National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 19 Highlights
U.S. Department of Transportation
DOT Headquarters/Nassif Building, Rooms 6332-6336
400 7th Street, S.W., Washington, D.C
October 23-25, 2000

INTRODUCTION

Welcoming remarks were conveyed by NAC Chairperson, George Rusch and Department of Transportation meeting host, George Cushmac. The Meeting Highlights for the NAC/AEGL Meeting 18 were reviewed and approved after minor changes (Appendix A). These changes are: (1) AEGL Phosgene 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 it should state what they propose to do to respond to the public and committee comments; and (2) Hydrogen cyanide: 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). Roger Garrett (Program Director) provided a perspective of the AEGL Program, its accomplishments, and future directions.

The highlights for NAC/AEGL-19 are presented below and the meeting agenda (Attachment 1) and attendee list (Attachment 2) are attached.

GENERAL INTEREST ITEMS

Status of SOPs and Final TSDs

A brief overview of the status of the Standing Operating Procedures (SOPs) and the five final Technical Support Documents was given by Ernest Falke and Roger Garrett. These are in final preparation for publication by the National Academy of Sciences Committee on Toxicology, Subcommittee on Acute Exposure Guideline Levels (NAS/COT).

Comments from the NAS/COT on AEGLs

Several issues identified by the NAS/COT regarding AEGL development were briefly commented on by Roger Garrett and referred to the summary sheets distributed prior to the meeting (Attachment 3). Many concerns expressed by the COT/AEGL subcommittee on AEGL's development are listed as follows: (1) choice of effect concentration, (2) choice of endpoint, (3) choice of exposure protocol, (4) AEGL definitions, (5) study quality, (6) TSD format; (7) values to be developed for AEGL-1, and that AEGL values are very low numbers that are not always consistent with the known toxicity of the chemicals and overall human experience.

RESPONSE TO COMMENTS ON THE *FEDERAL REGISTER* NOTICE

There was considerable discussion on how to address *Federal Register* comments. Three proposals were suggested:

Proposal No. 1: The TSD Development Team (author, chemical manager, and reviewers) could make changes to the content of the TSD and AEGL values and present these changes to NAC/AEGL for approval.

Proposal No. 2: The TSD Development Team could make changes to the content of the TSD but *not* AEGL values, and present these changes to NAC/AEGL for approval.

Proposal No. 3: The TSD Development Team could make recommendations to NAC/AEGL for the changes on the content of the TSD and AEGL values. After approval by NAC/AEGL, these recommendations will then be incorporated into the TSD and be ready for NAS/COT AEGL Subcommittee's final review.

Chairman Rusch asked the committee for show of hands for approval. The third proposal was unanimously approved. These was no support for either Proposal No. 1 or No. 2.

DEVELOPMENT OF 10-MINUTE AEGLS

AEGL values for 10-minute durations were proposed for several chemicals for which other AEGL values had already been developed and approved by NAC/AEGL in earlier meetings.

Allyl alcohol (CAS Reg. No. 107-18-6)
Mark McClanahan, chemical manager, presented the proposed 10-minute AEGL values for allyl alcohol and the values for the other time periods using the conservative values for *n* of 1 and 3 according to the SOP (Attachment 4). The AEGL-1 10-minute value based on the odor detection threshold is identical with that for the other time periods. The AEGL-2 10-minute value is identical to the 30-minute value of 1.8 ppm according to the SOP because the data are from a 7-hour exposure study based on irritation in rats. The AEGL-3 10-minute value of 9.6 ppm is an extrapolation of animal data based on a 1-hour exposure animal lethality study. The Committee unanimously approved (motion by George Rodgers, second by Bob Benson) adoption of the values for all three AEGL levels (Appendix B).

Boron trichloride (CAS Reg. No. 10294-34-5)
Mark McClanahan, chemical manager, presented the proposed 10-minute values for AEGL-1, AEGL-2, and AEGL-3 (Attachment 5). The AEGL-1 and AEGL-2 values previously adopted by the committee were derived values recommended as guidance values based on the hydrolysis product of boron trichloride, hydrochloric acid. Because, each mole of boron trichloride produces three moles of hydrochloric acid upon hydrolysis, the previously approved AEGL-1 and AEGL-2 values for hydrochloric acid were divided to obtain the corresponding values for boron trichloride. The hydrochloric acid AEGL-1 value is based on data for exercising humans and is 1.8 ppm for all time values. The boron trichloride value of 0.6 ppm for 30-minute through 8-hour, previously adopted by the NAC/AEGL committee was proposed as the 10-minute value. The proposed AEGL-2 10-minute value (34 ppm) was derived by dividing the hydrochloric acid AEGL-2 value by 3, based on mouse RD_{50} data and rat histopathology findings. The proposed AEGL-3 10-minute value (170 ppm) was developed by extrapolation based on one-third of the 1-hour boron trichloride LC_{50} value. The extrapolation to 10 minutes used the value of 1 for *n* obtained from hydrogen chloride lethality data. The committee

unanimously approved (motion by George Rodgers, second by Steve Barbee) adoption of the three proposed 10-minute values (Appendix C). There was a suggestion that the use of the 3 as a modifying factor for AEGL-2 levels should be explained more throughly in the TSD.

Chloromethyl methyl ether (CAS Reg. No. 107-30-2

The proposed 10-minute AEGL values were accepted (motion by Bob Benson, second by Richard Thomas) (YES: 16; NO: 1; ABSTAIN:0) (Appendix D). Cancer-based AEGLs have been re-calculated using an adjustment factor of 6 instead of 2.8 to account for uncertainty in the stages of the carcinogenic process. Ernie Falke, chemical manager, presented the proposed 10-minute values for AEGL-1 (not recommended), AEGL-2 (0.076 ppm), and AEGL-3 (1.2 ppm) according to SOP guidance of applying *n* of 1 and 3 in the time scale extrapolation. (Attachment 6). It was the consensus of the NAC/AEGL that the cancer risk levels be added as in Appendix section of TSD and that an explanation regarding confidence in these values also be included (motion by Bob Benson, second by Richard Thomas) (Appendix D).

Diborane (CAS Reg. No. 1928-45-7)

Jim Holler, chemical manager, presented the 10-minute AEGL values (Attachment 7). Following discussion on alternative approaches (i.e., use of 15-minute LC_{50} for the 10-minute AEGL-3 value), the following 10-minute AEGL values proposed were accepted: AEGL-1- not recommended due to the lack of data; AEGL-2 value was set at 2.0 ppm; and AEGL-3 value was set at 7.3 ppm. The 10-minute AEGL-2 & 3 values were set to equal to the 30-minute values (motion made by Richard Thomas, second by Jim Holler) (AEGL-1: YES, unanimously; AEGL-2: YES: 17; NO: 2; ABSTAIN: 0; AEGL-3: YES: 19; NO: 1; ABSTAIN: 0) (Appendix E).

Furan (CAS Reg. No. 111-00-9)

George Rodgers, chemical manager, presented the 10-minute AEGL values (Attachment 8) as well as AEGLs adjusted by application of default *n* values of 1 and 3 rather than 2. Ten-minute values of 18 ppm and 52 ppm for AEGL-2 and -3, respectively, were proposed based upon the 1-hour exposure data from Terrill et al. (1989) and an *n* of 3. The values were approved unanimously (motion by Mark McClanahan, second by David Belluck) (Appendix F). No AEGL-1 values were developed. It was recommended that the "ID" designation (insufficient data) for missing values be changed to "NR" (Not Recommended).

Propylene oxide (CAS Reg. No. 75-56-9)

Jim Holler, chemical manager, presented the proposed 10-minute AEGL values (Attachment 9). Due to concerns expressed regarding the use of the empirically-derived n of 0.87, the deliberations were tabled until the next meeting. It was suggested that a cover letter be added to the revised TSD to explain changes.

Tetrachloroethylene (CAS Reg. No. 127-18-4)

Bill Bress, chemical manager, presented the proposed 10-minute AEGL values (Attachment 10).
A motion (George Rodgers, second by David Belluck) was made to accept the proposed 10-minute values and 30-minute values as equal. Some NAC/AEGL members expressed concern that the NAS might send this chemical back because of the use of a chronic animal study for AEGL-2, when human studies were available and felt that the AEGL-3 was too low when you compared the numbers to human data (AEGL-1: YES: 19; NO: 1; ABSTAIN: 0; AEGL-2: YES: 16; NO: 4; ABSTAIN: 0; AEGL-3: YES: 16; NO: 2; ABSTAIN: 2) (Appendix G).

Tetranitromethane (CAS Reg. No. 509-14-8)

Ernest Falke presented the proposed 10-minute values for tetranitromethane (Attachment 11). The proposed values and the altered "n" value used to develop them were accepted (motion by George Rodgers, second by Richard Thomas) (AEGL-1, -2, and -3: YES: 17; NO: 2; ABSTAIN: 0) (Appendix H). It was suggested that the cancer risk values be added as an Appendix in the TSD and that justification be added regarding the 8-hr AEGL-1 reflecting a 1 in 10,000 cancer risk.

Perchloromethyl mercaptan (CAS Reg. No. 594-42-3)
Zarena Post, chemical manager, presented the AEGL adjusted 10-minute values using an *n* value of 1 or 3 according to the SOP (Attachment 12). A motion to accept the values as proposed was made by George Rodgers and seconded by Richard Niemeier. The motion passed (AEGL-1: YES: 17; NO: 1; ABSTAIN: 0; AEGL-2: YES: 17; NO: 1; ABSTAIN: 0; AEGL-3: YES: 18; NO: 0; ABSTAIN: 0) (Appendix I).

REVISIT/RE-ASSESSMENTS OF CHEMICAL-SPECIFIC AEGLS

Hydrogen sulfide
A reassessment of the AEGLs for hydrogen sulfide were necessitated by concerns of the NAS/COT/AEGL (COT/AEGL) Subcommittee regarding the quality of the study used to develop the AEGL-1 values. The COT/AEGL believed that the study of asthmatics would provide for more robust and appropriate AEGL-1 values. Cheryl Bast provided AEGL-1 values developed using this study (Jappinen, 1990). Several members of the NAC/AEGL indicated that the values (Attachment 13) presented by the World Health Organization (WHO) allowed for defensible AEGL-1 values that were in opposition to these values. As a result, no consensus was reached regarding the AEGL-1 values for H_2S.

☞**Action Item**: Following discussion, it was recommended that the COT/AEGL comments and the overall data on H_2S be reviewed by Cheryl Bast, Steve Barbee and George Alexeeff. Furthermore, a specific data analysis will be conducted by Mark Ruijten, Dave Belluck, and Zarena Post regarding the WHO values with attention given to a definitive demarcation of odor and annoyance thresholds. The results of this analysis will be presented at the next NAC/AEGL meeting. Steve Barbee will organize a conference call to discuss general issues of H_2S and to welcome the participation of NAC members.

AEGL PRIORITY CHEMICALS

Uranium hexafluoride, CAS Reg. No. 7783-81-5

Chemical Manager: George Rusch, Chair
Staff Scientist: Cheryl Bast, ORNL Staff Scientist

Cheryl Bast presented an overview of the pertinent data and development of the draft AEGL values (Attachment 14), noting that the toxicity of UF_6 included both a renal toxicity and radiological component. Discussion ensued regarding the most appropriate endpoint for AEGL-1. Additionally, it was decided that an available accident report had notable deficiencies making it unsuitable for development of AEGL values. For AEGL-3, the relevance of the hydrogen fluoride (HF) component (especially for shorter exposure periods) was discussed and the HF and UF_6 AEGL values compared; HF values were lower than those of UF_6 for times >1 hour, equivalent at 1 hour, but greater for 4- and 8-hour periods. A motion was made by George Rodgers (seconded by Ernest Falke) to accept UF_6 values of 550, 100, 36, 4.4, and 1.6 mg/m^3 for the 10-minute, 30-minute, 1-hr, 4-hr, and 8-hr values. It was noted that these values are consistent with the AEGL-3 values proposed for HF. The motion passed YES: 18; NO: 0; ABSTAIN: 0) (Appendix J). The AEGL-2 values were based upon renal toxicity in dogs and an

empirically-derived "*n*" value of 0.66. The AEGL values based on this UF_6 study would also be protective of toxicity due to the HF component of UF_6. The motion made by Ernest Falke, seconded by Steve Barbee) to accept the values of 28, 19, 9.6, 2.4 and 1.2 mg/m^3 for the 10-minute, 30-minute, 1-hr, 4-hr, and 8-hr passed (YES: 19; NO: 1; ABSTAIN: 0) (Appendix I). For AEGL-1, several options were considered; no AEGL values, AEGL values equivalent to HF, and use of the available accident reconstruction report. It was the consensus of the NAC/AEGL that for AEGL-1, HF values would be more appropriate for the shorter time periods (<4 hrs) but that UF_6 would be more relevant at 4 and 8 hours. Therefore, the 10-minute, 30-minute, and 1-hr AEGL values for HF of 3.6 ppm were applied for the same exposure durations for UF_6. For 4- and 8-hrs, no values were recommended for UF_6. A motion was made by Tom Hornshaw (seconded by Richard Thomas) to accept these values; the motion passed unanimously (YES: 19; NO: 0; ABSTAIN: 0) (Appendix J).

SUMMARY OF PROPOSED AEGL VALUES FOR URANIUM HEXAFLUORIDE (mg/m^3)						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint**
AEGL-1	3.6	3.6	3.6	NR	NR	Equivalent to HF
AEGL-2	28	19	9.6	2.4	1.2	Renal toxicity in dogs
AEGL-3	550	100	36	4.4	1.6	Lethality

G Agents (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, USAF
Staff Scientist: Annetta Watson, ORNL Staff Scientist

The presentation of the agent-specific data and development of the AEGL values for the G-agents was preceded by supporting introductory presentations.

Veronique Hauschild (USACHPPM) presented introductory information from an operational standpoint regarding issues and needs of the U.S. Army relative to AEGLs for chemical warfare agents (Attachment 15). Ms. Hauschild explained the need for expeditiously developed scientifically-based AEGLs, and the U.S. Army's appreciation for the NAC/AEGL role in this effort.

Coleen Weese (USACHPPM) presented a summary of the CDC Public Meeting on airborne exposure limits to nerve agents held in August, 2000, which affirmed that miosis (rather than ChE depression) was the most appropriate endpoint for assessing nerve agent exposure. The August public meeting also identified the most relevant and appropriate data sets, and approved the relative potency approach for developing toxicity values for the data-deficient Agent VX.

Glenn Leach also made a brief presentation noting the critical effects of concern for nerve agents, the most appropriate species for AEGL-3 determinations, and distinguishing derivative values presented in the TSD from those derived experimentally.

An elaboration on issue analyses relevant to nerve agent toxicity and development of AEGL values was presented by Robert Young (Attachment 16). This presentation focused on the toxicology of nerve agents, types of cholinesterases (ChE) and the relevance of ChE in development of AEGLs, and previous peer-reviewed analyses of appropriate endpoints used in developing toxicity values for nerve agents and organophosphate pesticides.

Annetta Watson provided an overview of the available data for the G-agents, noting that a more detailed presentation had been given at the previous NAC/AEGL meeting (NAC/AEGL 18) and that all presentation materials, as well as the TSDs, were previously made available to the NAC membership (Attachment 17). The presentation reflected input from several NAC reviewers and an Air Force review coordinated by John Hinz. Discussion focused on the partitioning of uncertainty factors with NAC consensus that the total uncertainty factor of 30 was appropriate for estimating AEGL-3, but the intraspecies UF should be 10 (greater sensitivity of female rats was not considered justification for a UF of 10) and the interspecies UF should be 3. There was also discussion on the data set selection and derivation of an n of 2 from recent studies of GB vapor exposure to rats (Mioduszewski et al., in press, 2000). A motion to accept the AEGL-3 values for Agent GB was made by Bill Bress and seconded by Loren Koller. The motion passed (AEGL-3: YES: 20; NO: 0; ABSTAIN: 0) (Appendix K).

The AEGL-1 values were based upon data from studies with informed human subjects exposed to GB vapor (0.05 mg/m^3 for 20 min) and experiencing only minimal effects. AEGL-2 effects were based upon a repeat study using informed volunteers (under Helsinki accords and clinical supervision) in which miosis, dyspnea, reduction of RBC-ChE to 60% of baseline, and small changes in single fiber electromyography of the forearm (considered a possible precursor to nondepolarising neuromuscular block) following exposure to 0.5 mg/m^3 GB for 30 minutes. For both AEGL-1 and AEGL-2 values an intraspecies uncertainty factor of 10 was applied, resulting in a composite UF of 10 (interspecies UF of 1 and intraspecies UF of 10; modifying factor not apply). Following discussions of the derivation logic, motions were made to accept the AEGL-2 values (motion made by Koller and seconded by Richard Thomas) (YES: 16; NO: 0; ABSTAIN: 2) (Appendix K) and AEGL-1 values (motion made by Loren Koller and seconded by Steve Barbee). Both motions passed unanimously (AEGL-1 and -2: YES: 20; NO: 0; ABSTAIN: 0) (Appendix K).

Following explanation by Annetta Watson of the process/rationale for the relative potency approach wherein AEGLs for Agents GA, GD and GF were developed relative to GB data, motions were made to accept the AEGLs as presented for these agents. The motion for Agent GA was made by Loren Koller and seconded by Glenn Leach. The motion for Agent GD was made by George Rodgers and seconded by Loren Koller, and the motion for Agent GF was made by Richard Thomas and seconded by Loren Koller. All of the motions passed [**Agent GA**: AEGL-1: YES: 19; NO: 1; ABSTAIN: 0; AEGL-2 and -3: YES: 21; NO: 0; ABSTAIN: 0 (Appendix L). **Agent GD**: AEGL-1: YES: 18; NO: 0; ABSTAIN: 0; AEGL-2 and -3: YES: 21; NO: 0; ABSTAIN: 0 (Appendix M); **Agent GF**: AEGL-2: YES: 18; NO: 0; ABSTAIN: 0; AEGL-2 and -3: YES: 21; NO: 0; ABSTAIN: 0 (Appendix N)].

SUMMARY OF PROPOSED AEGL VALUES (ppm[mg/m^3]) FOR AGENT GA

Classification	10 min	30 min	1 hr	4 hr	8 hr	Endpoint
AEGL 1	0.0010 [0.0069]	0.00060 [0.0040]	0.00042 [0.0028]	0.00021 [0.0014]	0.00015 [0.0010]	Based on relative potency from GB
AEGL 2	0.013 [0.087]	0.0075 [0.050]	0.0053 [0.035]	0.0026 [0.017]	0.0020 [0.013]	Based on relative potency from GB
AEGL 3	0.11 [0.76]	0.057 [0.38]	0.039 [0.26]	0.021 [0.14]	0.015 [0.10]	Based on relative potency from GB

SUMMARY OF PROPOSED AEGL VALUES (ppm[mg/m^3]) FOR AGENT GB						
Classification	**10 min**	**30 min**	**1 hr**	**4 hr**	**8 hr**	**Endpoint**
AEGL 1	0.0012 [0.0069]	0.00068 [0.0040]	0.00048 [0.0028]	0.00024 [0.0014]	0.00017 [0.0010]	Headache, eye pain, rhinorrhea, tightness in chest, cramps, nausea, malaise, miosis in human volunteers exposed to 0.05 mg/m^3 for 20 min. (Harvey, 1952; Johns, 1952)
AEGL 2	0.015 [0.087]	0.0085 [0.050]	0.0060 [0.035]	0.0029 [0.017]	0.0022 [0.013]	Miosis, dyspnea, RBC-ChE depression, electromyographic changes in human volunteers (0.5 mg/m^3 for 30 min; Baker and Sedgwick, 1996)
AEGL 3	0.064 [0.38]	0.032 [0.19]	0.022 [0.13]	0.012 [0.070]	0.0087 [0.051]	Rat lethality (Mioduszewski et al., in press; 2000)

SUMMARY OF PROPOSED AEGL VALUES (ppm[mg/m^3]) FOR AGENT GD						
Classification	**10 min**	**30 min**	**1 hr**	**4 hr**	**8 hr**	**Endpoint**
AEGL 1	0.00046 [0.0035]	0.00026 [0.0020]	0.00018 [0.0014]	0.000091 [0.00070]	0.000065 [0.00050]	Based on relative potency from GB
AEGL 2	0.0057 [0.044]	0.0033 [0.025]	0.0022 [0.018]	0.0012 [0.0085]	0.00085 [0.0065]	Based on relative potency from GB
AEGL 3	0.049 [0.38]	0.025 [0.19]	0.017 [0.13]	0.0091 [0.070]	0.0066 [0.051]	Based on relative potency from GB

SUMMARY OF PROPOSED AEGL VALUES (ppm[mg/m^3]) FOR AGENT GF						
Classification	**10 min**	**30 min**	**1 hr**	**4 hr**	**8 hr**	**Endpoint**
AEGL 1	0.00049 [0.0035]	0.00028 [0.0020]	0.00020 [0.0014]	0.00010 [0.00070]	0.000070 [0.00050]	Based on relative potency from GB

AEGL 2	0.0062 [0.044]	0.0035 [0.025]	0.0024 [0.018]	0.0013 [0.0085]	0.00091 [0.0065]	Based on relative potency from GB
AEGL 3	0.053 [0.38]	0.027 [0.19]	0.018 [0.13]	0.0098 [0.070]	0.0071 [0.051]	Based on relative potency from GB

Agent VX, CAS No. 50782-69-9

Chemical Manager: Glenn Leach, USACHPPM
Staff Scientist: Annetta Watson, ORNL Staff Scientist

Annetta Watson summarized the available data for Agent VX, noting the similarities in signs/symptoms of VX to the G-agents and providing an overview of the gradation of effects with increasing cumulative exposure (Attachment 18). There was considerable discussion regarding the data quality and how this impacted the relative potency approach. The comparative study of Callaway and Dirnhuber (1971) , which evaluated the potency of GB and VX vapor to produce miosis during direct exposure experiments to the eyes of albino rabbits, was interpreted by the NAC to support a relative potency factor of 12 (VX more potent than GB). This determination is different than the relative potency factor of 10 originally proposed in the TSD. In addition, the NAC recommended application of a modifying factor of 3 in the development of all AEGL values for agent VX to account for the incomplete VX data set. For both AEGL-1 and AEGL-2 values, an interspecies UF of 1 and an intraspecies UF of 10 were applied. With addition of the modifying factor of 3, the composite UF for AEGL-1 and AEGL-2 estimates was 30.

A motion to accept the resulting AEGL-1 values was made by Bill Bress and seconded by Ernie Falke. The motion passed (YES: 15; NO: 1; ABSTAIN: 3) (Appendix O). A motion to accept the AEGL-2 values was made by Bob Benson and seconded by Glenn Leach also passed (YES: 11; NO 3; ABSTAIN: 6) (Appendix O).

For AEGL- 3 values, rat lethality data for GB were used with the same relative potency method, but with an added modifying factor of 3 for database inadequacy which was of particular concern to several NAC members. With an interspecies UF of 3 and an intraspecies UF of 10, the composite adjustment was equal to 100. A motion was made by Bill Bress and seconded by Ernie Falke. The motion passed (YES: 16; NO: 1; ABSTAIN: 2) (Appendix O).

A lengthy discussion ensued regarding the adequacy of this adjustment to address the uncertainty associated with the assumption of relative potency and physiological/metabolic similarities between VX and GB. It was the consensus of the NAC/AEGL that the VX database is extremely weak, and was noted by previous National Research Council recommendations (NRC, 1997). To address these significant data gaps and yet provide some guidance for potential current real-world applications, it was the consensus of the NAC/AEGL to propose temporary AEGL values that would expire in 3 years from the date of NAS publication at which time a re-evaluation of any new data would be necessary.

SUMMARY OF PROPOSED TEMPORARY* AEGL VALUES (ppm[mg/m^3]) FOR AGENT VX						
Classification	**10 min**	**30 min**	**60 min**	**4 hr**	**8 hr**	**Endpoint**

Temporary* AEGL 1	0.000018 [0.00020]	0.000010 [0.00011]	0.0000073 [0.000080]	0.0000037 [0.000040]	0.0000026 [0.000028]	Based on relative potency from GB
Temporary* AEGL 2	0.00022 [0.0024]	0.00013 [0.0014]	0.000090 [0.00098]	0.000045 [0.00049]	0.000032 [0.00035]	Based on relative potency from GB
Temporary* AEGL 3	0.00088 [0.0096]	0.00045 [0.0049]	0.00030 [0.0033]	0.00016 [0.0017]	0.00012 [0.0013]	Based on relative potency from GB

*Due to significant data gaps, these values are temporary proposed. They will expire 3 years from the date of NAS publication.

ADMINISTRATIVE ISSUES

Plans for future NAC/AEGL meeting dates were discussed. The following were options:

January 8-10, 2001 (Washington, DC)
March 22-24, 2001 (in conjunction with SOT and the NAS/COT meeting)
June 18-20, 2001 (Oak Ridge, TN)
September 11-13, 2001 (Washington, DC)

Meeting highlights were 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. 19 Agenda
2. NAC/AEGL Meeting No. 19 Attendee List
3. NAS/COT/AEGL Subcommittee comments on AEGLs and TSDs
4. Data analysis of 10-minute AEGLs for Allyl alcohol
5. Data analysis of 10-minute AEGLs for Boron trichloride
6. Data analysis of 10-minute AEGLs for Chloromethyl methyl ether
7. Data analysis of 10-minute AEGLs for Diborane
8. Data analysis of 10-minute AEGLs for Furan
9. Data analysis of 10-minute AEGLs for Propylene oxide
10. Data analysis of 10-minute AEGLs for Tetrachloroethylene
11. Data analysis of 10-minute AEGLs for Tetranitromethane
12. Data analysis of 10-minute AEGLs for Perchloromethylmercaptan
13. Data analysis for Hydrogen sulfide
14. Data analysis for Uranium hexachloride
15. An Overview of Development of Nerve agent AEGLs by Veronique Hauschild
16. Issues for NAC/AEGL in Developing AEGLs for Nerve Agents
17. Data analysis for Nerve Agents (GA, GB, GD, and GF)
18. Data analysis for Nerve Agent VX

LIST OF APPENDICES

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-19
October 23-25, 2000

U.S. Department of Transportation
DOT Headquarters/Nassif Building, Rooms 6332-6336
400 7th Street, S.W., Washington, D. C.

AGENDA

Monday, October 23, 2000

10:00 AM	Introductory remarks and approval of NAC/AEGL-18 Highlights (George Rusch, Roger Garrett, and Paul Tobin)
10:15	AEGL Program Perspectives (Roger Garrett)
11:00	Status of SOP manual and final TSDs (Roger Garrett and Ernie Falke)
11:15	Summary of COT/AEGLs comments
12:00 PM	Lunch
1:00	Review of 10-minute AEGLs ✦ Allyl alcohol, Boron trichloride, Chloromethyl methyl ether, Diborane, Furan, Perchloromethyl mercaptan, Propylene oxide, Tetrachloroethylene, and Tetranitromethane
2:30	Break
3:00	Review of 10-minute AEGLs (continued)
4:00	Review of Uranium hexafluoride (George Rusch/Cheryl Bast)
5:00	Adjourn for the day

Tuesday, October 24, 2000

8:30 AM	Review of Uranium hexafluoride (continued)
9:30	Introduction and Summary of Army issues and needs (Veronique Hauschild)
9:45	Nerve agent issues analysis (Robert Young)
10:30	Break
11:00	Review of Nerve Agent G: GB, GA, GD, and GF (John Hinz/Annetta Watson)
12:00 PM	Lunch
1:00	Review of Nerve Agent G: GB, GA, GD, and GF (continued)
2:30	Break
3:00	Review of Nerve Agent VX (Glenn Leach/Annetta Watson)
5:00	Administrative matters
5:15	Adjourn for the day

Wednesday, October 25, 2000

8:30 AM	Review of Hydrogen sulfide (Steve Barbee/Cheryl Bast)
10:30	Break
11:00	Review of 10-minute AEGLs (continued)
12:00 PM	Adjourn meeting

NAC/AEGL-19
Oct 23-25, 2000

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NAC-AEGL 19

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ATTENDANCE SHEET

SUBJECT:

M09- 1100 PENN AVE

DATE:
TIME:

LOCATION: ~~Ariel Rios - Green Room~~

Name	Signature	Organization	Phone Number
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→ OVER

COT Subcommittee Comments on AEGLs and TSDs

Most of the comments provided by the NAS/COT Subcommittee have been positive. The TSDs are considered to be well-written and thorough, and both the TSDs and the presentations are considered positive assets in the COT review process. However, there have been points of contention, some of which are recurring.

Major Concerns Expressed by the COT Subcommittee on AEGLs

1. Choice of Effect Concentration
   For a given endpoint, the COT Subcommittee believes that the NAC/AEGL sometimes selects the lowest value available in the reviewed literature on upon which to base an AEGL level even when the preponderance of data shows that the value may be an outlier. An example is the basis for the AEGL-3 for 1,1,1-trichloroethane in which the chosen LC_{50} value is well below the regression line calculated from several similar studies with the same species. Furthermore, the key study (a translation from French) was not considered the best study for AEGL development. AEGL values need to be put into perspective with the overall data set. The AEGL-3 values approved by the NAC/AEGL are below concentrations routinely used for surgical anesthesia of persons of all ages. The same comment, i.e., using the lowest value rather than a value supported by the preponderance of the data, was applied to the 1,1,1-trichloroethane AEGL-2.

   Another example is hydrogen sulfide. Monitoring data from a mobile laboratory downwind from an oil refinery were utilized to derive AEGL-1 values. Minor throat, eye, and nasal irritation and headaches were reported by staff members in the monitoring van. These effects were reported at concentrations far below those producing effects in well controlled human experimental studies in healthy and asthmatic (sensitive) persons.

   Additionally, starting with their first meeting, the COT Subcommittee has expressed concern that the chosen endpoint be an effect level (or threshold for an effect) consistent with each AEGL tier definition. NOAELs should not be chosen as the endpoint when an effect at a higher concentration and meeting the definition of a specific AEGL tier is available.

2. Choice of Endpoint
   For chemicals for where considerable data are available, the chosen endpoint needs to be consistent with the known mechanism of action or continuum of toxic effects for that chemical. Occasionally, published studies address endpoints that are inconsistent with the chemical action or the overall weight-of-evidence for the toxic effects of that chemical. Notable concern was expressed regarding the use of a developmental toxicity endpoint in rodents as the basis for the AEGL-2 for chloroform, a chemical not known for its activity or potential as a developmental toxicant.

3. Choice of Exposure Protocol
The COT Subcommittee was in opposition with the NAC/AEGL decision to use data from a repeated exposure protocol in the development of the AEGL values for phosphine. Similarly, there was disagreement with the selection of 30-day, discontinuous exposure study as a driver for the AEGL-2 values for ethylenediamine.

4. AEGL Definitions
Initially there appeared to be some disagreement/confusion regarding the definitions for the various AEGL tiers. This has been clarified.

5. Study Quality
The quality of the key study has, at times, been questioned. For example, the key study selected by the NAC/AEGL as the basis for developing the AEGL-2 values for cyclohexylamine was an older (1950), poorly reported study (e.g., details regarding numbers of animals treated, mortality rate for a given exposure). The COT Subcommittee on AEGLs disagreed with the selection of this study and suggested that a more recent GLP study be used.

6. TSD Format
The TSDs now include additional standards and guidelines for comparison with AEGLs. An additional section, written in layman terms, has been added to address data quality and research needs. Verbiage pertaining to "confidence" in data or AEGLs has been deleted.

7. The COT Subcommittee continually expresses concern that AEGL-1 values be developed, even if for nothing more than to serve as notification levels.

8. The COT Subcommittee has, on more than one occasion, expressed concern that AEGL values are very low numbers that are not always consist with the known toxicity of the chemicals and overall human experience.

ALLYL ALCOHOL

- Changed "n" from default of n = 2 to default of n = 1 or 3

- Added 10-minute values:

  AEGL-2: flat-lined the 30-min value to 10 min because exposure duration was≥ 4 hr

  AEGL-3: extrapolated to 10 min

Summary of Proposed AEGL Values for Allyl Alcohol (ppm)						
Level	**10-m**	**30-m**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**
AEGL-1	1.8	1.8	1.8	1.8	1.8	Mean odor detection threshold
AEGL-2	9.6	9.6	7.7	4.8	3.5	Irritation in rats at 40 ppm for 7 hr
AEGL-3	36	25	20	10	7.1	NOEL for lethality in mice, rats, and rabbits exposed to 200 ppm for 1 hr

BORON TRICHLORIDE

- Updated the AEGL-1 and-2 levels: no derived values but ⅓ the NAC-approved HCl values recommended as guidance levels

- AEGL-3 level: Extrapolated to 10 minutes

Summary of Proposed AEGL Values for Boron Trichloride (ppm)						
Level	**10-m**	**30-m**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**
AEGL-1	0.6	0.6	0.6	0.6	0.6	Recommended as guidance levels: ⅓ the NAC-approved HCl values [No-adverse-effect-level of HCl in exercising human asthmatics]
AEGL-2	34	14	7.3	1.8	0.90	Recommended as guidance levels: ⅓ the NAC-approved HCl values [Mouse RD_{50}; Histopathology in rats]
AEGL-3	170	57	28	7.1	3.5	⅓ the 1-hour boron trichloride LC_{50} value of 2541 ppm in male rats

NAC/Draft 2: 10/00

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR CHLOROMETHYL METHYL ETHER, TECHNICAL GRADE

$H_3C–O–CH_2Cl$

Draft 2: October, 2000
Draft 1: March, 1998

ORNL Staff Scientist: Sylvia Milanez
Chemical Manager: Ernest Falke
Chemical Reviewers: Thomas Hornshaw, Robert Benson

INTRODUCTION

The chloromethyl methyl ether (CMME) TSD was originally presented March 1998 and AEGL values were accepted by the AEGL/NAC.

The key changes in Draft 2 compared to Draft 1 of the TSD are:

(1) 30-480 minute AEGL- and AEGL-3 values have been re-calculated using the new SOP scaling defaults: **n=3 or n=1** (go to shorter/longer times) vs. using **n=2** in 3/98 (NAC changed from n=1 in original TSD). AEGL-1 values were/are not recommended.

(2) New 10-minute AEGL-2 and AEGL-3 values have been derived: all were flat-lined from 30 minutes because exposure time in key studies was > 4 hours.

(3) Cancer-based AEGLs have been re-calculated using an adjustment factor of 6 instead of 2.8 to account for uncertainty in the stages of the carcinogenic process at which TNM acts.

ACUTE EXPOSURE GUIDELINE LEVELS FOR TECHNICAL GRADE CHLOROMETHYL METHYL ETHER (107-30-2)

AEGL-2 Key study: Drew et al., 1975. Rat, 30-exposures; use one 6 hr/day exp.
AEGL-3 Key study: Drew et al., 1975. Rat 7-hour exposure LC_{50} study

October 2000. **Summary of Proposed AEGL Values for CMME [ppm]**						
Level	**10 minute**	**30 minute**	**1 hour**	**4 hour**	**8 hour**	**Endpoint**
AEGL-1	Not Recommended (No studies consistent with AEGL-1 definition)					
AEGL-2	0.076	0.076	0.061	0.038	0.025	Tracheal/bronchial squamous metaplasia; regenerative lung hyperplasia
AEGL-3	1.2	1.2	0.94	0.59	0.43	Lethality threshold for rats

Scaling: $C^n \times t = k$ (ten Berge et al., 1986); used n=3 or n=1 to scale to <6 hrs and >6 hrs, respectively; ***10-min. values flat-lined from 30-minutes***

Total uncertainty/modifying factor: 30
Intraspecies: 3: Response to irritant gas hydrolyzed *in situ* will not vary greatly among humans
Interspecies: 3: Little interspecies variability was seen [AEGL-2, AEGL-3]; key study was repeat-exposure [AEGL-2]
Modifying factor: 3: Potential variability in BCME content of tech. grade CMME

COMPARISON OF 10/00 AND 3/98 AEGL VALUES

October 2000. Summary of AEGL Values for CMME [ppm]					
Level	**10 minute**	**30 minute**	**1 hour**	**4 hour**	**8 hour**
AEGL-1	Not Recommended				
AEGL-2	0.076	0.076	0.061	0.038	0.025
AEGL-3	1.2	1.2	0.94	0.59	0.43

n=3 or 1

March 1998. Summary of AEGL Values for CMME [ppm]					
Level	**10 minute**	**30 minute**	**1 hour**	**4 hour**	**8 hour**
AEGL-1	Not Recommended				
AEGL-2	Not derived	0.12	0.082	0.041	0.029
AEGL-3		1.8	1.3	0.65	0.46

n = 2

Note that the original TSD used n=1, which was subsequently changed by the AEGL/NAC to n=2. These values are not presented here.

PRELIMINARY CANCER ASSESSMENT OF TNM: COMPARISON OF 10/00 AND 3/99 AEGL VALUES

Key study: Kuschner et al., 1975. Rat 10-100 day exposures to 0.1 ppm BCME followed by lifetime observation. Divide BCME conc. by 0.08 to convert to 100% CMME (BCME is ≤ 8% of technical grade CMME).

Key difference between 3/98 and 10/00 cancer assessment:

Adjustment factor for uncertainty regarding the stages of the carcinogenic process at which TNM acts: used **2.8** in 3/99; use **6** in 10/00 TSD

Adjustment factor = 2.8 (3/98)	**Adjustment factor = 6 (10/00)**
½-hour exposure = 2.7 ppm 1-hour exposure = 1.4 ppm 4-hour exposure = 0.34 ppm 8-hour exposure = 0.17 ppm	½-hour exposure = 1.2 ppm 1-hour exposure = 0.62 ppm 4-hour exposure = 0.16 ppm 8-hour exposure = 0.078 ppm

***Compare the cancer-based values to AEGL-2 or AEGL-3*?????**

[In 3/98 TSD, compared to AEGL-3; in 10/00 TSD, compared to AEGL-2]

***October 2000.* Summary of AEGL Values for CMME [ppm]**					
Level	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-2	0.076	0.076	0.061	0.038	0.025
AEGL-3	1.2	1.2	0.94	0.59	0.43

DIBORANE

- Added 10-minute values:

  AEGL-1: NA/ level 1 values are not recommended

  AEGL-2: extrapolated to 10 min

  AEGL-3: flat-lined the 30-min value to 10 min because exposure duration was ≥ 4 hr

Summary of Proposed AEGL Values for Diborane (ppm)						
Level	**10-m**	**30-m**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**
AEGL-1	NR	NR	NR	NR	NR	Not recommended because proposed AEGL-2 value is below the odor threshold, and no other data pertaining to endpoints relevant to the AEGL-1 definition were available.
AEGL-2	6.0	2.0	1.0	0.25	0.13	LOAEL for pulmonary changes in male ICR mice; 5 ppm for 2 hr
AEGL-3	7.3	7.3	3.7	0.92	0.46	4-hour LC_{01} of 9.2 ppm estimated from a 4-hour LC_{50} in male ICR mice

FURAN

- Changed "n" from default of n = 2 to default of n = 1 or 3

- Added 10-minute values:

  AEGL-1: NA/ Insufficient data

  AEGL-2 and AEGL-3: extrapolated to 10 min

see SOP

Summary of Proposed AEGL Values for Furan (ppm)						
Level	**10-m**	**30-m**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**
AEGL-1	ID	ID	ID	ID	ID	Insufficient data
AEGL-2	18	13	10	2.5	1.3	1014 ppm for 1 hour: threshold for adverse effects in rats
AEGL-3	52	46	29	7.1	3.6	2851 ppm for 1 hour: threshold for lethality in rats

PROPYLENE OXIDE

♦ DERIVATION OF *n*

Currently use derived value of ***n = 1.2*** for ethylene oxide because of similar mechanisms (direct alkylating agent)

Ethylene oxide generally 2-3x more toxic than propylene oxide

Toxicity of propylene oxide may be more like epichlorohydrin (***n = 0.87***):

Both affect upper respiratory tract resulting in toxic lesions after single exposure and nasal tumors after repeated exposures.

Unlike ethylene oxide, neither epichlorohydrin nor propylene oxide has been found to be a developmental toxicant.

Both compounds produce similar clinical signs. However, epichlorohydrin 2-10x more toxic than propylene oxide

Summary of AEGL Values (ppm) Based on Ethylene Oxide n=1.2 (currently proposed)					
Level	Exposure Duration				
	10-min	30-min	1-hour	4-hour	8-hour
AEGL-1	110	110	60	19	11
AEGL-2	1400	510	290	91	51
AEGL-3	2700	1100	610	190	110

Summary of AEGL Values (ppm) Based on Epichlorohydrin n=0.87					
Level	Exposure Duration				
	10-min	30-min	1-hour	4-hour	8-hour
AEGL-1	260	260	120	24	11
AEGL-2	2900	830	370	76	34
AEGL-3	6600	1900	840	170	77

- Add 10-minute values:

  AEGL-1: flat-line the 30-min value to 10 min because exposure duration was ≥ 4 hr

  AEGL-2 and AEGL-3: extrapolate to 10 min

Current Summary of Proposed AEGL Values for Propylene Oxide (ppm) (using n=1.2)						
Level	**10-m**	**30-m**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**
AEGL-1	110	110	60	19	11	8-hour TWA of 31.8 ppm resulted in no worker complaints
AEGL-2	1300	510	290	91	51	Humans: Strong odor and irritation noted in monitoring study; average of AEGL-2 values using four exposure conc. and durations: 380 ppm for 177 min, 525 ppm for 121 min, 392 ppm for 135 min, 460 ppm for 116 min
AEGL-3	2700	1100	610	190	110	Humans: Highest recorded nonlethal concentration of 1520 ppm for 171 minutes

ISSUE FOR CONSIDERATION FOR PROPYLENE OXIDE AEGLs

Insufficient data currently exist from which to derive an n value for use in the scaling of propylene oxide AEGL values across time. In the current document, because of the lack of data for empirical derivation of *n* for propylene oxide, and based on a similar mechanism of action of propylene oxide as compared to ethylene oxide, the derived value of *n* for ethylene oxide was used in the scaling of propylene oxide AEGL values across time. The value of $n = 1.2$ for ethylene oxide was derived empirically from 1- and 4-hour LC_{50} values for rats. An approximate value of n is supported by data on propylene oxide exposure in guinea pigs (Tables 11 and 14 in TSD - not sufficient for calculation of n).

That being said, it has also been noted in the document that while ethylene oxide is a structurally-related chemical that also is a direct alkylating agent and undergoes similar biotransformation, propylene oxide is not as toxic ethylene oxide. Based on a comparison of the 4-hour LC_{50} values for the two chemicals, propylene oxide is 2-3 times less toxic than ethylene oxide. Ethylene oxide is mutagenic to germ cells as well as somatic cells in species such as rodents, monkeys, and rabbits, and has been found to be 5-10 times more effective than propylene oxide when considering gene conversion, reverse mutations, and sister chromatid conversion in yeast. The two chemicals have about the same potency for inducing *in vitro* point mutations in bacteria and sister chromatid exchanges in human lymphocytes. *In vivo*, ethylene oxide is more effective than propylene oxide at inducing chromosomal aberrations in humans and sister chromatid exchanges and chromosomal aberrations in monkeys. The number of hemoglobin adducts formed following exposure to propylene oxide has been estimated to be 4 times lower than the number formed by ethylene oxide exposure. Following intraperitoneal injection of each chemical, propylene oxide binding in mouse liver DNA was one-twentieth that of ethylene oxide [taken from Section 4.3 of TSD, see section for references if desired].

Kowetha is currently revising the epichlorohydrin AEGL TSD, and was investigating SARs. In her document, she points out that epichlorohydrin is a chloromethyl substituted oxirane (ethylene oxide) or chlorinated methyloxirane (propylene oxide). All three compounds are direct alkylating agents; however, the toxicity of epichlorohydrin is more like that of propylene oxide than ethylene oxide. Both epichlorohydrin and propylene oxide affect the upper respiratory tract resulting in toxic lesions after single exposure and nasal tumors after repeated exposures. Unlike ethylene oxide, neither epichlorohydrin nor propylene oxide has been found to be a developmental toxicant. Both compounds produce similar clinical signs. The LC_{50} values for 4-hour inhalation exposure to epichlorohydrin and propylene oxide, respectively, are as follows: 441–635 ppm and 3205–4197 ppm for rat and 820–1153 and 1160-1740 ppm for the mouse. These data suggest that the rat is 5–10 times more sensitive to epichlorohydrin than propylene oxide; the difference in sensitivity to the mouse, however, is less than a factor of ≤ 2. Although the clinical signs were similar the test concentrations eliciting clinical signs were much lower for epichlorohydrin than for propylene oxide. Therefore these data show that epichlorohydrin are qualitatively similar but quantitatively different. It may be more appropriate to use the n-value for epichlorohydrin rather than for ethylene oxide.

For epichlorohydrinm, the LC_{50} data for inhalation exposure to the rat was used to determine the relationship between concentration of epichlorohydrin and the exposure duration. LC_{50} values for the rat, and are as follows: 2798 (geometric mean of 3617 ppm for males and 2165 ppm for females) for a 1-hour exposure, 635 ppm for a 4-hour exposure, 360 ppm for a 6-hour exposure, and 250 ppm for a 8-hour exposure. A linear log-log relationship was observed over the 1- to 8-hour exposure duration. The calculated value of n was 0.87.

TETRACHLOROETHYLENE

- Added 10-minute values:

  AEGL-1: extrapolated to 10-min

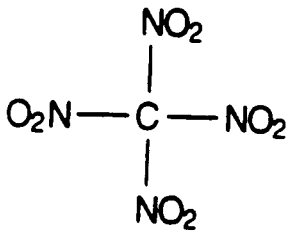
  AEGL-2 and AEGL-3: flat-lined 30-min value to 10 min because exposure duration was ≥ 4 hr

Summary of Proposed AEGL Values for Tetrachloroethylene (ppm)						
Level	**10-m**	**30-m**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**
AEGL-1	86	50	35	18	12	Mild eye irritation in 6 subjects exposed to 106 ppm for 1 hr
AEGL-2	330	330	230	120	81	No-effect level for ataxia in rats following exposure to 1150 ppm PCE for 4 hours/day, 5 days/week for 2 weeks (4 hr time period used for the derivation)

Summary of Proposed AEGL Values for Tetrachloroethylene (ppm)						
AEGL-3	690	690	490	240	170	No-effect-level for lethality in mice of 2450 ppm for 4 hrs and in rats of 2445 ppm for 4 hrs

NAC/Draft 2: 10/00

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR TETRANITROMETHANE (*TNM*)



Draft 2: October, 2000
Draft 1: March, 1999

ORNL Staff Scientist: Sylvia Milanez
Chemical Manager: 10/00: Ernest Falke (3/99: Kyle Blackman)
Chemical Reviewers: George Rodgers, Richard Thomas

INTRODUCTION

Tetranitromethane (TNM) TSD was originally presented March 1999 and AEGL-1, AEGL-2, and AEGL-3 values were accepted by the AEGL/NAC.

The key changes in Draft 2 compared to Draft 1 of the TSD are:

(1) 30-480 minute AEGL values have been re-calculated using the new SOP scaling defaults: **n=3 or n=1** (go to shorter/longer times) vs. using **n=2** in 3/99 TSD.

(2) New 10-minute AEGL values have been derived: all were flat-lined from 30 minutes because the exposure time in the key studies was > 4 hours.

(3) Cancer-based AEGLs have been re-calculated using an adjustment factor of 6 instead of 2.8 to account for uncertainty in the stages of the carcinogenic process at which TNM acts.

AEGL DERIVATION FOR TETRANITROMETHANE

Key study for ALL AEGL levels: NTP (1990). Rats and mice were exposed to 2, 5, 10, 25, (and mice to 50) ppm TNM for 2 weeks (6 hours/day, 5 days/week). Use single 6-hour exposure for derivation.

2 ppm: None in rats or mice (rats possibly, unlikely lethargic) **[AEGL-1]**
5 ppm: None in rats; ↓ body weights, red lungs in mice **[AEGL-2]**
10 ppm: ↓Weight gains, lethargy in both sp.; red lungs in mice **[AEGL-3]**
25 ppm: All rats die on day 1 (pulm. edema); 8/10 mice die on day 3, 4 (red lungs)
50 ppm (mice only): All die on day 2 (reddened lungs)

Scaling: $C^n \times t = k$ (ten Berge et al., 1986); used default n=3 or n=1 to scale to <6 hours and >6 hrs, respectively; ***10-min. values flat-lined from 30-min. values***

Total Uncertainty Factor: 10
Intraspecies: 3: response to an irritant gas will not likely vary greatly among humans
Interspecies: 3: toxicity of TNM did not vary greatly between two species [AEGL-1, AEGL-3] or the most sensitive species was used [AEGL-2]; key study was repeat-exposure

TABLE 7. Summary of AEGL Values for TNM [ppm]

Level	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	0.46	0.46	0.36	0.23	0.15
AEGL-2	1.1	1.1	0.91	0.57	0.38
AEGL-3	2.3	2.3	1.8	1.1	0.75

COMPARISON OF 10/00 AND 3/99 AEGL VALUES

October 2000. **Summary of AEGL Values for TNM [ppm]**					
Level	**10 minute**	**30 minute**	**1 hour**	**4 hour**	**8 hour**
AEGL-1	0.46	0.46	0.36	0.23	0.15
AEGL-2	1.1	1.1	0.91	0.57	0.38
AEGL-3	2.3	2.3	1.8	1.1	0.75

(n=3,1)

March 1999. **Summary of AEGL Values for TNM [ppm]**					
Level	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	not derived	0.69	0.49	0.24	0.17
AEGL-2		1.7	1.2	0.61	0.43
AEGL-3		3.5	2.4	1.2	0.87

(n=2)

PRELIMINARY CANCER ASSESSMENT OF TNM:
COMPARISON OF 10/00 AND 3/99 AEGL VALUES

Key study: NTP, 1990 (103-weeks; rats and mice)
Key difference between 3/99 and 10/00 cancer assessment:

Adjustment factor for uncertainty regarding the stages of the carcinogenic process at which TNM acts: used **2.8** in 3/99; use **6** in 10/00 TSD

Adjustment factor = 2.8 (3/99)	**Adjustment factor = 6 (10/00)**
½-hour exposure = 4.9 ppm 1-hour exposure = 2.4 ppm 4-hour exposure = 0.61 ppm 8-hour exposure = 0.31 ppm	½-hour exposure = 2.3 ppm 1-hour exposure = 1.1 ppm 4-hour exposure = 0.29 ppm 8-hour exposure = 0.14 ppm

Compare the cancer-based values to AEGL-2 or AEGL-3?????

[In 3/99 TSD, compared to AEGL-3; in 10/00 TSD, compared to AEGL-2]

Summary of AEGL Values for TNM [ppm]					
Level	**10 minute**	**30 minute**	**1 hour**	**4 hour**	**8 hour**
AEGL-1	0.46	0.46	0.36	0.23	0.15
AEGL-2	1.1	1.1	0.91	0.57	0.38
AEGL-3	2.3	2.3	1.8	1.1	0.75

PERCHLOROMETHYL MERCAPTAN

- Changed "n" from default of n = 2 to default of n = 1 or 3

- Added 10-minute values:

  AEGL-1 and AEGL-2: flat-lined the 30-min value to 10 min because exposure duration was ≥ 4 hr

  AEGL-3: extrapolated to 10 min

Summary of Proposed AEGL Values for Perchloromethyl Mercaptan (ppm)

Level	10-m	30-m	1-hr	4-hr	8-hr	Endpoint
AEGL-1	0.018	0.018	0.014	0.0090	0.0060	NOAEL of 0.079 ppm for 6 hr/d, 5 d/wk for 70-72 exposure days
AEGL-2	0.044	0.044	0.035	0.022	0.015	Treatment-related mild to minimal focal subacute interstitial pneumonia and slightly increased lung weights in rats exposed to 0.58 ppm for 6 h/d, 5 d/wk for 70 days

AEGL-3	0.54	0.38	0.30	0.075	0.038	No-effect level for lethality in rats (9 ppm for 1 hour)

HYDROGEN SULFIDE

Response to COT Comments

NAC/AEGL-20
October 23-25, 2000

Chemical Manager: Steve Barbee
ORNL Staff Scientist: Cheryl Bast

AEGL-1 FOR HYDROGEN SULFIDE (ppm [mg/m^3])					
AEGL Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	0.03 [0.04]	0.03 [0.04]	0.03 [0.04]	0.03 [0.04]	0.03 [0.04]

Species: Human
Concentration: 0.09 ppm
Time: Approx. 5 hours
Endpoint: Persistent odors, Eye irritation, Throat irritation, Headache, Nausea
Reference: TNRCC, 1998

Uncertainty Factor: Intraspecies = 3

Supporting Data (State of California, 1985):

0.008 ppm x 5 = 0.04 ppm

"Data summarized by the Health Department and experiments carried out by its staff showed that the geometric mean of threshold odor concentration for hydrogen sulfide was about 0.008 ppm."

"Factors responsible for annoyance can be categorized as the unpleasant odor sensation itself, its effects on social life, and the instigation of headache or nausea. As a provisional rule, it appears that when an unpleasant odor reaches about 5 times its detection threshold concentration, then this is the median threshold for odor annoyance."

It will be noted in the TSD that in order to avoid any complaints of odor from hydrogen sulfide, concentrations need to be in the range of 5-10 ppb. The WHO (1981) document and California geyser (1960-1980) data will be cited as support.

AEGL-1 FOR HYDROGEN SULFIDE (ppm [mg/m^3])					
AEGL Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	0.25 [0.35]	0.20 [0.28]	0.17 [0.24]	0.12 [0.17]	0.11 [0.15]

Species: Human- asthmatic
Concentration: 2 ppm
Time: 30 min.
Endpoint: Headache in 3/10 and increased Raw in 2/10 subjects with no significant effects on FVC, FEV_1, or FEF
Reference: Jappinen et al., 1990

n = 4.36

Interspecies UF = none
Intraspecies UF = 10 (effects more severe than defined by AEGL-1)

Interspecies = NA. Subjects were human
Intraspecies = NA. Subjects were sensitive population (asthmatic)

Supporting Data (Bambhani et al.):

No adverse effects observed in humans exposed to H_2S while exercising to exhaustion.

5 ppm for 30 minutes
10 ppm for 15 minutes

From:

Shusterman, D. 1992. Critical review: The health significance of environmental odor pollution. Arch. Environ. Health. 47: 76-87.

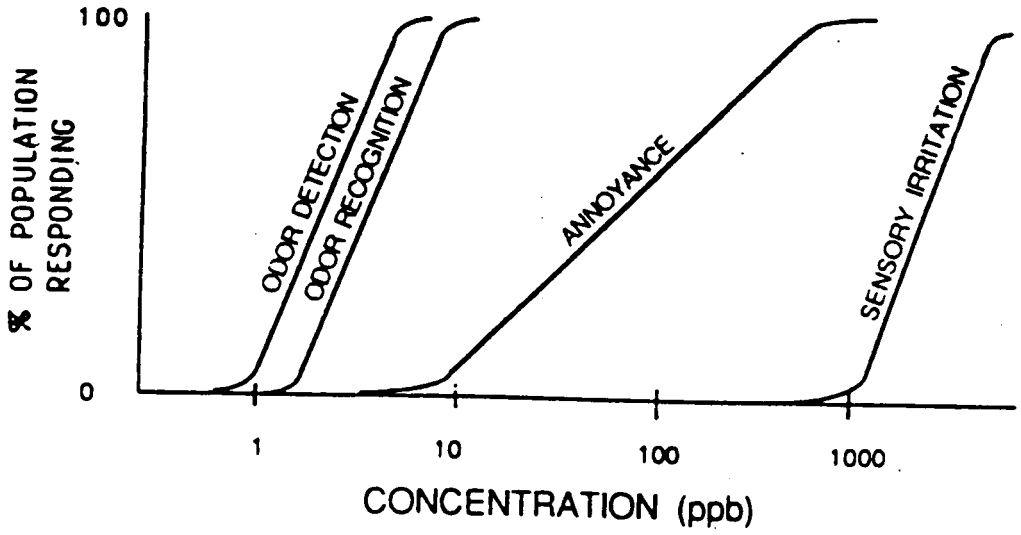


Fig. 2. Relationship of odor perception, annoyance, and sensory irritation for hydrogen sulfide. (Adapted from Flesh and Turk,[71] Amoore and Hautala,[43] and Ruth.[19])

AEGL-2 FOR HYDROGEN SULFIDE (ppm [mg/m^3])					
AEGL Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	42 [59]	32 [45]	28 [39]	20 [28]	17 [24]

Species: Rat
Concentration: 200 ppm
Time: 4 hr.
Endpoint: Perivascular edema and increased protein and LDH in lavage fluid in rats
References: Green et al., 1991; Khan et al., 1991

n = 4.36

Uncertainty Factor: 3 x 3 =10

Interspecies = 3 (Rat and mouse lethality data suggest little species variability)
Intraspecies = 3 (Well known mechanism of action)

AEGL-3 FOR HYDROGEN SULFIDE (ppm [mg/m^3])					
AEGL Level	*10-min*	30-min	1-hr	4-hr	8-hr
AEGL-3	76 [106]	60 [85]	50 [71]	37 [52]	31 [44]

Species: Rat
Concentration: 504 ppm
Time: 1 hour
Endpoint: No-effect-level for death
Reference: MacEwen and Vernot, 1972

n = 4.36

Uncertainty Factor = 3 x 3 = 10

Interspecies = 3 (Rat and mouse lethality data suggest little species variability)
Intraspecies = 3 (Well known mechanism of action)

Supporting Data (Toxigenics, 1983a):

No deaths in rats exposed to 80 ppm H_2S for 6 hr/day, 5 days/week, for 90 days.

Summary of Proposed AEGL Values for Hydrogen Sulfide						
	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1	0.25 ppm (0.35 mg/m^3)	0.20 ppm (0.28 mg/m^3)	0.17 ppm (0.24 mg/m^3)	0.12 ppm (0.17 mg/m^3)	0.11 ppm (0.15 mg/m^3)	Headache, increased Raw in asthmatic subjects (Jappinen et al., 1990)
AEGL-2	42 ppm (59 mg/m^3)	32 ppm (45 mg/m^3)	28 ppm (39 mg/m^3)	20 ppm (28 mg/m^3)	17 ppm (24 mg/m^3)	Perivascular edema and increased protein and LDH in lavage fluid in rats (Green et al., 1991; Khan et al., 1991)
AEGL-3	76 ppm (106 mg/m^3)	60 ppm (85 mg/m^3)	50 ppm (71 mg/m^3)	37 ppm (52 mg/m^3)	31 ppm (44 mg/m^3)	1-hour no-effect-level for death in rats (MacEwen and Vernot, 1972)

ACGIH TLV-TWA: 10 ppm
ACGIH TLV-STEL: 15 ppm

NIOSH IDLH: 100 ppm
NIOSH REL- 10 min. ceiling 10 ppm

OSHA PEL-TWA: 20 ppm
PEL- 10 min. peak: 50 ppm

ERPG-1: 0.1 ppm (Based on objectionable odor)
ERPG-2: 30 ppm
ERPG-3: 100 ppm

NAS EEGL- 10 min. 50 ppm
NAS EEGL- 24-hr. 10 ppm

ACUTE EXPOSURE GUIDELINE LEVELS FOR URANIUM HEXAFLUORIDE

NAC/AEGL-19
JULY 26-28, 2000

CHEMICAL MANAGER: GEORGE RUSCH
ORNL STAFF SCIENTIST: CHERYL BAST

$$UF_6 + 2H_2O \rightarrow UO_2F_2 + 4HF$$

CHEMICAL TOXICITY:

HF: Irritation, Pulmonary edema, Corrosion
(Fluoride ion may also contribute to renal toxicity)

U: Renal toxicity

RADIOLOGICAL TOXICITY:

U: Considered negligible for acute exposure to UF_6

Cancers in uranium workers are from *chronic* exposure

No carcinogenic (or noncarcinogenic) long-term effects at 38-year follow-up in two exposed workers

Lung deposition estimated at 59-74 mg UF_6

Rat LC_{50}

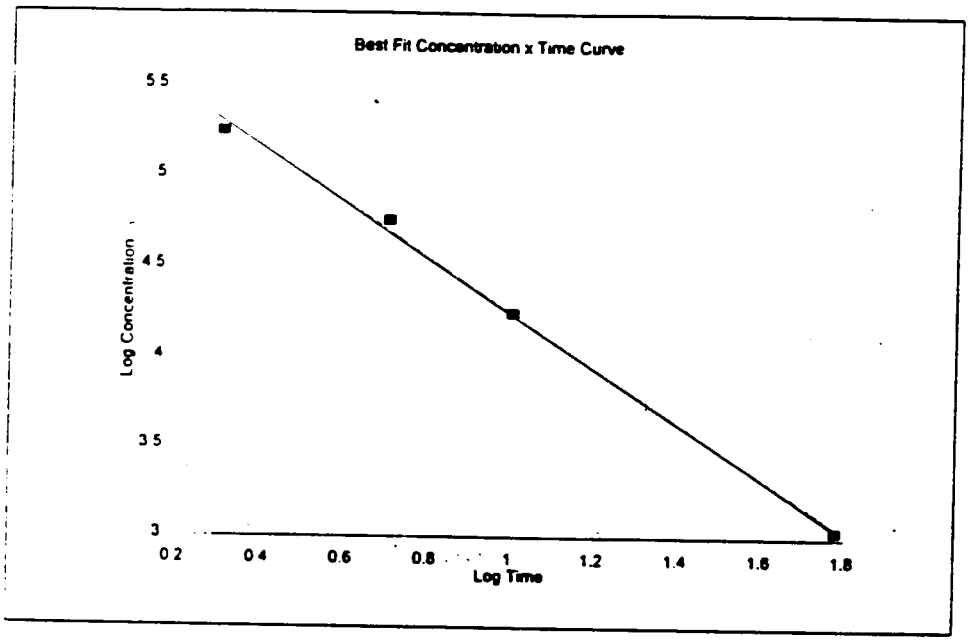
Time	Conc.	Log Time	Log Conc.
2	177515	0.3010	5.2492
5	57100	0.6990	4.7566
10	17751	1.0000	4.2492
60	1095	1.7782	3.0394

Regression Output:	
Intercept	5.7550
Slope	-1.5154
R Squared	0.9975
Correlation	-0.9988
Degrees of Freedom	2
Observations	4

n = 0.66
k = 6276

Minutes	Conc.
30	3285.15
60	1149.15
240	140.61
480	49.19

Hours	Conc.
0.5	**********
1.0	568813.67
4.0	69600.83
8.0	24346.51



TOXICOLOGIST	APPROACH	1-HR. NOEL (MG/M^3)	RENAL INJURY- 1 HR. (MG/M^3)	50% LETHALITY- 1 HR. (MG/M^3)
Dr. J. B. Hursh	"Used Leach rat and guinea pig data to correlate absorbed Uranium dose and C x T products to predict human health effects."	24.5	32	920
Dr. L. J. Leach	"Used Leach animal data and other applicable information to develop an absorbed-dose level corresponding to a predicted human health effect and to calculate a C x T product."	13.6	33.9	2272
Dr. P. E. Morrow		3.0	14.8	493
Dr. M. E. Wren		21.4	37	542
Average		15.6	29.4	1057
Range		3.0- 24.5	14.8- 37	542- 2272

CONSENSUS	9.6	18.5	862

JUST & ELMER, 1984; JUST, 1984

AEGL-1 FOR URANIUM HEXAFLUORIDE (mg/m^3)					
AEGL Level	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1	**11**	**4.3**	**1.5**	**0.18**	**0.064**

Species: Human
Concentration: 1.5 mg/m^3
Time: 1 hour
Endpoint: NOEL in 100 offsite residents
Reference: NRC, 1986

n = 0.66

Uncertainty Factor = none

Interspecies = NA. Subjects were human
Intraspecies = NA. Population of 100 residents was assumed to include sensitive individuals

Modifying Factor = 2: Applied to 10-min. value only to account for deficient data base for AEGL-1 effects at short durations

Supporting Data (Just and Elmer, 1984; Just, 1984):

Estimated 1-hour human NOEL: 9.6 mg/m^3
UF = 3 for sensitive individuals
MF = 2 for 10-minute value only

10-min	*30-min*	*1-hr*	*4-hr*	*8-hr*
23 mg/m^3	*8.9 mg/m^3*	*3.1 mg/m^3*	*0.39 mg/m^3*	*0.13 mg/m^3*

AEGL-2 FOR URANIUM HEXAFLUORIDE (mg/m^3)					
AEGL Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	100	19.2	6.8	0.82	0.28

Species: Dog
Concentration: 192 mg/m^3
Time: 30 minutes
Endpoint: Renal tubular pathology in dogs
References: Morrow et al., 1992

n = 0.66

Uncertainty Factor: 3 x 3 =10

Interspecies = 3 (Reversible pathology is mild AEGL-2 endpoint)
Intraspecies = 3 (Pathology not expected to vary greatly)

AEGL-3 FOR URANIUM HEXAFLUORIDE (mg/m^3)					
AEGL Level	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-3	**550**	**104**	**36**	**4.4**	**1.6**

Species: Rat
Concentration: 365 mg/m^3
Time: 1 hour
Endpoint: Estimated No-effect-level for death (1/3 LC_{50} of 1095 mg/m^3)
Reference: Leach et al., 1984

n = 0.66

Uncertainty Factor = 3 x 3 = 10

Interspecies = 3 (Moderately sensitive species, but poor concentration-response)
Intraspecies = 3
(Lethality is likely due to severe irritation/pulmonary edema from HF hydrolysis product and is not expected to vary greatly among individuals)

Supporting Data (Leach et al., 1984):

10-min. Rat LC_{50} = 17751 mg/m^3

Estimated NOEL for death (1/3 LC_{50} of 17751 mg/m^3) = 5971 mg/m^3

UF = 3 x 3

Supporting 10-minute AEGL-3 value = 592 mg/m^3

Summary of Proposed AEGL Values for Uranium Hexafluoride						
Classification	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1 (Nondisabling)	11 mg/m^3	4.3 mg/m^3	1.5 mg/m^3	0.18 mg/m^3	0.064 mg/m^3	NOEL in humans (NRC, 1986)
AEGL-2 (Disabling)	100 mg/m^3	19.2 mg/m^3	6.8 mg/m^3	0.82 mg/m^3	0.28 mg/m^3	Renal tubular pathology in dogs (Morrow et al., 1982)
AEGL-3 (Lethality)	550 mg/m^3	104 mg/m^3	36 mg/m^3	4.4 mg/m^3	1.6 mg/m^3	Estimated 1-hr NOEL for death in the rat (Leach et al., 1984)

ACGIH TLV-TWA (ACGIH, 1999): 0.2 mg/m^3 (soluble compounds as U) (0.30 mg/m^3 UF_6)

ACGIH TLV-STEL (ACGIH, 1999): 0.6 mg/m^3 (soluble compounds as U) (0.89 mg/m^3 UF_6)

NIOSH IDLH (NIOSH, 1997): 10 mg/m^3 (soluble compounds as U) (14.8 mg/m^3 UF_6)

NIOSH TWA (NIOSH, 1997): 0.05 mg/m^3 (soluble compounds as U) (0.07 mg/m^3 UF_6)

OSHA TWA (NIOSH, 1997): 0.05 mg/m^3 (soluble compounds as U) (0.07 mg/m^3 UF_6)

ERPG, 1-hour (AIHA, 1991):

- **ERPG-1:** 5 mg/m^3 UF_6
- **ERPG-2:** 15 mg/m^3 UF_6
- **ERPG-3:** 30 mg/m^3 UF_6

Nerve Agent AEGLs

- Army applications and needs are only part of the issue....
- There are 'existing values' but they have lost meaning and credibility – even within Army
- There are 3 general levels of data (Classified, Unclassified-Limited Distribution, Unclassified-Unlimited Distribution) which even together leaves gaps; however: Classified data provided no information pertinent to AEGLs beyond that available in Unclassified reports
- Detection Capabilities are not an issue – capabilities do exist
- Some of the same technical issues are being discussed by other groups....(CDC)

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

2

Nerve Agent Issues Analysis
An Overview

NAC/AEGL-19
U.S. Dept. of Transportation
DOT Headquarters/Nassif Bldg., Rms 6332-6336
400 7th Street, SW
Washington, D.C

October 23-25, 2000

Nerve Agent Issues Analysis

- Nerve Agent Toxicity Endpoints
  - Local effects
  - Systemic effects, OPIDN, and long-term sequelae
  - Appropriate test species
  - OPP weight-of-evidence approach

- Cholinesterases (ChE) & Nerve Agents
  - Types/functions of ChE
  - 'Aging' of enzyme/agent complex

- Blood ChE Activity Inhibition

Nerve Agents Toxicity Endpoints

- **Local Effects of Nerve Agents**
  - **local effects: miosis, rhinorrhea**

- **Systemic and Long-term Effects of Nerve Agents**
  - **overt toxic effects (tremors/convulsions, respiratory failure)**
  - **OPIDN/Intermediate Syndrome**
  - **Long-term sequelae of acute exposure**
    - **EEG alterations/behavioral effects**
    - **unlikely with asymptomatic exposures**

- **Appropriate Test Species**
  - **Rat: OPPTS 870.6200 Neurotoxicity Screening Battery**

Nerve Agents Toxicity Endpoints

- **Weight-of-Evidence Approach (OPP Science Policy; U.S. EPA, 2000)**
  - **clinical signs, physiological/behavioral effects in humans and animals**
  - **symptoms in humans**
  - **CNS ChE inhibition**
  - **peripheral NS AChE inhibition**
  - **RBC AChE inhibition**
  - **plasma ChE inhibition**

http://www.epa.gov/pesticides/trac/science/cholin.pdf

Types of Cholinesterases

- Acetylcholinesterase (AChE)
  - cholinergic neurons of peripheral & central nervous system
  - terminates action of ACh

- Butyrylcholinesterase (BuChE)
  - structurally similar to ACh but slower activity
  - encoded on different gene
  - plasma and tissues

- Alternate terminology
  - Plasma cholinesterase
    - BuChE and AChE
    - Species variability in ratio of above; humans mostly BuChE
  - Red blood cell (erythrocyte) cholinesterase
    - AChE
  - Pseudocholinesterase
    - non-specific cholinesterase
    - plasma, various tissues
  - Brain cholinesterase
    - AChE

ChE Inhibition

- **Biomarker of Exposure**
  - **ChE inhibition in blood is acceptable surrogate for peripheral and central NS AChE inhibition (U.S. EPA, 2000; Young et al., 1999)**
  - **RBC ChE preferred over plasma ChE**
  - **Cal-EPA/Dept. Pesticide Reg. (1998)**
    - **RBC AChE below 80% of baseline: workplace corrections**
    - **RBC AChE below 70% or plasma ChE below 60% of baseline: remove from OPs and carbamates**

- **Biomarker of Effect**
  - **Plasma ChE inhibition NOT appropriate as an effect**
  - **"Plasma ChE more labile and is thus less reliable in reflecting actual enzyme activity depression at neuro-effector sites"**
    Cal-EPA Guidelines for Physicians

ChE Inhibition

- **Aging of Enzyme-inhibitor Complex**
  - **resistance to reactivation; variable among nerve agents**

Aging Half-time of Nerve Agents

Nerve Agent	Aging Half-time
GA (human, in vitro)	>13.3 hrs
GB (human, in vitro)	3-5 hrs
GD (human, in vitro)	2-6 min
GF (human, in vitro)	7.5-40 hrs
VX (human, in vitro)	48 hrs

Dunn, M.A, Hackley, B.E., Jr. and Sidell, F.R. (1997). Pretreatment for nerve agent exposure. In: Sidell et al. (1997). Medical Aspects of Chemical and Biological Warfare Agents, p 183.

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

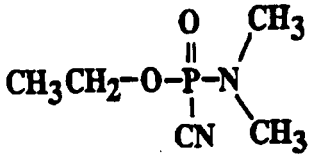
NAC/AEGL-19
U.S. Dept. of Transportation
DOT Headquarters/Nassif Bldg., Rms 6332-6336
400 7th Street, SW
Washington, D.C.

October 23-25, 2000

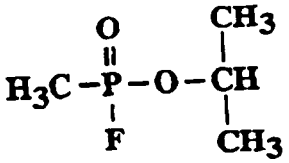
G-series Nerve Agents: Identification

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

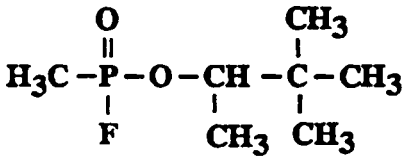
- Agent GA; tabun; Dimethylamidocyanophosphate; $C_5H_{11}N_2O_2P$; CAS. No. 77-81-6; contains cyanide group



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

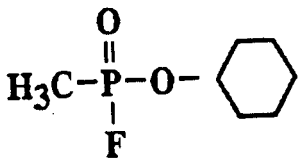


- Agent GD; soman; Pinacolyl methylphosphonofluoridate; $C_7H_{16}FO_2P$; CAS No. 96-64-0; contains fluoride group



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; AChE accumulation produces continuous post-synaptic action potentials; adverse PNS and CNS cholinergic effects + end organ stimulation

- no chronic neurological disorders after asymptomatic exposures

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

- 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; possible early indicator of Intermediate Syndrome development from similar NM change (non-depolarizing NM block)

- 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; local effect
NOSE:	runny (rhinorrhea); local effect
RESP:	"Tightness in chest," bronchoconstriction, secretions in airways, cough, breathing difficulty

Pupillary muscles very sensitive to vapor contact; miosis early local sign of nerve agent vapor exposure

MODERATE Effects

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

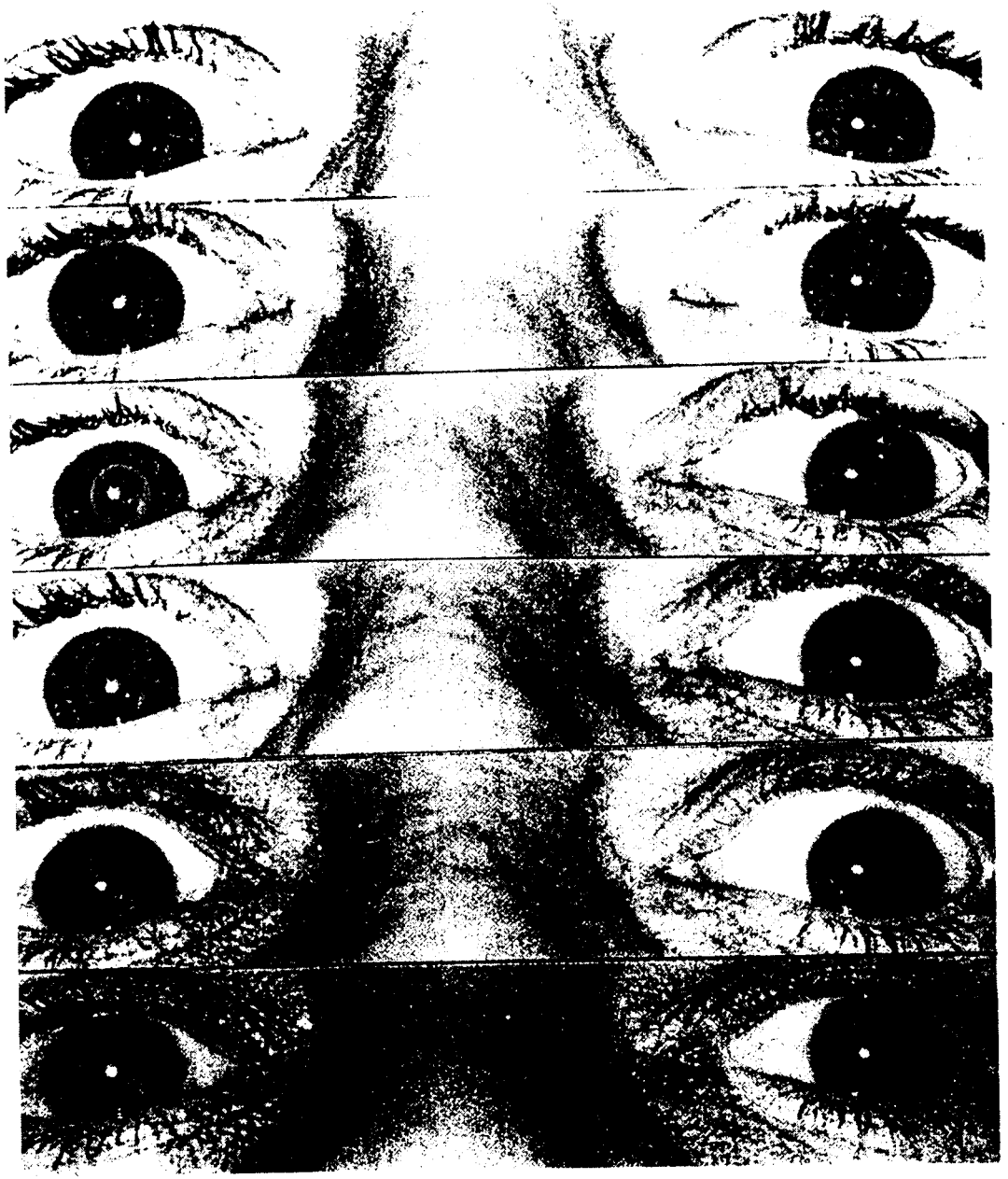


Fig. 5-4. This man was accidentally exposed to an unknown amount of nerve agent vapor. The series of photographs shows his eyes gradually recovering their ability to dilate. All photographs were taken with an electronic flash (which is too fast for the pupil to react) after the subject had been sitting 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 with eventual loss of muscle tone and capability to function (paralysis); cessation of breathing; systemic effects
RESP:	very copious secretions ("dry-land drowning")
ALL:	loss of consciousness, coma, death; systemic effects

Respiratory failure is chief cause of death following severe exposure; largely due to systemic effect cascade.

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

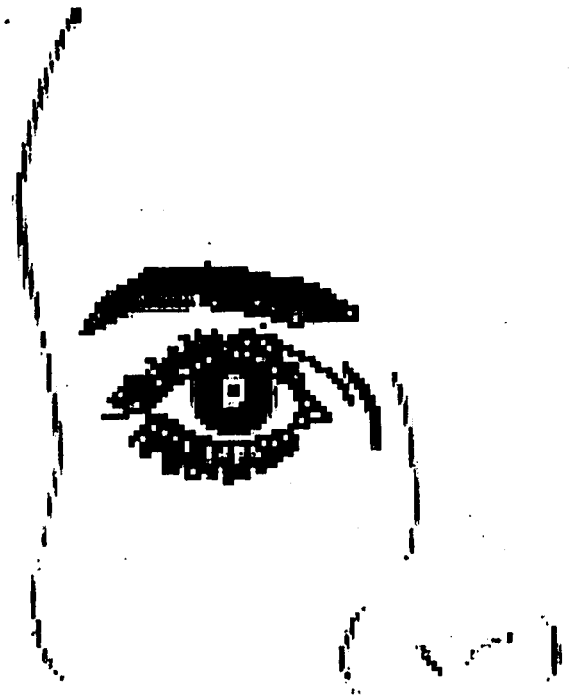
- Nonlethal Toxicity

  - 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.)

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 (0.7 mg-min/m^3; transient chest tightness, no miosis); 1.6 mg/m^3 for 2 min (3.2 mg-min/m^3; chest tightness, miosis); 3.2 mg-min/m^3<exposures <30 mg-min/m^3 (chest tightness, miosis + impaired vision; exposures>30 mg-min/m^3 (severe eye pain, headaches, nausea, vomiting) (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

DATA COMPLETENESS

- Available for multiple spp., including human experimental data (non-lethal effects)

- Non-lethal and lethal endpoints documented
  - endpoints possess exposure-response data

- Mechanism of toxicity known; all endpoints observed represent response continuum to anticholinesterase exposure (consistent with *OPP Science Policy*)

- The *n* value for agent GB derived from time-specific **experimental data** for all AEGL-pertinent intervals except 8 hrs (seven exposure times; 3, 10, 30, 60, 90, 240, 360 min)
  - nerve agent-specific and definitive endpoints (LC_{01} and LC_{50})
  - *n* value not based on methodological assumptions; is not a empirical default generated from non-agent specific data

- No uncertainties regarding reproductive and developmental effects

- No uncertainties regarding carcinogenicity

A WORD ABOUT
THE MILITARY LITERATURE

CLASSIFICATION

- All literature used in the TSDs is UNCLASSIFIED (not secret at any level, not confidential), including critical studies
  - The Reutter and Wade (1994) citation is to an unclassified summary table from the Reutter and Wade (1984) secret report
  - Document developer served on Army Science Board panel that reviewed the Reutter and Wade (1994) report and source documents; ASB Panel made unclassified brief to Ass't Sec Army in Dec 1994; unclassified report released by ASB
  - **Classified documents relevant to AEGL assessment of these agents contain no significant data that are not also found in unclassified reports**

A WORD ABOUT
THE MILITARY LITERATURE

CLASSIFICATION (cont'd)

- Reutter and Wade (1994) examined by Nat'l Res Council COT Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents chaired by Loren Koller
    - unclassified report of Subcommittee findings published 1997
    - report examined classified literature and performed comparisons; findings unclassified and published by National Academies Press (NRC 1997)
- TSD itself determined to be UNCLASSIFIED following examination by Intelligence and Security Office of the US Army Soldier and Biological Chemical Command, July 2000

ANOTHER WORD ABOUT THE MILITARY LITERATURE

LIMITED DISTRIBUTION

- Separate issue from "classification"

- Restricted distribution due to treaty restrictions on data access with Allies, concerns *re* distribution of engineering information characterizing agent dissemination/vapor generation, etc.

- To ensure public access to pertinent toxicity data originating from "limited distribution" materials, USACHPPM incorporated these data into nerve agent TSDs
  - If additional details desired, USACHPPM will assist any requestor on a 1-to-1 basis

  - POC is Ms. Veronique Hauschild, USACHPPM, Environmental Health Engineering (Ph. 410-436-5213; email: Veronique.Hauschild@apg.amedd.army.mil)

- TSD itself determined to be "cleared and approved for public access" by Intelligence and Security Office of the US Army Soldier and Biological Chemical Command, July 2000

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

ANALYTICAL APPROACH; AEGL-3

- 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; in press)

- 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
    - LC_{50} 18.10 mg/m^3 for 10 min
      8.51 mg/m^3 for 30 min
      6.39 mg/m^3 for 60 min
      3.03 mg/m^3 for 4 hr
      2.63 mg/m^3 for 6 hr

    - LC_{01} 11.54 mg/m^3 for 10 min
      5.84 mg/m^3 for 30 min
      4.01 mg/m^3 for 60 min
      2.09 mg/m^3 for 4 hr
      1.76 mg/m^3 for 6 hr

ANALYTICAL APPROACH; AEGL-3 (cont'd)

- Mioduszewski et al (in press) robust data set that supports regression determination of *n*
  - LC_{50}; $n = 1.88$; $r^2 = 0.9927$
  - LC_{01}; $n = 1.93$; $r^2 = 0.9948$

- $n = 2$ (derived from regression on experimental data, as above) for GB; used to extrapolate from 6 hr LC_{01} to derive 8 hr LC_{01} estimate ; time-scaling not necessary for estimating AEGL-3 values from 10 min to 4 hr

- Mioduszewski et al (in press) reports female rats as more sensitive to lethal endpoint, statistical significance at $p < 0.001$
  - in keeping with other rat lethality data (Callaway and Blackburn 1954) and unpublished non-lethal effects data of Mioduszewski et al for SD rats (miosis occurs at lower concentration in females); gender difference not appear to be endpoint-specific

  - Follows OPPTS 870.6200 *Neurotoxicity Screening Battery* protocol

- Interspecies UF = 10 (rat data)
  Intraspecies UF = 3 (selection of data characterizing most sensitive gender [females] considered to provide some additional protection for sensitive populations)

ANALYTICAL APPROACH (AEGL-2)

- 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
  - "Controls" = pre-exposure baseline readings for each subject; >15 mos., individual subject SFEMG readings not significantly different from individual subject baseline

ANALYTICAL APPROACH (AEGL-2) (cont'd)

- respiratory effects resolved w/in minutes; ocular effects resolved w/in 48 hrs

- authors find SFEMG changes to be reversible and subclinical, and possible early indicator/precursor of "non-depolarising neuromuscular block" found associated with "Intermediate Syndrome" paralysis in severe OP pesticide poisoning cases; protective definition of AEGL-2 effect

- Interspecies UF = 1 (human data)
  Intraspecies UF = 10 (sensitive populations)

- $n = 2$ (derived from experimental data of Mioduszewski et al, in press) for GB and same mechanism of toxicity

ANALYTICAL APPROACH; AEGL-1

- 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) symptoms of eye pain, headache, cramps, etc.

- Miosis and rhinorrhea NOT self-reported; miosis quantified as max. decrease in pupil diameter with modified fixed-focus prism telescope; rhinorrhea observed by clinicians

ANALYTICAL APPROACH; AEGL-1 (cont'd)

- Interspecies UF = 1 (human data)
  Intraspecies UF = 10 (sensitive populations)

- $n = 2$ (derived from experimental data of Mioduszewski et al, in press) for GB and same mechanism of toxicity

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 $mg\text{-}min/m^3$.

References

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

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.

Mioduszewski, R.J., et. al. 2000. Estimating the probability of sarin vapor toxicity in rats as a function of exposure concentration and duration. Presented at the 39th Annual Meeting of the Society of Toxicology, March, 2000, Philadelphia, PA. Toxicologist 54(1): 18 (# 84).

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).

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)

ANALYTICAL APPROACH; AGENTS GA, GD, GF

- Necessitates development of AEGL values for other G-series agents by comparative method from that of agent GB

  - **For AEGL-1 and AEGL-2** effects, GB and GA considered equipotent; GD and GF each considered MORE potent than GB by factor of 2 for miosis (review by Mioduszewski et al., 1998)

    GB mg/m^3 = GA mg/m^3
    GD mg/m^3 = (GB mg/m^3) ÷ 2
    GF mg/m^3 = (GB mg/m^3) ÷ 2

  - **For AEGL-3** effects, GB, GD and GF considered equipotent; GA considered LESS potent than GB by a factor of 2 (review by Mioduszewski et al., 1998). Assumption for agent GD lethal potency supported by analysis of rat lethality data of Aas et al. (1985) for GD dynamic chamber exposures

    GB mg/m^3 = GD mg/m^3 = GF mg/m^3
    GA mg/m^3 = (GB mg/m^3) × 2

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-disablin g)	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 (Disabli ng)	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-disablin g)	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 (Disabli ng)	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]

SUMMARY OF PROPOSED AEGL VALUES FOR AGENTS GA, GD and GF [ppm (mg/m^3)] (cont'd)							
Agent	**Class.**	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Ref.)**
GF	AEGL-1 (Non-disabling)	0.00049 ppm (0.0035 mg/m^3)	0.00028 ppm (0.002 mg/m^3)	0.0002 ppm (0.0014 mg/m^3)	0.0001 ppm (0.0007 mg/m^3)	0.00007 ppm (0.0005 mg/m^3)	Based on relative potency[c]
	AEGL-2 (Disabling)	0.0062 ppm (0.044 mg/m^3)	0.0035 ppm (0.025 mg/m^3)	0.0024 ppm (0.018 mg/m^3)	0.0013 ppm (0.0085 mg/m^3)	0.0008 ppm (0.0065 mg/m^3)	Based on relative potency[c]
	AEGL-3 (Lethal)	0.053 ppm (0.38 mg/m^3)	0.027 ppm (0.19 mg/m^3)	0.018 ppm (0.13 mg/m^3)	0.0098 ppm (0.070 mg/m^3)	0.0071 ppm (0.051 mg/m^3)	Based on relative potency[d]

[a] Based on relative potency equal to that of agent GB (see Section 4.3 and Mioduszewski et. al., 1998)
[b] Agent GA is considered approximately one-half as potent as GB in causing lethality; thus, AEGL-3 values for GA are estimated by multiplying each time-specific AEGL-3 value for agent GB by a factor of 2 (see Section 4.3 and Mioduszewski et. al., 1998)
[c] Agents GD and GF are considered approximately twice as potent as agents GA and GB for causing miosis, and equipotent to each other. Thus, AEGL-1 and AEGL-2 values are estimated by multiplying each time-specific AEGL-1 or AEGL-2 value for agent GB by a factor of 0.5 (see Section 4.3 and Mioduszewski et. al., 1998)
[d] Based on a relative potency for lethality of GD = GF = GB and lethality data of Aas et al. (1985) (which provides a 10-min AEGL-3 estimate of 0.34 mg/m^3 and a 30-min AEGL-3 value of 0.11 mg/m^3) (see Section 4.3, Appendix A and Mioduszewski et. al., 1998)

References

Aas, P., Sterri, S.H., Hjermstad, H.P., Fonnum, F. 1985. A method for generating toxic vapors of soman: Toxicity of soman by inhalation in rats. Toxicol. Appl. Pharmacol. 80:437-445.

Mioduszewski, R.J., Reutter, S.H., Thomson, S.A., Miller, L.L., Olajos, E.J. 1998. Evaluation of airborne exposure limits for G-agents: Occupational and general population exposure criteria. ERDEC-TR-489. U.S. Department of the Army, Edgewood Research, Development and Engineering Center, U.S. Army Chemical and Biological Defense Command, Aberdeen Proving Ground, MD

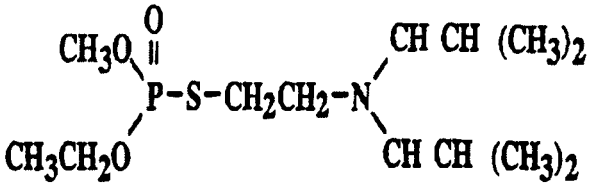
NERVE AGENT VX AEGLs
(CAS No. 50782-69-9)

NAC/AEGL-19
U.S. Dept. of Transportation
DOT Headquarters/Nassif Bldg., Rms 6332-6336
400 7th Street, SW
Washington, D.C.

October 23-25, 2000

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

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

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; local effect
NOSE:	runny (rhinorrhea); local effect
RESP:	"Tightness in chest," bronchoconstriction, secretions in airways, cough, breathing difficulty

Pupillary muscles very sensitive to vapor contact; miosis early local sign of nerve agent vapor exposure

MODERATE Effects

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

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; systemic effects
RESP:	very copious secretions ("dry-land drowning")
ALL:	loss of consciousness, coma, death; systemic effects

Respiratory failure is primary cause of death following severe exposure; largely due to systemic effect cascade.

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; **noncredible study**

DATA SUMMARY
VX NERVE AGENT
Human Data (Non-lethal Toxicity, cont'd)

- Bramwell et al (1963) study considered flawed, noncredible source
  - actual concentration to which subjects exposed in breathing zone could not be determined ("tunnel" protocol)
  - both C and t were varied (no replicate Cts)
  - Benzene used to help disperse agent VX in airstream to which subjects exposed (Bramwell not address potential effect of carrier solvent on agent absorption by subject)
  - Safe to say that human subjects "not in a rigorously controlled atmosphere" (Reutter et al 2000)
  - Surgeon General's Review panel convened by CDC in Atlanta (Aug 2000) considered Bramwell data "very suspect" and not recommended for use in deriving exposure estimates; include for completeness
- AEGL data analysis necessarily augmented by studies of human intravenous, oral, and percutaneous VX exposure

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, rats and guinea pigs over period of 2 weeks (6-hr/da, 5 da/wk) indicate wide range in species sensitivity (Crook, et al., 1983); **nonverifiable**

- 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); **nonverifiable**

  - 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
Animal Data (cont'd)

- Crook et al (1983) study considered nonverifiable (by Crook et al !)
  - not possible to verify agent VX concentrations due to
    - sampling technique employed
    - possible chlorine bleach contamination of sampling/detection apparatus
  - VX tends to "stick" to interior of equipment feed lines
  - Bleach is decon solution; degrades agent (instrument reading < actual exposure concentration)
  - Crook et al reported that VX concentrations "may vary by order of magnitude" from measured amounts
  - Surgeon General's Review panel convened by CDC in Atlanta (Aug 2000) considered Crook et al data "very suspect" and not recommended for use in deriving exposure estimates; include for completeness

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; evaluation by NRC 1997; McNamara et al 1973; review by Reutter et al. 2000)

RELATIVE POTENCY OF AGENT VX TO AGENT GB

- Direct vapor exposure, experimental data from Callaway and Dirnhuber (1971; *Estimation of the Concentrations of Nerve Agent Vapour Required to Produce Measured Degrees of Miosis in Rabbit and Human Eyes,* Porton Technical Paper #64)
  - Definitive endpoint of "90% miosis;" 90% decrement in pupil area from original baseline area of untreated pupil
  - eye exposure times range from 10 min to 5 hrs
  - Cumulative exposure to produce 90% miosis in white rabbits

    GB: 2.71 mg-min/m^3 (95% CI = 1.84 to 4.00)

    VX: 0.23 mg-min/m^3 (95% CI = 0.12 to 0.45)

    GB/VX = 11.8

RELATIVE POTENCY OF AGENT VX TO AGENT GB (cont'd)

- Evaluation performed by COT Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents (NRC 1997; *Review of Acute Human-Toxicity Estimates for Selected Chemical-Warfare Agents*) comparing human ECt_{50} "mild effects" (miosis and rhinorrhea) for vapor exposure to GB and VX

  - Subcommittee recommended "mild effects" ECt_{50}

    GB: 0.5 mg-min/m^3 "should be raised"

    VX: 0.09 mg-min/m^3 "is scientifically valid"

    GB/VX = >0.5/0.09 = >5.6

RELATIVE POTENCY OF AGENT VX TO AGENT GB (cont'd)

- Data from human IV studies of Kimura et al (1960); calculational model based on ChE activity recovery (McNamara et al 1973)
  - Considered applicable to direct eye effects + systemic effects through resp. tract absorption following VX vapor inhalation
- Analysis indicated
  - VX is 25 times potent than GB for miosis induction
  - Recovery from VX effects is 4 times faster than for GB (spontaneous enzyme recovery in absence of antidote; VX "ages" more slowly [days] than GB [hrs]
  - ∴ Allowable VX concentration is

    4/25 = 0.16 (times GB concentration)
  - Recommended ratio is 1/10 (or, 0.10 times GB concentration) for greater margin of safety

ANALYTICAL APPROACH FOR VX (AEGL-1)

- 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

  - Derivation also performed for $n = 2$

  - Interspecies UF = 1 (human data)
    Intraspecies UF = 10 (sensitive populations)

ANALYTICAL APPROACH FOR VX (AEGL-2)

- 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 as for AEGL-1

    - Interspecies UF = 1 (human data)
      Intraspecies UF = 10 (sensitive populations)

ANALYTICAL APPROACH FOR VX (AEGL-3)

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

- Interspecies UF = 10 (rat data for agent GB)
  Intraspecies UF = 3 (selection of agent GB data characterizing most sensitive gender [female rats] is considered to provide some additional protection for sensitive populations)

  - n = 1 for estimating from 6 hr time period (max exposure duration experimentally tested in Mioduszewski et al., 2000; in press) to 8 hr (also calculated for n = 2)

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 $mg\text{-}min/m^3$ (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 $mg\text{-}min/m^3$.

References

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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.

Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B., Muse, W., Crosier, R., Sommerville, D. 2000. Estimating the probability of sarin vapor toxicity in rats as a function of exposure concentration and duration. Presented at the 39th Annual Meeting of the Society of Toxicology, March, 2000, Philadelphia, PA. Toxicologist 54(1): 18 (# 84).

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).

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 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

NAC/AEGL Meeting 19: 10/23-25/2000

Chemical: ALLYL ALCOHOL (10 MIN) **CAS Reg. No.:** 107-18-6

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A	Glenn Leach			
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				Robert Snyder			
Larry Gephart				Thomas Sobotka	A	A	A
John Hinz				Kenneth Still			
Jim Holler				Judy Strickland			
Thomas C. Hornshaw				Richard Thomas			
Nancy Kim							
Loren Koller				Thomas Tuccinardi/ Doan Hansen			
				TALLY	UNANIMOUS		TO ACCEPT

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	1.8 ,( )	1.8 ,( )	1.8 ,( )	1.8 ,( )	1.8 ,( )
AEGL 2	9.6 ,( )	9.6 ,( )	7.7 ,( )	4.8 ,( )	3.5 ,( )
AEGL 3	36 ,( )	25 ,( )	20 ,( )	10 ,( )	7.1 ,( )

AEGL 1 Motion: George Rodgers **Second:** Bob Benson

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

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

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 10/23/00

NAC/AEGL Meeting 19: 10/23-25/2000

Chemical: BORON TRICHLORIDE (10 MIN) **CAS Reg. No.:** 10294-45-7

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A	Glenn Leach			
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				Robert Snyder			
Larry Gephart				Thomas Sobotka	A	A	A
John Hinz				Kenneth Still			
Jim Holler				Judy Strickland			
Thomas C. Hornshaw				Richard Thomas			
Nancy Kim							
Loren Koller				Thomas Tuccinardi/ Doan Hansen			
				TALLY	Unanimous to accept		

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.60 ,( )	0.60 ,( )	0.60 ,( )	0.60 ,( )	0.60 ,( )
AEGL 2	34 ,( )	14 ,( )	7.3 ,( )	1.8 ,( )	0.90 ,( )
AEGL 3	170 ,( )	59 ,( )	28 ,( )	7.1 ,( )	3.5 ,( )

AEGL 1 Motion: G. Rodgers **Second:** S. Barbee

AEGL 2 Motion: ↓ **Second:** ↓

AEGL 3 Motion: ↓ **Second:** ↓

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 10/23/00

NAC/AEGL Meeting 19: 10/23-25/2000

Chemical: CHLOROMETHYL METHYL ETHER (10 MIN) **CAS Reg. No.:** 107-30-2

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A	Glenn Leach	Y		
Steven Barbee	A			Mark A. McClanahan	Y		
Lynn Beasley	A			John S. Morawetz	Y		
David Belluck	P			Richard W. Niemeier	P		
Robert Benson	Y			Marinelle Payton	A		
Jonathan Borak	P			Zarena Post	A		
William Bress	P			George Rodgers	Y		
George Cushmac	Y			George Rusch, Chair	Y		
Ernest Falke	Y			Robert Snyder	P		
Larry Gephart	Y			Thomas Sobotka	A	A	A
John Hinz	A			Kenneth Still	Y		
Jim Holler	Y			Judy Strickland	A		
Thomas C. Hornshaw	Y			Richard Thomas	Y		
Nancy Kim	Y						
Loren Koller	A			Thomas Tuccinardi/ Doan Hansen	A A		
				TALLY	Unanimous except for John Morawetz (17 VS. 1 NO) Yes		

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR ,( )	NR ,( )	NR ,( )	NR ,( )	NR ,( )
AEGL 2	0.076 ,( )	0.076 ,( )	0.061 ,( )	0.038 ,( )	0.025 ,( )
AEGL 3	1.2 ,( )	1.2 ,( )	0.94 ,( )	0.59 ,( )	0.43 ,( )

NOTE: Bob Benson also moved to show 10^{-4}, 10^{-5} & 10^{-6} Cancer Values in appendix
Second by Ernie 14/14 VOTE YES.

AEGL 1 Motion: Bob Benson **Second:** Richard Thomas

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

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

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 10/23/00

NAC/AEGL Meeting 19: 10/23-25/2000

Chemical: DIBORANE (10 MIN) **CAS Reg. No.:** 19287-45-7

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A	Glenn Leach	Y	Y	Y
Steven Barbee	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
Lynn Beasley	A	A	A	John S. Morawetz	Y	Y	Y
David Belluck	Y	Y	Y	Richard W. Niemeier	Y	Y	Y
Robert Benson	Y	N	N	Marinelle Payton	A	A	A
Jonathan Borak	Y	Y	Y	Zarena Post	A	A	A
William Bress	Y	N	Y	George Rodgers	Y	Y	Y
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	Y	Y	Robert Snyder	Y	Y	Y
Larry Gephart	Y	?	Y	Thomas Sobotka	A	A	A
John Hinz	A	A	A	Kenneth Still	Y	Y	Y
Jim Holler	Y	Y	Y	Judy Strickland	A	A	A
Thomas C. Hornshaw	Y	Y	Y	Richard Thomas	Y	Y	Y
Nancy Kim	Y	Y	Y				
Loren Koller	A	A	A	Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
				TALLY	20/20	17/19	19/20

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR ,( )	NR ,( )	NR ,( )	NR ,( )	NR ,( )
AEGL 2	6.0 (20) ,( )	,( )	,( )	,( )	,( )
AEGL 3	7.3 ,( )	,( )	,( )	,( )	,( )

NR = Not Recommended

AEGL 1 Motion: R. Thomas **Second:** J. Holler

AEGL 2 Motion: ↓ **Second:** ↓

AEGL 3 Motion: ↓ **Second:** ↓

Approved by Chair: [signature] **DFO:** [signature] **Date:** 10/23/00

NAC/AEGL Meeting 19: 10/23-25/2000

Chemical: FURAN (10 MIN) **CAS Reg. No.:** 110-00-9

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A	Glenn Leach			
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				Robert Snyder			
Larry Gephart				Thomas Sobotka	A	A	A
John Hinz				Kenneth Still			
Jim Holler				Judy Strickland			
Thomas C. Hornshaw				Richard Thomas			
Nancy Kim							
Loren Koller				Thomas Tuccinardi/ Doan Hansen			
				TALLY	Unanimous		to accept

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	10 ,( )	10 ,( )	10 ,( )	10 ,( )	10 ,( )
AEGL 2	18 ,( )	13 ,( )	10 ,( )	2.5 ,( )	1.3 ,( )
AEGL 3	52 ,( )	46 ,( )	29 ,( )	7.1 ,( )	3.6 ,( )

10 = duration/severity data

AEGL 1 Motion: McClanahan **Second:** Belluck

AEGL 2 Motion: ↓ **Second:** ↓

AEGL 3 Motion: ↓ **Second:** ↓

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 10/23/00

NAC/AEGL Meeting 19: 10/23-25/2000

Chemical: TETRACHLORO ETHYLENE (10 MIN) **CAS Reg. No.:** 127-18-4

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A	Glenn Leach	Y	Y	Y
Steven Barbee	Y	Y	Y	Mark A. McClanahan	N	N	N
Lynn Beasley	A	A	A	John S. Morawetz	Y	N	N
David Belluck	Y	Y	Y	Richard W. Niemeier	Y	N	Y
Robert Benson	Y	Y	Y	Marinelle Payton	A	A	A
Jonathan Borak	Y	Y	Y	Zarena Post	A	A	A
William Bress	Y	Y	Y	George Rodgers	Y	N	Y
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	Y	Y	Robert Snyder	Y	Y	Y
Larry Gephart	Y	Y	P	Thomas Sobotka	A	A	A
John Hinz	A	A	A	Kenneth Still	Y	Y	Y
Jim Holler	Y	Y	Y	Judy Strickland	A	A	A
Thomas C. Hornshaw	Y	Y	Y	Richard Thomas	Y	Y	Y
Nancy Kim	Y	Y	P				
Loren Koller	A	A	A	Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
				TALLY	19/20	16/20	16/18

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	50 ,( )	,( )	,( )	,( )	,( )
AEGL 2	330 ,( )	,( )	,( )	,( )	,( )
AEGL 3	690 ,( )	,( )	,( )	,( )	,( )

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

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

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

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 10/23/00

NAC/AEGL Meeting 19: 10/23-25/2000

Chemical: TETRANITROMETHANE (10 MIN) **CAS Reg. No.:** 509-14-8

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A	Glenn Leach			
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	N		
George Cushmac				George Rusch, Chair			
Ernest Falke				Robert Snyder			
Larry Gephart	N			Thomas Sobotka	A	A	A
John Hinz				Kenneth Still			
Jim Holler				Judy Strickland			
Thomas C. Hornshaw				Richard Thomas			
Nancy Kim							
Loren Koller				Thomas Tuccinardi/ Doan Hansen			
				TALLY	*17/19	17/19	17/19

*Only 2 opposed of 19 present by show of hands

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.46 ,( )	0.46 ,( )	0.36 ,( )	0.23 ,( )	0.15 ,( )
AEGL 2	1.1 ,( )	1.1 ,( )	0.91 ,( )	~~0.57~~ 0.57 ,( )	0.38 ,( )
AEGL 3	2.3 ,( )	2.3 ,( )	1.8 ,( )	1.1 ,( )	0.75 ,( )

AEGL 1 Motion: G. Rodgers **Second:** R. Thomas

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

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

*Show 10^{-4}, 10^{-5} & 10^{-6} Cancer Calcns. in appendix. (Benson/Kim) Only McClanahan OPPOSED

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 10/23/00

To: Po-Yung | From: Paul Tobin
Dept./Agency: ORAL-LifeScan | Phone #: 202 260-1736
Fax #: 423-241-0397 | Fax #: 202 260-0981
NSN 7540-01-317-7368 5099-101 GENERAL SERVICES ADMINISTRATION
865 241-0397

Appendix I

ting 19: 10/23-25/2000

Chemical: Perchloromethyl mercaptan **CAS Reg. No.:** 594-42-3

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A
Steven Barbee	Y	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	Y	Y	Y
Robert Benson	Y	Y	Y
Jonathan Borak	A	A	A
William Bress	Y	Y	Y
George Cushmac	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	A	A	A
John Hinz	A	A	A
Jim Holler	Y	Y	Y
Thomas C. Hornshaw	Y	Y	Y
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	Y
John S. Morawetz	Y	Y	Y
Richard W. Niemeier	Y	Y	Y
Marinelle Payton	A	A	A
Zarena Post	Y	Y	Y
George Rodgers	N	N	Y
George Rusch, Chair	Y	Y	Y
Robert Snyder	Y	Y	Y
Thomas Sobotka	A	A	A
Kenneth Still	A	A	A
Judy Strickland	A	A	A
Richard Thomas	A	A	A
		1	
Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
TALLY	17/18	17/18	18/18

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.018, ( )	0.018, ( )	0.014, ( )	0.0090, ( )	0.0060, ( )
AEGL 2	0.044, ( )	0.044, ( )	0.035, ( )	0.022, ( )	0.015, ( )
AEGL 3	0.54, ( )	0.38, ( )	0.30, ( )	0.075, ( )	0.038, ( )

AEGL 1 Motion: G. Rodgers **Second:** R. Niemeier

AEGL 2 Motion: ↓ **Second:** ↓

AEGL 3 Motion: ↓ **Second:** ↓

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 11/25/00

NAC/AEGL Meeting 19: 10/23-25/2000

Chemical: ~~URANIUM~~ HEXAFLUORIDE **CAS Reg. No.:** 7783-81-5

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A A	A	A	Glenn Leach	N Y	Y	Y
Steven Barbee	N Y	Y	Y	Mark A. McClanahan	N Y	N	Y
Lynn Beasley	Y Y	Y	Y	John S. Morawetz	N Y	Y	Y
David Belluck	N Y	Y	P	Richard W. Niemeier	N Y	Y	Y
Robert Benson	P P	Y	Y	Marinelle Payton	A A	A	A
Jonathan Borak	A A	A	A	Zarena Post	A A	A	A
William Bress	N Y	Y	Y	George Rodgers	Y Y	Y	Y
George Cushmac	N Y	Y	Y	George Rusch, Chair	Y Y	Y	Y
Ernest Falke	Y Y	Y	Y	Robert Snyder	N Y	Y	Y
Larry Gephart	A A	A	A	Thomas Sobotka	A A	A	A
John Hinz	A A	A	A	Kenneth Still	N Y	Y	Y
Jim Holler	N Y	Y	Y	Judy Strickland	A A	A	A
Thomas C. Hornshaw	N Y	Y	Y	Richard Thomas	N Y	Y	Y
Nancy Kim	N Y	Y	Y				
Loren Koller	N P	Y	Y	Thomas Tuccinardi/ Doan Hansen	A A A A	A A	A A
				TALLY	4/19 (*18/18)	19/20	19/19

mg/m³ → NR*

~~PPM~~, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	3.6 ,( )	3.6 ,( )	3.6 ,( )	1.8 ,( )	NR ,( )
AEGL 2	28 ,( )	19 ,( )	9.6 ,( )	2.4 ,( )	1.2 ,( )
AEGL 3	550 ,( )	100 ,( )	36 ,( )	4.4 ,( )	1.6 ,( )

* Hornshaw * Thomas

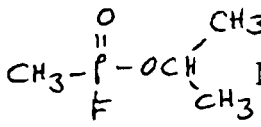
AEGL 1 Motion: Falke **Second:** Rodgers

AEGL 2 Motion: Falke **Second:** Barbee

AEGL 3 Motion: Rodgers **Second:** Falke

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 10/24/00

* = 2nd ballot



NAC/AEGL Meeting 19: 10/23-25/2000

Chemical: GB (SARIN) **CAS Reg. No.:** 107-44-8

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A	Glenn Leach	Y	Y	Y
Steven Barbee	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
Lynn Beasley	Y	Y	Y	John S. Morawetz	N	Y	Y
David Belluck	Y	Y	Y	Richard W. Niemeier	Y	Y	Y
Robert Benson	P	P	Y	Marinelle Payton	A	A	A
Jonathan Borak	A	A	A	Zarena Post	N	Y	P
William Bress	Y	Y	Y	George Rodgers	P	Y	Y
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	Y	Y	Robert Snyder	Y	Y	Y
Larry Gephart	A	A	A	Thomas Sobotka	A	A	A
John Hinz	A	A	A	Kenneth Still	Y	Y	Y
Jim Holler	Y	Y	Y	Judy Strickland	A	A	A
Thomas C. Hornshaw	Y	Y	Y	Richard Thomas	Y	Y	Y
Nancy Kim	P	Y	Y				
Loren Koller	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
				TALLY	16/18	20/20	20/20

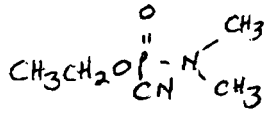
PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(0,0012)	,(0,00068)	,(0,00048)	,(0,0024)	,(0,00017)
AEGL 2	,(0,015)	,(0,0090)	,(0,0060)	,(0,0029)	,(0,0022)
AEGL 3	,(0,064)	,(0,032)	,(0,022)	,(0,012)	,(0,0087)

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

AEGL 2 Motion: L. Koller **Second:** R. Thomas

AEGL 3 Motion: W. Bress **Second:** L. Koller

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 10/24/00



NAC/AEGL Meeting 19: 10/23-25/2000

Chemical: GA (TABUN) **CAS Reg. No.:** 77-81-6

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A	Glenn Leach	Y	Y	Y
Steven Barbee	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
Lynn Beasley	Y	Y	Y	John S. Morawetz	N	Y	Y
David Belluck	Y	Y	Y	Richard W. Niemeier	Y	Y	Y
Robert Benson	Y	Y	Y	Marinelle Payton	A	A	A
Jonathan Borak	A	A	A	Zarena Post	N	Y	Y
William Bress	Y	Y	Y	George Rodgers	Y	Y	Y
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	Y	Y	Robert Snyder	Y	Y	Y
Larry Gephart	A	A	A	Thomas Sobotka	A	A	A
John Hinz	A	A	A	Kenneth Still	Y	Y	Y
Jim Holler	Y	Y	Y	Judy Strickland	A	A	A
Thomas C. Hornshaw	Y	Y	Y	Richard Thomas	Y	Y	Y
Nancy Kim	P	Y	Y				
Loren Koller	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
				TALLY	19/20	21/21	21/21

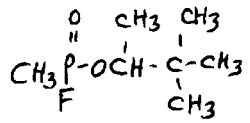
PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.0010, (~~0.0010~~)	0.00069, ( )	0.0042, ( )	0.0021, ( )	0.0015, ( )
AEGL 2	0.013, ( )	0.0080, ( )	0.0050, ( )	0.0026, ( )	0.0020, ( )
AEGL 3	0.11, ( )	0.059, ( )	0.039, ( )	0.021, ( )	0.015, ( )

AEGL 1 Motion: L. Koller **Second:** G. Leach

AEGL 2 Motion: ↓ **Second:** ↓

AEGL 3 Motion: ↓ **Second:** ↓

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 10/24/00



NAC/AEGL Meeting 19: 10/23-25/2000

Chemical: GD (SOMAN) **CAS Reg. No.:** 96-64-0

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A	Glenn Leach	Y	Y	Y
Steven Barbee	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
Lynn Beasley	Y	Y	Y	John S. Morawetz	N	Y	Y
David Belluck	Y	Y	Y	Richard W. Niemeier	Y	Y	Y
Robert Benson	Y	Y	Y	Marinelle Payton	A	A	A
Jonathan Borak	A	A	A	Zarena Post	N	Y	Y
William Bress	Y	Y	Y	George Rodgers	Y	Y	Y
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	Y	Y	Robert Snyder	Y	Y	Y
Larry Gephart	A	A	A	Thomas Sobotka	A	A	A
John Hinz	A	A	A	Kenneth Still	Y	Y	Y
Jim Holler	Y	Y	Y	Judy Strickland	A	A	A
Thomas C. Hornshaw	Y	Y	Y	Richard Thomas	Y	Y	Y
Nancy Kim	P	Y	Y				
Loren Koller	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
				TALLY	18/20	21/21	21/21

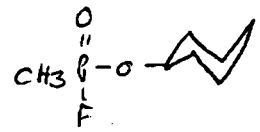
PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0,0046, ( )	0,00030, ( )	0,00018, ( )	0,0009, ( )	0,00007, ( )
AEGL 2	0,0057, ( )	0,0033, ( )	0,0022 ( )	0,0012, ( )	0,0008 , ( )
AEGL 3	0,049 , ( )	0,025 , ( )	0,017 , ( )	0,0091, ( )	0,0066 , ( )

AEGL 1 Motion: G. Rodgers **Second:** L. Koller

AEGL 2 Motion: ↓ **Second:** ↓

AEGL 3 Motion: ↓ **Second:** ↓

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 10/24/00



NAC/AEGL Meeting 19: 10/23-25/2000

Appendix N

Chemical: GF **CAS Reg. No.:** 329-99-7

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A	Glenn Leach	Y	Y	Y
Steven Barbee	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
Lynn Beasley	Y	Y	Y	John S. Morawetz	N	Y	Y
David Belluck	Y	Y	Y	Richard W. Niemeier	Y	Y	Y
Robert Benson	Y	Y	Y	Marinelle Payton	A	A	A
Jonathan Borak	A	A	A	Zarena Post	N	Y	Y
William Bress	Y	Y	Y	George Rodgers	Y	Y	Y
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	Y	Y	Robert Snyder	Y	Y	Y
Larry Gephart	A	A	A	Thomas Sobotka	A	A	A
John Hinz	A	A	A	Kenneth Still	Y	Y	Y
Jim Holler	Y	Y	Y	Judy Strickland	A	A	A
Thomas C. Hornshaw	Y	Y	Y	Richard Thomas	Y	Y	Y
Nancy Kim	P	Y	Y				
Loren Koller	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
				TALLY	18/20	21/21	21/21

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.00049, ( )	0.00028, ( )	0.002, ( )	0.001, ( )	0.0007, ( )
AEGL 2	0.0062, ( )	0.0035, ( )	0.0024 ( )	0.0013, ( )	0.0008, ( )
AEGL 3	0.053, ( )	0.027, ( )	0.018, ( )	0.009, ( )	0.0071, ( )

AEGL 1 Motion: R. Thomas **Second:** L. Koller

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

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

Approved by Chair: _____ **DFO:** Pam B. Noon **Date:** 10/24/00

NAC/AEGL Meeting 19: 10/23-25/2000

Chemical: VX **CAS Reg. No.:** 50782-69-9

NAC Member		AEGL 1	AEGL 2	AEGL 3
George Alexeeff *	A	A	A	A
Steven Barbee	Y	Y	Y	Y
Lynn Beasley	Y	Y	P	Y
David Belluck	Y	Y	N	Y
Robert Benson	Y	N	Y	Y
Jonathan Borak	A	A	A	A
William Bress	N	Y	Y	Y
George Cushmac	Y	Y	Y	Y
Ernest Falke	Y	Y	Y	Y
Larry Gephart	A	A	A	A
John Hinz	A	A	A	A
Jim Holler	Y	Y	P	Y
Thomas C. Hornshaw	Y	N	Y	Y
Nancy Kim	Y	N	Y	Y
Loren Koller	P	P	P	P

NAC Member		AEGL 1	AEGL 2	AEGL 3
Glenn Leach	Y	Y	Y	Y
Mark A. McClanahan	Y	Y	N	Y
John S. Morawetz	Y	N	P	N
Richard W. Niemeier	P	N	P	Y
Marinelle Payton	A	A	A	A
Zarena Post	Y	N	P	Y
George Rodgers	Y	N	Y	Y
George Rusch, Chair	P	P	Y	P
Robert Snyder	Y	N	Y	Y
Thomas Sobotka	A	A	A	A
Kenneth Still	A	A	A	A
Judy Strickland	A	A	A	A
Richard Thomas	A	A	N	A
Thomas Tuccinardi/ Doan Hansen	A A	A A	A A	A A
	TALLY	9/17	11/14	16/17

P/P NOT PASS mg/m³

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(0.00029)	,(0.00017)	,(~~0.000080~~ 0.000072)	,(0.000090 0.000060)	,(~~0.000038~~ 0.000043)
AEGL 2	,(0.0024)	,(0.0014)	,(0.00098)	,(0.00049)	,(0.00035)
AEGL 3	,(0.0096)	,(0.0049)	,(0.0033)	,(0.0017)	,(0.0013)

AEGL 1 Motion: ~~R. BENSON~~ Bress **Second:** ~~G. LEACH~~ Falke

AEGL 2 Motion: R. BENSON **Second:** G. LEACH

AEGL 3 Motion: Bress **Second:** Falke

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 10/24/00

PASSED

AEGL-1 Benson 0.00020 0.00011 0.000080 Rodgers