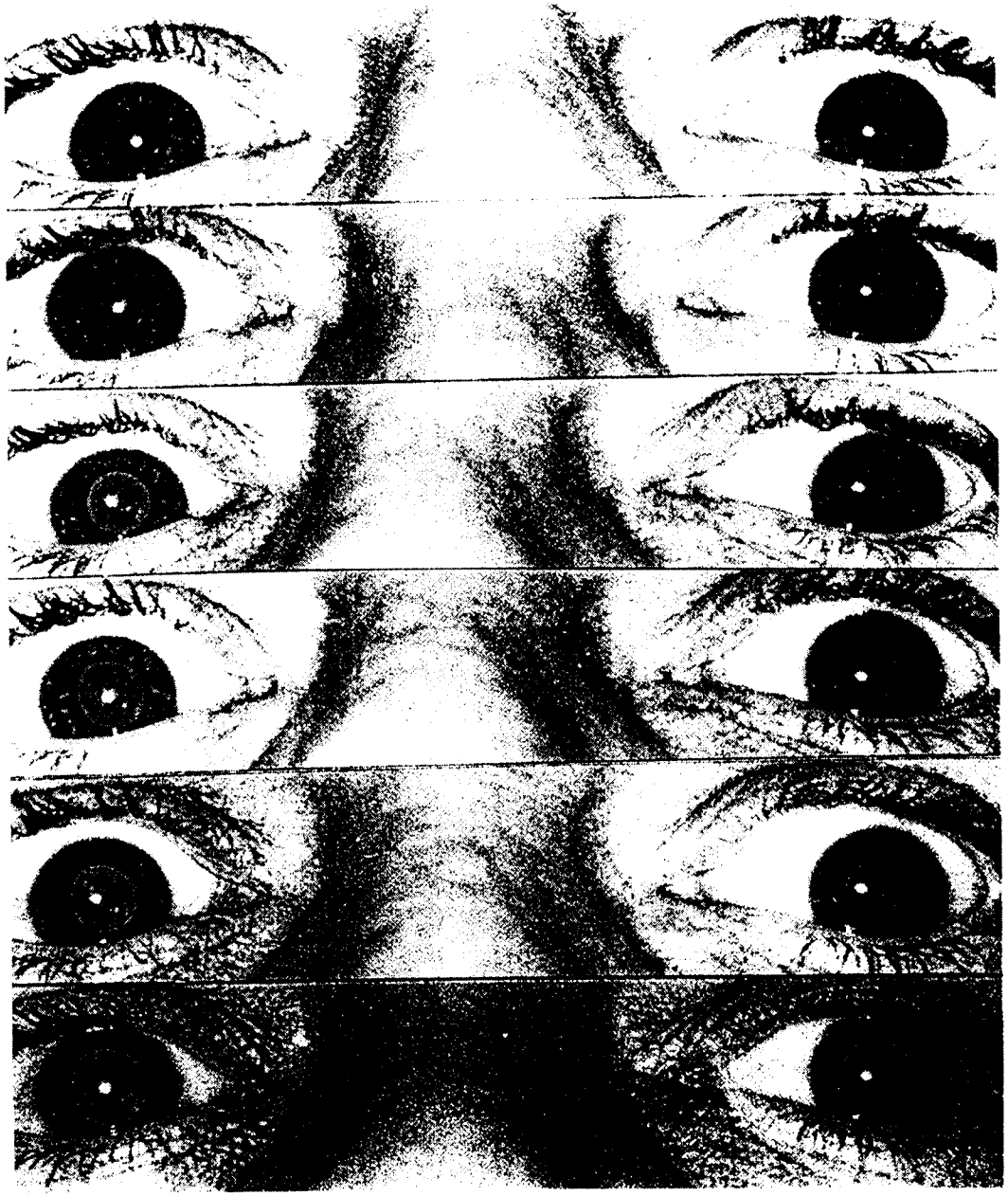


Fig. 5-4. This man was accidentally exposed to an unknown amount of nerve agent vapor. The series of photographs shows his eyes gradually recovering their ability to dilate. All photographs were taken with an electronic flash (which is too fast for the pupil to react) after the subject had been sitting in a totally dark room for 2 minutes. These photographs were taken (from top to bottom) at 3, 6, 13, 20, 41, and 62 days after the exposure. Subsequent photographs indicate that the eyes did not respond fully to darkness for 9 weeks; maximal dilation was reached on day 62 after the exposure. Reprinted with permission from Sidell FR. Soman and sarin: Clinical manifestations and treatment of accidental poisoning by organophosphates. *Clin Toxicol.* 1974;7:11.

Gradation of Signs/Symptoms with ↑ Cumulative Exposure

SEVERE Effects

MUSCLES:	convulsions, weakness w/eventual loss of muscle tone and capability to function (paralysis); cessation of breathing
RESP:	v. copious secretions ("dry-land drowning")
ALL:	loss of consciousness, coma, death

Respiratory failure is chief cause of death following severe exposure.

DATA SUMMARY
G-series NERVE AGENTS
Human Data

- Lethal Toxicity
  - clinical case reports from 2 incidents (1994, 1995) of chemical terrorism in Japan with lethal concentrations of agent GB ; prompt deaths, DOAs, and delayed deaths due to respiratory insufficiency and hypoxic brain damage (perhaps some NTE inhibition); no dose-response data

  - Available estimates of human lethal concentrations (LCt_{50}, etc.) derived/extrapolated from animal data

- Nonlethal Toxicity

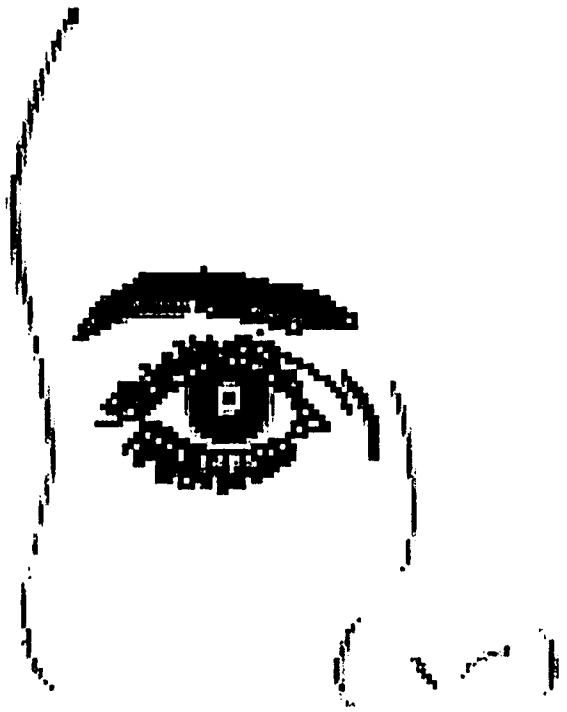
  - clinical case reports from chemical terrorist releases in Japan (Morita et al., 1995; Okumura et al., 1996); effects range in severity; miosis, headache, vision disturbances, decreased visual acuity, fatigue, dizziness, nausea, dyspnea, ocular pain, dysaesthesia of extremities, tachycardia, bradycardia, salivation, rhinorrhea, muscle fasciculations, abnormal eliptiform EEG; decrease in serum ChE and RBC-AChE

CLINICAL SIGNS AND SYMPTOMS NOTED by Hospital Personnel among Subway Passengers

(in decreasing order of frequency)

- Miosis* (pinpointing of the pupils)
- Headache
- Dyspnea (labored breathing)
- Nausea
- Vomiting
- Muscular Weakness
- Cough
- Rhinorrhea (runny nose)
- Chest oppression
- Muscular fasciculations
- Psychological disturbances (anxiety, etc.)

*observed in most patients



Source: Sidell, F.R., S.R. Lillibridge, S.S. Leffingwell and J.A. Liddle, "A Report by a U.S. Medical Team on the Casualties from the Tokyo Subway Incident." (May 1995.)

KNOWN CLINICAL STATUS OF CASUALTIES AS OF NOON, 21 March 1995

(Data supplied by Japanese Ministry of Health and Welfare)

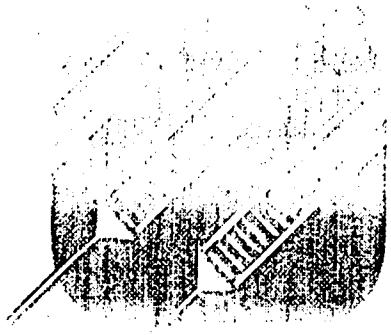
Effect	Number
Dead (4 more died later)	8
Critical (required mechanical ventilation and intensive care; 2 died on 22 March 1995)	17
Severe (miosis + GI signs or respiratory/neurological signs/symptoms; no assisted ventilation)	37
Moderate (miosis only)	984
Not hospitalized (examined and released)	4073
Unknown disposition (unaccounted for)	391
	5510

(2769 male; 1824 female; 917 unrecorded gender)

Source: Sidell, F.R., S.R. Lillibridge, S.S. Leffingwell and J.A. Liddle, "A Report by a U.S. Medical Team on the Casualties from the Tokyo Subway Incident." (May 1995.)

CHOLINESTERASE MONITORING

- Plasma ChE only (no RBC- ChE)
- ChE tests performed before and after treatment initiated
  - Mean ChE inhibition of patients ≈ 20%
  - % inhibition reflective of manifested toxic effects (Range ≈ 10 - 30%)
- Dramatic recovery to normal levels following 2 PAM-I treatment



DATA SUMMARY
G-series NERVE AGENTS
Human Data (cont'd)

- Nonlethal Toxicity (cont'd)
  - clinical case reports from accidental occupational exposures to agent workers (Sidell, 1974; 1997; Rengstorff, 1985); rhinorrhea, respiratory discomfort/distress, marked miosis w/ eye pain, salivation, labored breathing, cyanosis, convulsions, RBC-ChE depression (depression to 0%, 19%, 84%, of baseline with time), fasciculations

  - Epidemiologic studies
    - None suitable for deriving AEGL estimates (no dose-response data)

    - follow-up evaluations of chemical terrorist attacks in Japan (passive release of agent GB in subway cars/station platforms)

    - agent workers occupationally exposed to unknown concs. approx. 1 yr prior to exam

    - retrospective analysis of servicemen who had historically participated in agent effects/therapy testing at Edgewood Arsenal (questionnaire)

DATA SUMMARY
G-series NERVE AGENTS
Human Data (cont'd)

- Experimental exposures (human volunteers)
  - Agent GA: exposures to 0.35 mg/m^3 for 2 min (transient chest tightness, no miosis); 1.6 mg/m^3 for 2 min (chest tightness, miosis) (Uhde and Moore, 1945)

  - Agent GD: 0.3 mg/m^3 for 3 min (chest tightness, rhinorrhea; Fairley and Mumford, 1948)

  - Agent GB: multiple (approx. 10) studies published between 1948-1996 over wide concentration range for durations of < 1 min to 40 min reported headache, eye pain, vision dimness, miosis, eyelid twitching, rhinorrhea, salivation, throat irritation, chest tightness, sweating, cramps, nausea, vomiting, giddiness, concentration difficulty, malaise, ChE depression

DATA SUMMARY
G-series NERVE AGENTS
Animal Data

- Lethal toxicity
  - acute inhalation data for primates, dog, rabbit, guinea pig, rat, mouse (active and resting) exposed to agents GA, GB, GD

  - acute inhalation data for rats exposed to agent GF

- Nonlethal toxicity
  - short-term and subchronic inhalation exposures for baboons, dogs, rats (52 week study for rat), and mice exposed to agent GB

  - single inhalation exposure to multiple human LD_{50} of agent GD for baboons; cardiac arrhythmia, apnea, decreased BP

  - 40-hr exposure of rats to differing concs. GD; no clinical signs, inhibited AChE and Bu-ChE activity in all tissues except brain

  - Dog and rat studies indicate that exposures to 0.001 mg GB/m^3 for $\leq$6 hr/da unlikely to produce any signs of toxicity

ANALYTICAL APPROACH

- Overwhelming majority of data collected for single G-agent (GB; sarin; Isopropyl methylphosphono-fluoridate; $C_4H_{10}FO_2P$; CAS No. 107-44-8; contains fluoride group); most robust data set

- Perform AEGL determination for agent GB first

  - AEGL-1 based on human volunteer data from vapor exposure study of Harvey (1952); companion report (same study) of Johns (1952) characterizing miosis in human volunteers used as secondary study; military literature report (Army Chemical Center, Aberdeen Proving Ground, MD).

    - Exposure range:
      - 0.0 to 0.3 mg GB/m^3 for 20 min
      - 1.0 and 1.3 mg GB/m^3 for 4 min
      - 0.0 to 3.0 mg GB/m^3 for 2 min

    - "...normal human volunteers.." not otherwise described; appear to be males between ages of 22 and 59 years of age, with majority between 22 and 25

    - at 0.05 mg/m^3 for 20 min, response threshold for rhinorrhea and miosis signs + subjective eye pain, headache, cramps, etc., observed

ANALYTICAL APPROACH (cont'd)

- AEGL-2 based on human volunteer data from vapor exposure study of Baker and Sedgwick (1996); open literature (*Human and Experimental Toxicology* 15: 369-375)

    - Exposure: 0.5 mg GB/m^3 for 30 min
    - "Eight fit male servicemen...were fully informed about the nature of the project."
    - Study "ethically reviewed and approved...by the Medical Committee acting...as an Ethics Subgroup and adhering to the declaration of Helsinki and the Guidelines for Human Studies of the Royal College of Physicians."
    - miosis in all subjects, dyspnea and photophobia in some individuals, RBC-ChE inhibition to 60% baseline at 3 hr and 3 da post-exposure, measurable changes in single-fibre electromyography (SFEMG) of forearm muscle detectable in lab 4-15 mos post-exposure
    - respiratory effects resolved w/in minutes; ocular effects resolved w/in 48 hrs
    - authors find SFEMG changes to be reversible and subclinical, and possible sensitive indicator of "non-depolarising neuromuscular block" found associated with paralysis in severe OP poisoning cases; possible biomarker (protective definition of AEGL-2 effect)

ANALYTICAL APPROACH (cont'd)

- AEGL-3 based on female rat mortality data from vapor exposure study of Mioduszewski et al., (2000, in press); open literature (SOT Annual meeting presentation and abstract in *The Toxicologist* 54:18 [2000]; *Proceedings of the International Chemical Weapons Demilitarization Conference*, The Hague, NL [May 21-24, 2000]).

    - Inhalation of SD rats in dynamic mode exposure chamber
    - whole-body exposure to one of 5 concentrations (2-56 mg/m^3) for seven exposure times (3, 10, 30, 60, 90, 240, 360 min)
    - 10 animals /Ct combination, 50 animals per time point
    - 14-day lethality of females (females reported more sensitive, statistical significance at $p < 0.001$)

PROPOSED AEGL VALUES FOR AGENT GB (and comparison with ATEL)						
Classification	10-min.	30-min.	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Non-disabling)	0.0012 ppm 0.0069 mg/m^3	0.00068 ppm 0.004 mg/m^3	0.00048 ppm 0.0028 mg/m^3	0.00024 ppm 0.0014 mg/m^3	0.00017 ppm 0.0010 mg/m^3	Human headache, eye pain, rhinorrhea, tightness in chest, cramps, nausea, malaise, miosis (Harvey, 1952; Johns, 1952)
Agent Threshold Effects Level (ATEL/CDC; calculated)	0.0085 ppm 0.05 mg/m^3	0.0029 ppm 0.017 mg/m^3	0.0014 ppm 0.0083 mg/m^3	0.0036 ppm 0.0021 mg/m^3	0.00017 ppm 0.0010 mg/m^3	Derived from CDC Agent Threshold Effects Level for agent GB of 0.5 $mg\text{-}min/m^3$ (Thacker, 1994)
AEGL-2 (Disabling)	0.015 ppm 0.087 mg/m^3	0.009 ppm 0.05 mg/m^3	0.006 ppm 0.035 mg/m^3	0.0029 ppm 0.017 mg/m^3	0.0022 ppm 0.013 mg/m^3	Human miosis, dyspnea, inhibition of RBC-Che, changes in single fibre electromyography (SFEMG) (Baker and Sedgwick, 1996)
AEGL-3 (Lethal)	0.064 ppm 0.38 mg/m^3	0.032 ppm 0.19 mg/m^3	0.022 ppm 0.13 mg/m^3	0.012 ppm 0.070 mg/m^3	0.0087 ppm 0.051 mg/m^3	Based on rat lethality data (Mioduszewski et al., 2000; in press)

ATEL (Agent Threshold Effects Level) is a value of cumulative exposure considered by CDC (Thacker, 1994) to "form a prudent protective basis for planning and would be protective of public health and safety." The ATEL for agent GB is 0.5 $mg\text{-}min/m^3$.

SUMMARY OF PROPOSED AEGL VALUES FOR AGENTS GA, GD and GF [ppm (mg/m^3)]							
Agent	**Class.**	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Ref.)**
GA	AEGL-1 (Non-disabling)	0.0010 ppm (0.0069 mg/m^3)	0.0006 ppm (0.0040 mg/m^3)	0.00042 ppm (0.0028 mg/m^3)	0.00021 ppm (0.0014 mg/m^3)	0.00015 ppm (0.0010 mg/m^3)	Based on relative potency[a]
	AEGL-2 (Disabling)	0.013 ppm (0.087 mg/m^3)	0.008 ppm (0.050 mg/m^3)	0.005 ppm (0.035 mg/m^3)	0.0026 ppm (0.017 mg/m^3)	0.002 ppm (0.013 mg/m^3)	Based on relative potency[a]
	AEGL-3 (Lethal)	0.114 ppm (0.76 mg/m^3)	0.057 ppm (0.38 mg/m^3)	0.039 ppm (0.26 mg/m^3)	0.021 ppm (0.14 mg/m^3)	0.015 ppm (0.102 mg/m^3)	Based on relative potency[b]
GD	AEGL-1 (Non-disabling)	0.00046 ppm (0.0035 mg/m^3)	0.0003 ppm (0.002 mg/m^3)	0.00018 ppm (0.0014 mg/m^3)	0.00009 ppm (0.0007 mg/m^3)	0.00007 ppm (0.0005 mg/m^3)	Based on relative potency[c]
	AEGL-2 (Disabling)	0.0057 ppm (0.044 mg/m^3)	0.0033 ppm (0.025 mg/m^3)	0.0022 ppm (0.018 mg/m^3)	0.0012 ppm (0.0085 mg/m^3)	0.0008 ppm (0.0065 mg/m^3)	Based on relative potency[c]
	AEGL-3 (Lethal)	0.049 ppm (0.38 mg/m^3)	0.025 ppm (0.19 mg/m^3)	0.017 ppm (0.13 mg/m^3)	0.0091 ppm (0.070 mg/m^3)	0.0066 ppm (0.051 mg/m^3)	Based on relative potency and rat LC_{50} (Aas et al., 1985)[d]

NERVE AGENT VX AEGLs
(CAS No. 50782-69-9)

NAC/AEGL-18
U.S. Dept. of Transportation
DOT Headquarters/Nassif Bldg., Rms 8236-8240
400 7th Street, SW
Washington, D.C.

July 26-28, 2000

Nerve Agent VX: Toxicity

- Cholinesterase inhibitor; acetylcholine accumulation results in continuous post-synaptic action potentials leading to adverse cholinergic effects in PNS and CNS + end organ stimulation

- no chronic neurological disorders following asymptomatic exposures

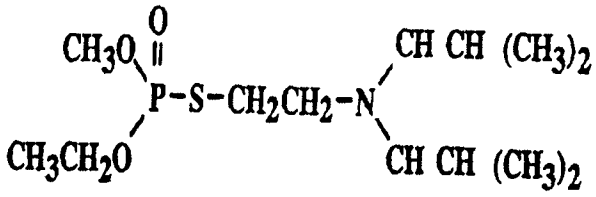
- shows no potential for inducing organophosphorous-induced delayed neuropathy (OPIDN)

- no data suggesting reproductive or developmental toxicity; no carcinogenicity evidence

- VX not genotoxic in microbial or mammalian bioassays

Nerve Agent VX: Identification and Characterization

- Organophosphate ester derivative of phosphonic acid containing a sulfur substituent group; O-ethyl-S-(isopropylaminoethyl) methyl phosphonothiolate; CAS No. 50782-69-9



- Code name derived from "Venom;" warfare agent developed by British and US scientists in the 1950's

- Persistent, "terrain denial" compound with deliberately formulated low volatility (considered "2000 times less volatile than nerve agent GB")

    - contaminated terrain can off-gas toxic concentrations for several days, depending on ambient temperature and weather; oily liquid in normal state

- Part of U.S. unitary stockpile undergoing Congressionally mandated destruction; listed as a material thought to be at non-stockpile sites undergoing installation restoration

- Considered potential military or terrorist threat

VX Similar to G-agents Regarding Gradation of Signs/Symptoms with ↑ Cumulative Exposure

SEVERE Effects

MUSCLES:	convulsions, weakness w/eventual loss of muscle tone and capability to function (paralysis); cessation of breathing
RESP:	v. copious secretions ("dry-land drowning")
ALL:	loss of consciousness, coma, death

Respiratory failure is primary cause of death following severe exposure.

VX Similar to G-agents Regarding Gradation of Signs/Symptoms with ↑Cumulative Exposure

MILD Effects

EYES:	miosis, pain ("deep in eye" or head), dim or blurred vision
NOSE:	runny (rhinorrhea)
RESP:	"Tightness in chest," bronchoconstriction, secretions in airways, cough, breathing difficulty

Pupillary muscles v. sensitive to vapor contact; miosis early sign of nerve agent vapor exposure

MODERATE Effects

EYES:	increased degree of miosis, pain, and dim or blurred vision
NOSE:	severe rhinorrhea, nasal congestion
RESP:	increasing bronchoconstriction and breathing difficulty, secretions more copious
MUSCLES:	feeling of generalized weakness, twitching of large muscle groups
GI:	nausea, vomiting, diarrhea, cramps

DATA SUMMARY
VX NERVE AGENT
Animal Data

- Lethal toxicity
  - Single 10-min LCt_{50} values reported for mouse and goat in summary source (no data)
  - multiple exposures to mice and guinea pigs over period of 2 weeks indicate wide range in species sensitivity (Crook, et al., 1983)

- Nonlethal toxicity
  - multiple exposures to a range of concentrations to both genders of SD rats, ICR Swiss mice, Hartley guinea pigs, NZ white rabbits over period of 2 weeks ; observed miosis, RBC-ChE activity inhibition; no lesions in multiple organ tissues; no physiological effects on body temp., BP, EEG, etc. (Crook, et al., 1983)
  - study of miosis induction potency in both genders of "albino" rabbits; comparison between VX and GB/GD vapor exposure to eye of rabbit to generate 50% and 90% reduction in pupil area; VX vapor range from 0.5 to 25$\mu g/m^3$ for durations of approx. 2 to 400 min; results presented in Cts of mg-min/m^3 (Callaway and Dirnhuber, 1971)

DATA SUMMARY
VX NERVE AGENT
Human Data

- Lethal Toxicity
  - no available information
  - Available estimates of human lethal concentrations (LCt_{50}, etc.) derived/extrapolated from animal data
- Nonlethal Toxicity
  - no case reports located
  - no epidemiological studies located
  - Experimental inhalation exposures (human volunteers)
    - odor detection study (Koon et al., 1959); 4 "sniff" exposures with est. total doses of 0.01 to 0.13 µg/kg; headaches, transitory chest "tightness," dry mouth, nasal irritation; 16 persons
    - vapor exposures of 0.23 mg/m^3 to 5 mg/m^3 for durations of 2.25 sec to 24 min (Ct range of 0.7 to 25.6 $mg\text{-}min/m^3$) (Bramwell, et. al., 1963); time-dependent development of ChE inhibition, miosis, eyelid twitch, sweating, GI upset, malaise, rhinorrhea, salivation; 8 persons
- AEGL data analysis augmented by studies of human intravenous, oral, and percutaneous VX exposure

ANALYTICAL APPROACH FOR VX (cont'd)

- AEGL-3 for VX based on recent inhalation studies in which lethality of agent GB evaluated for multiple time periods in female SD rats (Mioduszewski et al., 2000; in press); LC_{01} for VX estimated for data-derived LC_{01} for GB by factor of 10 reduction.

    - GB LC_{01} for 10 min = 11.54 mg/m^3
      Est. VX LC_{01} for 10 min = 1.15 mg/m^3
    - GB LC_{01} for 30 min = 5.84 mg/m^3
      Est. VX LC_{01} for 30 min = 0.58 mg/m^3
    - GB LC_{01} for 60 min = 4.01 mg/m^3
      Est. VX LC_{01} for 60 min = 0.40 mg/m^3
    - GB LC_{01} for 4 hr = 2.09 mg/m^3
      Est. VX LC_{01} for 4 hr = 0.21 mg/m^3
    - GB LC_{01} for 6 hr = 1.76 mg/m^3
      Est. VX LC_{01} for 6 hr = 0.18 mg/m^3

    - n = 1 for estimating from 6 hr time period (max exposure duration experimentally tested in Mioduszewski et al., 2000; in press) to 8 hr

ANALYTICAL APPROACH FOR VX

- Sparse animal and human toxicity data insufficient to support AEGL analysis

- AEGLs for agent VX are derived from AEGLs for agent GB by a relative potency method

- Literature indicates that VX is considered approximately 10 times more potent than agent GB for a number of toxic endpoints (Callaway and Dirnhuber, 1971; Reutter et al., 2000)

    - AEGL-1 based on Harvey (1952) and Johns (1952) study of human volunteers in which minimal effects occurred at 0.05 mg GB/m^3 for 20 min exposure; comparable effects concentration for agent VX assumed to equal 0.005 mg VX/m^3.
        - Subsequent derivation based on n = 1 (default since no experimental determination of "n" value for VX) and ten Berge et al. (1986) equation

    - AEGL-2 based on study of Baker and Sedgwick (1996) study of human volunteers; multiple respiratory and ocular effects, RBC-ChE depression, long-lasting SFEMG changes at 0.5 mg GB/m^3 for 30 min; comparable effects concentration for agent VX assumed to equal 0.05 mg VX/m^3.
        - Same assumptions for "n" and ten Berge et al.

References

Baker, D.J., Sedgwick , E.M. 1996. Single fibre electromyographic changes in man after organophosphate exposure. Hum. Exp. Toxicol. 15:369-375.

Callaway, S. and Dirnhuber, P. 1971. Estimation of the concentration of nerve agent vapour required to produce measured degrees of miosis in rabbit and human eyes. Technical Paper No. 64, Chemical Defence Establishment, Porton Down, Salisbury, Wilts., UK

Harvey, J.C. 1952. Clinical observations on volunteers exposed to concentrations of GB. Medical Laboratories Research Report No. 114, Publication Control No. 5030-114 (CMLRE-ML-52), MLCR 114. Army Chemical Center, MD.

Johns, R.J. 1952. The effect of low concentrations of GB on the human eye. Research Report No. 100, Publication Control No. 5030-100 (CMLRE-ML-52). Chemical Corps Medical Laboratories, Army Chemical Center, MD.

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Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B. Muse, W., Thomson, S., Sommerville, D. and Crosier, R. In press. Estimating the probability of sarin vapor toxicity in rats as a function of exposure concentration and duration. Proceedings of the International Chemical Weapons Demilitarization Conference (CWD-2000), The Hague, NL (May 21-24, 2000).

PROPOSED AEGL VALUES FOR AGENT VX (and comparison with ATEL)

Classification	10-min.	30-min.	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Non-disabling)	0.000091 ppm 0.0010 mg/m^3	0.000030 ppm 0.00033 mg/m^3	0.000016 ppm 0.00017 mg/m^3	0.0000037 ppm 0.000041 mg/m^3	0.0000019 ppm 0.000021 mg/m^3	Derived from study of multiple minimal effects to human volunteers exposed to GB vapor; headache, eye pain, rhinorrhea, tightness in chest, cramps, nausea, malaise, miosis (Harvey, 1952; Johns, 1952)
AEGL-2 (Disabling)	0.0014 ppm 0.015 mg/m^3	0.00046 ppm 0.005 mg/m^3	0.00023 ppm 0.0025 mg/m^3	0.000058 ppm 0.00063 mg/m^3	0.000028 ppm 0.00031 mg/m^3	Derived from study of GB vapor exposure to exercising human volunteers resulting in miosis, dyspnea, inhibition of RBC-ChE, changes in single fibre electromyography (SFEMG) (Baker and Sedgwick, 1996)
Agent Threshold Effects Level (ATEL/CDC; calculated)	0.0037 ppm 0.04 mg/m^3	0.0012 ppm 0.013 mg/m^3	0.00061 ppm 0.0067 mg/m^3	0.00016 ppm 0.0017 mg/m^3	0.000076 ppm 0.00083 mg/m^3	Derived from CDC Agent Threshold Effects Level for agent VX of 0.4 mg-min/m^3 (Thacker, 1994)
AEGL-3 (Lethal)	0.0035 ppm 0.038 mg/m^3	0.0017 ppm 0.019 mg/m^3	0.0012 ppm 0.013 mg/m^3	0.00064 ppm 0.0070 mg/m^3	0.00041 ppm 0.0045 mg/m^3	Based on rat lethality data (Mioduszewski et al., 2000; in press)

ATEL (Agent Threshold Effects Level) is a value of cumulative exposure considered by CDC (Thacker, 1994) to "form a prudent protective basis for planning and would be protective of public health and safety." The ATEL for agent VX is 0.4 mg-min/m^3.

References (cont'd)

Thacker, S.B., Assistant Surgeon General, Acting Director, National Center for Environmental Health, Centers for Disease Control and Protection, U.S. Department of Health and Human Services, 1994. Letter establishing "Recommended Acute Threshold Effects Levels for Determining Emergency Evacuation Distances in the CSEPP Program," to COL J.M. Coverstone, Deputy for Chemical Demilitarization, Office of the Assistant Secretary (I, l, and E), the Pentagon, Washington, D.C. (24 June, 1994)

Appendix A

National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 17 Highlights
Environmental & Occupational Health Sciences Institute
Rutgers University
Piscataway, New Jersey
April 26-28, 2000

INTRODUCTION

Dr. Robert Snyder, meeting host, welcomed the NAC/AEGL on behalf of the Environmental and Occupational Health Sciences Institute (EOSHI).

Dr. George Rusch (NAC Chairperson) opened the meeting with comments regarding the application of AEGLs in fire codes (National Institute for Fire Prevention) and that upon approval by the National Research Council the AEGLs will be considered as lead values for emergency programs. It was also stated that the New Jersey on-scene coordinator for training and emergency response expressed an interest in using AEGLs.

The highlights of the meeting are noted below, and the meeting agenda (Attachment 1) and an attendee list (Attachment 2) are attached. Highlights of the NAC Meeting 16 (December 6-8, 1999) were reviewed (with a brief discussion and minor correction) and were approved (Appendix A).

GENERAL INTEREST ITEMS

Paul Tobin provided brief comments about the second list of priority chemicals (186 chemicals), noting that production volumes and emergency release data (Reportable Quantity release data) were focal points.

Ernest Falke provided brief status remarks of the most recent revision SOPs.

RESPONSE TO COMMENTS ON THE *FEDERAL REGISTER* NOTICE

Discussions were held regarding comments (Attachment 3) on the *Federal Register* notice for eight chemicals: HFC-134a, 1,1,1-trichloroethane, Agent HD (sulfur mustard), 1,2-dichloroethylenes (*cis* and *trans*), Otto Fuel, HCFC-141b, hydrogen fluoride, and hydrogen sulfide. The dispositions of these comments are summarized in the following sections.

HFC-134a

In response to comments received from three sources on the *Federal Register* notice, there was discussion regarding the overall data set and its support of the proposed AEGL values. One submitter (Michigan Air Quality Division) indicated concurrence with the AEGLs. For AEGL-1, these discussions revolved around the appropriateness of an uncertainty factor of 1 from a study of 8 young health adults. A motion (moved by Loren Koller; seconded by John Hinz) passed [YES: 16; NO: 3; ABSTAIN: 0 (Appendix B)]

to accept the original AEGL-1 value of 8,000 ppm for all time points as an Interim AEGL-1. Similarly, there was discussion focusing on the available data and their support of the previously proposed AEGL-2 and AEGL-3 values. Specifically, the discussion focused on the use of cardiac sensitization as a predictor for adverse effects. A motion (moved by John Morawetz and seconded by Mark McClanahan) passed unanimously [YES: 19; NO: 0; ABSTAIN: 0] (Appendix B) to accept the AEGL-2 and AEGL-3 values as Interim and respond accordingly to the *Federal Register* comments.

INTERIM AEGL VALUES FOR HFC-134a					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	8,000 ppm	8,000 ppm	8,000 ppm	8,000 ppm	8,000 ppm
AEGL-2	13,000 ppm	13,000 ppm	13,000 ppm	13,000 ppm	13,000 ppm
AEGL-3	27,000 ppm	27,000 ppm	27,000 ppm	27,000 ppm	27,000 ppm

1,1,1-Trichloroethane

Two submissions were received. The Michigan Air Quality Division expressed concurrence with the AEGLs. The International Chemical Workers Union Council contended that the proposed AEGL values were too high and that this contention is supported by monitoring data from reconstruction of a fatility. Following discussions, a motion to accept the originally proposed values as Interim AEGLs was made by Robert Snyder (seconded by Steve Barbee). The motion passed [YES: 13; NO: 6; ABSTAIN: 0] (Appendix C). For the AEGL-3 values, it was also decided to remove the modifying factor (3-fold adjustment to achieve a reasonable concentration at which humans might experience life-threatening effects) and change the interspecies uncertainty factor from 3 to 1. This results in a total uncertainty factor of 3 (rather than 3.3) based on differences in sensitivity among humans. The reduction of the interspecies uncertainty factor to 1 is based on the 2-fold difference in uptake between the rat and humans. This change in rationale altered the 10- and 30-minute, and 1-, 4-, and 8-hour values from 4800, 4800, 3800, 2400, and 1900 ppm, respectively, to 4200, 4200, 4200, 2700, and 2100 ppm.

INTERIM AEGL VALUES FOR 1,1,1-TRICHLOROETHANE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	230 ppm	230 ppm	230 ppm	230 ppm	230 ppm
AEGL-2	930 ppm	670 ppm	600 ppm	380 ppm	310 ppm
AEGL-3[a]	4,200 ppm	4,200 ppm	4,200 ppm	2,700 ppm	2,100 ppm

[a] The 10- and 30-minute AEGL-3 values were flatlined to the 1-hour value so as not to exceed the threshold of 5,000 ppm for cardiac sensitization observed in dogs.

Agent HD (Sulfur Mustard)

The only comment submitted in response to the *Federal Register* notice was in support of the proposed values for sulfur mustard. A motion (Mark McClanahan, seconded by Richard Niemeier) to change the proposed AEGLs for Agent HD to Interim status passed unanimously (Appendix D).

INTERIM AEGL VALUES FOR SULFUR MUSTARD (AGENT HD)					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	0.060 ppm	0.020 ppm	0.010 ppm	0.0026 ppm	0.0012 ppm
AEGL-2	0.090 ppm	0.030 ppm	0.015 ppm	0.0038 ppm	0.0020 ppm
AEGL-3	0.92 ppm	0.63 ppm	0.32 ppm	0.080 ppm	0.041 ppm

1,2-Dichloroethylene

Comments from the Michigan Air Quality Division, PPG Industries, and Pinnacle West Capital Corp. were received in response to the *Federal Register* notice. The cis-values presented in the document were derived by a modification of the trans- values. Comments were received suggesting that cis-data be used for deriving cis-values. However, after deliberations, the NAC decided that data for the cis- isomer were sparse and it was appropriate to retain the modified trans-isomer values as cis-isomer values. Comments were also received concerning the selection of key studies. A human study from 1936 was used for derivation of all AEGL-1 values and AEGL-2 and AEGL-3 values for 10-min, 30-min, and 1-hr. The comments suggested the use of more recent controlled animal studies in place of the less robust human data. After much deliberation the NAC decided that the human data, could not be ignored and voted to elevate the values to interim status. In response to other comments, the introduction was changed to correctly summarize current uses and production methods; the previous introduction contained historical information. Summary information from genotoxicity studies were added. These data suggest that the trans-isomer is negative in both in vivo and in vitro tests and that the cis-isomer is negative in in vivo tests and equivocal in in vitro tests. A motion was made by Mark McClanahan (seconded by David Belluck) that the proposed AEGLs for this chemical be elevated to interim status and that the NAC/AEGL is satisfied with the explanations provided by Cheryl Bast and Ernie Falke in response to the *Federal Register* comments and that most of the issue had been addressed during the previous deliberations. The motion passed unanimously (Appendix E).

INTERIM AEGL VALUES FOR *trans-cis* 1,2-DICHLOROETHYLENE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	280 ppm	280 ppm	280 ppm	280 ppm	280 ppm
AEGL-2	1,000 ppm	1,000 ppm	1,000 ppm	690 ppm	450 ppm
AEGL-3	1,700 ppm	1,700 ppm	1,700 ppm	1,200 ppm	620 ppm

INTERIM AEGL VALUES FOR *cis* 1,2-DICHLOROETHYLENE

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	140 ppm	140 ppm	140 ppm	140 ppm	140 ppm
AEGL-2	500 ppm	500 ppm	500 ppm	340 ppm	230 ppm
AEGL-3	850 ppm	850 ppm	850 ppm	620 ppm	310 ppm

Otto Fuel

A comment from the International Chemical Workers Union Council to the *Federal Register* notice indicated that the 10-minute AEGL-2 value may be too high. This was based upon the contention that data in humans demonstrated severe headaches following a 3.5-hour exposure to 1.5 ppm and that this effect was too severe to be discounted. A motion was made by Robert Benson and seconded by Richard Niemeier to flatline the 30-minute and 10-minute AEGL-2 at 2 ppm and the 10- and 30-minute AEGL-3 at 16 ppm. The motion passed unanimously (Appendix F). The 10-minute AEGL-3 was flatlined from the 30-minute values because the key study utilized a 6-hour exposure duration. All of the AEGLs for Otto fuel were elevated to interim status.

INTERIM AEGL VALUES FOR OTTO FUEL					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	0.33 ppm	0.33 ppm	0.17 ppm	0.05 ppm	0.03 ppm
AEGL-2	2.0 ppm	2.0 ppm	1.0 ppm	0.25 ppm	0.13 ppm
AEGL-3	16 ppm	16 ppm	13 ppm	8.0 ppm	5.3 ppm

HCFC-141b

In response to a comment submitted by the International Chemical Workers Union Council to the *Federal Register* notice, initial discussion focused on the data set used to develop AEGL1- values. Specifically, an issue was raised regarding the reliability of an uncertainty factor of 1 from 8 young healthy adults. In response to this issue, it was explained that the subjects experienced no evidence of nasal irritation, and no specific unpleasant odor. Additionally, blood concentrations reach equilibrium very quickly and, therefore, development of effects at notably later time points is not likely. A motion was submitted by Mark McClanahan (seconded by Bob Benson) that the originally proposed AEGL-1 values be elevated to interim status. The motion passed [YES: 17; NO: 2; ABSTAIN: 0] (Appendix G). Mark McClanahan moved that the AEGL-2 and AEGL-3 values be elevated to interim status. The motion was seconded by Bob Benson and approved by the NAC/AEGL: [YES: 17; NO: 2; ABSTAIN: 0] (Appendix G).

INTERIM AEGL VALUES FOR HFC-141b					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	1,000 ppm	1,000 ppm	1,000 ppm	1,000 ppm	1,000 ppm
AEGL-2	1,700 ppm	1,700 ppm	1,700 ppm	1,700 ppm	1,700 ppm
AEGL-3	3,000 ppm	3,000 ppm	3,000 ppm	3,000 ppm	3,000 ppm

Hydrogen fluoride

Comments from the American Petroleum Institute, and BP Amoco on the *Federal Register* notice indicated concern regarding consistency between the endpoints used for AEGL development and the AEGL definitions. There was also concern regarding the use of data from the Rosenholtz et al. (1963) study in dogs as opposed to using the PERF (Dalbey, 1996) study for development of 30- and 60-minute AEGL-2 values. The Michigan Air Quality Division indicated that interspecies and intraspecies uncertainty factors for AEGL-2 and AEGL-3 values should be increased 3-fold. Discussion ensued regarding the AEGLs proposed by those submitting comments (BP Amoco, EM/API, State of Michigan, API). The comments/concerns from BPA and Michigan were addressed and comments from API and the recently available study by Lund et al. (1999) will be discussed at the next meeting.

Hydrogen sulfide

Comments were received from six organizations (American Petroleum Institute, Michigan Air Quality Division, American Forest and Paper Association, IBP, Inc., and the Chemical Manufacturers Association). Cheryl Bast summarized the comments and provided background information regarding the development of the proposed AEGLs. Comments on the hydrogen sulfide AEGLs were basically partitioned between AEGL-1, -2 and -3. For AEGL-1, many of the comments suggested the use of a study in asthmatics or withdrawal of the AEGLs. Following discussions, it was decided to retain the AEGL-1 values but to strengthen the rationale and justifications. A motion to retain the AEGL-1 values and elevate them to interim status was made by Dave Belluck (seconded by Ernest Falke) was voted upon and passed unanimously (Appendix H). For AEGL-2 and -3, the NAC/AEGL addressed several comments, including the use of endpoints with higher exposure concentrations, the use of a default *n* value for time scaling rather than the empirically derived *n* of 4.5, and the incorporation of a CIIT developmental neurotoxicity study recommended by the American Petroleum Institute. Following detailed discussions of each responder's comments, a motion was made by Bob Benson (seconded by Ernest Falke) to retain the AEGL-2 and -3 values and elevate them to interim status. AEGL-2 was also passed unanimously (Appendix H) and AEGL-3 was also passed [YES: 16; NO: 1; ABSTAIN: 0] (Appendix H).

INTERIM AEGL VALUES FOR HYDROGEN SULFIDE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	0.03 ppm	0.03 ppm	0.03 ppm	0.03 ppm	0.03 ppm
AEGL-2	42 ppm	32 ppm	28 ppm	20 ppm	17 ppm
AEGL-3	76 ppm	60 ppm	50 ppm	37 ppm	31 ppm

Hydrogen cyanide

George Rodgers summarized the *Federal Register* comments. It was suggested that the AEGL-1 values be flatlined based upon a cross-sectional study of cyanide salt workers by Lesser et al. (1990). Following discussions on the comments pertaining to AEGL-1, a motion was made by George Rodgers (seconded by Tom Hornshaw) that the comments were adequately addressed and to elevate to interim status the AEGL-1 value of 1 ppm for all time points (10 minutes, 30 minutes, 1-, 4-, and 8 hours). Later, the motion was withdrawn and the discussion was tabled pending receipt of studies. For AEGL-2 and -3, discussion focused on the appropriate endpoints and exposure concentrations. It was the consensus of the NAC/AEGL that the comments were adequately addressed but that the TSD be revised to show that both a probit analysis and benchmark dose analysis provided similar values. A motion to elevate the AEGL-2 and AEGL-3 values to interim status was made by Ernest Falke (seconded by Bob Benson). The motions passed [YES: 21; NO: 1; ABSTAIN: 0] (Appendix I).

INTERIM AEGL VALUES FOR HYDROGEN CYANIDE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	–	–	–	–	–
AEGL-2	17 ppm	10 ppm	7.1 ppm	3.5 ppm	2.5 ppm
AEGL-3	27 ppm	21 ppm	15 ppm	8.6 ppm	6.6 ppm

DEVELOPMENT OF 10-MINUTE AEGLS

In response to the need for 10-minute AEGLs, TSDs were revised to incorporate the development of 10-minute AEGLs. These values were developed by assessing data available for time periods less than 30 minutes, by temporal extrapolation from exposure with durations of 4 hours or less, or by flatlining from the previously established 30-minute AEGL. In the course of the discussions, it was agreed that extrapolation to 10-minute values would be limited to exposure data of less than 4 hours duration. If the AEGLs were developed using a key exposure of 4 hours or greater and no shorter duration data were available, the 10-minute AEGL would be flatlined from the 30-minute value. The 10-minute AEGLs and their rationales were presented by ORNL staff scientists or the chemical manager. Discussions were focused primarily on the newly derived 10-minute values and their relational consistency with the previously derived AEGLS.

Crotonaldehyde

Sylvia Milanez provided an overview of the available data pertinent to development of 10-minute AEGL values (Attachment 4). For AEGL-1, the same value was flatlined for 30 minutes to 8 hours was used for 10 minutes. AEGL-2 and AEGL-3 values were both based on studies that encompassed ≤10-minute exposures. Therefore, the 10-minute values were extrapolated using the *n* values previously used to derive 30 minute–8 hour values (Attachment 4). The NAC/AEGL approved development of the values as motioned by George Rogers and seconded by John Hinz (Appendix J). The resulting AEGLS for crotonaldehyde are shown below.

PROPOSED AEGL VALUES FOR CROTONALDEHYDE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	0.19 ppm	0.19 ppm	0.19 ppm	0.19 ppm	0.19 ppm
AEGL-2	27 ppm	8.9 ppm	4.4 ppm	1.1 ppm	0.56 ppm
AEGL-3	44 ppm	27 ppm	14 ppm	2.6 ppm	1.5 ppm

Allylamine

Pertinent data and development of AEGLS were reviewed by Sylvia Milanez (Attachment 5). Specifically, the AEGL-1 values were developed based upon the Shell Oil Co. (1992) study of occupational exposures that showed an 8-hour exposure to 0.20 ppm was nonirritating. The AEGL-1 was flatlined at 0.20 ppm.

A slight modification of previously accepted AEGL-2 was made using a newly calculated value of $n = 1.71$ based upon the endpoint of cardiotoxicity. These revised values and the newly developed 10-minute values were accepted and are shown below. For AEGL-1, the motion was made by Mark McClanahan and seconded by Loren Koller. For AEGL-2 and -3, the motion was made by Loren Koller and seconded by John Hinz (Appendix K). The 10-minute values for AEGL-2 were flatlined from the 30-minute numbers.

PROPOSED AEGL VALUES FOR ALLYLAMINE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	0.20 ppm	0.20 ppm	0.20 ppm	0.20 ppm	0.20 ppm
AEGL-2	4.2 ppm	4.2 ppm	2.8 ppm	1.2 ppm	0.83 ppm
AEGL-3	140 ppm	40 ppm	18 ppm	3.5 ppm	2.3 ppm

Ethylenediamine

The data and rationale pertinent to development of 10-minute AEGLS were summarized by Sylvia Milanez (Attachment 6). These values and a revision of the AEGL-2 and AEGL-3 values were discussed. AEGL-1 values were not recommended due to insufficient data. The AEGL-2 values were based upon an 8-hour animal exposure to approximately 484ppm. Due of the 8-hour duration, the 10-minute values were flatlined from the 30-minute value. Because the AEGL values were based on 8-hour exposures, the

10-minute AEGL-3 values were flatlined from the 30-minute value. Both the AEGL-2 and AEGL-3 values are supported by a multiple-exposure rat study. The accepted values are shown below (Appendix L). For AEGL-1, the motion was made by Bob Benson and seconded by Bob Snyder. For AEGL-2 and -3, the motion was made by Zarena Post and seconded by George Rodgers.

PROPOSED AEGL VALUES FOR ETHYLENEDIAMINE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	12 ppm	12 ppm	9.7 ppm	6.1 ppm	4.8 ppm
AEGL-3	25 ppm	25 ppm	20 ppm	13 ppm	10 ppm

Cyclohexylamine

The rationale for development of 10-minute AEGLS was presented by Sylvia Milanez (Attachment 7). The AEGL-1 values were flatlined at 1.8 ppm. The AEGL-2 values were calculated based upon a well-defined study. The 10-minute values for AEGL-2 and AEGL-3 were flatlined from the 30-minute values. The values as presented below were accepted by the NAC/AEGL. A motion was made by George Rodgers and seconded by John Hinz to accept the proposed 10-minute AEGLS. The voting records for AEGL-1 through -3 are: AEGL-1: [YES: 18; NO: 3; ABSTAIN: 0]; AEGL-2: [YES: 19; NO: 2; ABSTAIN: 0]; for AEGL-3: [YES: 19; NO: 2; ABSTAIN: 0], respectively (Appendix M).

PROPOSED AEGL VALUES FOR CYCLOHEXYLAMINE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm
AEGL-2	11 ppm	11 ppm	8.6 ppm	5.4 ppm	2.7 ppm
AEGL-3	38 ppm	38 ppm	30 ppm	19 ppm	9.4 ppm

2,4- and 2,6-Toluene diisocyanate

The AEGL values for these chemicals were revised based upon an *n* of 1 (longer time periods) or 3 (shorter time periods) for time scaling rather than the previously applied *n* of 2. For AEGL-3 the 10-minute AEGL was set equivalent to the 30-minute value due to the use of a 4-hour exposure duration for the AEGL determinant. The 10-minute AEGLS were approved unanimously by the NAC/AEGL (motion made by Steve Barbee and seconded by Robert Niemeier) (Appendix N). The accepted values are shown below.

PROPOSED AEGL VALUES FOR 2,4, AND 2,6-TOLUENE DIISOCYANATE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**

AEGL-1	0.02 ppm	0.02 ppm	0.02 ppm	0.02 ppm	0.02 ppm
AEGL-2	0.24 ppm	0.17 ppm	0.083 ppm	0.021 ppm	0.021 ppm
AEGL-3	0.65 ppm	0.65 ppm	0.51 ppm	0.32 ppm	0.16 ppm

Iron pentacarbonyl

Robert Young presented a review of the iron pentacarbonyl AEGLS explaining the need for minor adjustments in the previously accepted values (Attachment 8). The development of the 10-minute values was also presented. Because data consistent with a 10-minute exposure period were unavailable, 10-minute values were derived using an *n* of 1 which was based upon analysis of the available data. AEGL-1 values were not developed due to the steep exposure-response relationship and the apparently narrow margin between exposures causing no observable effects and those resulting in lethal responses. The 8-hour AEGLS, as previously decided, were not developed due to the rapid decomposition of the chemical under ambient conditions. A motion was made by George Rodgers and seconded by David Belluck to adopt the 10-minute AEGLS. The voting records (Appendix O) for AEGL-1 and AEGL-3 were unanimously approved; AEGL-2: [YES: 19; NO: 3, ABSTAIN: 0], respectively (Appendix O). The resulting accepted values are shown below.

PROPOSED AEGL VALUES FOR IRON PENTACARBONYL					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	NA	NA	NA	NA	NA
AEGL-2	1.2 ppm	0.40 ppm	0.19 ppm	0.050 ppm	NA
AEGL-3	3.5 ppm	1.2 ppm	0.58 ppm	0.15 ppm	NA

Nickel carbonyl

Robert Young presented a review of the nickel carbonyl AEGLS explaining the need for minor adjustments due to the use of default *n* values of 1 and 3 rather than the previously applied *n* of 2 (Attachment 8). The 10-minute values were developed by time scaling. Values for 8 hours, as determined at initial NAC/AEGL deliberations, were not developed because the chemical would not likely persist for that time under ambient conditions. The accepted values are presented in the following table. A motion was made by George Rogers and seconded by David Belluck. The motion passed unanimously [YES: 22; NO: 0; ABSTAIN: 0] (Appendix P).

PROPOSED AEGL VALUES FOR NICKEL CARBONYL					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	NA	NA	NA	NA	NA
AEGL-2	0.096 ppm	0.042 ppm	0.021 ppm	0.005 ppm	NA
AEGL-3	0.46 ppm	0.32 ppm	0.16 ppm	0.040 ppm	NA

Phosphorus oxychloride

As explained by Robert Young (Attachment 8), the previously proposed AEGLS were adjusted due to the use of default *n* values of 1 and 3 rather than the previously applied *n* of 2. Only AEGL-3 values were developed for this chemical due to the lack of data. Consistent with the procedure previously adopted by the NAC/AEGL, the 10-minute AEGL-3 was flatlined with the 30-minute AEGL-3 due to the use of data from a 4-hour exposure period. A motion was made by Zarena Post and seconded by David Belluck to adopt the proposed value. It was approved unanimously [YES: 18; NO: 0; ABSTAIN: 0] (Appendix Q). The proposed values are presented below.

PROPOSED AEGL VALUES FOR PHOSPHORUS OXYCHLORIDE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	NR	NR	NR	NR	NR
AEGL-3	1.1 ppm	1.1 ppm	0.85 ppm	0.54 ppm	0.27 ppm

Phosphorus trichloride

The previously proposed AEGLS were adjusted due to the use of default *n* values of 1 and 3 rather than the formerly applied *n* of 2. Only AEGL-3 values had been developed for this chemical due to the lack of data. Consistent with the procedure previously adopted by the NAC/AEGL (Attachment 8), the 10-minute AEGL-3 was flatlined with the 30-minute AEGL-3 due to the use of data from a 4-hour exposure period. The proposed values are presented below. During the deliberations it was stated that an industry study was available that might be useful in the development of the AEGL-1 and/or AEGL-2 values. This will be pursued and the development of AEGLs for this chemical revisited if necessary. A motion was introduced by Ernie Falke and seconded by Mark McClanahan to adopt the 10-minute AEGL-3 value. It was passed unanimously [YES: 20; NO: 0; ABSTAIN: 0] (Appendix R).

PROPOSED AEGL VALUES FOR PHOSPHORUS TRICHLORIDE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	NR	NR	NR	NR	NR
AEGL-3	1.1 ppm	1.1 ppm	0.88 ppm	0.56 ppm	0.28 ppm

Hydrogen chloride

Cheryl Bast provided an overview of the hydrogen chloride AEGLS (Attachment 9) and the derivation 10-minute values. For AEGL-1, the 10-minute values was flatlined with the AEGLS for other time points at 1.8 ppm. The NAC/AEGL briefly reviewed the available key data sets for this chemical. AEGL-1 values are based on a NOAEL in exercising human asthmatics. AEGL-2 levels for 30 minutes to 8 hours are based on nasal and lung histopathology in rats. The 10-minute AEGL-2 value is based on a modification of the mouse RD_{50} to obtain a concentration corresponding to irritation. AEGL-3 values are based on an estimated NOEL for death in rats. A motion was made by Mark McClanahan and seconded by John Hinz to adopt the proposed 10-minute AEGL values. In summary, AEGL-1 passed unanimously [YES: 20; NO: 0; ABSTAIN: 0]; AEGL-2: [YES: 16; NO: 3, ABSTAIN: 0]; AEGL-3: [YES: 18; NO: 2; ABSTAIN: 0], respectively (Appendix S). The 10-minute AEGLS presented in the following table were accepted.

PROPOSED AEGL VALUES FOR HYDROGEN CHLORIDE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm
AEGL-2	100 ppm	43 ppm	22 ppm	5.4 ppm	2.7 ppm
AEGL-3	620 ppm	210 ppm	100 ppm	26 ppm	13 ppm

Methyltrichlorosilane

Cheryl Bast presented an overview for the derivation of 10-minute AEGLS for methyltrichlorosilane (Attachment 10). The accepted values are shown in the table below. The 10-minute values for AEGL-2 and -3 were developed by extrapolation from the 1-hour key study. Motion was made by Loren Koller and seconded by Richard Niemeier. AEGL-1 was approved unanimously; AEGL-2: [YES: 16; NO: 4; ABSTAIN: 0]; AEGL-3: [YES: 18; NO: 2; ABSTAIN: 0], respectively (Appendix T).

PROPOSED AEGL VALUES FOR METHYLTRICHLOROSILANE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm
AEGL-2	37 ppm	12 ppm	6.2 ppm	1.6 ppm	0.78 ppm
AEGL-3	170 ppm	56 ppm	28 ppm	7.0 ppm	3.5 ppm

Dimethyldichlorosilane

Cheryl Bast presented an overview for the derivation of 10-minute AEGLS for dimethyldichlorosilane (Attachment 11). For the AEGL-1, the values were flatlined at 0.90 ppm for all time periods. The 10-minute values for AEGL-2 and -3 were developed by extrapolation from the 1-hour key study. A motion was made by Bob Benson and seconded by Mark McClanahan to accept the following AEGL values: AEGL-1: unanimously accepted; AEGL-2: [YES: 15; NO: 5; ABSTAIN: 0]; AEGL-3: [YES: 18; NO: 2; ABSTAIN: 0] (Appendix U).

PROPOSED AEGL VALUES FOR DIMETHYLDICHLOROSILANE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm
AEGL-2	78 ppm	26 ppm	13 ppm	3.3 ppm	1.6 ppm
AEGL-3	320 ppm	110 ppm	53 ppm	13 ppm	6.6 ppm

Methyl isocyanate

Ten-minute AEGLS for this chemical were based upon time scaling using an empirically-derived *n* value of 1 which is based upon exposures with durations as low as 7 minutes. The 10-minute AEGLS were approved as shown in the following table. No AEGL-1 values were developed because the exposures resulting in irritation would exceed AEGL-2 levels. A motion was made by Bob Benson and seconded by Loren Koller and all proposed 10-minute AEGL values were approved unanimously (Appendix V).

PROPOSED AEGL VALUES FOR METHYL ISOCYANATE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	NA	NA	NA	NA	NA
AEGL-2	0.40 ppm	0.13 ppm	0.067 ppm	0.017 ppm	0.008 ppm
AEGL-3	1.2 ppm	0.40 ppm	0.20 ppm	0.05 ppm	0.25 ppm

AEGL PRIORITY CHEMICALS

Deliberations (other than development and approval of 10-minute values) took place for two additional priority chemicals. In both instances, the discussions were a revisit of chemicals that were, to varying extent, addressed at prior meetings.

Bromine, CAS Reg. No. 7726-95-6

Chemical Manager: Zarena Post, Texas NRCC
Staff Scientist: Sylvia Talmage, ORNL

Bromine was first reviewed in 1998 and no AEGLS were developed pending data development. Zarena Post presented an overview of the pertinent data on bromine. Following discussion of the data (especially that by Henschler [Attachment 12]) and uncertainty factor applications, a motion was made by Mark McClanahan (seconded by Bob Benson) to use a 0.1 ppm exposure for 30 minutes as an estimate of the threshold for ocular and nasopharyngeal irritation. The AEGL-1 values were derived using an uncertainty factor of 3 and extrapolation using an *n* value of 2.2 from a lethality study. The motion passed to accept AEGL-1 values of 0.055, 0.033, 0.024, 0.013, and 0.009 ppm, respectively for 10-minutes, 30-minutes, and 1-, 4-, and 8 hours [YES: 15; NO: 5; ABSTAIN: 0] (Appendix V). There was discussion of Henschler's interpretation of data and the exposure that would be considered a threshold for AEGL-2 effects. The determinant of AEGL-2 was a 30-minute exposure of human subjects to 1 ppm that resulted in severe sensory irritation of the eyes, nose, and throat, which was considered by the NAC/AEGL as appropriate AEGL-2 effects. An interspecies uncertainty factor of 3 was applied and time scaling performed using $n = 2.2$ to obtain the AEGL-2 values. A motion to accept the AEGL-2 values of 0.55, 0.33, 0.24, 0.13, and 0.095 ppm was made by Larry Gephart and seconded by Richard Niemeier. The motion passed [YES: 16: NO: 4; ABSTAIN: 0] (Appendix W). For AEGL-3, there was discussion regarding the relative toxicity of bromine and chlorine and the issue of bromination. Following the discussions, there was a motion made by Zarena Post and seconded by Larry Gephart to accept the following AEGL-3 values based on a lethality study with the mouse, time scaling using $n = 2.2$: 19, 12, 8.5, 4.5, and 3.2 ppm. The motion passed [YES: 18; NO: 1: ABSTAIN: 1] (Appendix W).

SUMMARY OF PROPOSED AEGL VALUES FOR BROMINE

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint
AEGL-1	0.055 ppm	0.033 ppm	0.024 ppm	0.013 ppm	0.0095 ppm	Threshold for ocular and nasopharyngeal irritation in humans (Rupp and Henschler,1967)
AEGL-2	0.55 ppm	0.33 ppm	0.24 ppm	0.13 ppm	0.095 ppm	Threshold for irreversible effects in humans (Rupp and Henschler,1967)
AEGL-3	19 ppm	12 ppm	8.5 ppm	4.5 ppm	3.2 ppm	Mouse LC_{01} (Schlagbauer and Henschler, 1967)

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

Chemical Manager: Ernest Falke, U.S. EPA
Staff Scientist: Cheryl Bast, ORNL

Cheryl Bast explained that comments from the NAS/COT Subcommittee on Acute Exposure Guideline Levels necessitated revisions/reconsideration of the phosphine AEGLS (Attachment 13). These comments included: (1) reconsideration of key study selection of AEGL-2 (i.e., no repeat exposures); (2) justification for an uncertainty factor of 3 for AEGL-2, and (3) development of AEGL-1 values. Following a review of available data and discussions, the NAC/AEGL unanimously decided that there were insufficient data with which to develop AEGL-1 values (motion made by Bob Benson; seconded by David Belluck). For AEGL-2 issues, discussion focused on data describing AEGL-2 type endpoints and the effects of the exponent, *n,* on the time scaling. The AEGL-2 values were based upon a NOAEL for histopathologic changes in mice following exposure to 5 ppm, 6 hrs/day for 4 days (a single 6-hour exposure was assumed for AEGL development). The AEGL-2 values were developed using an uncertainty factor of 30 (3 for interspecies and 10 for intraspecies) and time scaling performed using an *n* of 1 or 3. A motion to accept the resulting AEGL-2 values was made by Steve Barbee and seconded by Richard Niemeier. The motion passed [YES: 17; NO: 1; ABSTAIN: 0] (Appendix X). For AEGL-3 values, a 6-hour exposure of rats to 18 ppm was considered a NOAEL for lethality. The AEGL-3 values were developed using this endpoint, uncertainty factors of 3 for interspecies variability and 10 for intraspecies variability, and an *n* of 1 or 3 (the *n* of 1 as suggested by the COT Subcommittee was not used because the experimental data were from a time to death study which may not have revealed the actual mortality). A motion was made by Richard Niemeier and seconded by Bob Benson that the AEGL-3 values derived by the aforementioned process be accepted. The motion passed [YES: 19; NO: 1; ABSTAIN: 0] (Appendix X).

SUMMARY OF PROPOSED AEGL VALUES FOR PHOSPHINE						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint**
AEGL-1	NA	NA	NA	NA	NA	Not applicable; insufficient data
AEGL-2	0.38 ppm	0.38 ppm	0.30 ppm	0.19 ppm	0.13 ppm	NOAEL for histopathologic changes
AEGL-3	1.4 ppm	1.4 ppm	1.1 ppm	0.69 ppm	0.45 ppm	Estimated lethality threshold.

ADMINISTRATIVE ISSUES

Plans for future NAC/AEGL meeting dates were discussed. The next proposed meeting date is

July 26-28, 2000 Washington, D.C.

There was also some discussion regarding the possibility of holding a meeting in San Antonio, Texas. John Hinz is working on preliminary investigations regarding feasibility. A possible date for this meeting is the first week in December.

Submitted by Bob Young and Po-Yung Lu
Oak Ridge National Laboratory

LIST OF ATTACHMENTS

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

1. NAC/AEGL Meeting No. 17 Agenda
2. NAC/AEGL Meeting No. 17 Attendee List
3. Public comments from *Federal Register* Notice
4. Data Analysis for Crotonaldehyde - Sylvia Milanez
5. Data Analysis for Allylamine - Sylvia Milanez
6. Data Analysis for Ethylenediamine - Sylvia Milanez
7. Data Analysis for Cyclohexamine - Sylvia Milanez
8. Data Analysis for Iron Pentacarbonyl, Nickel Carbonyl, Phosphorus Oxychloride, and Phosphorus Trichloride - Bob Young
9. Data Analysis for Hydrogen Chloride - Cheryl Bast
10. Data Analysis for Methyltrichlorosilane - Cheryl Bast
11. Data Analysis for Dimethyldichlorosilane - Cheryl Bast
12. Data Analysis for Bromine from Henschler publication
13. Data Analysis for Phosphine - Cheryl Bast

LIST OF APPENDICES

A. Approved NAC/AEGL-16 Meeting Highlights
B. Ballot for HFC-134a
C. Ballot for 1,1,1-Trichloroethane
D. Ballot for Agent HD
E. Ballot for 1,2-Dichloroethylene
F. Ballot for Otto Fuel
G. Ballot for HCFC-141b
H. Ballot for Hydrogen Sulfide
I. Ballot for Hydrogen Cyanide
J. Ballot for Crotonaldehyde
K. Ballot for Allylamine
L. Ballot for Ethylenediamine
M. Ballot for Cyclohexylamine
N. Ballot for 2,4- and 2,6-Toluene Diisocyanate
O. Ballot for Iron Pentacarbonyl
P. Ballot for Nickel Carbonyl
Q. Ballot for Phosphorus Oxychloride
R. Ballot for Phosphorus Trichloride
S. Ballot for Hydrogen Chloride
T. Ballot for Methyltrichlorosilane
U. Ballot for Dimethyldichlorosilane
V. Ballot for Methyl Isocyanate
W. Ballot for Bromine
X. Ballot for Phosphine

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** HCN 74-90-8

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	N			Glenn Leach	A	A	A
Steven Barbee	Y			Mark A. McClanahan	N		
Lynn Beasley	A			John S. Morawetz	N		
David Belluck	A			Richard W. Niemeier	Y		
Robert Benson	P			Marinelle Payton	Y		
Jonathan Borak	A			Zarena Post	N		
William Bress	Y			George Rodgers	A		
George Cushmac	Y			George Rusch, Chair	Y		
Ernest Falke	Y			Michelle Schaper	A		
Larry Gephart	Y			Bob Snyder	A	A	A
John Hinz	Y			Thomas Sobotka	Y		
Jim Holler	Y			Kenneth Still	A		
Thomas C. Hornshaw	Y			Judy Strickland	(Y)		
Nancy Kim	Y			Richard Thomas	Y		
Loren Koller	Y			Thomas Tuccinardi/ ~~Doan Hansen~~	A		
				TALLY	15/19		

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	25 ,( )	2.5 ,( )	2.0 ,( )	1.3 ,( )	1.0 ,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

AEGL 1 **Motion:** R. Niemeier **Second:** S Barbee

AEGL 2 **Motion:** previously approved **Second:** _____

AEGL 3 **Motion:** previously approved **Second:** _____

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 7/26/00

7664-39-3 **Appendix C**

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** HF

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	Y		Glenn Leach	A	A	A
Steven Barbee	Y	Y		Mark A. McClanahan	N	N	
Lynn Beasley	A	A		John S. Morawetz	Y	Y	
David Belluck	A	A		Richard W. Niemeier	N	Y	
Robert Benson	Y	Y		Marinelle Payton	Y	Y	
Jonathan Borak	A	A		Zarena Post	Y	Y	
William Bress	Y	Y		George Rodgers	A	A	
George Cushmac	Y	Y		George Rusch, Chair	Y	Y	
Ernest Falke	Y	Y		Michelle Schaper	A	A	
Larry Gephart	Y	N		Bob Snyder	A	A	A
John Hinz	Y	N		Thomas Sobotka	P	N	
Jim Holler	A	Y		Kenneth Still	A	A	
Thomas C. Hornshaw	N	Y		Judy Strickland	(Y)	(Y)	
Nancy Kim	Y	Y		Richard Thomas	Y	Y	
Loren Koller	N	N		Thomas Tuccinardi/ Doan Hansen	A A	A A	
				TALLY	14/18	15/20	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	1.0 ,( )	1.0 ,( )	1.0 ,( )	0.50 ,( )	0.50 ,( )
AEGL 2	95 ,( )	34 ,( )	24 ,( )	12 ,( )	8.6 ,( )
AEGL 3	170 ,( )	62 ,( )	44 ,( )	22 ,( )	13 ,( )

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

AEGL 2 **Motion:** G. Alexeeff **Second:** R. Benson (MOTION TO MAINTAIN 10 MIN + 30 MIN AEGL)

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

Approved by Chair: _____ **DFO:** _____ **Date:** 7/27/00

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** 107-02-8 ACROLEIN 10 Min AEGL-1,2,3 values

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	P			Glenn Leach	A	A	A
Steven Barbee	Y			Mark A. McClanahan	Y		
Lynn Beasley	A			John S. Morawetz	N		
David Belluck	A			Richard W. Niemeier	Y		
Robert Benson	Y			Marinelle Payton	Y		
Jonathan Borak	A			Zarena Post	Y/N		
William Bress	Y			George Rodgers	A		
George Cushmac	Y			George Rusch, Chair	Y		
Ernest Falke	Y			Michelle Schaper	A		
Larry Gephart	N			Bob Snyder	A	A	A
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	A		
Thomas C. Hornshaw	~~Y~~ N	~~Y~~	~~Y~~	Judy Strickland	(Y)		
Nancy Kim	Y			Richard Thomas	N		
Loren Koller	A			Thomas Tuccinardi/ Doan Hansen	A A		
				TALLY	12/17		

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	0.03 ,( )	,( )	,( )	,( )	,( )
AEGL 2	0.44 ,( )	,( )	,( )	,( )	,( )
AEGL 3	6.2 ,( )	,( )	,( )	,( )	,( )

AEGL 1 **Motion:** J. Hinz **Second:** M. McClanahan

AEGL 2 **Motion:** ↓ **Second:** ↓

AEGL 3 **Motion:** ↓ **Second:** ↓

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 7/26/00

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** ClF_3 Chlorine Trifluoride

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	P			Glenn Leach	A	A	A
Steven Barbee	Y			Mark A. McClanahan	N		
Lynn Beasley	A			John S. Morawetz	P		
David Belluck	A			Richard W. Niemeier	Y		
Robert Benson	Y			Marinelle Payton	P		
Jonathan Borak	A			Zarena Post	N		
William Bress	Y			George Rodgers	A		
George Cushmac	Y			George Rusch, Chair	Y		
Ernest Falke	Y			Michelle Schaper	A		
Larry Gephart	Y			Bob Snyder	A	A	A
John Hinz	Y			Thomas Sobotka	N		
Jim Holler	Y			Kenneth Still	A		
Thomas C. Hornshaw	Y			Judy Strickland	(Y)		
Nancy Kim	Y			Richard Thomas	Y		
Loren Koller	Y			Thomas Tuccinardi/ Doan Hansen	A A		
				TALLY	14/17		

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	0.70 ,( )	,( )	,( )	,( )	,( )
AEGL 2	6.2 ,( )	,( )	,( )	,( )	,( )
AEGL 3	81 ,( )	,( )	,( )	,( )	,( )

AEGL 1 **Motion:** E. Falke **Second:** J. Hinz

AEGL 2 **Motion:** E. Falke **Second:** J Hinz

AEGL 3 **Motion:** E. Falke **Second:** J. Hinz

Approved by Chair: [signature] **DFO:** [signature] **Date:** 7/27/00

ce

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** EPICHLOROHYDRIN 10 MIN

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	Y	N	Glenn Leach	A	A	A
Steven Barbee	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
Lynn Beasley	A			John S. Morawetz	Y	Y	N
David Belluck	A			Richard W. Niemeier	Y	Y	Y
Robert Benson	Y	Y	Y	Marinelle Payton	Y	Y	Y
Jonathan Borak	A			Zarena Post	Y	Y	N
William Bress	Y	Y	Y	George Rodgers	A		
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	Y	Y	Michelle Schaper	A		
Larry Gephart	Y	N	Y	Bob Snyder	A	A	A
John Hinz	Y	Y	Y	Thomas Sobotka	N	N	Y
Jim Holler	A			Kenneth Still	A		
Thomas C. Hornshaw	Y	P	Y	Judy Strickland	(Y)	(Y)	(N)
Nancy Kim	Y	Y	Y	Richard Thomas	Y	Y	Y
Loren Koller	Y	Y	Y	Thomas Tuccinardi/ ~~Doan Hansen~~	Y	Y	Y
				TALLY	19/20	17/19	17/20

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	5 ,( )	,( )	,( )	,( )	,( )
AEGL 2	53 ,( )	,( )	,( )	,( )	,( )
AEGL 3	570 ,( )	,( )	,( )	,( )	,( )

AEGL 1 **Motion:** Tom Hornshaw M. McClanahan **Second:** E. Falke R Thomas

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

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

Approved by Chair: [signature] **DFO:** Paul S. Miller **Date:** 7/27/00

H
N
151-56-4

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** ETHYLENIMINE 10 MIN

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff		Y	Y	Glenn Leach	A	A	A
Steven Barbee		Y	Y	Mark A. McClanahan		Y	Y
Lynn Beasley		A	A	John S. Morawetz		Y	Y
David Belluck		A	A	Richard W. Niemeier		Y	Y
Robert Benson		Y	Y	Marinelle Payton		Y	Y
Jonathan Borak		A	A	Zarena Post		Y	Y
William Bress		Y	Y	George Rodgers		A	A
George Cushmac		Y	Y	George Rusch, Chair		Y	Y
Ernest Falke		Y	Y	Michelle Schaper		A	A
Larry Gephart		Y	Y	Bob Snyder	A	A	A
John Hinz		Y	Y	Thomas Sobotka		Y	Y
Jim Holler		A	A	Kenneth Still		A	A
Thomas C. Hornshaw		Y	Y	Judy Strickland		P	P
Nancy Kim		A	A	Richard Thomas		Y	Y
Loren Koller		Y	Y	Thomas Tuccinardi/ Doan Hansen		Y	Y
				TALLY			

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	— ,( )	,( )	,( )	,( )	,( )
AEGL 2	33 ,( )	,( )	,( )	,( )	,( )
AEGL 3	48 ,( )	,( )	,( )	,( )	,( )

AEGL 1 **Motion:** D. Gephart **Second:** J. Hinz

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

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

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 7/27/00

Appendix H

75-21-8

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** ETHYLENE OXIDE (10 MIN)

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	P	P
Steven Barbee	Y	Y	N
Lynn Beasley	A	A	A
David Belluck	A	A	A
Robert Benson	Y	N	N
Jonathan Borak	A	A	A
William Bress	Y	Y	Y
George Cushmac	A	A	A
Ernest Falke	Y	Y	N
Larry Gephart	Y	Y	N
John Hinz	Y	Y	Y
Jim Holler	Y	Y	Y
Thomas C. Hornshaw	Y	Y	P
Nancy Kim	Y	Y	Y
Loren Koller	Y	Y	Y

NAC Member	AEGL 1	AEGL 2	AEGL 3
Glenn Leach	A	A	A
Mark A. McClanahan	Y	Y	N
John S. Morawetz	Y	Y	Y
Richard W. Niemeier	Y	Y	Y
Marinelle Payton	Y	Y	Y
Zarena Post	Y	Y	Y
George Rodgers	A	A	A
George Rusch, Chair	Y	Y	Y
Michelle Schaper	A	A	A
Bob Snyder	A	A	A
Thomas Sobotka	Y	Y	Y
Kenneth Still	A	A	A
Judy Strickland	(Y)	(Y)	(N)
Richard Thomas	A	A	A
Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
TALLY	18/18	16/17	11/16

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	NR, ( )	NR, ( )	NR, ( )	NR, ( )	NR, ( )
AEGL 2	60, ( )	80, ( )	45, ( )	14, ( )	7.9, ( )
AEGL 3	360, ( )	360, ( )	200, ( )	63, ( )	35, ( )

AEGL 1 **Motion:** J Hinz **Second:** M. McClanahan

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

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

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 7/28/00

CEN
78-82-0

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** ISOBUTYRONITRILE

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	Y	Y	Glenn Leach	A	A	A
Steven Barbee	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
Lynn Beasley	A	A	A	John S. Morawetz	Y	Y	Y
David Belluck	A	A	A	Richard W. Niemeier	Y	Y	Y
Robert Benson	Y	Y	Y	Marinelle Payton	A	A	A
Jonathan Borak	A	A	A	Zarena Post	Y	Y	Y
William Bress	Y	Y	Y	George Rodgers	A	A	A
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	Y	Y	Michelle Schaper	A	A	A
Larry Gephart	Y	Y	Y	Bob Snyder	A	A	A
John Hinz	Y	Y	Y	Thomas Sobotka	Y	Y	Y
Jim Holler	Y	Y	Y	Kenneth Still	A	A	A
Thomas C. Hornshaw	Y	Y	Y	Judy Strickland	(Y)	(Y)	(Y)
Nancy Kim	Y	Y	Y	Richard Thomas	Y	Y	Y
Loren Koller	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
				TALLY	19/19	19/19	19/19

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	*N/A ,( )	,( )	,( )	,( )	,( )
AEGL 2	13 ,( )	,( )	,( )	,( )	,( )
AEGL 3	40 ,( )	,( )	,( )	,( )	,( )

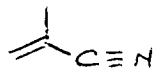
* = not assigned - insufficient data

AEGL 1 **Motion:** B. Benson **Second:** R. Thomas

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

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

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 7/27/00



126-98-7

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** METHACRYLONITRILE

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	P	P	P	Glenn Leach	A	A	A
Steven Barbee	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
Lynn Beasley	A	A	A	John S. Morawetz	Y	Y	Y
David Belluck	A	A	A	Richard W. Niemeier	Y	Y	Y
Robert Benson	P	P	P	Marinelle Payton	A	A	A
Jonathan Borak	A	A	A	Zarena Post	Y	Y	Y
William Bress	Y	Y	Y	George Rodgers	A	A	A
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	Y	Y	Michelle Schaper	A	A	A
Larry Gephart	Y	Y	Y	Bob Snyder	A	A	A
John Hinz	Y	Y	Y	Thomas Sobotka	N	N	N
Jim Holler	Y	Y	Y	Kenneth Still	A	A	A
Thomas C. Hornshaw	Y	Y	Y	Judy Strickland	(Y)	(Y)	(Y)
Nancy Kim	Y	Y	Y	Richard Thomas	Y	Y	Y
Loren Koller	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
				TALLY	16/17	16/17	16/17

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	*N/A ,( )	,( )	,( )	,( )	,( )
AEGL 2	1.5 ,( )	,( )	,( )	,( )	,( )
AEGL 3	4.5 ,( )	,( )	,( )	,( )	,( )

* N/A = Not assigned - insufficient data

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

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

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

Approved by Chair: _____ **DFO:** _____ **Date:** 7/27/00

Appendix K

$CH_3C(=O)OOH$ 79-21-0

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** PERACETIC ACID (10 MIN.)

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	N	Y	Y	Glenn Leach	A	A	A
Steven Barbee	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
Lynn Beasley	A	A	A	John S. Morawetz	Y	Y	N
David Belluck	A	A	A	Richard W. Niemeier	Y	Y	N
Robert Benson	Y	Y	Y	Marinelle Payton	Y	Y	Y
Jonathan Borak	A	A	A	Zarena Post	Y	Y	Y
William Bress	Y	Y	Y	George Rodgers	A	A	A
George Cushmac	A	A	A	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	Y	Y	Michelle Schaper	A	A	A
Larry Gephart	Y	Y	Y	Bob Snyder	A	A	A
John Hinz	P	P	P	Thomas Sobotka	A	A	A
Jim Holler	Y	Y	Y	Kenneth Still	A	A	A
Thomas C. Hornshaw	Y	Y	Y	Judy Strickland	(Y)	(Y)	(Y)
Nancy Kim	Y	Y	N	Richard Thomas	A	A	A
Loren Koller	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
				TALLY	15/16	16/16	13/16

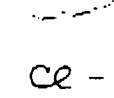
PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	0.17 ,( )	0.17 ,( )	0.17 ,( )	0.17 ,( )	0.17 ,( )
AEGL 2	0.50 ,( )	0.50 ,( )	0.50 ,( )	0.50 ,( )	0.50 ,( )
AEGL 3	19 ,( )	9.6 ,( )	4.8 ,( )	2.0 ,( )	1.3 ,( )

AEGL 1 **Motion:** L Gephart **Second:** B. Benson

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

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

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 7/28/00



75-44-5

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** PHOSGENE (10 min)

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexceff	Y	N	Y	Glenn Leach	A	A	A
Steven Barbee	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
Lynn Beasley	A	A	A	John S. Morawetz	Y	Y	Y
David Belluck	A	A	A	Richard W. Niemeier	Y	Y	Y
Robert Benson	Y	Y	Y	Marinelle Payton	Y	Y	Y
Jonathan Borak	A	A	A	Zarena Post	Y	Y	Y
William Bress	Y	Y	Y	George Rodgers	A	A	A
George Cushmac	A	A	A	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	Y	Y	Michelle Schaper	A	A	A
Larry Gephart	Y	Y	Y	Bob Snyder	A	A	A
John Hinz	Y	Y	Y	Thomas Sobotka	Y	Y	P
Jim Holler	Y	Y	Y	Kenneth Still	A	A	A
Thomas C. Hornshaw	Y	Y	Y	Judy Strickland	(Y)	(Y)	(Y)
Nancy Kim	Y	Y	Y	Richard Thomas	A	A	A
Loren Koller	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
				TALLY	18/18	17/18	17/17

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	NA ,( )	NA ,( )	NA ,( )	NA ,( )	NA ,( )
AEGL 2	0.60,( )	0.60 ,( )	0.30 ,( )	0.08 ,( )	0.04 ,( )
AEGL 3	3.6 ,( )	1.5 ,( )	0.75 ,( )	0.20 ,( )	0.09 ,( )

AEGL 1 **Motion:** Hinz **Second:** Gephart

AEGL 2 **Motion:** ↓ **Second:** ↓

AEGL 3 **Motion:** ↓ **Second:** ↓

Approved by Chair: [signature] **DFO:** [signature] **Date:** 7/28/00

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** ~C≡N PROPIONITRILE

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	Y	Y	Glenn Leach	A	A	A
Steven Barbee	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
Lynn Beasley	A	A	A	John S. Morawetz	Y	Y	Y
David Belluck	A	A	A	Richard W. Niemeier	Y	Y	Y
Robert Benson	Y	Y	Y	Marinelle Payton	A	A	A
Jonathan Borak	A	A	A	Zarena Post	Y	Y	Y
William Bress	Y	Y	Y	George Rodgers	A	A	A
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	Y	Y	Michelle Schaper	A	A	A
Larry Gephart	Y	Y	Y	Bob Snyder	A	A	A
John Hinz	Y	Y	Y	Thomas Sobotka	Y	Y	Y
Jim Holler	Y	Y	Y	Kenneth Still	A	A	A
Thomas C. Hornshaw	Y	Y	Y	Judy Strickland	(Y)	(Y)	(Y)
Nancy Kim	Y	Y	Y	Richard Thomas	Y	Y	Y
Loren Koller	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
				TALLY	16/16	16/16	16/16

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	*N/A ,( )	,( )	,( )	,( )	,( )
AEGL 2	9.6 ,( )	,( )	,( )	,( )	,( )
AEGL 3	51 ,( )	,( )	,( )	,( )	,( )

* Not assigned due to inadequate data

AEGL 1 **Motion:** J. Hinz **Second:** R. Niemeier

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

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

Approved by Chair: _____ **DFO:** _____ **Date:** 7/27/00

75-55-8 HN

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** Propyleneimine

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff		N	N	Glenn Leach	A	A	A
Steven Barbee		Y	Y	Mark A. McClanahan		Y	Y
Lynn Beasley		A	A	John S. Morawetz		Y	Y
David Belluck		A	A	Richard W. Niemeier		Y	Y
Robert Benson		P	P	Marinelle Payton		Y	Y
Jonathan Borak		A	A	Zarena Post		Y	N
William Bress		Y	Y	George Rodgers		A	A
George Cushmac		Y	Y	George Rusch, Chair		Y	Y
Ernest Falke		Y	Y	Michelle Schaper		A	A
Larry Gephart		Y	Y	Bob Snyder	A	A	A
John Hinz		Y	Y	Thomas Sobotka		Y	Y
Jim Holler		A	A	Kenneth Still		A	A
Thomas C. Hornshaw		Y	Y	Judy Strickland		(P)	(P)
Nancy Kim		A	A	Richard Thomas		Y	Y
Loren Koller		Y	Y	Thomas Tuccinardi/ Doan Hansen		Y	Y
				TALLY		17/18	16/18

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	— ,( )	,( )	,( )	,( )	,( )
AEGL 2	63 ,( )	,( )	,( )	,( )	,( )
AEGL 3	167 ,( )	,( )	,( )	,( )	,( )

AEGL 1 **Motion:** J. Hinz **Second:** R. Niemeier

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

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

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 7/27/00

MOVING ... (16 MEMBERS PRESENT – UNANIMOUS)

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** ALLYLAMINE, CYCLOHEXYLAMINE, CROTONALDEHYDE, IRON PENTACARBONYL, NICKEL CARBONYL

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	✓		
Steven Barbee	✓		
Lynn Beasley			
David Belluck			
Robert Benson	✓		
Jonathan Borak			
William Bress	✓		
George Cushmac	✓		
Ernest Falke			
Larry Gephart	✓		
John Hinz	✓		
Jim Holler	✓		
Thomas C. Hornshaw	✓		
Nancy Kim	✓		
Loren Koller	✓		

NAC Member	AEGL 1	AEGL 2	AEGL 3
Glenn Leach	A	A	A
Mark A. McClanahan	✓		
John S. Morawetz	✓		
Richard W. Niemeier	✓		
Marinelle Payton			
Zarena Post	✓		
George Rodgers			
George Rusch, Chair			
Michelle Schaper			
Bob Snyder	A	A	A
Thomas Sobotka	✓		
Kenneth Still			
Judy Strickland			
Richard Thomas			
Thomas Tuccinardi/ Doan Hansen			
TALLY			

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )

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

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

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

Approved by Chair: _____ **DFO:** _____ **Date:** 9/27/00

Reaffirm current values following public comments.
(17 voting members) All "Yes"

Dimethyldichlorosilane

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** 75-78-5

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff				Glenn Leach	A	A	A
Steven Barbee				Mark A. McClanahan			
Lynn Beasley				John S. Morawetz			
David Belluck				Richard W. Niemeier			
Robert Benson				Marinelle Payton			
Jonathan Borak				Zarena Post			
William Bress				George Rodgers			
George Cushmac				George Rusch, Chair			
Ernest Falke				Michelle Schaper			
Larry Gephart				Bob Snyder	A	A	A
John Hinz				Thomas Sobotka			
Jim Holler				Kenneth Still			
Thomas C. Hornshaw				Judy Strickland			
Nancy Kim				Richard Thomas			
Loren Koller				Thomas Tuccinardi/ Doan Hansen			
				TALLY			

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

AEGL 1 **Motion:** Hinz **Second:** McClanahan

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

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

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 7/27/00

Reaffirm current values following public comment
Unanimous "Yes" - 17 member Voting

Appendix Q

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** ETHYLENEDIAMINE 107-15-3

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff				Glenn Leach	A	A	A
Steven Barbee				Mark A. McClanahan			
Lynn Beasley				John S. Morawetz			
David Belluck				Richard W. Niemeier			
Robert Benson				Marinelle Payton			
Jonathan Borak				Zarena Post			
William Bress				George Rodgers			
George Cushmac				George Rusch, Chair			
Ernest Falke				Michelle Schaper			
Larry Gephart				Bob Snyder	A	A	A
John Hinz				Thomas Sobotka			
Jim Holler				Kenneth Still			
Thomas C. Hornshaw				Judy Strickland			
Nancy Kim				Richard Thomas			
Loren Koller				Thomas Tuccinardi/ Doan Hansen			
				TALLY			

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

AEGL 1 **Motion:** Hinz **Second:** McClanahan

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

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

Approved by Chair: _____ **DFO:** Paul S. Date: 7/27/00

Maintain values following public comments - 17 voting members All "Yes"

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** HCl 7647-01-0

Appendix R

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff			
Steven Barbee			
Lynn Beasley			
David Belluck			
Robert Benson			
Jonathan Borak			
William Bress			
George Cushmac			
Ernest Falke			
Larry Gephart			
John Hinz			
Jim Holler			
Thomas C. Hornshaw			
Nancy Kim			
Loren Koller			

NAC Member	AEGL 1	AEGL 2	AEGL 3
Glenn Leach	A	A	A
Mark A. McClanahan			
John S. Morawetz			
Richard W. Niemeier			
Marinelle Payton			
Zarena Post			
George Rodgers			
George Rusch, Chair			
Michelle Schaper			
Bob Snyder	A	A	A
Thomas Sobotka			
Kenneth Still			
Judy Strickland			
Richard Thomas			
Thomas Tuccinardi/ Doan Hansen			
TALLY			

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

AEGL 1 **Motion:** Hinz **Second:** McClanahan

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

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

Approved by Chair: _____ **DFO:** _____ **Date:** 7/27/00

Reaffirm current values following public comment.
"Yes" unanimous - 17 members voting

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** Methyl isocyanate 624-83-9

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff				Glenn Leach	A	A	A
Steven Barbee				Mark A. McClanahan			
Lynn Beasley				John S. Morawetz			
David Belluck				Richard W. Niemeier			
Robert Benson				Marinelle Payton			
Jonathan Borak				Zarena Post			
William Bress				George Rodgers			
George Cushmac				George Rusch, Chair			
Ernest Falke				Michelle Schaper			
Larry Gephart				Bob Snyder	A	A	A
John Hinz				Thomas Sobotka			
Jim Holler				Kenneth Still			
Thomas C. Hornshaw				Judy Strickland			
Nancy Kim				Richard Thomas			
Loren Koller				Thomas Tuccinardi/ Doan Hansen			
				TALLY			

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

AEGL 1 **Motion:** J Hinz **Second:** M. McClanahan

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

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

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 7/27/00

Reaffirm current values following public comment.
(17 voting members) All "Yes"

75-79-6

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** Methyltrichlorosilane

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff				Glenn Leach	A	A	A
Steven Barbee				Mark A. McClanahan			
Lynn Beasley				John S. Morawetz			
David Belluck				Richard W. Niemeier			
Robert Benson				Marinelle Payton			
Jonathan Borak				Zarena Post			
William Bress				George Rodgers			
George Cushmac				George Rusch, Chair			
Ernest Falke				Michelle Schaper			
Larry Gephart				Bob Snyder	A	A	A
John Hinz				Thomas Sobotka			
Jim Holler				Kenneth Still			
Thomas C. Hornshaw				Judy Strickland			
Nancy Kim				Richard Thomas			
Loren Koller				Thomas Tuccinardi/ Doan Hansen			
				TALLY			

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

AEGL 1 **Motion:** Hinz **Second:** McClanahan

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

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

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 7/27/00

Reaffirm current values following public comment. -17 member voting "Yes" unanimous

584-84-9 91-08-7

Appendix U

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** 2,4 + 2,6- Toluenediisocyanate

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff			
Steven Barbee			
Lynn Beasley			
David Belluck			
Robert Benson			
Jonathan Borak			
William Bress			
George Cushmac			
Ernest Falke			
Larry Gephart			
John Hinz			
Jim Holler			
Thomas C. Hornshaw			
Nancy Kim			
Loren Koller			

NAC Member	AEGL 1	AEGL 2	AEGL 3
Glenn Leach	A	A	A
Mark A. McClanahan			
John S. Morawetz			
Richard W. Niemeier			
Marinelle Payton			
Zarena Post			
George Rodgers			
George Rusch, Chair			
Michelle Schaper			
Bob Snyder	A	A	A
Thomas Sobotka			
Kenneth Still			
Judy Strickland			
Richard Thomas			
Thomas Tuccinardi/ Doan Hansen			
TALLY			

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

McClanahan Hinz

AEGL 1 **Motion:** J. Hinz **Second:** M. McClanahan

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

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

Approved by Chair: _____ **DFO:** _____ **Date:** 7/27/00

75-86-5

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** ACETONE CYANOHYDRIN

NAC Member	AEGL 1 (C) (B) (A)	AEGL 2	AEGL 3
George Alexeeff	P N Y	P	Y
Steven Barbee	Y Y N	Y	Y
Lynn Beasley	A A A	A	A
David Belluck	A A A	A	A
Robert Benson	P Y N	Y	Y
Jonathan Borak	A A A	A	A
William Bress	Y Y N	Y	Y
George Cushmac	Y Y Y	Y	Y
Ernest Falke	Y Y N	Y	Y
Larry Gephart	Y Y N	Y	Y
John Hinz	N N N	Y	P
Jim Holler	Y Y Y	Y	Y
Thomas C. Hornshaw	Y Y N	Y	Y
Nancy Kim	Y N Y	Y	Y
Loren Koller	A Y N	Y	Y

NAC Member	AEGL 1 (C) (B) (A)	AEGL 2	AEGL 3
Glenn Leach	A	A	A
Mark A. McClanahan	N N Y	N	Y
John S. Morawetz	Y Y N	Y	Y
Richard W. Niemeier	Y N Y	Y	Y
Marinelle Payton	Y Y N	Y	Y
Zarena Post	Y Y N	Y	Y
George Rodgers	A A A	A	A
George Rusch, Chair	Y P Y	Y	Y
Michelle Schaper	A A A	A	A
Bob Snyder	A	A	A
Thomas Sobotka	A A A	A	Y
Kenneth Still	A A A	A	A
Judy Strickland	Y Y N	Y	P
Richard Thomas	Y Y N	Y	Y
Thomas Tuccinardi/ Doan Hansen	A A A A A A	A A	A A
TALLY	(C) 14/16 (B) 12/19 (A) 8/18	17/18	19/19

EGL-1 * (C) PASSES (B) DID NOT PASS (A) DID NOT PASS
NOTE

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1 (C) (B) *	1.1 2.1 0.76 ,( )	1.1 2.1 0.76 ,( )	0.84 1.7 2.61 ,( )	0.53 1.1 0.38 ,( )	0.33 0.69 0.25 ,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

(C) N. Kim
(B) S. Barbee
(A) N. Kim

R. Thomas
R. Niemeier

AEGL 1 **Motion:** N. Kim **Second:** R. Thomas

AEGL 2 **Motion:** R. Benson **Second:** S. Barbee

AEGL 3 **Motion:** E. Falke **Second:** R. Niemeier

Approved by Chair: George M. Rusch **DFO:** Paul S. Tobin **Date:** 7/26/00

Appendix W

$CH_2 = CH - COOH$

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** ACRYLIC ACID 79-10-7

NAC Member	AEGL 1	AEGL 2 (A) (B)	AEGL 3
George Alexeeff	N	Y N N	Y
Steven Barbee	Y	Y Y Y	Y
Lynn Beasley	A	A A A	A
David Belluck	A	A A A	A
Robert Benson	N	Y P P	Y
Jonathan Borak	A	A A A	A
William Bress	Y	Y N N	Y
George Cushmac	Y	Y Y Y	Y
Ernest Falke	Y	Y Y Y	Y
Larry Gephart	Y	N Y Y	Y
John Hinz	P	Y P N	Y
Jim Holler	Y	Y Y Y	Y
Thomas C. Hornshaw	N	Y N N	Y
Nancy Kim	Y	Y N N	Y
Loren Koller	Y	N Y Y	Y

NAC Member	AEGL 1	AEGL 2 (A) (B)	AEGL 3
Glenn Leach	A	A A A	A
Mark A. McClanahan	Y	N Y Y	N
John S. Morawetz	N	Y N N	Y
Richard W. Niemeier	Y	Y N N	Y
Marinelle Payton	A	A A A	A
Zarena Post	N	Y N N	Y
George Rodgers	A	A A A	A
George Rusch, Chair	Y	Y Y P	Y
Michelle Schaper	A	A A A	A
Bob Snyder	A	A A A	A
Thomas Sobotka	N	Y N N	Y
Kenneth Still	A	A A A	A
Judy Strickland	(P)	(Y)(N)(N)	(Y)
Richard Thomas	Y	Y N N	Y
Thomas Tuccinardi/ Doan Hansen	A A	A A A A A A	A
TALLY	12/18	(A) 8/17 (B) 7/17	18/19

* (C) 16/19 Passes

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	1.0 ,( )	1.0 ,( )	1.0 ,( )	1.0 ,( )	1.0 ,( )
AEGL 2 (A)	99 ,( )	99 ,( )	68 ,( )	31 ,( )	21 ,( )
AEGL 3	480 ,( )	260 ,( )	180 ,( )	85 ,( )	58 ,( )
AEGL 2 (B)	68 30	68 30	46 20	21 9.4	14 6.4
AEGL 2 (C)					

AEGL 1 **Motion:** R. Thomas Barbee **Second:** Sobotka

AEGL 2 **Motion:** (A) S Barbee (B) (C) McCLANAHAN THOMAS Benson **Second:** M. McClanahan S. Barbee BRESS

AEGL 3 **Motion:** [illegible] **Second:** Sobotka

Approved by Chair: [signature] **DFO:** [signature] **Date:** 7/27/00

Appendix X

NAC/AEGL Meeting 18: 7/26-28/2000 **Chemical:** CH_3OH METHANOL 67-56-1

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	P	Y	P
Steven Barbee	Y	Y	Y
Lynn Beasley	A	A	A
David Belluck	A	A	A
Robert Benson	Y	Y	Y
Jonathan Borak	A	A	A
William Bress	Y	Y	Y
George Cushmac	A	A	A
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
John Hinz	Y	Y	Y
Jim Holler	Y	Y	Y
Thomas C. Hornshaw	Y	Y	Y
Nancy Kim	Y	Y	P
Loren Koller	Y	Y	Y

NAC Member	AEGL 1	AEGL 2	AEGL 3
Glenn Leach	A	A	A
Mark A. McClanahan	Y	Y	Y
John S. Morawetz	A	A	A
Richard W. Niemeier	Y	Y	Y
Marinelle Payton	Y	Y	Y
Zarena Post	P	P Y	P
George Rodgers	A	A	A
George Rusch, Chair	Y	Y	Y
Michelle Schaper	A	A	A
Bob Snyder	A	A	A
Thomas Sobotka	Y	Y	Y
Kenneth Still	A	A	A
Judy Strickland	(Y)	(Y)	(Y)
Richard Thomas	A	A	A
Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
TALLY	15/15	17/17	14/14

* PASSES * 11/16 Y FOR 4,000 10' 10/17 Y for 10 MIN 11,000

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8Hr
AEGL 1	670 ,( )	670 ,( )	530 ,( )	340 ,( )	270 ,( )
AEGL 2	~~11000~~ 4,000 ,( )	4000 ,( )	2100 ,( )	720 ,( )	510 ,( )
AEGL 3	15,000,( )	15,000 ,( )	7900 ,( )	2500 ,( )	1600 ,( )

AEGL 1 **Motion:** L. Koller **Second:** R. Niemeier

AEGL 2 **Motion:** R. Benson (10 MIN 4,000) Z. Post **Second:** ~~D. Bress~~ M. McClanahan J. Hinz

AEGL 3 **Motion:** L Koller **Second:** S. Barbee

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 7/28/00