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

June 17-19, 2002

Final Meeting-25 Highlights

Environmental & Occupational Health Sciences Institute, Conference Room C
Rutgers University
170 Frelinghuysen Road
Piscataway, NJ 08854

INTRODUCTION

George Rusch, NAC/AEGL Chair, opened the meeting with brief remarks and along with AEGL Program Director, Roger Garrett, welcomed the committee members and guests and expressed thanks to Bob Snyder for hosting the meeting and inviting speakers. Then Bob Snyder welcomed NAC/AEGL to Rutgers University and gave a brief overview of Environmental and Occupational Health Sciences Institute (EOHSI). EOHSI was established in l986. The institute sponsors research, education, and service programs in a setting that facilitates interaction among experts in the areas of environmental health, toxicology, occupational health, exposure assessment, public policy and health education.

George Rusch thanked the Chemical Managers and authors for making timely contributions to the meeting highlights preparation. The draft meeting highlights of NAC/AEGL-24 were reviewed. A motion was made by John Hinz and seconded by David Belluck to accept the aforementioned draft meeting highlights without modifications. The motion passed unanimously by a show of hands.

The revised highlights of NAC/AEGL-24 are attached (Appendix A). The highlights of the NAC/AEGL-25 meeting are presented below along with the meeting agenda (Attachment 1) and the attendee list (Attachment 2). The meeting highlights are presented by subject categories of discussion and do not necessarily follow the order in the agenda.

Status Report of G-Agents and VX from COT/AEGL Review

John Hinz provided a brief status report on the response of the COT/AEGL to the CW agents in their Seventh Interim Report (May 2002). He distributed two handouts: (1) addressing the CW AEGL issues by an e-mail of June 11 signed by Glenn Leach and John Hinz to NAC/AEGL and (2) a summary of the response to COT/AEGL comments (Attachment 3). He also stated that the AEGL Development Team is requesting additional information from COT/AEGL at their July meeting to further clarify and consolidate their commentary on the CW agents in the COT/AEGL's Seventh Interim report. John later distributed the detailed response to COT comments that states that the outstanding issues requiring input from NAC/AEGL will be brought to the Sept. NAC/AEGL meeting (Attachment 4).

Technical Issue Discussion: Question of critical health effects starting points for AEGL determination

George Alexeeff presented an analysis evaluating the consistency in the document development process for AEGLs. The specific concern was that the starting points for many compounds appeared to be inconsistent with the Standing Operating Procedures (SOPs) and with AEGL definitions. The analysis was based on the justifications provided in 51 AEGL documents (Attachment 5). He outlined the sections of the SOPs pertaining to use of a no-observed-adverse-effect-level (NOAEL) as the starting point for AEGL development. The AEGL-3 values have consistently used a starting point that is equivalent to or adjusted to the "highest exposure level that does not cause lethality" as described in the SOPs. The AEGL-2 values appeared to be inconsistent in 22 of the documents by identifying a starting point that is a severe LOEL instead of a NOAEL (or NOEL), without the incorporation of an adjustment factor. For AEGL-1 values, nine of the documents appeared to identify a starting point concentration that produced an AEGL-1 effect, instead of a NOAEL (Attachment 6). George Alexeeff pointed out that many of these inconsistencies may be addressed by additional clarifications in the documents. In other cases, a new starting point may need to be identified. Roger Garret presented a further evaluation of this information indicating which documents could be addressed by further clarification, which documents are already being revised and which values may require revision (Attachment 7). He requested that comments on this subject be sent to Paul Tobin by July 18, 2002, so that the table could be revised.

Invited Technical Presentations from EOHSI

Neurobehavioral Function and the Regulatory Process
Nancy Fiedler

Neurobehavioral tests are used to assess sensory and cognitive behavioral function among humans exposed acutely and chronically to neurotoxicants. The purpose of this talk was to review the validity of these tests for predicting functions that are relevant for the AEGL regulatory process. Subtle decrements in behavioral function (e.g., latency of response) can be

documented using neurobehavioral tests and can be benchmarked to known neurologic conditions (e.g., multiple sclerosis) and to substances such as alcohol. Dr. Fiedler specifically reviewed the data on toluene, noting the subtlety of the neurobehavioral endpoints in many of the studies.

Weight of Evidence Application to AEGL Development
Mike Gallo

ATSDR defines weight of evidence (WOE) as the following: "A weight -of-evidence analysis involves the balanced review and integration of relevant exposure, toxicological, medical and health outcome data to help determine whether exposures under site-specific conditions might result in harmful effects." Weight of evidence as applied to assessment scenarios always involves two major factors, namely, expert opinion and informed judgement. All relevant qualitative and quantitative toxicity data as well as uncertainty factors must be applied in making informed decisions.

Analysis of the Fallouts of the World Trade Center Disaster
Paul Lioy

There was significant damage to many buildings within the 16-acre World Trade center complex. A consequence of the pulverization of these buildings and the fires was the release of a large plume of particles and gases into the atmosphere. Dust was collected and analyzed to determine chemical and physical characteristics of the atmospheric particles, and further, to determine if these pollutants could have acute or long-term human health consequences. The following contaminants were identified: asbestos, glass fibers, benzene, chromium, copper, diesel fumes, freons, lead, mercury, PAHs, PCBs, and sulfur dioxides. Materials of health concern included asbestos, PAHs, lead and glass fiber. Analysis of long-term problems of these materials should focus on the indoor environment for poorly cleaned residences or workplaces and unprotected cleanup workers.

Concept and Methodologies for Short Term Exposure Limits
for European Land Use Planning
Annick Pichard

In Europe, in the frame of the Seveso Directive, Acute Exposure Threshold limits are necessary to determine safety distances either for land use planning or emergency situations. Presently, US AEGLs are developed for emergency situations. Therefore, the range of applicability of these values is somewhat limited specifically in the case of land use planning. In the context of land-use planning, a European project is underway and aims to elaborate "a methodology to develop acute exposure threshold levels in case of chemical release."

RESPONSES TO *Federal Register Notice* COMMENTS ON THE PROPOSED AEGL VALUES

Comments from the *Federal Register Notice* of February 15, 2002, on the proposed AEGL values for carbon tetrachloride, chlorine, chlorine dioxide, and propylene oxide were received and discussed. The NAC/AEGL deliberations of these chemicals were briefly summarized as follows.

Carbon Tetrachloride
CAS Reg. No. 65-23-5

Chemical Manager: Bill Bress, ASTHO
Staff Scientist: Robert Young, ORNL

Two comments were received on the proposed AEGL values. They were submitted by George Alexeeff, Office of Environmental Health Hazard Assessment, CA, and John Morawetz of The International Chemical Workers Union. George Alexeeff had concern regarding the carcinogenicity calculation and the AEGL-1 and -2 values (Attachment 8). J. Morawetz's concerns involve the AEGL-2 and -3 values recommended by the NAC/AEGL (Attachment 9). Bill Bress represented the AEGL Development Team's resolutions to these comments, and the AEGL values were revisited (Attachment 10).

For AEGL-1, the use of a lower exposure concentration (76 ppm), identified as the NOAEL in the study, was considered as the starting point for AEGL-1 development. This would have resulted in essentially the same AEGL-1 values (22, 14, 11, 6.3, and 4.8 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr periods, respectively). However, it was motioned by Robert Snyder, seconded by John Hinz to retain the current (previously approved) AEGL-1 levels, based on a LOAEL in the study, for 10-min of 25 ppm, 30-min of 16 ppm, 1-hr of 12 ppm, 4-hr of 6.9 ppm and 8-hr of 5.2 ppm. The motion passed [YES: 17; NO: 2; Abstain: 0] (Appendix B). The proposed AEGL-2 levels were based on a human subject study of exposure to 1,191 ppm by Davis (1934).

It was pointed out from Davis (1934) study that for 3 of 4 individuals the exposure duration of the volunteer subjects was limited to less than 15 minutes (originally reported as only one individual left the chamber before 15 minutes) and that the 9-min exposure that was intolerable for one individual was more appropriate for development of the AEGL-2 values. The revised AEGL-2 values of 114 ppm, 74 ppm, 56 ppm, 32 ppm and 24 ppm for 10 minutes, 30 minutes, 1 hour, 4 hours, and 8 hours, respectively. Ernest Falke made a motion to accept these values and seconded by Mark McClanahan. The motion passed [YES:17; NO:1; Abstain: 0](Appendix B).

Following discussions revolving around the quality of a human lethality case report by Norwood et al. (1950), it was moved by John Hinz and seconded by Loren Keller to reaffirm the original values. The motion failed [YES:16; NO:9; Abstain:3](Appendix B). After further discussion, another motion was made by George Rodgers and seconded by Bob Benson to adapt the downward adjustment of the AEGL-3 10-minute value from the 30-minute value proposed for 230 ppm, and reaffirm all other AEGL values. Again, the motioned did not pass [YES:17;

NO:10; Abstain:2](Appendix B). Later, Susan Ripple, American Chemistry Council liaison, presented new exposure data to clarify the concern of Norwood study which she will make available to the committee at a later date. Afterwards, a motion was made by Tom Hornshaw and seconded by Richard Niemeier to reaffirm the proposed AEGL-3 values as published in the *Federal Register Notice* 350, 230, 170, 99, and 75 ppm for 10-min, 30-min, 1-hr, 4-hr, and 8-hr, respectively. The motion passed [YES:16; NO:2; Abstain:0](Appendix B). Finally, a motion was made by George Rusch and seconded by Bill Bress to elevate the TSD from Proposed to Interim status. The motion was approved unanimously by show of hands (Appendix B).

Chlorine
CAS Reg. No. 7782-50-5

Chemical Manager: Larry Gephart, Exxonmobil
Staff Scientist: Sylvia Talmage, ORNL

One comment was received from George Alexeeff, Office of Environmental Health Hazard Assessment, CA. The comment in part reads, 'For chlorine the AEGL-2 starting point appears inconsistent with the AEGL-2 definition. The chlorine document states "...an exercising susceptible individual exhibited effects consistent with the definition of the AEGL-2." Specifically, it states that "a susceptible individual experienced an asthmatic-like attack (shortness of breath and wheezing) at a concentration of 1 ppm after 4 hour of exposure (Rotman et al. 1983)." The document suggests that an asthmatic attack is an AEGL-2 response. This is inconsistent with discussions of the committee. However, the document uses this AEGL-2 effect as a starting point instead of using the NOAEL. Thus, the appropriate NOAEL, possibly 0.5 ppm for 4 hours should have been used as the starting point for AEGL-2 level.' (Attachment 8).

The TSD Development Team responded by pointing out that the chlorine TSD was written before the present AEGL definitions were adopted. The text will be rewritten to conform with the present definitions. The Development Team further clarified that the asthmatic attack did not occur during the first 4 hours of exposure and therefore, the 1.0 ppm concentration for 4 hours was a NOAEL for the symptoms and therefore a NOAEL for the AEGL-2 (Attachment 11).

It was moved by Mark McClanahan and seconded by John Hinz to elevate the chlorine values to Interim status. The motion passed unanimously by a show of hands (Appendix C).

Chlorine dioxide
CAS Reg. No. 10049-04-4

Chemical Manager: Bob Benson, EPA
Staff Scientist: Cheryl Bast, ORNL

One comment was received from George Alexeeff, Office of Environmental Health Hazard Assessment, CA (Attachment 8). The comment stated that the derivation of the proposed AEGL-1 value started from an effect level, rather than a no-effect level, for an AEGL-1 response. The comment further stated the NAC's SOP document (page 42) indicates that the starting point for AEGL-1 development is the 'highest experimental exposure without an AEGL-1 effect'

(Attachment 8). Bob Benson led the discussion for the TSD Development Team. The NAC/AEGL Committee discussed both the comments and the responses (Attachment 12). It was suggested that the rationale be modified to state that the modifying factor was also used because the effect exceeded the definition of an AEGL-1 effect. A motion was made by Mark McClanahan and seconded by John Hinz to retain the AEGL-1 values but modify the rationale and to elevate chlorine dioxide from Proposed to Interim status. The motion passed unanimously (Appendix D).

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

Chemical Manager: Jim Holler, ATSDR
Staff Scientist: Claudia Troxel, ORNL

The committee received two sets of comments regarding the *Federal Register* notice for propylene oxide. The American Chemistry Council raised several concerns regarding the carcinogenicity information contained in Appendix C, such as outdated carcinogenicity information and appropriateness of the factor for the multistage model and the computation of the cancer slope factor (Attachment 13). John Morawetz suggested lowering the AEGL-1 values based on limitations of the data set. These limitations are identified as failure to question workers regarding effects from exposure, the small sample size of individuals in the highest exposure category, and the fact that the data came from unpublished reports (Attachment 14).

Jim Holler led the discussion for the TSD Development Team (Attachment 15). The NAC/AEGL reviewed the employee monitoring data set in the technical support document as provided by the manufacturer, and discussed the limitations of the information. The committee also discussed the supporting study in mice with dyspnea as endpoint for AEGL-1 development. Then, a motion was made by Steven Barbee and seconded by Loren Koller to reaffirm the AEGL-1 values as previously approved by NAC/AEGL. The motion failed [YES:9; NO:5; Abstain: 4] (Appendix E). After further discussion of the concern and clarification and with additional members present, there was a revote of the motion to reaffirm the proposed AEGL-1 values. The motion was approved [YES:14; NO:5; Abstain: 0] (Appendix E). Several follow up actions are to be taken to address carcinogenicity issues. Contacts will be made with the TSD Development Team to identify more recent carcinogenicity data if possible. The most recent factors for the multistage model will be used. This discussion of derivation and presentation of carcinogenicity data by the committee raised an issue of whether such an approach is currently appropriate given the international representation on the committee. A workgroup is to be formed to review the committee policy and Standing Operating Procedures with respect to carcinogenicity information. Finally, a motion was made by George Rodgers and seconded by Mark McClanahan to elevate the AEGL values from Proposed to Interim status. The motion was approved unanimously (Appendix E).

REVIEW OF PRIORITY CHEMICALS FOR AEGL VALUES

Benzene
CAS Reg. No. 71-43-2

Chemical Manager: Bob Snyder, Rutgers University
Staff Scientist: Marcel van Raaij, RIVM, The Netherlands

The first draft of the TSD on Benzene was introduced by Marcel van Raaij (Attachment 16). Values for AEGLs 1, 2, and 3 at 10 min. and 30 min. and at 1, 4, and 8 hrs were suggested but there was no in-depth discussion owing to the delay in sending the draft document to the members. The major difficulty in preparing the TSD was that, although the data base for chronic benzene toxicity and leukemogenesis is extensive, there are very little data of good quality, either descriptive or quantitative, for acute toxicity. A specific problem arises with respect AEGL-1 values where it was suggested that the odor threshold might be used to establish the value. This raises the question of the validity of using odor thresholds in lieu of other effects, especially when the chemical is not an irritant at low levels. There is a search on for further data from the American Petroleum Institute. Additional comments were made that the TSD description of the Midzenski, Kraut and Greenberg papers had some inaccuracies in their use in Section 5 and 6 of TSD. A broad-ranging discussion is anticipated when the Benzene TSD returns to the next meeting.

RESPONSE TO NAS/COT/AEGL COMMENTS

Hydrogen Fluoride and Hydrogen Chloride

Chemical Managers: Ernest Falke (HF), EPA and John Hinz (Hcl), DoD
Staff Scientists: Sylvia Talmage (HF) and Cheryl Bast (Hcl), ORNL

The COT/AEGL Subcommittee in their Seventh Interim Report (Attachment 18) suggested that for both HF and HCl, time scaling of the AEGL-2 and AEGL-3 values from a 1-hour starting point to 4 and 8 hours resulted in values that were too low or inconsistent with the human and animal data. Therefore, they suggested adjustment of these values. Specifically, the COT/AEGL Subcommittee suggested that the 4 and 8 hour values be similar for the respective chemicals and that the 4-hour values be only slightly lower than the respective 1-hour values. The values also must reflect the relative toxicity of these two chemicals. The AEGL development team response was to set the 4-hour HCl AEGL-2 value equal to half of the 1-hour value (based on chemical similarity to HF) and then, for both HF and HCl, set the 8-hour AEGL-2 and AEGL-3 values equal to the respective 4-hour values (Attachment 17). Appropriate reasoning for these changes based on the human data was added to the respective TSDs. The reasoning for making the 4- and 8-hour values equal will also address the relative water solubilities and resulting nasal scrubbing of the chemicals at low concentrations. The suggested changes were approved by the NAC. HF: (Appendix F); HCl: (Appendix G). The revised Interim values appear in the table below.

AEGL INTERIM VALUES FOR HYDROGEN FLUORIDE AND HYDROGEN CHLORIDE (ppm)					
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL–1					
HF	1.0	1.0	1.0	1.0	1.0
HCl	1.8	1.8	1.8	1.8	1.8
AEGL–2					
HF	95	34	24	12	12
HCl	100	43	22	11	11
AEGL–3					
HF	170	62	44	22	22
HCl	620	210	100	26	26

Tetrachloroethylene
CAS Reg. No. 127-18-4

Chemical Manager: Bill Bress, ASTHO
Staff Scientist: Claudia Troxel, ORNL

Bill Bress presented the COT/AEGL comments on tetrachloroethylene (TCE) and led the discussion on revisiting the values (Attachment 19). AEGL-1 and -3 values were changed from the original Interim values, and the AEGL-2 values remained the same. The AEGL-1 value for 10 min through 8 hours at 35 ppm was proposed by Bob Snyder and seconded by Mark McClanahan. Because the endpoint was sensory irritation, the same number was used throughout the AEGL-1 time periods. The motion passed [YES: 15; NO:1 ; Abstain: 1] (Appendix F). AEGL-2 values of 10 min through 1 hr of 230 ppm, 4 hour at 120 ppm and 8 hour at 81 ppm were not changed. The 10-min 1-hr numbers were the same because of a Rowe 1962 study, which mentioned serious motor impairment at 280 ppm for up to 2 hours. AEGL-3 values of 1,600 ppm for 10 min and 30 min, 1,200 ppm for 1 hr, 580 ppm for 4 hr, and 410 ppm for 8 hr were proposed by Bob Snyder and seconded by Mark McClanahan. The numbers were based on an LC_{50} value divided by 3. For time scaling, an n=2 was retained. The n value was calculated by ten Berge from the Rowe lethality study for TCE. The motion was approved [YES:12; NO: 4; Abstain: 2] (Appendix H).

Nickel Carbonyl
CAS Reg. No. 13463-39-3

Chemical Manager: Kyle Blackman, FEMA
ORNL Staff Scientist: Robert Young, ORNL

Responding to comments by the COT/AEGL, the development of AEGL-2 values for nickel

carbonyl was revisited. Specifically, concern had been expressed in the COT/AEGL review regarding the validity of using developmental toxicity in compromised dams (hamsters) as the critical effect for AEGL-2 development (Sunderman et al., 1980). Robert Young provided an overview of the issue and pertinent data, and outlined three options for revision of the AEGL-2 (Attachment 20). These included: (1) a recommendation that no AEGL-2 values be developed due to limited data, (2) a three-fold reduction of the AEGL-3 values which could be supported by the developmental toxicity studies, and (3) the use of a developmental toxicity study in rats wherein a NOAEL (11.2 ppm, 15-min. on gestation Day 8; eye malformations) for developmental effects was reported (Sunderman et al., 1979). Following discussion of the relevance/validity of using developmental toxicity as a critical effect for AEGL-2 development and the strengths and weaknesses of the three proposed approaches, it was the consensus of the NAC/AEGL that the AEGL-2 values should be driven by the data from the rat developmental toxicity study. Because the approach of the three-fold reduction of the AEGL-3 values provided AEGL-2 values similar to those using the rat developmental toxicity study, it would be relegated to supporting information. In addition to the revision of the AEGL-2 values, 8-hr AEGL-2 and AEGL-3 values were also derived in response to COT/AEGL concerns that these 8-hr values may be appropriate with respect to possible prolonged, pressurized releases of nickel carbonyl (the 8-hour values were previously not recommended due to the rapid decomposition of nickel carbonyl in ambient air). A motion was made by Ernie Falke and seconded by Richard Niemeier to accept the proposed values for AEGL-2 of 0.13, 0.056, 0.028, 0.0070, and 0.0035 ppm for 10 min., 30 min., 1 h, 4h and 8 h, respectively and AEGL-3 of 0.020 ppm for 8 h. The motion passed [YES:17; NO:0; Abstain:1] (Appendix I). The following table summarizes the revisions of the AEGLs for nickel carbonyl. The values in bold are the revised numbers.

Summary of Interim AEGL Values For Nickel Carbonyl [ppm]						
Classification	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	not recommended
AEGL-2 (Disabling)	**0.13**	**0.056**	**0.028**	**0.0070**	**0.0035**	NOAEL (11.2 ppm, 15-min. on gestation Day 8) for eye malformations in rats (Sunderman et al., 1979)
AEGL-3 (Lethal)	0.46	0.32	0.16	0.040	**0.020**	estimated lethality threshold (LC_{01} of 3.17 ppm); mouse lethality data (Kincaid et al., 1953)

NR: Not recommended. Numeric values for AEGL-1 are not recommended because the lack of available data. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

Chemical Manager: Kyle Blackman, FEMA
ORNL Staff Scientist: Robert Young, ORNL

The COT/AEGL questioned the absence of 8-hour values for iron pentacarbonyl. Specifically, concern was expressed regarding the possibility of a continuous pressurized release which may necessitate an 8-hour value regardless of the known instability of iron pentacarbonyl under normal atmospheric conditions. In response to the query, Robert Young presented 8-hour AEGL-2 and AEGL-3 values based upon temporal extrapolation using a default n of 1 (Attachment 21). A motioned was made by Mark McClanahan and seconded by Richard Niemeier to accept the proposed values for 8 h AEGL-2 and 3 as 0.024 and 0.073 ppm. The values were accepted unanimously (Appendix J) and are summarized in the following table in bold.

Summary of Interim AEGL Values For Iron Pentacarbonyl [ppm (mg/m^3)]						
Classification	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended; insufficient data
AEGL-2 (Disabling)	1.2 (9.6)	0.40 (3.2)	0.19 (1.5)	0.050 (0.40)	**0.024 (0.19)**	Based upon a three-fold reduction in the AEGL-3 values
AEGL-3 (Lethal)	3.5 (28)	1.2 (9.6)	0.58 (4.6)	0.15 (1.2)	**0.073 (0.59)**	Estimated lethality threshold in rats (6-hr exposure to 2.91 ppm) (BASF, 1995). *n* = 1; UF=30 (10 for interspecies variability, 3 for individual variability)

NR: Not recommended. Numeric values for AEGL-1 are not recommended because (1) the lack of available data, and (2) an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

Allylamine
CAS Reg. No. 107-11-9

Chemical Manager: Loren Koller, OSU
ORNL Staff Scientist: Sylvia Milanez, ORNL

Loren Koller led the discussion of issues raised by COT/AEGL at the February 2002 meeting. The revised TSD incorporated mechanistic studies published since 1994 and adjusted UFs in deriving AEGL-1 and 2 values (Attachment 22).

The AEGL-1 value was revised by using the same endpoint (irritation) and a total uncertainty factor of 6 (3 intraspecies, 2 modifying factor). The value was 0.42 ppm for all time points because it is an irritant. A motion was made Bob Benson and seconded by Mark McClanahan to

accept the revised AEGL-1 values. The motion was approved unanimously (Appendix K).

For AEGL-2 values, NAC/AEGL favored using an UF of 30 rather than 50. However, when 30 was used, the 8 hour AEGL-2 and AEGL-3 values became very close. This was unacceptable to most committee members. The ensuing discussion focused on changing the AEGL-3 values. However, it was determined that these values most likely could not be increased (COT had also accepted them) but the committee recommended to change the n from 0.85 to 1.0 for consistency purposes. Time expired before this recommendation reached a vote. Later, Loren Koller presented a different approach for the AEGL-2 values which appeared favorable to most who remained in attendance (no quorum). Chairman George Rusch requested that this TSD be recycled. The revised TSD will be distributed electronically. The NAC/AEGL members are requested to provide a prompt reply for any recommendations or disapproval, listing reasons why and suggestions for revision, of the numbers presented in an attempt to minimize discussion on the chemical at the September meeting.

Allyl Alcohol
CAS Reg. No. 107-18-6

Chemical Manager: Mark McClanahan, CDC
Staff Scientist: Claudia Troxel, ORNL

Mark McClanahan reviewed the status of the development of values for allyl alcohol as a follow up from the last meeting, including development of an n value based on the reported LC_{50} data, and creating a categorical plot of the data (Attachment 23). The AEGL-2 values were developed using a 40 ppm, 7 hours/day, 60-exposure study that showed reversible irritation in rats, and the AEGL-3 values were based on a 200 ppm 1-hour exposure to rats, mice, and rabbits that produced no mortality. The empirical value for n, (LC_{50} data, Union Carbide 1951) equaled 0.78. Using this n for time scaling and the two cited data sets, produced AEGL-3 values lower than the corresponding AEGL-2 values (except the 10-minute value).

Rounding the value of n to 1 had resolved the conflicting values on the previous occasion. The starting data for derivation of AEGL-3 values was the highest concentration causing no mortality in mice, rats, and rabbits (200 ppm for 1 hour). The interspecies uncertainty factor was set to 1 because of three species had the same exposure and experienced no mortality. At higher exposures each of these species had mortality. These data suggest little difference between species in response to allyl alcohol exposure. An intraspecies uncertainty factor of 3 was chosen. Although the traditional approach for uncertainty factors in a case such as this would argue for an uncertainty factor of 10 because of the lack of data addressing inter-individual variability, this would result in a composite uncertainty factor of 10. An uncertainty factor of 10 would drive the AEGL-3 values to a level that would be inconsistent with available data.

Repeat 7-hour and 8-hour exposures at 100 ppm required 32 or more days for all rats to die, while at 150 ppm, all rats in one study, and 8 of 10 of the rats, in the other study died by the end of the first two exposures. Because of these data, the calculated 10-minute value of 400 ppm

was set equal to the 30-minute value, in order not to exceed the 150 ppm concentration that killed almost all the animals in only two 7- or 8-hour exposures.

TABLE 1. AEGL-3 Values For Allyl Alcohol (using n=1, UF=3, 200 ppm, 1-hour exposure)					
Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	130 ppm	130 ppm	67 ppm	17 ppm	8.3 ppm

It was moved by John Hinz and seconded by Dave Belluck to accept these proposed AEGL-3 values. The motion passed unanimously (Appendix L).
The basis for derivation of AEGL-2 values was human data (Dunlap et al., 1958) that reported slight to moderate nose irritation in 7 of 7 volunteers exposed to 12.5 ppm allyl alcohol for 5 minutes (Table 5). At 25 ppm 5 of 5 subjects reported severe eye irritation. The 12.5 ppm was taken as a no-effect-level for severe eye irritation. An intraspecies uncertainty factor of 3 was used because irritation is not likely to vary greatly among individuals.

TABLE 2. AEGL-2 Values For Allyl Alcohol (UF=3, 12.5 ppm, 5-minute human exposure)					
Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	4.2 ppm	4.2 ppm	4.2 ppm	4.2 ppm	4.2 ppm

It was moved by Bob Benson and seconded by Loren Koller to accept these proposed AEGL-2 values. The motion was approved [YES:15; NO: 0; Abstain: 0] (Appendix L).
They moved it

Table 3. AEGL-1 Values For Allyl Alcohol (UF=3, 6.25 ppm, 5-minute human exposure)					
Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	2.1 ppm	2.1 ppm	2.1 ppm	2.1 ppm	2.1 ppm

It was moved by Steven Barbee and seconded by John Hinz to accept these proposed AEGL-1 values. The motion passed unanimously (Appendix L). Values appear in the summary table below.

TABLE 4. SUMMARY OF APPROVED AEGL VALUES FOR ALLYL ALCOHOL (ppm [mg/m^3])						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	2.1 [5.1]	2.1 [5.1]	2.1 [5.1]	2.1 [5.1]	2.1 [5.1]	Slight to moderate irritation in humans at 6.25 ppm for 5 minutes (Dunlap et al., 1958)
AEGL-2 (Disabling)	4.2 [10]	4.2 [10]	4.2[10]	4.2 [10]	4.2 [10]	NOAEL Serve eye irritation in humans at 12.5 ppm for 5 minutes. (Dunlap et al., 1958)

AEGL-3 (Lethality)	130 [310]	130 [310]	67 [160]	17 [41]	8.3 [20]	NOEL for lethality in mice, rats, and rabbits exposed to 200 ppm for 1 hr (Union Carbide, 1951)

Administrative Matters

The next meeting, NAC/AEGL-26, has been set for September 10-12, 2002, in Washington, D.C. More information about the lodging will be provided soon by Po-Yung Lu. The tentative NAC/AEGL-27 meeting is proposed for December 9-11, 2002, in Washington, D.C.

The meeting highlights were prepared by Po-Yung Lu and Sylvia Talmage, Oak Ridge National Laboratory, with input from the respective chemical managers.

LIST OF ATTACHMENTS

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

Attachment 1. NAC/AEGL-25 meeting agenda
Attachment 2. NAC/AEGL-25 attendee list
Attachment 3. CW AEGL issues from Gleen Leach and John Hinz
Attachment 4. CW Agents: Deatiled response to COT/AEGL's Seventh Interim Report
Attachment 5. Alexeeff memo of 2/6/2002 to George Rusch
Attachment 6. Improving Consistency in Selecting AEGL Starting Points
Attachment 7. Identification of Starting Points for AEGL Development Relative to NOAEL and LOAEL
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Attachment 1

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-25
June 17-19, 2002

Environmental & Occupational Health Sciences Institute, Conference Room C
Rutgers University
170 Frelinghuysen Road
Piscataway, NJ 08854

Betty Davis, 732-445-0202, davisbe@eohsi.rutgers.edu

AGENDA

Monday, June 17, 2002

9:30 a.m.	Welcome to Environmental and Occupational Health Sciences Institute (Bob Snyder) Introductory remarks and approval of NAC/AEGL-24 Highlights (George Rusch, Roger Garrett, and Paul Tobin)
9:45	Question of critical health effects starting points for AEGLs determination: * George Alexeeff perspective * AEGL Program staff analysis * Presentation on "Impairment to escape" related to AEGL values (Nancy Fiedler)
11:45	Status report regarding G-Agents and VX from COT/AEGL review (Gleen Leach, John Hinz/Annetta Watson)
12:15 p.m.	Lunch
1:15	Issues regarding HCl/HF from COT/AEGL review (John Hinz/Cheryl Bast, Larry Gephart/Sylvia Talmage)
2:00	Revision of Tetrachloroethylene (Bill Bress/Claudia Troxel)
3:00	Break
3:15	Review of comments received from February 15, 2002, *Federal Register Notice* - Carbon tetrachloride, Chlorine, Chlorine dioxide, and Propylene oxide
5:15	Adjourn for the day

Tuesday, June 18, 2002

8:30 a.m.	Summary of Biological & Chemical Terrorism: a New Jersey Perspective (Bob Snyder)
8:45	Weight of Evidence Application to AEGL Development (Mike Gallo)
9:45	Revision of Allylamine (Loren Koller/Sylvia Milanez)
10:30	Break
10:45	Issues regarding Nickel carbonyl: AEGL-2 and revisit of Iron pentacarbonyl: 8- hours AEGL values (Kyle Blackman/Bob Young))
12:00 noon	Lunch
1:00	Revision of Toluene (Larry Gephart/Sylvia Talmage)
2:30	Revision of Allyl alcohol (Mark McClanahan/Claudia Troxel)
3:15	Break
3:30	Review of Benzene (Bob Snyder/Marcel Raaij)
5:00	Adjourn for the day

Wednesday, June 19, 2002

8:30 a.m.	Review of Benzene (continued)
9:30	Revisit of Chlorine trifluoride: AEGL-1 and related issues (Bob Benson/Sylvia Talmage)
10:15	Break
10:30	Analysis of the Fallouts of the World Trade Center Disaster (Paul Lioy)
11:15	Administrative matters
11:30	Adjourn meeting

NAC/AEGL-25

June 17-19, 2002

Attachment 2

Name	Affiliation	Phone NO.
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George Woodall	API	202 682-8067
Paul J. Lioy	EOHSI	732-445-0150

Seventh Interim Report (May 02) of the COT Subcommittee on AEGLs; Review of Interim Values for the G-series Nerve Agents (GA, GB, GD, GF) and Nerve Agent VX

John Hinz
AEGL Chemical Manager, G-series agents
17 June 2002

Nerve Agent AEGL Development Team Request for Clarification

- *Seventh Interim Report*
  - –requests additional information
  - –expresses differing opinions on similar issues
- Request for clarification and consolidated comment submitted to COT by Nerve Agent AEGL Development Team, 30 May
  - –request accompanied by summary response addressing each major issue of COT concern

Status (17 June 02)

- Development Team has since received preliminary comments from individual Subcommittee primary and secondary reviewers, who consider the Team response to be appropriate
- Current Development Team response under consideration by all COT Reviewers
- Formal COT determination will await next scheduled Subcommittee meeting (15-17 July 02)
- Outstanding issues requiring input by NAC will be brought to September NAC meeting

Hinz John P Civ AFIERA/RSRE

From: Leach, Glenn J Dr USACHPPM [Glenn.Leach@APG.AMEDD.ARMY.MIL]
Sent: Tuesday, June 11, 2002 9:28 AM
To: 'falke.ernest@epa.gov'; 'garrett.rodger@epa.gov'; 'tobin.paul@epa.gov'; 'george.rusch@honeywell.com'; 'tahan.letty@epa.gov'; 'kollerl@pacifier.com'; 'vdh.state.vt.us'; 'lpy@ornl.gov'; 'kenneth.still@wpafb.af.mil'
Cc: 'john.hinz@brooks.af.mil'; 'watsonap@ornl.gov'; Hauschild, Veronique D Ms USACHPPM
Subject: CW AEGL Issues

Dear NAC Members,

You are all probably aware that the Interim AEGLs for the chemical warfare nerve agents GA, GB, GD, GF and VX were presented to the COT Subcommittee on AEGLs in February, 2002. At present, the COT Subcommittee is still considering an official position on several significant issues.

Potential consideration of nerve agents for decision-making at the June 2002 meeting of the National Advisory Committee (NAC) was initially based on the assumption that the NAC leadership and TSD authors would receive a definitive determination on all issues of concern from the COT/AEGL by mid-May. This did not occur in the Seventh Interim Report of the COT Subcommittee on AEGLs. The DoD sponsor acknowledges that a full AEGL evaluation of these compounds demands care and caution, and that sufficient time must be allowed for completion of this task.

It is also observed that the Federal Register notice announcing the next meeting of the National Advisory Committee for AEGLs (67FR 38269-38270; 3 June 2002), to be held 17-19 June at Rutgers University, does not include mention of nerve agents as a topic for discussion. The Nerve Agent AEGL Chemical Managers, who also represent the DoD sponsor, prefer that all discussions of nerve agent AEGLs before the National Advisory Committee be announced to the public in advance and in sufficient time for the public to be adequately informed. In our opinion, to do otherwise would send the wrong message to the public, be contrary to the basic principles of the Standing Operating Procedures, and not reflect the extraordinary care to maintain transparency that has characterized all previous AEGL discussions of these compounds in open Committee meetings. For all these reasons, the Nerve Agent AEGL Chemical Managers conclude that consideration of nerve agent AEGL estimates at the 17-19 June meeting of the National Advisory Committee would be premature.

We expect the COT to finalize their position on the key issues during their July meeting in Woods Hole. Following the July COT meeting, the Chemical Managers believe that any outstanding issues requiring input by the NAC can be resolved at the September NAC meeting with no significant changes in the publication schedule.

Glenn Leach
John Hinz

SUMMARY RESPONSE (3 Jun 02 Pagination UpGrade)
Nerve Agent AEGL Development Team
30 May 2002

Annetta Watson, Corresponding Author
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN

to

Seventh Interim Report of the Subcommittee on Acute Exposure Guideline Levels

National Research Council May 2002

SUMMARY RESPONSE
Nerve Agent AEGL Development Team
30 May 2002

Background:

At the recommendation of the COT Program Director, the nerve agent Technical Support Document (TSD) authors respectfully request clarification on several technical issues identified in the nerve agent portions of the Seventh Interim Report. Due to national concern regarding potential chemical terrorist use of nerve agents, this communication has been prepared as one means of facilitating and expediting the AEGL review process for these compounds.

The principal issues for which clarification and consolidated comments are requested include:

1) Relative potency determination for GB: VX
2) Value of "n" for agent GB time scaling
3) Selection of critical study for developing agent GB AEGL-1 estimates

In some cases, the Seventh Interim Report expresses different opinions on the same issue.

In other cases, issue resolution and author guidance resulting from TSD author response to Subcommittee queries at the Beckman Center meeting (6-8 Feb 2002), coupled with COT Subcommittee discussion and consultation with the SOPs that took place at the same meeting, are not reflected in the review comments provided in the Seventh Interim Report.

In a separate case, the TSD authors were requested to perform additional literature review and report back their appraisal on the issue of carboxylesterases as a factor in estimating interspecies uncertainty factors (rat-to-human; AEGL-3 determinations). This appraisal was completed in March, 2002, and provided to the COT Subcommittee at that time. It is respectfully requested that the COT Subcommittee provide a "reading" of that previous analysis in sufficient time to update the TSD as appropriate and prior to the July COT Subcommittee meeting at Woods Hole.

The authors appreciate your time in responding to our requests for clarification on these important issues.

Please note that detailed individual responses to each review comment contained in the Seventh Interim Report have also been prepared by the nerve agent TSD authors, and are being provided to the COT Subcommittee under separate cover.

Comparative analyses illustrating the AEGL-1 and AEGL-2 estimates resulting when either "n" = 1 or "n" = 3 are substituted into the ten Berge et al (1986) equation were presented as plots to the COT Subcommittee as part of the Beckman Center discussions. These plots also included designation of the experimental human and animal data, with emphasis on data points provided by the critical studies. Of the three "n" values considered, the plots drawn for "n" = 2 were most reflective of the available human and animal database. The reviewer withdrew his comment at the Beckman Center discussion table, and retention of the "n" value of 2 seemed acceptable to the COT Subcommittee at the time.

Since early February, a more recent study on GB vapor-induced miosis in SD rats was presented at the Nashville SOT meeting (Mioduszewski et al, 2002, in press; "Low-level sarin vapor exposure in rats: Effect of exposure concentration and time on pupil size," ECBC-TR-235, US Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD; publication expected in June 2002). Miosis response data (female SD rat) from this report have been subjected to regression analysis to determine a best-fit concentration x time curve. The resulting "n" value is 2.00. These recent miosis data from a well-conducted and well-calibrated study support the use of an "n" = 2 when time scaling for non-lethal endpoints following vapor exposure to nerve agents. (Plots and further information are in detailed individual responses being provided to the COT Subcommittee under separate cover).

Clarification Request: After group discussion and author presentation of plots illustrating the results of various "n" evaluations, the COT reviewer's comment was withdrawn at the Beckman Center meeting. Further, the March file of preliminary COT Subcommittee comments (GAgents 2_6_02.doc) provided to the authors also indicated that this comment had been withdrawn. If additional information known to the reviewer and/or the COT Subcommittee has resulted in retention of this comment after consideration of the Beckman Center record, please advise the authors such that adequate preparation can be made to present necessary supporting logic at the July COT meeting.

3) Critical study for supporting GB AEGL-1 estimates

COT Subcommittee Comments: On **pp. 16-17**, paragraphs 1 and 2 ("The most difficult point in this document....This flawed study should not be used to derive AEGL-1 values"), and **p. 17, paragraph #3** ("The Harvey (1952) study is very old.....use of the van Helden (1999) marmoset study is recommended").

Author Analysis: At the Beckman Center meeting, the authors recommended that the very excellent and state-of-the art study of marmoset threshold miosis prepared by Van Helden et al (2001), and for which there is highly credible documentation for GB vapor generation and measurement, be substituted as the critical study for AEGL-1 estimation. The authors further recommended that Harvey (1952) and Johns (1952) would be retained as secondary and supportive studies.

As previously stated, a more recent study on GB vapor-induced miosis in SD rats was presented at the Nashville SOT meeting (Mioduszewski et al, 2002, in press, and cited above). A preprint of this report has provided a 3rd data set to consider for the miosis endpoint. Results are summarized in Table 1 below. Current Interim values are **bolded**.

TABLE 1. AEGL-1 Estimates for Nerve Agent GB (15 May 2002)

Time Period	**Interim Value (66 FR 21940 (2 May 2001)[a]; human data (mg/m^3)**	Alternate #1 [b]; marmoset miosis data (mg/m^3)	Alternate # 2 [c]; female SD rat miosis data (mg/m^3)
10 min	**0.0069**	0.0045	0.0068
30 min	**0.0040**	0.0026	0.0039
1 hr	**0.0028**	0.0019	0.0020
4 hr	**0.0014**	0.00092	0.0012
8 hr	**0.0010**	0.00065	0.0010

[a] Harvey, JS, 1952. Clinical observations on volunteers exposed to concentrations of GB. Medical Laboratories Research Report No. 114, Publication Control No. 5030-114, MLCR 114 (CMLRE-ML-52), Army Chemical Center, MD. Johns, RJ, 1952. The effect of low concentrations of GB on the human eye. Chemical Corps Medical Laboratories Research Report No. 100, Publication Control No. 5030-100 (CMLRE-ML-52), Army Chemical Center, MD. **[20 min exposures]**

[b] van Helden HPM et al., 2001. Low-level Exposure to GB vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, and Performance Incapacitation. Proceedings NATO Conference on Operational Medical Issues in Chemical and Biological Defense, Lisbon, Portugal (14-17 May, 2001; in press). **[5 hour exposures]**

[c] Mioduszewski R et al., 2002. Low-level sarin vapor exposure in rats: Effect of exposure concentration and time on pupil size. ECBC-TR-235. Edgewood Research Development and Engineering Center, U.S. Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD (in press). **[10 min, 1 hr, and 4 hr exposures]** [report will hopefully be published in time for distribution at the July COT meeting]

Assumptions: n = 2; interspecies UF = 1 (van Helden of TNO and staff of Porton Down consider miosis response in all mammal eyes exposed to nerve agent vapors to be similar across species; the AEGL Nerve Agent Development Team concurs); intraspecies UF = 10 (adjustment for possible susceptible individuals); • UF = 10

At the present time, the authors consider Mioduszewski et al (2002, in press) to be the most robust data set (3 exposure durations, all of which match AEGL exposure durations of interest; sufficiently large number of animals) available for use in developing an AEGL-1 for nerve agent GB vapor exposure. The authors recommend that the Mioduszewski et al (2002, in press) report be used as the critical study for GB AEGL-1 estimation, with retention of van Helden et al (2001), Harvey (1952), and Johns (1952) as secondary and supportive studies. If this recommendation is acceptable, there will be little to no change in the numerical values of AEGL-1 for agent GB.

Further information is provided in detailed individual responses being transmitted to the COT Subcommittee under separate cover.

Clarification Request: Please provide specific guidance regarding selection of a key (non-human) study from which to develop GB AEGL-1 estimates (van Helden et al 2001; and/or Mioduszewski et al 2002). Please also address whether substitution of the (recent) miosis data for marmosets and/or female rats results in AEGL-1 estimates that are significantly different from the existing Interim values.

4) Interspecies UF for rat to human

COT Subcommittee Comments: For GB: On **p. 17** of the Seventh Interim Report, paragraph **#2** ("Even though the respiratory uptake....interspecies UF of at least 10 should be used."), as well as **p. 19**, Specific Comment **#11** on the page **("Page 64, line 17..."**"With different detoxification mechanisms, why was the interspecies UF of 3 applied instead of 10?").

For VX: On **p. 21**, paragraph **#1**, (**"Page 31..."** reference to aliesterases and an UF of 10)

Author Analysis: At the Beckman Center meeting, the authors were requested to perform some "homework" and expand evaluations of carboxylesterases (CaE) as a potential factor in the development of an interspecies UF. Since early February, the authors have contacted a number of investigators in the field who identified additional literature sources, one of which had not yet been published at the time of the Beckman Center meeting (Chanda et al 2002). Further, the TSD authors have more closely examined the available lethal inhalation toxicity data for rats, primates and dogs; and developed several interspecies comparisons as a means of evaluating whole-organism response.

In summary,

- An expanded examination of the literature regarding CaE in lab animals and humans indicates that CaE is present in human plasma as well as numerous other human tissues and organs (including those where exposure and distribution leading to death by G-agent vapor toxicity would likely occur).

- The known detoxification potential of carboxylesterases is multifaceted and encompasses consideration of CaE amount, affinity, and inhibitor resistant esterase activity. The present state of incomplete characterization for human CaE precludes accurate prediction regarding CaE detoxification potential in a population of humans exposed to anticholinesterase compounds.

- Interspecies data for comparison of the whole organism response of lethality indicates that, when challenged with a lethal concentration of GB vapor, adult female SD rats are more robust than adult dogs or monkeys by approximate factors of 2.0-2.5. Species differences in carboxylesterase concentrations may account for the more robust response of adult female rats. Model predictions of human LCt_{50} indicate a rat: human ratio of between 3.0 and 3.5.

DETAILED RESPONSE
Nerve Agent AEGL Development Team
30 May 2001

Annetta Watson, Corresponding Author
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN

to

Seventh Interim Report of the Subcommittee on Acute Exposure Guideline Levels

National Research Council
May 2002

Seventh Interim Report of the Subcommittee on Acute Exposure Guideline Levels

BACKGROUND

In 1991, the U.S. Environmental Protection Agency (EPA) and the Agency for Toxic Substances and Disease Registry (ATSDR) asked the National Research Council (NRC) to provide technical guidance for establishing community emergency exposure levels (CEELs) for extremely hazardous substances (EHSs) pursuant to the Superfund Amendments and Reauthorization Act of 1986. In response to that request, a subcommittee of the NRC Committee on Toxicology (COT) prepared a report titled *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993). That report provides step-by-step guidance for the derivation of CEELs for EHSs.

In 1995, EPA, several other federal and state agencies, and several private organizations convened an advisory committee—the National Advisory Committee on Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances (referred to as the NAC)—to develop, review, and approve AEGLs (similar to CEELs) for up to 400 EHSs. AEGLs developed by the NAC have a broad array of potential applications for federal, state, and local governments and for the private sector. AEGLs are needed for prevention and emergency response planning for potential releases of EHSs either unintentionally from accidents or as a result of terrorist activities.

THE CHARGE TO THE SUBCOMMITTEE

The NRC convened the Subcommittee on Acute Exposure Guideline Levels to review the AEGL documents approved by the NAC. The subcommittee members were selected for their expertise in toxicology, pharmacology, medicine, industrial hygiene, biostatistics, risk assessment, and risk communication.

The charge to the subcommittee is to (1) review AEGLs developed by the NAC for scientific validity, completeness, and conformance to the NRC (1993) guidelines report, (2) identify priorities for research to fill data gaps, and (3) identify guidance issues that may require modification or further development based on the toxicological database for the chemicals reviewed.

This interim report presents the subcommittee's comments concerning the draft AEGL documents for 14 chemicals: phosgene, hydrogen chloride, hydrogen fluoride, hydrogen sulfide, G nerve agents, VX, diborane, *cis*- and *trans*-crotonaldehyde, perchloromethyl mercaptan, iron pentacarbonyl, nickel carbonyl, allylamine, cyclohexylamine, and ethylenediamine.

COMMENTS ON G NERVE AGENTS

At its February 6-8, 2002 meeting, the subcommittee reviewed the AEGL document on G nerve agents. The document was presented by Annetta Watson and Robert Young of Oak Ridge National Laboratory. The subcommittee recommends a number of revisions.

General Comments

1) COT SUBCOMMITTEE COMMENT: Page 55, line 23 and page 56, line 28: The most difficult point in this document is the choice of the Harvey (1952) study as the key reference for the development of AEGL-1 values. There are two reasons for this difficulty:

(1) Harvey (1952) could not monitor or control air concentrations of the test material at the time of the study. The concentrations were estimated to be 0.05 mg/m^3 but may have been 0.01 or 0.2 mg/m^3.

(2) The effects Harvey (1952) measured in subjects were almost totally subjective and were not quantifiable.

This flawed study should not be used to derive AEGL-1 values.

AUTHORS' RESPONSE: *At the February 6-8, 2002, meeting in the Beckman Center, the technical support document (TSD) authors recommended that the very excellent and state-of-the art study of marmoset threshold miosis prepared by Van Helden et al (2001; "Low-level exposure to GB vapor in air; Diagnosis/dosimetry, lowest observable effect levels, and performance incapacitation," Proceedings of the NATO Conference on Operational Medical Issues in Chemical and Biological Defense. Lisbon, Portugal, 14-17 May 2001), and for which there is highly credible documentation for GB vapor generation and measurement, be substituted as the critical study for AEGL-1 estimation. The TSD authors further recommended that Harvey (1952) and Johns (1952) would be retained as secondary and supportive studies. It is further noted by the TSD authors that the van Helden et al (2001a, b) study became available after the NAC made its Interim decision in June 01, that the AEGL-1 analysis of the van Helden data has already been circulated among the TSD Development Team for concurrence, and that the derivation was documented in the status report sent to each member of the COT Subcommittee on AEGLs in their briefing books. It was noted by the Subcommittee members present that there is concordance for the AEGL-1 estimates from the non-human primate (marmosets) when compared to that derived from the human data set of Harvey (1952) and Johns (1952).*

In the intervening months, a more recent study on GB vapor-induced miosis in SD rats was presented at the Nashville SOT meeting (Mioduszewski et al, 2002, in press; "Low-level sarin vapor exposure in rats: Effect of exposure concentration and time on pupil size," ECBC-TR-235, US Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD; publication expected in June 2002). A preprint of this report has provided a 3rd data set to consider for the miosis endpoint. Both genders of SD rat were tested for 3 time durations of

AEGL interest (10 min, 1 hr, 4 hr), and the female rat appeared to be more susceptible than the male. The ORNL Team has calculated the AEGL-1 estimations from the female rat data set.

For your information, the current Interim AEGL-1 estimates and the alternate estimates from the van Helden (marmoset; 5 hr exposure) and Mioduszewski et al (female SD rat; 10 min, 1 hr and 4 hr exposures) data sets are summarized in the table below. The ***current Interim values are bolded.***

TABLE 1. AEGL-1 Estimates for Nerve Agent GB (15 May 2002)

Time Period	***Interim Value (66 FR 21940 (2 May 2001)[a]; human data (mg/m³)***	*Alternate #1[b]; marmoset miosis data (mg/m³)*	*Alternate # 2[c]; female SD rat miosis data (mg/m³)*
10 min	***0.0069***	*0.0045*	*0.0068*
30 min	***0.0040***	*0.0026*	*0.0039*
1 hr	***0.0028***	*0.0019*	*0.0020*
4 hr	***0.0014***	*0.00092*	*0.0012*
8 hr	***0.0010***	*0.00065*	*0.0010*

[a] Harvey JS, 1952. Clinical observations on volunteers exposed to concentrations of GB. Medical Laboratories Research Report No. 114, publication Control No. 5030-114, MLCR 114 (CMLRE-ML-52), Army Chemical Center, MD. Johns, RJ, 1952. The effect of low concentrations of GB on the human eye. Chemical Corps Medical Laboratories Research Report No. 100, Publication Control No. 5030-100 (CMLRE-ML-52), Army Chemical Center, MD. ***[20 min exposures]***

[b] van Helden HPM et al., 2001. Low-level Exposure to GB vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, and Performance Incapacitation. Proceedings NATO Conference on Operational Medical Issues in Chemical and Biological Defense, Lisbon, Portugal (14-17 May, 2001; in press). ***[5 hour exposures]***

[c] Mioduszewski R et al., 2002. Low-level sarin vapor exposure in rats: Effect of exposure concentration and time on pupil size. ECBC-TR-235. Edgewood Research Development and Engineering Center, U.S. Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD (in press). ***[10 min, 1 hr, and 4 hr exposures]*** *[report will hopefully be published in time for distribution at the July COT meeting]*

Assumptions: *n = 2; interspecies UF = 1 (van Helden of TNO and staff of Porton Down consider miosis response in all mammal eyes exposed to nerve agent vapors to be similar across species; the AEGL Nerve Agent Development Team concurs); intraspecies UF = 10 (adjustment for possible susceptible individuals); • UF = 10*

AUTHORS' CONCLUSIONS: *At the present time, the most robust data set available for use in developing an AEGL-1 for nerve agent GB vapor exposure is that of Mioduszewski et al (in press; publication expected in June 2002). A total of 423 rats were used in this well-conducted study, of which 130 were controls. Three vapor exposure time periods, each of which is an AEGL exposure interval (10 min, 1 hr, 4 hr), were incorporated into the study design, and a sufficient number of individuals were exposed at each interval (10 min, 52 female SD rats; 1 hr, 35 female SD rats; 4 hr, 55 female SD rats). Further, the inhalation exposure chamber design and air concentration monitoring are highly credible and well-calibrated to current standards. The authors recommend that the Mioduszewski et al (in press) report be used as the critical*

study for GB AEGL-1 estimation, with retention of van Helden et al (2001), Harvey (1952), and Johns (1952) as secondary and supportive studies.

2) COT SUBCOMMITTEE COMMENT: Even though the respiratory uptake is 3.5-fold greater in rats compared to humans (providing relative protection to humans when the AEGL is based on rat data), rats possess an active carboxylesterase in the blood plasma, the compartment that the nerve gases first encounter after respiratory uptake. Carboxylesterase is especially important in protection from nerve gas toxicity and it is totally absent in humans (Augustinsson, 1959). Because of the absence of that enzyme and because of all other known and unknown differences between the rat and human in enzymes controlling the level of the toxic component, an interspecies UF of at least 10 should be used.

***AUTHORS' RESPONSE**: Since early February, the authors have contacted a number of investigators in the field, including Stephanie Padilla (USEPA Neurotoxicology Division at RTP), Carey Pope (Dept. Physiological Sciences, College of Veterinary Medicine, Oklahoma State Univ.), William Sette (USEPA Office of Pesticide Programs), and others. These investigators identified additional literature sources, one of which had not yet been published at the time of the Beckman Center meeting. Further, the TSD authors have more closely examined the available lethal inhalation toxicity data for rats, primates and dogs; and developed several interspecies comparisons as a means of evaluating whole-organism response.*

***Interspecies differences in carboxylesterase:** While carboxylesterases are widely considered to be absent from the blood plasma of humans, the G-agent TSD points out that carboxylesterases are, indeed, present in human erythrocytes and monocytes as well as in human liver, kidney, lung, skin and nasal tissue (Cashman et al 1996; p. 51 of the G-agent TSD, lines 3-4). Additional literature search completed since the Feb 2002 COT Subcommittee meeting has identified studies documenting the presence of carboxylesterases in many human tissues and fluids, including brain, milk, mammary gland, pancreas, small intestine, colon, stomach, placenta, as well as plasma and serum (Chanda et al 2002; Kaliste-Korhonen et al 1996). The lung carboxylesterases are associated with alveolar macrophages (Munger et al 1991). It would appear that some of the older literature quoted regarding the absence of CaE in human blood plasma (Augustinsson 1959) is not fully accurate. Further, carboxylesterases are present in human tissues and organs where exposure to nerve agent vapors would likely first occur (nasal tissues and the lung), be distributed (erythrocytes, monocytes, plasma), and generate effects (brain, stomach, colon, etc.). Carboxylesterase is also present in human serum. Recent studies indicate that full characterization of the OP-protective capabilities of carboxylesterases requires assessment not only of the **amount**, but also of the **affinity** exhibited by carboxylesterases for the inhibitor, as well as the total carboxylesterase activity unlikely to be inhibited (**inhibitor resistant esterase** activity, or IRE) (Chanda et al 2002). The detoxification potential of carboxylesterases is multifacted, and is an area requiring further experimental characterization.*

It is acknowledged that the CaE profile in humans is not well known and that there are few data from which to characterize the contributions that CaE may make to human protection from anticholinesterase poisoning. Chanda et al (2002) consider that full characterization of CaE amount, affinity and IRE in human tissues will be necessary before accurate predictions can be made regarding CaE detoxification potential following anticholinesterase exposures to humans.

Interspecies lethality estimates: *Given that the AEGL-3 estimation for the G-series nerve agents is derived from a lethal inhalation toxicity study of adult female SD rats (Mioduszewski et al 2000a,b; 2001), it is reasonable to consider the whole-organism response of lethality as an appropriate endpoint by which to compare data for rats (a CaE-rich species) with that for monkeys and dogs, two experimental species considered in earlier studies to possess no plasma carboxylesterase (Augustinsson 1959). Available experimental LCt_{50} data for the monkey, dog and rat are presented in Table 8 ("Acute inhalation lethality values for Agent GB in Animals," p. 20) of the G-agent TSD. In addition, Mioduszewski et al (2000a,b; 2001) published 5-min rat LCt_{50} values (female SD rat: 164 mg-min/m^3; male SD rat = 230 mg-min/m^3), which can be converted by use of the ten Berge et al (1986) expression (using an n value of 2) to 2-min LCt_{50} values (female SD rat: 104 mg-min/m^3; male SD rat = 145.5 mg-min/m^3). The resulting 2-min LCt_{50} ratios are*

- *Female SD rat: monkey = 104/42 = 2.5*
- *Female SD rat: dog = 104/56 = 1.9*

These comparisons indicate that, when challenged with a lethal concentration of GB vapor, adult female SD rats (Mioduszewski et al 2000a,b; 2001) are more robust than adult dogs or monkeys (Oberst et al 1961) by approximate factors of 2.0-2.5. Species differences in carboxylesterase concentrations may account, in part, for the more robust response of the adult female rats.

Human lethality estimates: *Bide et al (1999) estimate GB inhalation toxicity values for humans by application of allometric model extrapolation from extensive experimental animal data. Their study estimates that a 2-min adult human LCt_{50} approximates 31 mg-min/m^3. The resulting 2-min LCt_{50} ratio with the female SD rat is*

- *Female SD rat: human (est) = 104/31 = 3.4*

This comparison indicates that, when challenged with a lethal concentration of GB vapor, adult female SD rats (Mioduszewski et al 2000a,b; 2001) are likely to be more robust than adult humans by a factor between 3.0 and 3.5.

Comparison of AEGL estimates: *Full consideration of the reviewer's suggestion that the composite UF for estimating AEGL-3 values should be raised from 30 to 100 requires comparison of the resultant AEGL-3 estimates with those already derived for AEGL-2 and AEGL-1. In addition, AEGL-3 estimates calculated with a composite UF = 100 (for ease of reference, we will refer to these as AEGL-3X) need to be compared with available experimental data for humans and animals. These comparisons have been performed and plotted in the attached figures "Nerve Agent GB Animal Data" and "Nerve Agent GB Human Data" following the bibliography of this Authors' Response. The solid line connecting the solid black triangular points illustrates the AEGL-3 estimates calculated with a composite UF = 30 (presented as Interim AEGL-3 estimates to the COT Subcommittee on AEGLs at the Beckman Center meeting, 6-8 Feb 02). The dotted line connecting the solid black rectangular points illustrates the AEGL-3X estimates calculated with a composite UF = 100 (as recommended by reviewers who support the full default value of 10 as the interspecies UF for AEGL-3 estimation*

from the rat vapor inhalation lethality data). Application of the composite UF = 100 would "drop down" the AEGL-3 values over those for AEGL-2, making the AEGL-3X values largely indistinguishable from those for AEGL-2. Further, the resulting AEGL-3X estimates would be very much lower than most experimental data identifying concentrations where human discomfort occurs, and is thus inconsistent with the definition of AEGL-3 levels ("above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death." NRC 2001, p. 3).

AUTHORS' SUMMARY RESPONSE TO COMMENT 2):

- *An expanded examination of the literature regarding carboxylesterase (CaE) in lab animals and humans indicates that CaE is, indeed, present in human plasma as well as numerous other human tissues and organs (including those where exposure and distribution leading to death by G-agent vapor toxicity would likely occur). This expanded analysis will be added to the TSD.*

- *The known detoxification potential of carboxylesterases is multifaceted and encompasses consideration of CaE amount, affinity, and inhibitor resistant esterase activity. The present state of incomplete characterization for human CaE precludes accurate prediction regarding CaE detoxification potential in a population of humans exposed to anticholinesterase compounds.*

- *Interspecies data for comparison of the whole organism response of lethality indicates that, when challenged with a lethal concentration of GB vapor, adult female SD rats are more robust than adult dogs or monkeys by approximate factors of 2.0-2.5. Species differences in carboxylesterase concentrations may account for the more robust response of adult female rats. Model predictions of human LCt_{50} indicate a rat: human ratio of between 3.0 and 3.5.*

- *Plotted comparisons of the AEGL-3 values (AEGL-3 with a composite UF = 30 versus AEGL-3X with a composite UF = 100) indicates that application of the full default interspecies UF of 10 would make the AEGL-3X estimates largely indistinguishable from those derived for AEGL-2. Further, the AEGL-3X values are inconsistent with the results of existing human (and animal) experimental data.*

AUTHORS' CONCLUSIONS REGARDING COMMENT 2): Recent literature indicates that CaE detoxification potential exists in numerous human organs and tissue, including blood plasma. It is acknowledged that further experimental characterization of CaE detoxification potential in humans will be necessary before accurate prediction of the contributions CaE may make to human protection from anticholinesterase poisoning. Interspecies comparisons of calculated values for AEGL-3 (AEGL-3 versus AEGL 3X) with experimental GB vapor exposure lethality data for rats and monkeys (as well as estimated human LCt_{50} values) has been performed. ***The results indicate that an interspecies UF of approximately 3 for AEGL-3 determination is a reasonable characterization of the present state of knowledge for this parameter.***

3) COT SUBCOMMITTEE COMMENT: Page 56, line 30: The Harvey (1952) study is very old. Is the NAC confident of the exposure measurements? Are there any more recent studies? This is especially critical because the VX AEGLs are also based on Harvey (1952). The Baker and Sedgwick (1996) study is more complete, although it has fewer exposures. At a minimum, those studies should be tied together. The use of the Van Helden (1999) marmoset data is recommended.

AUTHORS' RESPONSE: *Please see previous response to first GB comments in this section, repeated below:*

At the February 6-8, 2002 meeting in the Beckman Center, the technical support document (TSD) authors recommended that the very excellent and state-of-the art study of marmoset threshold miosis prepared by Van Helden et al (2001; "Low-level exposure to GB vapor in air; Diagnosis/dosimetry, lowest observable effect levels, and performance incapacitation," Proceedings NATO Conference on Operational Medical Issues in Chemical and Biological Defense. Lisbon, Portugal, 14-17 May 2001), and for which there is highly credible documentation for GB vapor generation and measurement, be substituted as the critical study for AEGL-1 estimation. Further, Harvey (1952) and Johns (1952) would be retained as secondary and supportive studies. It is further noted by the TSD authors that the van Helden et al (2001a, b) study became available after the NAC made its Interim decision in June 01, that the AEGL-1 analysis of the van Helden data has already been circulated among the TSD Development Team for concurrence, and that the derivation is documented in the status report sent to each member of the COT Subcommittee on AEGLs in their briefing books. It was noted by the Subcommittee members present that there is concordance for the AEGL-1 estimates from the non-human primate (marmosets) when compared to that derived from the human data set of Harvey (1952) and Johns (1952).

In the intervening months, a more recent study on GB vapor-induced miosis in SD rats was presented at the Nashville SOT meeting (Mioduszewski et al, in press; "Low-level sarin vapor exposure in rats: Effect of exposure concentration and time on pupil size," ECBC-TR-235, US Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD; publication expected in June 2002). A preprint of this report has provided a 3rd data set to consider for the miosis endpoint. Both genders of SD rat were experimentally tested for 3 time durations of AEGL interest (10 min, 1 hr, 4 hr), and the female rat appears to be more susceptible. The ORNL Team has calculated the AEGL-1 estimations from the female rat data set.

For your information, the current Interim AEGL-1 estimates and the alternate estimates from the van Helden (marmoset; 5 hr exposure) and Mioduszewski et al (female SD rat; 10 min, 1 hr and 4 hr exposures) data sets are summarized in Table 1 provided earlier. The ***current Interim values are bolded****.*

AUTHORS' CONCLUSIONS: *At the present time, the most robust data set available for use in developing an AEGL-1 for nerve agent GB vapor exposure is that of Mioduszewski et al (in press; publication expected in June 2002). A total of 423 rats were used in this well-conducted study, of which 130 were controls. Three vapor exposure time periods, each of which is an AEGL exposure interval (10 min, 1 hr, 4 hr), were incorporated into the study design, and a sufficient number of individuals were exposed at each interval (10 min, 52 female SD rats; 1 hr,*

35 female SD rats; 4 hr, 55 female SD rats). Further, the inhalation exposure chamber design and air concentration monitoring are highly credible and well-calibrated to current standards. The authors recommend that the Mioduszewski et al (2002, in press) report be used as the critical study for GB AEGL-1 estimation, with retention of van Helden et al (2001), Harvey (1952), and Johns (1952) as secondary and supportive studies.

4) COT SUBCOMMITTEE COMMENT: Page 57, lines 24-29: What is the specific justification for the use of the Mioduszewski et al. (2000b) data for calculating the *n* value? While cholinesterase inhibition is the mechanism used as the basis for AEGL-2 and AEGL-3, there is no correlation between the decrease in cholinesterase inhibition and miosis.

AUTHORS' RESPONSE: *In the absence of other signs, miosis is a local effect and the result of direct inhibition to the cholinesterases involved in controlling contraction of the pupillary muscles. Because miosis is a local effect and confined to the tissues of the eye, there is usually little to no measurable simultaneous depression of cholinesterase activity in the blood. Because miosis is observable and measurable prior to any detectable inhibition of blood cholinesterase, it is a preferred clinical sign for early diagnosis of vapor exposures to nerve agents or pesticides with anticholinesterase properties. This was recognized by clinicians treating victims of the Tokyo Subway Incident in 1995, when cases were triaged according to whether miosis only or miosis plus other signs or symptoms were exhibited. If additional signs, such as vomiting, breathing difficulty, etc, were noted, the case was considered to have experienced systemic exposure and treated aggressively. The standard medical practice for cases of "miosis only" is to consider miosis as evidence of localized vapor exposure to the eye(s), and observe without treatment (Sidell, 1995; Sidell et al 2000).*

With greater exposures, a cascade of signs and symptoms can develop, including increasing bronchoconstriction, copious respiratory secretions, abdominal cramps, convulsions, etc. These are all the consequence of cholinesterase inhibition at synapses controlling smooth and skeletal muscles as well as glandular activity. At appropriately high agent concentrations, the chief cause of death is respiratory failure largely due to systemic effect cascade.

Thus, all toxicological endpoints identified as critical in developing AEGL-1, AEGL-2, or AEGL-3 estimates for these agents are the consequence of cholinesterase activity inhibition, and the same mechanism of toxicological action is operant at all AEGL levels. All endpoints observed in human and animal studies represent a response continuum to anticholinesterase exposure. Accordingly, it is valid to apply an "n" value derived from GB lethality data to time scaling for non-lethal endpoints. As a consequence, the "n" value developed from the well-conducted and data-rich study of SD rat lethality performed by Mioduszewski and his colleagues is appropriate for application to time-scaling for AEGL-1 and AEGL-2 endpoints.

This position is consistent with that of the Science Policy of the USEPA Office of Pesticide Programs (USEPA 2000; Office of Pesticide Programs Science Policy on the Use of Data on Cholinesterase Inhibition for Risk Assessments for Organophosphorous and Carbamate Pesticides, Aug 19, 2000).

Further, the use of an "n" derived from lethality data is supported by the AEGL SOPs (NRC 2001; p. 99); this is particularly appropriate when the mechanism of toxicity is the same.

Comparative analyses illustrating the AEGL-1 and AEGL-2 estimates resulting when either "n" = 1 or "n" = 3 were substituted into the tenBerge et al (1986) equation and presented as plots to the COT Subcommittee at the Beckman Center meeting in February. The plots also included designation of the experimental human and animal data, with emphasis on data points provided by the critical studies. Of the three "n" values considered, the plots drawn for "n" = 2 were most reflective of the available human and animal database. Retention of the "n" value of 2 seemed acceptable to the COT Subcommittee at the time.

In the intervening months, a more recent study on GB vapor-induced miosis in SD rats was presented at the Nashville SOT meeting (Mioduszewski et al, 2002, in press; "Low-level sarin vapor exposure in rats: Effect of exposure concentration and time on pupil size," ECBC-TR-235, US Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD; publication expected in June 2002). Both genders of SD rat were tested for 3 time durations of AEGL interest (10 min, 1 hr, 4 hr), and the female rat appears to be more susceptible. Miosis response data (female SD rat) from this report have been subjected to regression analysis to determine a best-fit concentration x time curve (please see regression analysis and plot "GB Vapor Mioduszewski et al 2002" provided as the last page of this package). The resulting "n" value is 2.00. These recent miosis data from a well-conducted and well-calibrated study support the use of an "n" = 2 when time scaling for non-lethal endpoints following vapor exposure to nerve agents.

Additional text expanding on the concept of an effects continuum linking the AEGL endpoints can readily be included in the next edition of the TSD.

Specific Comments

5) COT SUBCOMMITTEE COMMENT: Exposure to acetylcholinesterase inhibitors (AChEI), or organophosphates, may lead—in addition to their well-known acute effects—to long-term delayed sequelae on the peripheral nervous system. This is an important effect to consider when setting AGEL-2 values. This delayed toxicity should also be mentioned in Sections 2.3 (page 17) and 3.3 (page 33). The concept of NTE inhibition is obsolete and should only be mentioned in combination with more recent opinions on the mechanism of organophosphate-induced delayed neuropathy (OPIDN) (page 9, line 47; page 10, line 5; Sections 4.2 and 4.5.2).

AUTHORS' RESPONSE: *The authors will re-write the TSD sections where NTE is mentioned, using more recent literature already provided by the reviewer.*

Sections 2.3 and 3.3 include by reference an extensive review of nerve agent toxicity (Opresko et al 1998). The SOPs for AEGL Technical Support Document development encourage inclusion of material by reference rather than individual scholarly evaluations of all pertinent topics. The Opresko et al (1998) paper provided an examination of the literature (up to late 1997) on delayed neuropathy following experimental nerve agent exposures to laboratory species. When

supralethal doses of GA (120 X LD_{50}; mild neuropathic signs), or GB (30-60 X LD_{50}), or GD (not at 38 X LD_{50}; but delayed neuropathy observed at 120-150 X LD_{50} in a single surviving hen) are administered to adult chickens previously protected from lethality by large antidote doses, delayed neuropathy was observed for these G agents (Gordon et al 1983; Willems et al 1984). Since chickens are considered a sensitive species for this effect, it would appear that the potential for delayed neuropathy would be a concern only for those individuals surviving a greater than 30 X LD_{50} exposure to the G-agents.

The observed presence of (long-lasting but reversible) single-fibre electromyographic changes (SFEMG) in the Baker and Sedgewick (1996) report, chosen as the critical study for AEGL-2 derivation, is considered by the TSD authors to be a possible early indicator or precursor of the Intermediate Syndrome. Intermediate Syndrome is a delayed effect of some severe organophosphorous insecticide exposure cases. While not considered debilitating or permanent effects in themselves, SFEMG changes are considered in the AEGL-2 analysis to be an early indicator of exposures that could potentially result in more significant effects. Selection of the SFEMG effect as a protective definition of an AEGL-2 level is considered appropriate given the steep dose-response toxicity curve of nerve agents. The observed SFEMG change is essentially a NOAEL for AEGL-2; this determination is consistent with the AEGL SOPs (NRC 2001).

Thus, the issue of delayed neuropathic effects has been considered (by reference) and accommodated by the selection of the SFEMG effect as a protective definition of AEGL-2.

Treatment of these points can be expanded in the next edition of the TSD.

6) **COT SUBCOMMITTEE COMMENT:** Page viii, line 26: Is a UF of 10 sufficient to protect individuals with inherited pseudocholinesterase deficiency? (The incidence of the heterozygous condition low is about 3%, and the incidence of the homozygous condition low is about 1:4,000, as suggested on page 48, Section 4.5.3.)

AUTHORS' RESPONSE: *It is acknowledged that the distribution of enzyme activity variants in human populations exhibits polymorphism. Even so, the SOP analyses and guidelines regarding intraspecies uncertainty factors (Section 2.5.3.3, pp. 75-91; NRC 2001) states "the maximum variation in responses in susceptible subpopulations are believed to generally range between 3-fold and 10-fold of the responses for healthy individuals" (p. 88). Further, "a default UF of 10 is used in the development of AEGLs to account for susceptible human subpopulations" (p. 88). In keeping with the AEGL SOP, the most appropriate value for calculating AEGL estimates for nerve agents is an intraspecies UF of 10.*

This logic and SOP guidance were discussed at the Beckman Center meeting, and seemed acceptable to the COT Subcommittee at the time.

The COT Subcommittee position on intraspecies UF, as stated in the "COT SUBCOMMITTEE COMMENT 36" of this response document, indicates that "the use of a UF of 10 appears reasonable."

7) **COT SUBCOMMITTEE COMMENT:** Page ix, line 7: It is true that for the acute effects, the biochemical mechanism of toxicity in rats and humans is the same; it is not true for

the delayed peripheral neurotoxicity as shown by the large interspecies differences in response.

AUTHORS' RESPONSE: *Given that supralethal doses of the G-series agents are required to generate delayed neuropathic responses in sensitive laboratory species (hens), it would appear that the potential for delayed neurotoxicity would be a concern only for those individuals surviving a greater than 30 X LD_{50} exposure to the G-agents. As a consequence, the employment of uncertainty factors protective for the AEGL-3 endpoint would also be protective for an endpoint of delayed neurotoxicity.*

Please see earlier discussion of this point: When supralethal doses of GA (120 X LD_{50}; mild neuropathic signs), or GB (30-60 X LD_{50}), or GD (not at 38 X LD_{50}; but delayed neuropathy observed at 120-150 X LD_{50} in a single surviving hen) are administered to adult chickens previously protected from lethality by large antidote doses, delayed neuropathy was observed for these G agents (Gordon et al 1983; Willems et al 1984).

8) **COT SUBCOMMITTEE COMMENT:** Page A-2, line 32: A UF of 10 may not be sufficient to protect ACHE-deficient subjects.

AUTHORS' RESPONSE: *It is acknowledged that the distribution of enzyme activity variants in human populations exhibits polymorphism. Even so, the SOP analyses and guidelines regarding intraspecies uncertainty factors (Section 2.5.3.3, pp. 75-91; NRC 2001) states "the maximum variation in responses in susceptible subpopulations are believed to generally range between 3-fold and 10-fold of the responses for healthy individuals" (p. 88). Further, "a default UF of 10 is used in the development of AEGLs to account for susceptible human subpopulations" (p. 88). In keeping with the AEGL SOP, the most appropriate value for calculating AEGL estimates for nerve agents is an intraspecies UF of 10.*

This logic and SOP guidance were discussed at the Beckman Center meeting, and seemed acceptable to the COT Subcommittee at the time.

The COT Subcommittee position on intraspecies UF, as stated in the "COT SUBCOMMITTEE COMMENT 36" of this response document, indicates that "the use of a UF of 10 appears reasonable."

9) **COT SUBCOMMITTEE COMMENT:** A-4, lines 8-10: Is there a difference in observed effects for AEGL-1 and AEGL-2 values? Expand the text discussion to address either the degree of effect or the number of personnel affected.

AUTHORS' RESPONSE: *Text description will be expanded to more fully emphasize endpoints observed in the critical study (Baker and Sedgewick 1996) from which AEGL-2 estimates were developed (e.g, the number of subjects exhibiting miosis, dyspnea and photophobia, single-fibre electromyographic changes, and RBC-ChE inhibition). Care will be taken to point out that observed endpoints illustrate a continuum of response, and are indicative of systemic exposure. Further, as a consequence of COT Subcommittee guidance, the critical study for calculation of AEGL-1 estimates will now be one for a laboratory species exhibiting quantitative and*

significant miosis. Thus the difference between observed effects for the AEGL-1 and AEGL-2 determinations will be far more marked in the next edition of the TSD.

10) COT SUBCOMMITTEE COMMENT: Page 2, line 46 and page 3, line 9: (3×10^{-6} mg/m^3)(480 min) = 0.00144 mg-min/m^3(CDC-CSEPP). That is significantly less than the 0.5 mg-min/m^3 on line 9 and also on page 12, line 30.

AUTHORS' RESPONSE:

The two Cts under consideration do not have equivalent toxicological endpoints; they are defined differently and have different applications.

The current control limit for general public exposure to agents GB and GA of 3×10^{-6} mg/m^3 is a no-adverse-health-effect level for continuous exposure (24 hours/da) (see 53 FR 8504, 15 Mar 1988). This concentration would represent a GB Ct of 0.004 mg-min/m^3 for a 24-hour continuous exposure. Please note that the CDC considers a GB/GA air concentration of 3×10^{-6} mg/m^3 would pose no adverse health risk to the public (including sensitive subpopulations) for extended time periods in excess of 24 hours' duration.

The Agent Threshold Effect Level identified in line 9 of page 3 is a Ct of 0.5 mg-min/m^3 for agent GB, and is considered, for the purposes of emergency planning, to be a "lowest-observed-effect-level" that could be exceeded without danger. However, if projected GB concentrations resulting from a release event would result in Cts >0.5 mg-min/m^3, then evacuation procedures are considered warranted to provide maximal protection to safeguard the general public. The CDC considered that the steep slope of the dose-response toxicity curve for nerve agents justifies this caution.

Please see an existing discussion of these concepts in Section 8.2, pp. 72-73, of the G-series agent TSD under review at the Beckman Center meeting.

11) COT SUBCOMMITTEE COMMENT: Page iv and further: General comment on respiratory uptake: It seems that all calculations are based on the assumption that the minute volume remains constant. However, in a case of calamity, respiratory rate may increase considerably through physical exertion during attempts to escape, thus leading to increased pulmonary uptake.

AUTHORS' RESPONSE: *Minute volumes up to about 25 L/min should cover most situations involving civilian populations; however, as the reviewer points out, breathing rates may be higher under stressful evacuation conditions. Dosimetric adjustments based on breathing rate are not normally considered by the AEGL protocol (please see Sect. 2.4, p. 57, of the SOP; NRC 2001). In the case of the G-series agents, such a dosimetric adjustment would not be necessary for the AEGL-1 (and to some extent, the AEGL-2) values, which are based on a local effect to the eye (miosis) as the most sensitive indicator of exposure toxicity. Changes in respiratory rate would not affect the miosis endpoint.*

12) COT SUBCOMMITTEE COMMENT: Page 3, line 2: What is the validity of miosis as a primary adverse health effect? Is it because it can be measured quite well, or is it really

the most sensitive parameter? Rhinorrhea could be more sensitive, but it is difficult to measure (page 47, line 41) (see also Hardy 1952).

AUTHORS' RESPONSE: *A number of investigators consider both miosis and rhinorrhea to be early signs of exposure to cholinesterase inhibitors. The presence of rhinorrhea can be indicative of inhalation exposure and/or development of systemic effects, while miosis only in the absence of other signs or symptoms is a local effect to the pupillary muscles of the eye. As a consequence, the presence of miosis is considered an appropriately sensitive indicator of direct vapor exposure, with the additional advantage of being readily recognized and quantifiable.*

13) **COT SUBCOMMITTEE COMMENT:** Page 4: Whole-body exposure experiments are a combination of inhalation and dermal/mucosal uptake; thus, the results may not always be relevant for setting air standards.

AUTHORS' RESPONSE: *The reviewer may be referring to p. 4 of the Status Report accompanying the TSD.*

Agreed. Nevertheless, it is generally acknowledged that a specific toxicological endpoint for vapor exposure to nerve agents will be achieved at a lower concentration exposure for the inhalation route than for other routes (e.g., the estimated human LCt_{50} for percutaneous vapor exposure to agent GB is 10,000 mg-min/m^3, while the estimated human LCt_{50} for inhalation vapor exposure to agent GB is <35 mg-min/m^3; NRC 1997).

14) **COT SUBCOMMITTEE COMMENT:** Page 4: The way the AEGL values are expressed using a large number of zeros after the decimal point suggests certain degree of accuracy that does not exist. These values should be rounded to the nearest 0 or 5 and expressed in micrograms per m^3.

AUTHORS' RESPONSE: *The recommended presentation of AEGL values is to provide two significant figures. In addition, the primary users of nerve agent AEGL values are employing emergency response models and training based on air concentration values provided in units of mg/m^3 (state and federal regulatory agencies and the DoD). As a consequence, the AEGL estimates are provided both in units of mg/m^3 and ppm.*

At the Beckman Center meeting it was further agreed that introduction of a new unit such as micrograms/m^3, while scientifically accurate, would be unfamiliar to the end users (who are used to working with mg/m^3), and unnecessary errors would likely be introduced in end user applications.

15) **COT SUBCOMMITTEE COMMENT:** Page 5, line 3: In the chemical name, "ethyl" is missing.

AUTHORS' RESPONSE: *Thank you for catching this error. Corrections will be made in Table 1, line 5 (p. 5) and the Executive Summary (p. vi, line 8).*

16) **COT SUBCOMMITTEE COMMENT:** Page 11, line 34: The most sensitive effect is apparently rhinorrhea, but it is apparently difficult to quantify accurately.

AUTHORS' RESPONSE: *A number of investigators consider both miosis and rhinorrhea to be early signs of exposure to cholinesterase inhibitors. The presence of rhinorrhea can be indicative of inhalation exposure and/or development of systemic effects, while miosis only in the absence of other signs or symptoms is a local effect to the pupillary muscles of the eye. As a consequence, the presence of miosis is considered an appropriately sensitive indicator of direct vapor exposure, with the additional advantage of being readily recognized and quantifiable.*

17) **COT SUBCOMMITTEE COMMENT:** Page 13, line 20-21: Again, miosis is not the earliest effect.

AUTHORS' RESPONSE: *A number of investigators consider both miosis and rhinorrhea to be early signs of exposure to cholinesterase inhibitors. The presence of rhinorrhea can be indicative of inhalation exposure and/or development of systemic effects, while miosis only in the absence of other signs or symptoms is a local effect to the pupillary muscles of the eye. As a consequence, the presence of miosis is considered an appropriately sensitive indicator of direct vapor exposure, with the additional advantage of being readily recognized and quantifiable.*

18) **COT SUBCOMMITTEE COMMENT:** Page 13, line 42: RBC or plasma ACHE?

AUTHORS' RESPONSE: *Morita et al (1995) reported findings for both "Acetylcholinesterase in erythrocytes (E-AchE)" and "serum ChE."*

19) **COT SUBCOMMITTEE COMMENT:** Page 17, line 31: add "and peripheral nervous system."

AUTHORS' RESPONSE: *This additional material will be added to the next edition of the TSD.*

20) **COT SUBCOMMITTEE COMMENT:** Page 33, line 21: add "and peripheral nervous system."

AUTHORS' RESPONSE: *This additional material will be added to the next edition of the TSD.*

21) **COT SUBCOMMITTEE COMMENT:** Page 39, line 35 to page 40, line 37: With respect to the metabolism issues that are confusing (including the fact that the respective studies were spread over decades during which names and sometimes assignments of identity of enzymes changed), it would be helpful to the reader if the following editorial changes were performed: (1) give the entire metabolism information here (under the heading "metabolism") and do not provide part of it in other sections (such as "species differences"); (2) give a complete synopsis of all enzymes (substantially) contributing to detoxication of the toxic compounds and of their differences among the animal species used for the toxicity studies and humans; (3) give all synonyms of the enzymes (and point out where assignments of the identity of the enzyme is uncertain) rather than leave it up to the reader to distinguish whether a different name in a later paragraph refers to the same enzyme mentioned before.

AUTHORS' RESPONSE: *The authors appreciate these specific suggestions to improve the text presentation, and will address Dr. Oesch's recommendations. Dr. Oesch points out text reflective of changes in the evolution of enzyme naming conventions throughout the time period*

covered by the cited literature. In particular, the synonymy between "aliesterase" and "carboxylesterase" requires clarification in the text. The scientific community acknowledges that the nomenclature and classification of mammalian carboxylesterases needs greater clarity (Satoh and Hosokawa 1998). Edited text incorporating contemporary naming conventions is being prepared to address this comment, and will be substituted for existing text.

22) **COT SUBCOMMITTEE COMMENT:** Page 40, lines 23-33: Beside the 6-fold differences in human paraoxonase observed by Kujiraoka et al. (2000), it may be advantageous to also mention the much larger (40-fold) differences observed by Furlong et al. (1989).

AUTHORS' RESPONSE: *This additional point regarding 40-fold differences observed in Furlong et al (1989) will be added to the next edition of the TSD.*

23) **COT SUBCOMMITTEE COMMENT:** Page 41, line 26: OPIDN, or dying back phenomenon, is not due to ACHE inhibition.

AUTHORS' RESPONSE: *The next edition of the TSD will include new text describing the "dying back" neuropathy in terms of axonal transport blockage, as clarified in new reference material provided to the TSD authors by Dr. de Wolff (de Wolff et al, 2002).*

24) **COT SUBCOMMITTEE COMMENT:** Page 46, line 9: The argument is not convincing as to why RBC-CHE was rejected as a critical end point.

AUTHORS' RESPONSE: *Additional text describing population and individual variability of RBC-ChE activity will be incorporated here.*

25) **COT SUBCOMMITTEE COMMENT:** Page 47, lines 40-41: See remarks on page 11 and page 13; miosis is not the most sensitive indicator.

AUTHORS' RESPONSE: *A number of investigators consider <u>both</u> miosis and rhinorrhea to be early signs of exposure to cholinesterase inhibitors. The presence of rhinorrhea can be indicative of inhalation exposure and/or development of systemic effects, while miosis only in the absence of other signs or symptoms is a local effect to the pupillary muscles of the eye. As a consequence, the presence of miosis is considered an appropriately sensitive indicator of direct vapor exposure, with the additional advantage of being readily recognized and quantifiable.*

26) **COT SUBCOMMITTEE COMMENT:** Page 47, lines 48-50: The neuropathy target esterase (NTE) theory is obsolete; the current literature on this point should be reviewed and the entire section should be rewritten and updated.

AUTHORS' RESPONSE: *The authors will re-write the TSD sections where NTE is mentioned, using more recent literature already provided by the reviewer (de Wolff, et al 2002).*

27) **COT SUBCOMMITTEE COMMENT:** Page 48, line 40: Incidence may be much higher, but it is in a recognizable susceptible group.

AUTHORS' RESPONSE: *Agreed.*

28) **COT SUBCOMMITTEE COMMENT:** Page 53, line 23: Not only skin absorption of vapor but, more importantly, percutaneous uptake of the aerosol droplets should be considered here.

AUTHORS' RESPONSE: *While it is recognized that droplets and/or aerosols may be present during certain release events (as they may be for numerous other industrial compounds reviewed during the AEGL process), the focus of the present AEGL activity (and the community emergency preparedness need) for these compounds is vapor exposure.*

29) **COT SUBCOMMITTEE COMMENT:** Page 54, Section 4.5.7, line.33: Protective clothing can have an adverse effect. Some materials absorb the organophosphates, and because of occlusion of the skin, the proposed "protection" afforded by certain types of clothing will work as an absorption-promoting device.

AUTHORS' RESPONSE: *Agreed.*

Nevertheless, the percutaneous vapor concentrations necessary to reach the same endpoint is far in excess of the respiratory concentrations required, as discussed earlier (e.g., the estimated human LCt_{50} for percutaneous vapor is 10,000 mg-min/m^3, while the estimated human LCt_{50} for inhalation vapor is <35 mg-min/m^3; NRC 1997). If emergency response control limits for the public (not equipped with personal protective clothing) are developed so as to safeguard against an adverse inhalation exposure, then the public will also be simultaneously safeguarded against a percutaneous vapor exposure. This is a protective position.

Further, emergency responders suited in personal protective clothing operate under additional safeguards in the form of limited stay times, observer and atmospheric monitoring, etc.

30) **COT SUBCOMMITTEE COMMENT:** Page 54, line 48: Casualty Management and Care. The section is not relevant, and it should be deleted.

AUTHORS' RESPONSE: *The section on casualty management and care was added at the express direction of the NAC. At the Beckman Center meeting, the TSD authors agreed that this material is inappropriate for inclusion in an analysis of AEGL values, and that the identified text (Sect. 4.5.7) would be deleted.*

31) **COT SUBCOMMITTEE COMMENT:** Page 60, line 5: The most relevant parameter for long-term adverse health effects for the derivation of AEGL-2 values is peripheral neurotoxicity.

AUTHORS' RESPONSE: *Literature review that took place during the development of the Technical Support Document revealed no controlled nerve agent vapor exposure studies in animal or human subjects for the specific endpoint of peripheral neurotoxicity.*

The critical study by Baker and Sedgewick (1996) was selected because it did examine single fibre electromyographic (SFEMG) changes as a possible early indicator of the nondepolarizing neuromuscular block found associated with the Intermediate Syndrome paralysis noted in some cases of severe organophosphorous insecticide poisoning. The Baker and Sedgewick (1996) study concluded that the SFEMG changes were persistent (>15 months), but reversible and

subclinical. While not considered debilitating or permanent effects in themselves, the TSD authors consider SFEMG changes to be an early indicator of agent exposures that could potentially result in more significant effects at a slightly greater concentration. The TSD authors further consider selection of this effect to be a protective definition of an AEGL-2 effect level.

32) **COT SUBCOMMITTEE COMMENT:** Page 64, line 17 and page 65, line 1: With different detoxification mechanisms, why was the interspecies UF of 3 applied instead of 10?

AUTHORS' RESPONSE: *This comment has been previously addressed in the response to an earlier, General Comment (see p. 5 of this Authors' Response for an extensive response regarding analysis of interspecies differences in carboxylesterases, etc.)*

33) **COT SUBCOMMITTEE COMMENT:** Page 70, lines17-19: Reconsider the AEGL value in light of the SOP definition.

AUTHORS' RESPONSE: *The cross-comparison of AEGL estimates with the existing data characterizing toxic response in experimental animals and volunteer human subjects reveals that the Interim AEGL-1, -2, and -3 estimates for these compounds are highly protective determinations.*

As a consequence, many would consider that consideration of additional reductions in the Interim AEGL estimates for the G-series nerve agents would not be well supported by existing toxicological data.

34) **COT SUBCOMMITTEE COMMENT:** Page 79, line 16: Is that the current document? Consider the recent non-stockpile EIS.

AUTHORS' RESPONSE: *DA (1988) is the final Programmatic EIS document for the* ***stockpile*** *disposal program. Thank you for the citation to the non-stockpile EIS.*

35) **COT SUBCOMMITTEE COMMENT:** Page 91, line 38: Is that the current version?

AUTHORS' RESPONSE: *The citations (USACMDA 1993 a,b) refer to two preliminary survey reports identifying the presence and extent of the non-stockpile problem; experimental data were not sourced to either of these reports. If more recent surveys have been published, the TSD authors would appreciate the citations.*

36) **COT SUBCOMMITTEE COMMENT:** The subcommittee recommends that this chapter provide tables that compare properties, human and animal toxicity data, and epidemiologic data for all of the agents. It is apparent that the bulk of the data was generated for GB. Relatively few empirical data exist for the remainder of the congeners in this series. The cancer summary on page 38 and the general summary on the same page are important and the subcommittee concurs that the AEGL values for GA, GD, and GF must be derived by extrapolation of the GB values. GA is potentially more toxic than GB. Sidell (1974) claims that the reason the workers exposed to GB and treated within 20 min survived (page 14), whereas others exposed to GA and treated within the same time died is because the half-life of GB is longer than that of GA (70 min vs 11 min). The discussion of the "Desert Storm illness" etiology was balanced, but not

contributory. The subcommittee would like to see a scholarly evaluation of potential biomarkers and other end points for evaluating exposure in the epidemiology and relative potency sections.

The NRC subcommittee agrees that RBC cholinesterase is a poor indicator of toxicity (see Storm et al., 2000), and the subcommittee believes that NAC's comments on OP insecticides strengthen this section. Organophosphates exhibit gender differences in susceptibility, much like the G agents (Table 15), and there are probably also significant age differences in susceptibility. Therefore, the use of a UF of 10 appears reasonable.

VX could also be included with the G agents because the NAC uses the Harvey (1952) study for developing AEGL-1 values and the Baker and Sedgewood (1996) study for AEGL-2 values, but it is not clear why there is an additional UF of 3 for poor quality of data for VX and not for GA, GD, or GF. The NAC should eliminate the anecdotal reports on Desert Storm.

Although the subcommittee understands that the NAC's charge was to address inhalation exposures, these agents may have a strong dermal-exposure component that cannot be ignored. Percutaneous absorption will be especially important for some victims in the immediate vicinity of GB release and for remedial investigation and cleanup responders to an incident involving release and dispersion of those materials.

AUTHORS' RESPONSE: *As existing data allow, tables summarizing the requested parameters, and an examination of biomarkers for evaluating exposure (epidemiology and relative potency sections) can be developed.*

The discussion of "Desert Storm" reports and anecdotes will be deleted.

The above comment "The subcommittee would like to see a scholarly evaluation of potential biomarkers and other end points for evaluating exposure in the epidemiology and relative potency sections" appears to be drawn from Dr. Doull's written review comments distributed at the Beckman Center meeting and read into the meeting record in Dr. Doull's absence. His written comments state "...I like the scholarly evaluation of potential end points for evaluating exposure in the epidemiology and relative potency sections." It would appear that the "scholarly evaluation" is already present to a large extent in the Technical Support Document. If the Subcommittee wishes the authors to address additional and specific points or reference materials in the epidemiology and relative potency sections, please advise.

The TSD authors concur with the COT Subcommittee position that "the use of a [intraspecies] UF of 10 appears reasonable."

The TSD authors concur with the COT Subcommittee position that the analysis for VX can be incorporated into the analysis for the G-series agents.

The NAC considered that agent VX possessed sufficiently different physical and chemical properties to be deserving of separate database consideration, while still acknowledging that the primary mechanisms of toxicity are the same for all nerve agents. The NAC further considered that the G-series agents are all sufficiently similar in volatility and chemical properties such that the preponderance of similar data for the G-agents allowed these compounds to be logically considered together (and differing primarily in the matter of relative toxic potency).

It is understood and acknowledged that the agents may have a dermal exposure component of concern. This is an issue for other, commercial hazardous materials evaluated by the AEGL process, as well. The issue of percutaneous exposure is taken seriously and is stressed in decontamination and training requirements for nerve agent emergency responders as well as residents in host communities adjacent to the unitary stockpile sites. At present, the AEGL SOPs (NRC 2001) do not address a protocol for developing "dermal AEGLs."

COMMENTS ON NERVE AGENT VX

At its February 6-8, 2002 meeting, the subcommittee reviewed the AEGL document on VX. The presentation was made by Annetta Watson of Oak Ridge National Laboratory. The subcommittee recommends a number of revisions.

General Comments

1) **COT SUBCOMMITTEE COMMENT:** Although considerable data are presented, the AEGL values for VX are based on the relative potency of VX and GB; VX is considered to be 12 times more acutely toxic than GB. Although there are data to support the contention for 12 times greater potency for miosis (applicable to AEGL-2 and AEGL-3 values in one species), the evidence does not appear to be sufficient to support the potency factor of 12 for AEGL-3 values if ChE_{50} is used as the indicator of lethality. In addition, the GB base study is questionable. Data are presented in Table 8, page 25, that contradict the 12-times greater potency relationship. The NRC subcommittee recommends using a value of 5-7 for relative potency in deriving AEGL-3 values. It should also be noted that the CDC recommendation is the same as that for GB.

   Another consideration in the relative potency factor for miosis appears on page 36, line 20: VX is more potent than GB for miosis in one species only. This observation might not hold for other toxic effects in other species. The subcommittee therefore recommends rounding the relative potency factor to 10.

AUTHORS' RESPONSE: *The available experimental data base for comparing the potency of agent GB relative to agent VX is summarized in Tables 7 and 8 (pp. 24-25) of the TSD for agent VX; the Table entries in* ***bold*** *are those for experimental and primary sources; the non-bolded ratios are those found in secondary or derivative sources. Primary data for GB-to-VX comparisons (same endpoint) are available for 3 mammalian species. In all cases, agent VX is more potent than agent GB.*

Human inhalation (Oberst et al 1961; Bramwell et al 1963) and human oral (Grob and Harvey 1958; Sidell and Groff 1974) exposures are included in the experimental data base summarized in Tables 7 and 8 of the TSD for agent VX; reported endpoints for each human study were ChE_{50}. The Bramwell et al (1963) study of VX inhalation toxicity is considered a flawed and nonverifiable source because the human subjects were not exposed to a rigorously controlled atmosphere [breathing zone concentrations could not be determined, potential effects of the carrier solvent (benzene) on agent absorption by subject not evaluated, etc.]. As a consequence, the GB: VX ratio for inhalation ChE_{50} [which includes the VX Ct from Bramwell et al (1963)] is

not as credible as the comparable ratio derived from the well-conducted human oral exposure studies of Grob and Harvey (1958) and Sidell and Groff (1974). In addition, the oral exposure studies evaluate the effects of known agent doses (• g/kg). Of the values derived from available human data, the GB: VX ratio calculated from oral dose exposures needed to achieve RBC-ChE_{50} is the most credible.

With no adjustments for differences in recovery or reversibility ("aging"), direct application of experimental data from human subjects for the ChE_{50} endpoint supports a GB: VX relative potency estimate of 4.2. Because the ChE_{50} endpoint is part of the continuum of response for these anticholinesterase compounds, it is consistent to apply the same RP for estimating AEGL-1, AEGL-2 and AEGL-3 values for agent VX.

The authors recommend a RP of 4.2 (rounded to 4.0) to characterize the GB: VX potency ratio for all AEGL levels.

With regard to the CDC recommendation, one reviewer at the Beckman Center meeting cited the relative GB: VX potency of 12 as given in a CDC Federal Register notice (67 FR 894: 8 Jan 2002). The TSD authors also provided a file of this notice to the COT Program Director in the first weeks following the Beckman Center meeting. In that FR notice, the CDC cited the NAC/AEGL Technical Support Document as its source for this relative potency determination of 12, as well as the Callaway and Dirnhuber (1971) paper on rabbit miosis as the critical study for relative potency determination. The CDC cited no new information or analyses regarding relative potency, but repeated the analysis contained in the NAC/AEGL TSD for agent VX. Thus, the CDC analysis for VX relative potency as contained in the FR notice of 8 Jan 02 is duplicative of the NAC relative potency argument contained in the Interim VX AEGL Technical Support Document under review by the COT Subcommittee.

2) **COT SUBCOMMITTEE COMMENT:** Page 31, lines 22-24 and page 32, lines 1-4: It is not clear whether the NAC recommendation to use a UF of 10 also applies to VX. If the "aliesterases" on page 32, line 1, refer to the same entity as "carboxylesterases" of page 31, line 22, then the proposed UF of 3 for interspecies differences pertinent to AEGL-3 determination is appropriate. If the two names refer to two different entities, it is likely that the NAC's recommendation to increase the UF for interspecies differences relevant to AEGL-3 determination for GB to 10 also apply to VX. A revised description in the text would be helpful including clarification of whether the reference to "these compounds" in line 2 of page 32 means "these enzymes."

AUTHORS' RESPONSE: *Dr. Oesch points out where the TSD text reflects changes in the evolution of enzyme naming conventions throughout the time period covered by the cited literature. In particular, the synonymy between "aliesterase" and "carboxylesterase" requires clarification in the text. The scientific community acknowledges that the nomenclature and classification of mammalian carboxylesterases needs greater clarity (Satoh and Hosokawa 1998). Edited text incorporating contemporary naming conventions is being prepared to address this comment, and will be substituted for existing text.*

The detoxification potential of endogenous carboxylesterase to protect against the lethal effects of nerve agent exposure was tested by Maxwell (1992) in (male) SD rats. Nerve agents GA, GB,

GD, or VX in isotonic saline were administered by s.c. injection. The degree of in vivo CaE inhibition was measured in the plasma, lung and liver of exposed rats. In vivo protection provided by endogenous CaE was estimated by comparing differences in LD_{50} following nerve agent exposures to rats with inhibited CaE activity [following administration of the probe, 2-(O-cresyl)-4H-1,3,2-benzodioxaphosphorin-2-oxide] versus nerve agent exposures to rats without inhibited CaE activity. Maxwell determined that endogenous CaE in the rat provided no significant protection against in vivo lethal exposures to nerve agent VX under the experimental protocol employed; further, Maxwell concluded that "CaE detoxification does not appear to be important" against exposures to lethal concentrations of agent VX.

AUTHORS' CONCLUSIONS REGARDING COMMENT 2): *The SD rat in vivo experimental results of Maxwell (1992) indicate that endogenous CaE in this species confers no protection against lethal exposures of nerve agent VX. Thus, rats exposed to VX should not be considered more robust than other species possessing a different CaE profile.*

3) COT SUBCOMMITTEE COMMENT: Dermal absorption could be a major potential source of exposure, so the subcommittee recommends the addition of a section to address this hazard. Although initial exposure would likely be to vapor or aerosol, site remediation efforts would expose response personnel to the dermal hazards of VX.

The NAC should also address the issue of exposure to aerosols versus vapors. There may or may not be a difference in delivered dose and, therefore, toxicity. Although there are no experimental data, the issue should be addressed, if only in a theoretical framework (U.S. EPA, 1987; Oxo-Process Panel, 1995). It could also be discussed and submitted as a research need.

AUTHORS' RESPONSE: *New text providing greater emphasis on the percutaneous hazard posed by VX surface contamination and the potential for aerosol generation during an energetic release can be added to the TSD. Further, specific research necessary to more fully characterize the vapor toxicity as well as the percutaneous toxicity of agent VX can be highlighted in the document.*

Greater emphasis can be placed on the fact that the AEGL estimates are for vapor exposure only, and cautions to that point emphasized in AEGL summary tables.

At present, AEGL guidelines have been developed with an emphasis on vapor exposures. Specific protocols for aerosol exposures may be considered at some future date, and would apply not only to agent VX, but also to the numerous other, industrial, hazardous materials that are likely to exhibit an aerosol component during release events.

The documents identified are being located for author consideration.

4) COT SUBCOMMITTEE COMMENT: VX is 10 times as acutely toxic as GB on a mechanistic basis; however, the low volatility, lipophilicity, and persistence increase the risk of VX dermal absorption in comparison with GB. Therefore, overall risk of VX exposure may therefore be much higher than the 10 or 12 times cited. The text should indicate that the 10- or 12-times greater potency is appropriate for vapor exposures.

AUTHORS' RESPONSE: *There is no question that agent VX poses a dermal absorption risk; this point can be more specifically emphasized in the TSD, as addressed in "Authors' response" to Comment 3) above. Nevertheless, the sponsor has noted that the more immediate need is for an agent VX vapor emergency guideline level, with the potential for developing a comparable guideline for agent VX aerosol exposure at some future time.*

Text can be added to emphasize that the current AEGL determinations are intended for application to vapor exposure only.

5) **COT SUBCOMMITTEE COMMENT:** Delayed, long-term peripheral VX neurotoxicity cannot be excluded. The relative potency compared with GB for this effect may also be higher and rigorous discussion of this end point should be presented.

AUTHORS' RESPONSE: *Literature on this point is summarized in Section 4.5.2, "Delayed Neuropathy," pp. 29-30 of the nerve agent VX TSD. In tests with chickens, a susceptible species, delayed neuropathy was not observed in 3 strains of antidote-protected chickens given a single s.c. dose of VX equivalent to 5-10 times the lethal dose. Further, repeated supralethal i.m. injections of VX (each injection being equivalent to 1.3 times the LD_{50}) for either 3 days/wk over 30 days, or 5 days/wk over 90 days, produced no signs of organophosphate-induced delayed neuropathy (Goldman et al 1988; Wilson et al 1988). It is true that, in rats, continuous s.c. exposure via osmotic pump to a daily supralethal dose equivalent to 1.3 times the s.c LD_{50} is reported to generate myopathy in the soleus muscle (Lenz et al 1996). Nevertheless, application of the Lenz et al (1996) results seems appropriate only for individuals who survive lethal concentration exposures (which are well above Interim AEGL-3 values).*

6) **COT SUBCOMMITTEE COMMENT:** The NAC selected UFs of 3 or 10 for intraspecies extrapolation rather randomly. The NAC should provide a sound rationale for the selection of every uncertainty factor used. Include the literature reference for the 12-times greater potency of VX relative toxicity for miosis in the executive summary. Although the argument presented is convincing, it is buried in the document.

AUTHORS' RESPONSE: *Additional text can be added to the Executive Summary identifying the specific study and logic employed for development of the relative potency factor.*

The logic used to develop an uncertainty factor estimate to address interspecies variability in the AEGL-3 determination is the same for both agent GB and agent VX. Any potency difference in agent elicitation of the same response (lethality) in the same species (SD rat) is intended to be accommodated by the relative potency factor, since there are insufficient experimental data from which to derive a direct interspecies comparison. Agent VX database limitations are accommodated by the application of an (additional) modifying factor (MF = 3) in the AEGL estimation. Thus, the concern is still that of comparing the lethality responses of female SD rats to the estimated human lethality response for agent GB. This issue was addressed at length in the companion authors' response for the G-agents

Further, there appears to be insufficient evidence on which to base an interspecies uncertainty factor of a value greater than 3 for the rat-to-human extrapolation performed in the Agent VX Interim TSD for AEGL-3 effects under review. As previously discussed in the earlier response to

COT Subcommittee Comment 2), the SD rat in vivo experimental results of Maxwell (1992) indicate that endogenous CaE in this species confers no protection against lethal exposures of nerve agent VX. Thus, rats exposed to VX should not be considered more robust than other species possessing a different CaE profile (e.g., humans).

Briefly, then, interspecies comparisons of calculated values for AEGL-3 (AEGL-3 versus AEGL 3X) with experimental GB vapor exposure lethality data for rats and monkeys and dogs (as well as estimated human LCt_{50} values) has been performed. The results indicate that an interspecies UF of approximately 3 for AEGL-3 determination is a reasonable characterization of the present state of knowledge for this parameter, for all the nerve agents under consideration (G-series as well as VX).

Specific Comments

7) **COT SUBCOMMITTEE COMMENT:** Page vii, lines 7-18: Include the Callaway and Dirnhuber (1971) citation, and state that this is based on rabbit data.

AUTHORS' RESPONSE: *Can do.*

8) **COT SUBCOMMITTEE COMMENT:** Page vii, lines 33-34: AEGL-1 and AEGL-2 values for VX are not based on human data. They are based on human exposure to GB.

AUTHORS' RESPONSE: *Additional clarifying text can be added to these lines.*

9) **COT SUBCOMMITTEE COMMENT:** Page 7, lines 43-46: How can the NAC justify including the results of unethical experiments?

AUTHORS' RESPONSE: *First,* ***the referenced study*** *(Kimura, KK, BP McNamara and VM Sim. 1960, Intravenous administration of VX in man. U.S. Army Chemical Research and Development Laboratory, Technical Report No. 3017. Army Chemical Center, MD)* ***is not considered "unethical."*** *This experiment was performed with the informed consent of the participants, under full clinical supervision, and in a hospital setting considered suitable for the time (resuscitation team at bedside "to administer atropine, oximes, oxygen, artificial resuscitation and tracheotomy if indicated"). Many of the observed effects summarized on p. 7 of the Interim TSD are those noted for the single subject of the dose-response range-finding study—Dr. Van Sim, MD, a principal investigator of the reported study. Dr. Sim, a physician, was an internationally known investigator in this field, had previously performed research at Porton Down on nerve agent induced miosis, and volunteered to be the subject for the reported investigation. Dr. Sim was most certainly an informed volunteer. The same Technical Report No. 3017 included summaries of observed effects noted for 6 additional volunteers, identified by subject codes, who were also similarly monitored under the Clinical Research Division Volunteer Program.*

When this issue was brought up by the COT Subcommittee reviewer at the Beckman Center meeting, the AEGL SOPs for the application of human data to AEGL estimation (Sect. 2.3.2, "Evaluation, Selection, and Documentation of Key and Supporting Data," especially material on

p. 53; NRC 2001) were discussed. Key to acceptance of human subject data for use by the AEGL process is evidence that subjects provided informed consent, and that the studies were performed under appropriate clinical supervision. All these criteria can be met by the Kimura et al 1960 study.

This determination seemed to be acceptable to the COT Subcommittee at the time.

Please note that the Kimura et al (1960) report has not been used in the TSD as a critical study for the development of AEGL estimates.

10) **COT SUBCOMMITTEE COMMENT:** Page 8, line 34: How relevant is dermal vapor absorption for this low-volatility substance? Dermal absorption of aerosol droplets may be more relevant as it is a potentially high-risk mode of exposure.

AUTHORS' RESPONSE: *Dermal vapor absorption is a low priority for this compound, although there are certain release events that will generate a dermal vapor threat. It is generally acknowledged that a specific toxicological endpoint for vapor exposure to nerve agent VX will be achieved at a lower concentration exposure for the inhalation route than for other routes (e.g., the estimated human LCt_{50} for percutaneous vapor exposure to agent VX is 150 mg-min/m^3, while the estimated human LCt_{50} for inhalation vapor exposure to agent VX is <15 mg-min/m^3; NRC 1997). Thus, AEGL estimates based on non-dermal exposures are considered protective for both inhalation and dermal routes.*

Please see also earlier response to COT Subcommittee Comment 3).

11) **COT SUBCOMMITTEE COMMENT:** Page 10, line 6-8: How were these symptoms quantified? They appear subjective.

AUTHORS' RESPONSE: *As stated in lines 10-12, mood alterations were determined by results of Clyde Mood card sort (Bowers et al 1964).*

Intellectual impairment was determined as follows: impairment of ability to perform simple arithmetic tasks, inability to perform serial sevens, impairment of performance in reading or standard games of concentration, and other, subjective, symptoms ("impairment in orientation") (Bowers et al 1964).

Anxiety was determined by the appearance of palpitations, coupled with other, subjective symptoms ("restlessness").

Psychomotor depression was determined by the appearance of reply latency, slowed speech, and evidence of fatigue; in addition to other, subjective, symptoms (reported feelings of being "slowed down").

12) **COT SUBCOMMITTEE COMMENT:** Page 17, lines 27-33: This statement needs to be revised and clarified.

AUTHORS' RESPONSE: *Descriptions of blood cholinesterase depression will be clarified (from that used by the Crook et al 1983) so that "reduced to 92% of control" will be replaced by*

decrement language such as "decreased by 8% from baseline control." Similarly, "[reduced] to 24% of control" will be replaced by "decreased by 76% from baseline control."

13) **COT SUBCOMMITTEE COMMENT:** Page ix: What is the practical use of these homeopathic levels? Can these end points be analyzed in any rigorous fashion? AEGL-1 for 8 h = 28 ng/m^3. Does the NAC mean to imply that exposure to 27 ~~ppm~~ is safe and 29 ~~ppm~~ ~~is~~ toxic?

AUTHORS' RESPONSE: *AEGLs are considered predictive values, and, as such, are not intended to be definitive thresholds. This concept is true for all hazardous compounds considered in the AEGL program, and is not confined to chemical warfare agents only.*

The primary users of nerve agent AEGL values are developing and running emergency response models for pre-incident identification of hazard zones and protective actions (shelter-in-place, etc.). Effect-level estimates such as AEGL values are considered valuable as decision criteria for advance planning and identification of hazard zone boundaries.

In addition, emergency response planning and training by end users (state and federal regulatory agencies and the DoD) are based on air concentration values provided in units of mg/m^3. As a consequence, the AEGL estimates for the chemical warfare agents are provided both in units of mg/m^3 and ppm (the precedent was established for the chemical warfare agent sulfur mustard by the COT Subcommittee some time ago).

At the Beckman Center meeting it was further agreed that introduction of a new concentration unit such as nanograms/m^3, while scientifically accurate, would be unfamiliar to the end users (who are used to working with mg/m^3), and unnecessary errors would likely be introduced in end user applications.

14) **COT SUBCOMMITTEE COMMENT:** Page 21, line 4: Two species—what about the rats mentioned on page 13?

AUTHORS' RESPONSE: *For clarity, the text on p. 21, line 4, will be edited to read "**Credible** acute lethality data for inhalation exposure to agent VX vapors are available for only two species (mice and goats)..."*

The rat data inhalation exposure data summarized on p. 13 (Crook et al 1983) are not considered credible (see Section 2.2 and Table 5, p. 15). The other rat data summarized in Section 3.1.1 on p. 13 are for non-inhalation or non-vapor exposure routes (aerosols, subcutaneous, or intragastric).

15) **COT SUBCOMMITTEE COMMENT:** Page 39, line 17: Two species—what about the rat data on page 13?

AUTHORS' RESPONSE: *Please see response to COT Subcommittee Comment 14) above.*

16) **COT SUBCOMMITTEE COMMENT:** Page 44, line 32: Delete this title.

AUTHORS' RESPONSE: *Agree. Title will be deleted from the next edition of the TSD. Research needs described will be incorporated into Section 8.3 "Data Adequacy and Research Needs."*

17) COT SUBCOMMITTEE COMMENT: Page 44, line 34: Delete "The NAC has noted that"

AUTHORS' RESPONSE: *Agree. Identified text will be deleted from the next edition of the TSD. Research needs described will be incorporated into Section 8.3 "Data Adequacy and Research Needs."*

18) COT SUBCOMMITTEE COMMENT: Page 45, lines 1-6: Delete that paragraph

AUTHORS' RESPONSE: *Agree. Identified text will be deleted from the next edition of the TSD.*

Editorial Comments

19) COT SUBCOMMITTEE COMMENT: Page vi, lines 17-18: "VX is odorless, so overt toxicity could occur after exposures below those of odor detection." Rewrite these sentences to reflect the poor warning properties of this material.

AUTHORS' RESPONSE: *Suggested new text, "Because Agent VX is considered odorless, this compound possesses no olfactory warning properties."*

20) COT SUBCOMMITTEE COMMENT: Page 4, line 4: Chemical name: should be diisopropyl.

AUTHORS' RESPONSE: *Agree; edit change will be made in new edition text.*

21) COT SUBCOMMITTEE COMMENT: Page 16, line 13: Change "0.000005" to "5×10^{-6}."

AUTHORS' RESPONSE: *The concentrations were summarized in this TSD text as provided by the author of the original study (Crook et al 1983). The new edition of the TSD can include scientific notation of this value as well.*

22) COT SUBCOMMITTEE COMMENT: Page 17, lines 22-23: Change "highest" to "higher." A similar change should be made on page 16 in the discussion of the write-ups for rat and mouse data.

AUTHORS' RESPONSE: *To increase clarity, new text will read "...but none at 0.00006 mg/m^3."*

23) COT SUBCOMMITTEE COMMENT: Page 17, lines 27-30: To clarify the intended meaning, indicate actual inhibition of plasma ChE rather than percentage plasma ChE activity remaining after inhibition.

AUTHORS' RESPONSE: *Please see previous response to COT Subcommittee Comment 12) above.*

24) COT SUBCOMMITTEE COMMENT: Page 18, Section 3.3, line 15: Add possible peripheral neurotoxicity.

AUTHORS' RESPONSE: *New text on lines 19-20 will read "...on both smooth and skeletal muscle function as well as the central* ***and peripheral*** *nervous system."*

18) COT SUBCOMMITTEE COMMENT: Page 44, line 39: Do not put "miosis" and "lethality" on one line.

AUTHORS' RESPONSE: *Wording will be clarified.*

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Attachment 5

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February 6, 2002

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Dear Dr. Rusch:

This letter is a follow-up to an issue I raised at the National Advisory Committee on Acute Exposure Guideline Levels (NAC/AEGL) for Hazardous Substances meeting on December 3, 2001. At the meeting I indicated my concern regarding the unevenness in the document development process, possibly due to the preparation of the Standing Operating Procedures (SOPs) after the NAC/AEGL committee had already developed a large number of documents. Specifically, this letter focuses on one issue, the inconsistency in selection of a starting point for AEGL determination.

As stated in the SOPs (page 36), "in the development of the AEGLs, the NAC/AEGL Committee selects the highest exposure level from animal or human data where the effects used to define a given AEGL tier are not observed." This point is reiterated in the Chapter subheading 2.2.1 "Selection of the Highest Exposure Level at Which the Effects that Define an AEGL are not Observed." Also as stated on page 40, "for reasons discussed earlier in this chapter, the NAC/AEGL Committee generally selects the highest experimental concentration that does not elicit the symptoms or effects defined by the AEGL tier in question. This concentration represents the starting point for AEGL development."

The SOPs discuss various ways of identifying this starting point. For example, page 36 describes the no-observed-adverse-effect-level (NOAEL) concept, and page 37 discusses the benchmark concentration (BMC) approach. Using the NOAEL or BMC approach is consistent with the AEGL definitions on page 35 of the SOPs. Each definition defines a level "above which" effects may be experienced. The recent documents follow this general approach. Unfortunately, in many of the earlier documents reviewed by the NAC/AEGL committee, concentrations producing the effect of a specific tier were chosen as the starting point for AEGL development, instead of NOAELs. In some of these documents, the AEGL definition is also different in that it defines a level "at or above which" effects may be experienced; examples include the documents for allylamine, 1,2-dichloroethylene, ethylene oxide, hydrazine, hydrogen chloride, sulfur mustard, tetrachloroethylene and 1,1,1-trichloroethane. For these reasons, I am asking the NAC/AEGL committee to consider this issue and suggest revisions that are consistent with the current SOPs. Since a number of the

documents are in the process of being reviewed by the National Academy of Sciences (NAS) Subcommittee on Acute Exposure Guideline Levels, I am providing this information to the NAS subcommittee as well, so that the issue can be resolved before the documents are finalized.

I prepared the attached table listing the type of starting point for AEGL development, highlighting in bold the chemicals with an AEGL starting point that appears to be inconsistent with the SOPs and with AEGL tier definition. The table consists of 51 substances that have reached interim status and thus have or will soon be brought to the NAS subcommittee's attention. The description of the starting point comes directly from the document, and there was no attempt on my part to reinterpret the understanding of the NAC/AEGL Committee on this point. In some cases, as discussed below, the issue may be resolved by providing additional clarity in the document, however, in most cases it would appear the starting point requires adjustment or reevaluation. When the documents indicated the starting point produced an AEGL level effect, this is designated in the attached table as a lowest-observed-adverse-effect level (LOAEL) or lowest-observed-effect level (LOEL). When the document indicated the starting level was below the AEGL effect level, this was designated in the table as a NOAEL (or NOEL, no-observed-effect level). The document version utilized was cited, in case the version available to the rest of the NAC/AEGL or the subcommittee is different. This review will discuss the starting points identified for these 51 substances in developing AEGL-3, AEGL-2 and AEGL-1 values.

AEGL-3

The NAC/AEGL committee documents are most consistent with the SOPs for the AEGL-3 values. In almost every case, the documents identify a starting point that is equivalent to or adjusted to the "highest exposure level that does not cause lethality" as described in the SOPs (page 44-45). In almost all cases the documents identify the NOEL for lethality, estimate the lethality NOEL using a BMC approach, or identify the LC_{50}, and divide by 3. These three approaches are described in the SOPs and all appear to be consistent with the AEGL-3 definition since they either identify a "NOEL" for lethality or estimate the "NOEL" through modeling or dividing an effect level (LC_{50}) by an adjustment factor. One exception is the AEGL-3 value for iron pentacarbonyl where a concentration which produced lethality was used as the starting point without an adjustment factor. Thus, in contrast to the rest of the AEGL-3 evaluations, the starting point for this compound is inconsistent with the SOPs, and appears to be inconsistent with AEGL-3 definition.

AEGL-2

The inconsistency in identifying starting points appears to be greatest in the development of the AEGL-2 values. Although the SOPs (page 42) clearly state "in developing AEGL-2 values, the NAC/AEGL Committee estimates a NOAEL for serious or irreversible effects or effects that impair escape," 22 of the documents appear to identify a starting point that is a severe LOEL instead of a NOAEL (or NOEL), without the incorporation of an adjustment factor. As indicated in the attached table, the compounds with AEGL-2 starting points that are not NOAELs, or adjusted to NOAELs,

are allylamine, carbon monoxide, chlorine, chlorine trifuoride, crotonaldehyde, diborane, 1,2-dichloroethylene, dimethyldichlorosilane, ethylene oxide, ethylenediamine, HCFC 141b, hydrazine, hydrogen chloride, hydrogen sulfide, methyl trichlorosilane, nickel carbonyl, otto fuel, phosgene, propionitrile, sulfur mustard, toluene, and 1,1,1-trichloroethane.

A few examples from the table demonstrate that the starting point selected is a severe LOEL instead of a NOAEL (or NOEL). One example is allylamine, where the starting point for AEGL development is the concentration where rats developed cardiovascular lesions. Another example is 1,2-dichloroethylene where the 4- and 8-hour values are based on the starting point concentration that produces narcosis in the rat. In the case of nickel carbonyl the starting point, a single 15-minute exposure of pregnant hamsters on GD 4 or 5, resulted in increased malformations in offspring. As a final example, the starting point for 1,1,1-trichloroethane was the calculated EC_{50} for ataxia in rats. These examples indicate a wide variety of severe effects occurring at the starting point concentration. It is important to emphasize that the documents describe these effects as severe, AEGL-2 effects, and an adjustment factor from effect level to no effect level was not incorporated. For most of the remaining 29 compounds AEGL-1 effects occur at the AEGL-2 starting point, but that is expected and is described in the SOPs.

AEGL-1

The inconsistent selection of starting points occurs to fairly high extent in the development of the AEGL-1 levels. The SOPs (page 42) indicate that the starting point for AEGL-1 development is the "highest experimental exposure without an AEGL-1 effect." Chemical documents consistent with this approach are noted in the table with a NOAEL. However, nine of the documents appear to identify a starting point concentration that produced an AEGL-1 effect (indicated in the table with a LOAEL), instead of a NOAEL. The compounds with AEGL-1 starting points that are not NOAELs, but produce AEGL-1 level effects are: chlorine trifluoride, crotonaldehyde, hydrazine, nerve agent GB, sulfur mustard, tetrachloroethylene, toluene, toluene diisocyanate, 1,1,1-trichloroethane.

Several examples from the table demonstrate this point. One example is cyclohexylamine where the starting point concentration produced respiratory and ocular effects (labored breathing, red nasal discharge, and partially closed eyes) in rats. For the nerve agent GB the starting point concentration produced rhinorrhea, headache, tightness in chest, cramps, nausea and miosis in human volunteers. In the case of toluene diisocyanate the starting point concentration produced chest tightness, eye and throat irritation, cough, rhinitis, dyspnea, and/or headache lasting for up to several hours post exposure in 15 asthmatics. A final example is 1,1,1-trichloroethane where the starting point concentration produced eye irritation, slight dizziness, and a decline in perceptual acuity in humans. The effects reported are clearly AEGL-1 effects, and the documents indicate that the starting point concentration produces these health effects.

It is important that this inconsistent selection of the starting point be addressed, since it may have repercussions on the planning or response phase of a chemical accident. Most agencies addressing environmental issues are used to target levels that are no-effect or "safe" levels; and most

environmental standards are designed in this manner. The SOPs are consistent with this approach. However, developing some AEGL values in a manner that indicates the AEGL value may cause the effect for that tier, while other AEGLs are developed in a manner indicating they do not cause the effect for that tier, is likely to be confusing to the ultimate user of the values. In some cases it may result in the incorporation of additional factors by the end user, and in other cases it may threaten the public health.

As described above, the starting points for many compounds are inconsistent with the SOPs, and appear to be inconsistent with AEGL definitions. I hope this letter and table have been helpful in identifying those compounds. While it was not my intent to provide alternative values for any of the documents, there are several ways that this inconsistency can be addressed. The best alternative is to identify appropriate no effect levels (NOAELs for tiers 1, 2 or 3) for the studies, if they are available, or to predict NOAELs using the BMC methodology, and use the BMC as the starting point. For a number of the compounds, NOAELs are available from the same study; these compounds include allylamine, carbon monoxide, chlorine trifluoride (L-2), crotonaldehyde (L-2), diborane, ethylene oxide, HCFC 141b, iron pentacarbonyl, otto fuel, phosgene, sulfur mustard (L-2), and toluene. A second alternative is to apply an appropriate adjustment factor to the LOEL or LOAEL. This has been done for the methyl isocyanate AEGL-2 value, for two AEGL-1 values, and in a number of cases for AEGL-3 values. A third possibility is that the document lacks clarity or is in error and that the starting point selected is actually below the AEGL tier and is not a LOEL or LOAEL.

I thank you for your attention to these issues and would be happy to answer any other questions about my analysis. Please feel free to contact me at my Oakland office (510) 622 3202, Sacramento office (916) 322-2067 or by e-mail galexeef@oehha.ca.gov.

Sincerely,

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Identification of Starting Points for AEGL Development Relative to NOAELs and LOAELs

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
1	Allyl alcohol	L-1	Mean odor detection threshold of 1.8 ppm for humans (AIHA, 1989).	not applicable	not applicable	Dec-00
	Allyl alcohol	L-2	Exposure of 40 ppm for 7 hours/day did not result in severe effects in rats (Dunlap et al., 1958)	NOEL	not applicable	Dec-00
	Allyl alcohol	L-3	No lethality in mice, rats and rabbits exposed for 1 hour to 200 ppm (Union Carbide, 1951).	NOEL	not applicable	Dec-00
2	Allylamine	L-1	Exposure to 0.2 ppm allylamine for 3-4 hours a day was not associated with worker detection or complaints, but exposure to higher but undefined concentrations caused mucous membrane irritation in >20 workers (Shell Oil Co., 1992).	NOAEL	not applicable	May-00
	Allylamine	**L-2**	**Four rats exposed to 60 ppm for 14 hours developed cardiovascular lesions including scattered myofibril fragments with loss of striation, perivascular edema, and cellular infiltration. (Guzman et al., 1961)**	**LOEL**	**No**	May-00
	Allylamine	L-3	Estimated the lethality NOEL in rats by calculating LC_{01}s (533 ppm for a 1- hour, 286 ppm for 4 hours, 69.2 for 8 hours) using the lethality dose response curve (LC_{50}s were 1933 ppm, 286 ppm and 177 ppm respectively). LC01 derived by probit analysis (Hine et al., 1960).	NOEL	not applicable	May-00
3	Boron trichloride	L-1	Based on relative toxicity to hydrogen chloride.	not applicable	not applicable	Dec-00
	Boron trichloride	L-2	Based on relative toxicity to hydrogen chloride.	not applicable	not applicable	Dec-00

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
	Boron trichloride	L-3	1-hour rat LC_{50} of 2,541 ppm (Vernot, 1977)	LOEL	Yes, 3	Dec-00
4	Carbon monoxide	L-1	Not recommended	not applicable	not applicable	Feb-01
	Carbon monoxide	**L-2**	**Decrease in time to onset of angina pectoris during physical exercise at 4 % COHb produced from a 253 ppm exposure for 50-70 minutes in humans (Allred et al. 1989a,b; 1991; Sheps et al 1990, 1991).**	**LOEL**	**No**	Feb-01
	Carbon monoxide	L-3	Concentrations estimated to result in a COHb of 40% in humans, not expected to produce life-threatening effects, based on human studies of Chiodi et al. (1941) and Haldane (1895).	NOEL	not applicable	Feb-01
5	Chlorine	L-1	No effect in 31 human subjects at 0.5 ppm for 4 hours (Anglen 1981, Rotman et al. 1983)	NOAEL	not applicable	Oct-01
	Chlorine	**L-2**	**Exposure of a susceptible subject to 1 ppm for 4 hours resulted in serious asthmatic-like symptoms and pulmonary function changes (Rotman et al. 1983).**	**LOEL**	**No**	Oct-01
	Chlorine	L-3	Estimated the lethality NOEL by averaging the 1-hour NOELs in rats (213 ppm and 302 ppm) with the 1-hour NOEL in mice (150 ppm) (MacEwen and Vernot 1972, Zwart and Woutersen 1988)	estimated NOEL	not applicable	Oct-01
6	**Chlorine trifluoride**	**L-1**	**"Dogs had a definite sign of irritancy within the first 45 minutes of exposure (nasal discharge); lacrimation occurred after three hours of exposure (presumably during the first day of exposure)" (p. 11 of document), to 1.17 ppm. The starting point is based on a 3-hour exposure. (Horn and Weir, 1956)**	**LOAEL**	**No**	Aug-00
	Chlorine trifluoride	**L-2**	**Strong irritation in two dogs exposed to 5.15 ppm for 6 hours, may be extremely uncomfortable but are reversible; however, they could possibly impair the ability to escape. (Horn and Weir, 1955).**	**LOEL**	**No**	Aug-00

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
	Chlorine trifluoride	L-3	Estimated the lethality NOEL in mice by calculating an LC_{01} of 135 ppm for a 1-hour exposure using the lethality dose response curve (LC_{50} was 178 ppm). LC_{01} derived by probit analysis, using (MacEwen and Vernot, 1970).	estimated NOEL	not applicable	Aug-00
7	Chloromethyl methyl ether	L-1	Not recommended	not applicable	not applicable	Dec-00
	Chloromethyl methyl ether	**L-2**	**Pulmonary hyperplasia, broncheotracheal squamous metaplasia in rats exposed to 1 ppm for 6 hours for 30 exposures (Drew et al., 1975).**	**LOEL (but effect was following 30 exposures)**	**No**	Dec-00
	Chloromethyl methyl ether	L-3	Estimated the lethality NOEL in rats by calculating an LC_{01} of 14.8 ppm for a 7-hour exposure using the lethality dose response curve (LC_{50} was 55 ppm). LC_{01} derived by probit analysis (Drew et al. 1975).	estimated NOEL	not applicable	Dec-00
8	**Crotonaldehyde (cis and trans)**	**L-1**	**Mild eye irritation (lacrimation) in workers at 0.56 ppm during the workday. (Frannick, 1982)**	**LOAEL**	**No**	May-00
	Crotonaldehyde (cis and trans)	**L-2**	**Rat impaired pulmonary function (manifest as a 20-40% reduction in carbon monoxide and ether uptake rates compared to pre-exposure value) and bronchiole lesions at 8000 ppm-min (Rinehart, 1967).**	**LOEL**	**No**	May-00
	Crotonaldehyde (cis and trans)	L-3	Estimated the lethality NOEL in rats by calculating an LC_{01}s of 440 ppm for 10-min, 268 ppm for 30-min, 138 ppm for 1- hour, and 26 ppm for 4-hour exposures using the lethality dose response curves (LC_{50}s were 1480 pp, 593 ppm, 391 ppm, and 88 ppm respectively). LC_{01} derived by probit analysis. (Rinehart, 1967)	estimated NOEL	not applicable	May-00
9	Cyclohexylamine	L-1	Respiratory and ocular effects (labored breathing, red nasal discharge, and partially closed eyes) in rats exposed for 4 hours to 54.2 ppm (Bio/dynamics, Inc., 1990)	LOAEL	Yes, 3	May-00
	Cyclohexylamine	L-2	Respiratory and ocular effects (labored breathing, red nasal discharge, and partially closed eyes) in rats exposed for 4 hours to 54.2 ppm. NOEL for irreversible ocular lesions (bio/dynamics, Inc., 1990)	NOEL	not applicable	May-00

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
	Cyclohexylamine	L-3	No rats died from 567 ppm 4-hour exposure (Bio/dynamics, Inc., 1990)	NOEL	not applicable	May-00
10	Diborane	L-1	Not recommended	not applicable	not applicable	Dec-00
	Diborane	**L-2**	**Inflammatory epithelial degeneration in the bronchioles in male ICR mice (4/10) exposed to 5 ppm for 2 hours (Nomiyama et al., 1995)**	**LOAEL**	**No**	Dec-00
	Diborane	L-3	Estimated the lethality NOEL in mice by calculating an LC_{01} of 9.17 ppm for a 4-hour exposure using the lethality dose response curves (LC_{50}s was 31.5 ppm). LC_{01} derived by probit analysis. (Uemura et al. 1995).	estimated NOEL	not applicable	Dec-00
11	1,2-Dichloroethylene (cis and trans)	L-1	In 2 human subjects 825 ppm for 5 minutes caused slight dizziness but no eye irritation (Lehman and Schmidt-Kehl, 1936). The NOAEL for eye irritation was chosen as the starting point.	NOAEL	not applicable	Jan-00
	1,2-Dichloroethylene (cis and trans)	**L-2**	**For 10-min to 1-hour AEGLs, dizziness produced in 2 human subjects after 10-min exposure to 1000 ppm was used (Lehman and Schmidt-Kehl, 1936). For 4- and 8-hour AEGLs, narcosis in rats at 6000 ppm for a 6-hour exposure was used (Hurtt et al., 1993)**	**LOEL**	**No**	Jan-00
	1,2-Dichloroethylene (cis and trans)	L-3	For 10-min to 1-hour AEGLs, non-lethal effects produced in 2 human subjects after 3-min exposure to 1700 ppm was used (Lehman and Schmidt-Kehl, 1936). For 4- and 8-hour AEGLs, level of 12,300 ppm which produced no lethality in rats exposed for 4 hours was used (Kelly, 1999)	NOEL	not applicable	Jan-00
	Dimethyldichlorosilane	L-1	Modification of hydrogen chloride AEGL-1 values (U.S. EPA 1997a)	NOAEL	not applicable	May-00
	Dimethyldichlorosilane	**L-2**	**Necrotic and swollen paws, corneal opacity, grey areas on lungs, and other effects in rats exposed to 1309 ppm for 1 hour (Dow Corning, 1997a)**	**LOEL**	**No**	May-00

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
	Dimethyldichlorosilane	L-3	Estimated the lethality NOEL in rats by calculating an LC_{01} of 1589.5 ppm for a 1-hour exposure using the lethality dose response curves (LC_{50}s was 2092 ppm). LC_{01} derived by probit analysis. (Dow Corning, 1997a)	estimated NOEL	not applicable	May-00
12	Ethylene oxide	L-1	Not Recommended.	not applicable	not applicable	Apr-00
	Ethylene oxide	**L-2**	**Fetal growth retardation in rats manifested by a statistically significant decrease in fetal weight and non-statistically significant increase in the incidence of delayed ossification at 100 ppm. (Snellings et al., 1982a)**	**LOEL**	**No**	Apr-00
	Ethylene oxide	L-3	Estimated the lethality NOEL in rats by calculating an LC_{01} of 625 ppm for a 4-hour exposure using the lethality dose response curves (LC_{50}s was 1460 ppm). LC_{01} derived by probit analysis. (Jacobson et al., 1956) .	estimated NOEL	not applicable	Apr-00
13	Ethylenediamine	L-1	Not recommended.	not applicable	not applicable	Aug-00
	Ethylenediamine	**L-2**	**Bronchiolar edema, and light cloudy kidney swelling in rats from ~484 ppm for 6 hours. (Carpenter et al., 1948)**	**LOEL**	**No**	Aug-00
	Ethylenediamine	L-3	No lethality in 6 rats at ~1000ppm for 8 hours. (Smyth et al., 1951)	NOEL	not applicable	Aug-00
14	Ethylenimine	L-1	Derived from L-2 values.	not applicable	not applicable	Aug-01
	Ethylenimine	L-2	No effect for respiratory difficulty or escape impairment from an exposure of 10 ppm for 4 hours in guinea pigs (Carpenter et al., 1948)	NOEL	not applicable	Aug-01

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
	Ethylenimine	L-3	Estimated the lethality NOEL in rats by calculating an LC_{01} of 15 ppm for an 8-hour exposure using the lethality dose response curves (LC_{50}s was 35 ppm). LC_{01} derived by probit analysis. (Carpenter et al., 1948)	estimated NOEL	not applicable	Aug-01
15	Fluorine	L-1	No eye and skin irritation in 5 humans at 10 ppm for 15 min; no respiratory difficulty (Keplinger and Suissa 1968)	NOAEL	not applicable	Nov-99
	Fluorine	L-2	NOEL (67ppm for 30 min) for severe effects of irritation, dyspnea, and lung congestion. (Keplinger and Suissa 1968)	NOEL	not applicable	Nov-99
	Fluorine	L-3	No lethality in mice at 75 ppm for 1-hour, which is 1/2 the LC_{50} (Keplinger and Suissa 1968)	NOEL	not applicable	Nov-99
16	Furan	L-1	Not Recommended	not applicable	not applicable	Dec-00
	Furan	L-2	Exposure of rats to 1014 ppm for 1 hour produced respiratory distress, increased secretory response (Terril et al., 1989).	could not be determined	No	Dec-00
	Furan	L-3	No lethality to rats exposed to 2851 ppm for 1 hour (Terril et al., 1989).	NOEL	not applicable	Dec-00
17	HCFC 141b	L-1	No effects in one exercising subject at 1000 ppm for 6 hours. (Utell et al., 1997)	NOAEL	not applicable	Jan-00
	HCFC 141b	**L-2**	**Cardiac response on 1/10 dogs at 5200 ppm, exposed for 10 minutes, for cardiac arrhythmia (Mullin, 1977)**	**LOEL**	**No**	Jan-00

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
	HCFC 141b	L-3	Highest concentration (19000 ppm) tested for 10 minutes that did not result in lethality in the cardiac sensitization test on 1-2 dogs. (Hardy et al., 1989a).	NOEL	not applicable	Jan-00
18	HFC 134A	L-1	No effects in eight human subjects exposed to 8000 ppm for 1 hour (Emmen and Hoogendijk, 1998)	NOAEL	not applicable	Jan-00
	HFC 134A	L-2	No effect in six dogs at 40,000 ppm for cardiac sensitization (Hardy et al., 1991)	NOEL	not applicable	Jan-00
	HFC 134A	L-3	Not lethal at 80,000 ppm for 10 minutes in six dogs (Hardy et al., 1991)	NOEL	not applicable	Jan-00
19	**Hydrazine**	**L-1**	**Skin flushing and swollen eyes in monkeys at 0.4 ppm for 24 hours (House, 1964)**	**LOAEL**	**No**	Mar-00
	Hydrazine	**L-2**	**Lesions of the nasal transitional epithelium (minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, and mild apoptosis) from a 1 hour exposure to 750 ppm of rats (Latendresse et al., 1995)**	**LOEL**	**No**	Mar-00
	Hydrazine	L-3	1-hour rat LC_{50} of 3,192ppm (HR, 1993)	LOEL	Yes, 3	Mar-00
20	Hydrogen chloride	L-1	No adverse effects in exercising human asthmatics exposed to 1.8 ppm for 45 minutes (Stevens et al., 1992)	NOAEL	not applicable	May-00
	Hydrogen chloride	**L-2 (10min)**	**RD50 value of 309 for mice (Barrow , 1977) was divided by 3 to produce a significant irritation level.**	**LOEL**	**No**	May-00

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
	Hydrogen chloride	**L-2 (1-, 4-, 8-hour)**	**Histopathology observed in rats exposed to 1300 ppm for 30 minutes included severe necrotizing rhinitis, turbinate necrosis, thrombosis of nasal submucosa vessels (nose breathers) and severe ulcerative tracheitis accompanied by necrosis and luminal ulceration (mouth breathers) (Stavert et al., 1991)**	**LOEL**	**No**	**May-00**
	Hydrogen chloride	L-3	1-hour rat LC_{50} of 3124 ppm (Wohlslagel et al, 1976; Vernot et al., 1977)	LOEL	Yes, 3	May-00
21	Hydrogen cyanide	L-1	Serious effects may occur below detectable concentrations or concentrations causing discomfort (NA)	not applicable	not applicable	Jan-00
	Hydrogen cyanide	L-2	Slight central nervous system depression evident by a change in brain wave activity in monkeys from 30 minute exposure to 60 ppm. (Purser, 1984)	NOEL	not applicable	Jan-00
	Hydrogen cyanide	L-3	Estimated the lethality NOEL in rats by calculating an LC_{01}s of 138, 127, and 88 ppm for a 15-, 30- and 60- minute exposures, respectively using the lethality dose response curves (LC_{50}s were 196, 173, and 139 ppm for 15-, 30- and 60- minute exposures, respectively). LC_{01} derived by probit analysis. (E.I. du Pont de Nemours, 1981)	estimated NOEL	not applicable	Jan-00
22	Hydrogen fluoride	L-1	Subthreshold concentration for inflammation of 3 ppm (0.85-2.9 ppm) for 1 hour which was without sensory irritation (Lund et al. 1997, 1999).	NOAEL?	No	Jan-02
	Hydrogen fluoride	L-2 (10min)	NOEL (950 ppm, for 10 minutes) for lethal effects which produced lung effects in rats include small increases in myeloperoxidase and polymorphonuclear leukocytes in the BAL were observed along with histologic changes in the trachea. (Dalbey, 1996)	NOEL	not applicable	Jan-02
	Hydrogen fluoride	L-2 (30min, 1 hour, 4-, 8-hour)	Reversible irritation in dogs exposed to 243 ppm for 1 hour (Rosenholtz et al. 1963)	NOEL	No	Jan-02

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
23	**Hydrogen fluoride**	**L-3 (10min)**	**Lethality (1/20) in orally cannulated rats exposed to 1764 ppm for 10 minutes (Dalby, 1996).**	**LOEL (but oral cannulation is said to eliminate scrubbing by the nose)**	**No**	Jan-02
	Hydrogen fluoride	L-3 (30min, 1 , 4-, 8-hour)	No lethal effects at 263 ppm for a 1-hour exposure in mice (Wohlslagel et al., 1976)	estimated NOEL	not applicable	Jan-02
	Hydrogen sulfide	L-1	Headache (3/10), increased airway resistance (8/10) in asthmatic humans at 2 ppm for 30 minutes (Jappinen et al., 1990)	LOAEL	Yes, 10	Sep-00
24	**Hydrogen sulfide**	**L-2**	**Minor perivascular edema and increased protein and LDH in lavage fluid in rats exposed to 200 ppm for 4 hours (Green et al., 1991; Khan et al., 1991)**	**LOEL**	**No**	Sep-00
	Hydrogen sulfide	L-3	Highest concentration (504 ppm) causing no mortality in the rat after a 1-hour exposure (Mac Ewen and Vermot, 1972)	NOEL	No	Sep-00
	Iron pentacarbonyl	L-1	Not recommended; insufficient data.	not applicable	No	May-00
25	Iron pentacarbonyl	L-2	Based upon a three-fold reduction in the AEGL-3 values.	not applicable	No	May-00
	Iron pentacarbonyl	**L-3**	**10% mortality (1/10) in rats exposed to a single 6-hour exposure of 2.91 ppm (BASF, 1995)**	**LOEL**	**No**	May-00
	Isobutyronitrile	L-1	Insufficient data to derive L-1 values.	not applicable	not applicable	Aug-00

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
26	Isobutyronitrile	L-2	No maternal or fetal toxicity in rats exposed to 100 ppm for 6 hours (Saillenfait et al., 1993)	NOEL	not applicable	Aug-00
	Isobutyronitrile	L-3	LC_{50} of 1800 ppm for a 1-hour exposure in rats (Eastman Kodak, 1986a)	LOEL	Yes, 3	Aug-00
	Methacrylonitrile	L-1	Insufficient data to derive L-1 values.	not applicable	not applicable	Aug-00
	Methacrylonitrile	L-2	1/3 of AEGL-3 values	not applicable	not applicable	Aug-00
27	Methacrylonitrile	L-3	No lethality in mice exposed for 4 hours to 19 ppm (Pozzani et al., 1968)	NOEL	not applicable	Aug-00
	Methanol	L-1	Pharmacologic study exposing 3 female and 12 male subjects to 800 ppm methanol for 8 hours (Batterman et al. 1998; Franzblau 1999, 2000, personal communication). One of the study's coauthors stated in a personal communication that none of the subjects reported symptoms.	NOAEL	not applicable	Feb-01
	Methanol	L-2	No significant increase in cervical ribs, exencephaly, or cleft palate in mice exposed to a single 2000 ppm exposure for 7 hours. (Rogers et al., 1997, 1999, personal communication). The end of exposure methanol blood concentration of 487 mg/l (Rogers et al 1993,) was the starting point for AEGL development.	NOEL	not applicable	Feb-01
28	Methanol	L-3	Lowest calculated peak blood concentration resulting in death was 1109 mg/L (Naraqi et al. 1979)	LOEL	Yes, 2	Feb-01
	Methyl isocyanate	L-1	Not derived.	not applicable	not applicable	May-00

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
	Methyl isocyanate	L-2	Based on decreased fetal body weights at 2 ppm for single 3-hour exposure (Varma, 1987) and cardiac arrhythmias in rats after 2-hour exposure to 3 ppm (Tepper et all, 1987)	LOEL	Yes, 3	May-00
	Methyl isocyanate	L-3	Exposure of 1 ppm for 6 hours on GDs 14-17 produced a NOEL for pup survival during lactation but increased the number of dead fetuses at birth. (Schwetz et all, 1987)	NOEL	not applicable	May-00
	Methyl trichlorosilane	L-1	Modification of hydrogen chloride AEGL-1 values (U.S. EPA 1997a)	not applicable	not applicable	May-00
29	**Methyl trichlorosilane**	**L-2**	**Ocular opacity, irritation, hunched posture, and NOEL for lethality in rats exposed to 622 ppm for 1 hour (Dow Corning, 1997a). "This level was considered to be the threshold for impairment of escape and onset of serious long-term effects."**	**LOEL**	**No**	May-00
	Methyl trichlorosilane	L-3	Estimated the lethality NOEL in mice by calculating the 1 hour LC_{01} of 844 in rats. The LC_{50} was 1365 ppm (Dow Corning, 1997a)	estimated NOEL	not applicable	May-00
	Nerve Agent GA	L-1	Based on relative toxicity to Nerve Agent GB.	not applicable	not applicable	Oct-00
30	Nerve Agent GA	L-2	Based on relative toxicity to Nerve Agent GB.	not applicable	not applicable	Oct-00
	Nerve Agent GA	L-3	Based on relative toxicity to Nerve Agent GB.	not applicable	not applicable	Oct-00
	Nerve Agent GB (Sarin)	**L-1**	**Rhinorrhea, headache, tightness in chest, cramps, nausea and miosis observed in human volunteers exposed to 0.05 mg GB/m^3 for 20 minutes (Harvey, 1952).**	**LOAEL**	**No**	Oct-00

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
31	Nerve Agent GB (Sarin)	L-2	Miosis, dyspnea and photophobia, 60% RBC-CHE inhibition in eight male servicemen exposed to 0.5 mg GB/m^3 for 30 minutes, walking at a rate of 96 paces/min and breathing normally. However, effects were not considered to be debilitating or permanent (Baker and Sedgwick, 1996).	NOEL	not applicable	Oct-00
	Nerve Agent GB (Sarin)	L-3	Estimated the lethality NOEL in rats by calculating LC_{01}s (11.54 mg/m^3 for 10 min, 5.84 mg/m^3 for 30 min, 4.01 mg/m3 for 1- hour, 2.09 mg/m^3 for 4 hours, 1.76 mg/m^3 for 8 hours) using the lethality dose response curve (LC_{50}s were 18.1, 8.51, 6.39, 3.03, and 2.63 mg/m^3 respectively). LC_{01} derived by probit analysis (Mioduszewski et al., 2000b).	NOEL	not applicable	Oct-00
	Nerve Agent GD	L-1	Based on relative toxicity to Nerve Agent GB.	not applicable	not applicable	Oct-00
32	Nerve Agent GD	L-2	Based on relative toxicity to Nerve Agent GB.	not applicable	not applicable	Oct-00
	Nerve Agent GD	L-3	Based on relative toxicity to Nerve Agent GB.	not applicable	not applicable	Oct-00
	Nerve Agent GF	L-1	Based on relative toxicity to Nerve Agent GB.	not applicable	not applicable	Oct-00
33	Nerve Agent GF	L-2	Based on relative toxicity to Nerve Agent GB.	not applicable	not applicable	Oct-00
	Nerve Agent GF	L-3	Based on relative toxicity to Nerve Agent GB.	not applicable	not applicable	Oct-00
	Nerve Agent VX	L-1	Based on relative toxicity to Nerve Agent GB.	not applicable	not applicable	Oct-00

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
34	Nerve Agent VX	L-2	Based on relative toxicity to Nerve Agent GB.	not applicable	not applicable	Oct-00
	Nerve Agent VX	L-3	Based on relative toxicity to Nerve Agent GB.	not applicable	not applicable	Oct-00
	Nickel carbonyl	L-1	Not recommended. Qualitative data are limited and quantitative data consistent with AEGL-1 effects are unavailable.	not applicable	not applicable	May-00
35	**Nickel carbonyl**	**L-2**	**Single 15-minute exposure of pregnant hamsters to 8.4 ppm on GD 4 or 5 resulted in a significant increased malformations, increased proportions of litters with malformed fetuses, and serious cavity hemorrhage in offspring, (Sunderman et al. 1980).**	LOEL	No	May-00
	Nickel carbonyl	L-3	Estimated the lethality NOEL in mice by calculating an LC_{01} of 3.17 ppm for a 30-minute exposure using the lethality dose response curves (LC_{50}s was 33.6 ppm). LC_{01} derived by Litchfield and Wilcoxon method (HRC, 1953)	estimated NOEL	not applicable	May-00
	Nitric acid	L-1	No changes in pulmonary function in humans (Sackner and Ford, 1981)	NOAEL	not applicable	Aug-96
36	Nitric acid	L-2	Irritation with cough; increased pulse and respiratory rates (Lehmann and Hasegawa, 1913)	NOEL	not applicable	Aug-96
	Nitric acid	L-3	30-min LC_{50} in the rat (Gray, et al., 1954)	LOEL	Yes, 3	Aug-96
	Otto Fuel (mainly Propylene glycol dinitrate CAS #6423-43-4)	L-1	No headache in 2 human subjects at 0.03 ppm for a 6-hour exposure (Stewart et al., 1974)	NOAEL	not applicable	Jan-00

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
37	**Otto Fuel (mainly Propylene glycol dinitrate CAS #6423-43-4)**	L-2	**Severe headaches in humans, and one subject reported dizziness, at 0.5 ppm for a 6 hour exposure. Slight loss of equilibrium occurred after 6.25 hours. Starting point was at 6 hours. (Stewart et al., 1974)**	LOEL	No	Jan-00
	Otto Fuel (mainly Propylene glycol dinitrate CAS #6423-43-4)	L-3	Severe but non-lethal effects in monkeys exposed to 70 ppm for 6 hours (Jones et al., 1972)	NOEL	not applicable	Jan-00
	Perchloromethyl mercaptan	L-1	No focal subacute interstitial pneumonia, no increase in lung weights or any other adverse effects in rats exposed to 0.079 ppm for 6 hours/day, 5 days/week for 70-72 days (Knapp and Thomassen, 1987).	NOAEL	not applicable	Dec-00
38	Perchloromethyl mercaptan	L-2	No severe effects in rats, such as hair coat stains, pulmonary edema, increased mucous secretions, alveolitis, or interstitial fibroplasia, at 0.58 ppm for 6 hours, 5 days/week for 70 days. The severe effects occurred at a higher exposure concentration of 1.15 ppm, after a 6 hour/day, 5 day/week, 2 week exposure.	NOEL	not applicable	Dec-00
	Perchloromethyl mercaptan	L-3	No lethality in rats exposed to 9 ppm for 1 hour (Stauffer Chemical Co., 1973).	NOEL	not applicable	Dec-00
	Phenol	L-1	No clinical, hematological or histopathological effects in rats exposed to 25 ppm for 6 hours/day, 5 days/week for 2 weeks (CMA, 1998; Hoffmann et al. 1999, abstract)	NOAEL	not applicable	Feb-01
39	Phenol	L-2	No severe effects in rats exposed to 25 ppm for 6 hours/day, 5 days/week for 2 weeks (CMA, 1998). At a higher exposure concentration, 234 ppm, rats exhibited ocular and nasal irritation, muscle spasms and a slight loss of coordination within 4 hours and tremors and prostration in 1 of 6 animals after 8 hours (Flickinger, 1976).	NOEL	not applicable	Feb-01
	Phenol	L-3	No lethality in rats exposed to 234 ppm for 8 hours (Flickenger, 1976).	NOEL	not applicable	Feb-01
	Phosgene	L-1	none developed	not applicable	not applicable	Aug-00

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
40	**Phosgene**	**L-2**	**Chemical pneumonia occurred in rats exposed to 2 ppm for 1.5 hours (Gross et al. 1965).**	**LOEL**	**No**	Aug-00
	Phosgene	L-3	No effect level for death in rats was 15 ppm for a 30-minute exposure (Zwart et al. 1990); this was used for 30-min, 1-, 4-, and 8-hour values. No effect level for death in rats of 36 ppm for a 10-minute exposure was used for the 10-minute value.	NOEL	not applicable	Aug-00
	Phosphine	L-1	Appropriate data not available	not applicable	not applicable	Dec-00
41	Phosphine	L-2	No severe respiratory effects in rats exposed to 10 ppm phosphine for 6 hours. (Newton et all, 1993)	NOEL	No	Dec-00
	Phosphine	L-3	No lethality in rats exposed to 18 ppm phosphine for 6 hours. (Newton, 1991)	NOEL	not applicable	Dec-00
	Propionitrile	L-1	Insufficient data to derive L-1 values	not applicable	not applicable	Aug-00
42	**Propionitrile**	**L-2**	**Headache, nausea, vomiting, dizziness, confusion in a human subject exposed to 33.8 ppm for 2 hours who had to be admitted to a hospital and given an antidote. (Scholnick et al., 1993)**	**LOEL**	**No**	Aug-00
	Propionitrile	L-3	No lethality in rats exposed to 690 ppm for 4 hours (Younger Labs, 1978)	NOEL	not applicable	Aug-00
	Propylenimine	L-1	No values derived directly for AEGL-1. Based on ethylenimine.	not applicable	not applicable	Aug-01

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
43	Propylenimine	L-2	Based on relative toxicity to ethylenimine.	not applicable	not applicable	Aug-01
	Propylenimine	L-3	No lethality in 6 guinea pigs exposed for 30 minutes to 500 ppm (Carpenter et al. 1948)	NOEL	not applicable	Aug-01
	Sulfur Mustard	**L-1**	**An exposure of 6 mg/ m^3 for 2 minutes produced a band of fine injection across exposed bulbar conjuctiva in 3 of 4 human subjects. Trace angular conjunctivitis in one of 4 subjects. Absence of irritation. (Anderson, 1942)**	**LOAEL**	**No**	Jan-00
44	**Sulfur Mustard**	**L-2**	**An exposure of 4.5 mg/ m^3 for 13.5 minutes produced irritation, soreness, widespread conjunctivitis, photophobia, and chemosis, necessitating medical treatment in 3 human miltary volunteers. Ocular effects could be characterized as military casualities and such personnel might be ineffective for up to 7 days. Effects were severe enough to impair escape (Anderson, 1942)**	**LOEL**	**No**	Jan-00
	Sulfur Mustard	L-3	Absence of lethality in mice exposed to 21.2 mg/m^3 for one hour. (Kumar and Vijayaraghavan, 1998).	NOEL	not applicable	Jan-00
	Tetrachloroethylene	**L-1**	**106 ppm for 1 hour resulted in eye irritation in the exposed volunteers, and slight fullness in the head reported by one subject (Rowe et al., 1952).**	**LOAEL**	**No**	Dec-00
45	Tetrachloroethylene	L-2	No ataxia reported in rats exposed to 1150 ppm for 4 hours/day, 5 days a week for 2 weeks (Goldberg et al, 1964). Overt ataxia was noted following the first 4-hour exposure to the next highest concentration of 2300 ppm.	NOEL	not applicable	Dec-00
	Tetrachloroethylene	L-3	No lethality in mice exposed at 2450 ppm for 4 hours and no lethality in rats exposed at 2445 ppm for 4 hours (Frieberg et al., 1953, NTP, 1986).	NOEL	not applicable	Dec-00
	Tetranitromethane	L-1	No effects in mice or rats (possibly but not likely lethargic) at 2 ppm for 6 hours/day for 2 weeks (5 days/week), (NTP, 1990).	NOAEL	not applicable	Dec-00

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
46	Tetranitromethane	L-2	No clear lethargy effects in rats or mice at 5 ppm for 6 hours/day for 2 weeks (5 days/week), (NTP, 1990).	NOEL	not applicable	Dec-00
	Tetranitromethane	L-3	No lethality in rats or mice exposed to 10 ppm for 6 hours/day for 2 weeks (5 days/week), (NTP, 1990).	NOEL	not applicable	Dec-00
	Toluene	**L-1**	**In humans, eye and nose irritation, headache with no significant effects on psychomotor function at 100 ppm for a 6 hour exposure (Andersen et al 1983).**	**LOAEL**	**No**	Dec-00
47	**Toluene**	**L-2**	**Headache, nausea, incoordination, decreased reaction time in humans exposed to 200 ppm for 8 hours (Wilson, 1943). The studies by Wilson (1943) and von Oettingen et al. (1942) establish that toluene concentration at 200 or above 200 for an 8-hour exposure produce mental confusion, incoordination, lassitude, nausea and headache in humans.**	**LOEL**	**No**	Dec-00
	Toluene	L-3	Exposure for 1-hour to 19,018 ppm in mice was the LC_{50} (Moser and Balster 1985).	LOEL	Yes, 3	Dec-00
	Toluene 2,4-diisocyanate	**L-1**	**Chest tightness, eye and throat irritation, cough, rhinitis, dyspnea, and/or headache lasting for up to several hours post exposure in 15 asthmatics exposed to 0.01 ppm for 1 hour. (Baur, 1985)**	**LOAEL**	**No**	May-00
48	Toluene 2,4-diisocyanate	L-2	Severe eye and throat irritation, lacrimation in 1 of 6 humans exposed to 0.5 ppm for 30 minutes. (Henschler et al., 1962)	NOEL	No	May-00
	Toluene 2,4-diisocyanate	L-3	4-hour LC_{50} of 9.7 ppm in the mouse (Duncan et al., 1962)	LOEL	Yes, 3	May-00
	Toluene 2,6-diisocyanate	**L-1**	**Chest tightness, eye and throat irritation, cough, rhinitis, dyspnea, and/or headache in 15 asthmatics exposed to 0.01 ppm for 1 hour. (Baur, 1985)**	**LOAEL**	**No**	Apr-00

#	Chemical	AEGL Level	Starting Point for AEGL Development	NOAEL/ NOEL or LOAEL/ LOEL?	Applied LOAEL to NOAEL Uncertainty Factor?	NAC Draft Date
49	Toluene 2,6-diisocyanate	L-2	Severe eye and throat irritation, lacrimation in 1 of 6 humans exposed to 0.5 ppm for 30 minutes. (Henschler et al., 1962)	NOEL	not applicable	Apr-00
	Toluene 2,6-diisocyanate	L-3	4-hour LC_{50} of 9.7 ppm in the mouse (Duncan et al., 1962)	LOEL	Yes, 3	Apr-00
	1,1,1-Trichloroethane	**L-1**	**Eye irritation, slight dizziness, and a decline in perceptual acuity in humans exposed to 450 ppm for 4 hours (Salvini et al. 1971)**	**LOAEL**	**No**	Sep-99
50	**1,1,1-Trichloroethane**	**L-2**	**EC_{50} for ataxia in rats, of 6740, 6000, 4240, and 3780 ppm for 30 minutes, 1 hour, 2 hours, and 4 hours respectively. (Mullin and Krivanek 1982)**	**LOEL**	**No**	Sep-99
	1,1,1-Trichloroethane	L-3	LC_0 of 7000 ppm extrapolated from LC_{50} graph (Bonnet et al. 1980).	NOEL	not applicable	Sep-99
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Improving Consistency in Selecting AEGL Starting Points

George Alexeeff

June 17, 2002

Overview

- Identified starting points for AEGLs 1-, 2- and 3-, for 51 chemicals at interim status.
- Identified starting point justification
  - Especially whether NOAEL or LOAEL
- Reviewed SOP documentation
- Found starting point selection has been inconsistent with SOPs, especially for AEGL-2.

SOP Statement on Selecting AEGL Starting Point

- 2.2.1 "Selection of the Highest Exposure Level at Which the Effects that Define an AEGL are not Observed." (p. 36)
- "in the development of the AEGLs, the NAC/AEGL Committee selects the highest exposure level from animal or human data where the effects used to define a given AEGL tier are not observed."

SOP Statement on Selecting AEGL Starting Point (cont.)

- "for reasons discussed earlier in this chapter, the NAC/AEGL Committee generally selects the highest experimental concentration that does not elicit the symptoms or effects defined by the AEGL tier in question. This concentration represents the starting point for AEGL development." (p. 40)

Definition Issue

- Some documents identify a level
  "*at or above which an effect will occur*"
  instead of a level
  "*above which an effect will occur*".
- allylamine, 1,2-dichloroethylene, ethylene oxide, hydrazine, hydrogen chloride, sulfur mustard, tetrachloroethylene and 1,1,1-trichloroethane.

Approaches Consistent with Definition and SOPs

- Choosing for each level
  - NOAEL or NOEL
  - Benchmark concentration
  - Divide a LOAEL or LOEL with an adjustment factor

AEGL-3 Issue

- SOPs: the starting points are equivalent to "highest exposure level that does not cause lethality" (pp. 44-45)
  - NOEL for lethality
  - BMC approach
  - LC_{50} divided by 3
- 50 of 51 documents are consistent with SOPs
- Iron pentacarbonyl starting point produced lethality

AEGL-2 Issues

- SOPs: "in developing AEGL-2 values, the NAC/AEGL Committee estimates a NOAEL for serious or irreversible effects or effects that impair escape" (p. 42)
- 22 documents appear to identify a starting point that is an AEGL-2 LOEL without an adjustment factor.
- Documents describe starting points as severe AEGL-2 effects

AEGL-2 Issues (cont.)

- Example: Allylamine
  - the starting point is the concentration where rats developed cardiovascular lesions
- Example: 1,2-dichloroethylene
  - the 4- and 8-hour starting point is the concentration that produced narcosis in the rat.
- Example: 1,1,1-trichloroethane
  - The starting point is the calculated EC_{50} for ataxia in rats

AEGL-1 Issues

- SOPs: the AEGL-1 starting point is the "highest experimental exposure without an AEGL-1 effect." (p. 42)
- Nine documents appear to identify a starting point concentration that produced an AEGL-1 effect, without incorporating an adjustment factor.

AEGL-1 Issues (cont.)

- Example: cyclohexylamine
  - the starting point concentration produced respiratory and ocular effects in rats.
- Example: nerve agent GB
  - the starting point concentration produced rhinorrhea, headache, tightness in chest, cramps, nausea and miosis in human volunteers.

Possible Solutions

- Clarify document or fix errors in document
- Identify appropriate no effect levels, i.e., NOAELs for AEGLs 1-, 2- or 3-
  - allylamine, carbon monoxide, chlorine trifluoride (L-2), crotonaldehyde (L-2), diborane, ethylene oxide, HCFC 141b, iron pentacarbonyl, otto fuel, phosgene, sulfur mustard (L-2), and toluene
- Calculate BMCs if possible
- Apply LOEL to NOEL adjustment factor

ANALYSIS OF GEORGE ALEXEEFF LIST OF CHEMICALS WITH POSSIBLE NOAEL/LOAEL CONSISTENCY CONCERNS FOR AEGL DEVELOPMENT

Issue: George Alexeeff has concerns that the NAC/AEGL Committee is not following their own guidance as laid down in the 2001 Standing Operations Procedures manual (SOP). He cites the SOP language, "... in the development of the AEGLs, the NAC/AEGL Committee selects the highest level from animal or human data where the effects used to define a given AEGL tier are not observed." (p. 36) He further states that, "... this concentration represents the starting point for AEGL development"(p. 40). Concerning each chemical and respective AEGL value, he cites the SOP that, "the starting point for AEGL development is the "highest experimental exposure without that AEGL effect." (p. 42) The chemicals presented herein are examples of his concern that the NAC/AEGL Committee did not identify the NOAEL, but rather used the LOAEL as the starting point (the critical health effect endpoint) for AEGL development, without an additional safety factor correction to obtain a "NOAEL," or the true critical health effect endpoint. He claims this appears to be inconsistent with the AEGL definitions. He is requesting that the Committee reexamine these chemicals in light of this.

Generic Responses: George Alexeeff submitted a list of 33 chemicals where he is concerned that the NAC/AEGL Committee incorrectly selected the LOAEL instead of the NOAEL. The first point of clarification is what is meant by the NOAEL. The NOAEL used to derive AEGL numbers is not the classic toxicologic no-observed-adverse-effect level. The 2001 Standing Operating Procedures Manual specifically defines the "AEGL-NOAEL" starting points for AEGL development. For example, the AEGL-2 endpoint is defined as "the threshold between reversible effects that cause discomfort and serious or irreversible health effects or effects that impair escape." Above the AEGL-2 value, there is an increasing likelihood that people may become disabled or are increasingly likely to experience serious or irreversible effects. The Committee "estimates a NOAEL for serious or irreversible effects or effects that impair escape. If minor reversible effects are seen at one level of exposure and disabling effects at a higher exposure, the former is used to set the AEGL-2 value. If the exposure cannot be determined from experimental data, then the highest level causing reversible effects and discomfort may be used to set the AEGL-2 value." (SOP, p. 42)

For ease of review, the 33 chemicals in question are subdivided into the categories described below and comments are addressed in tern.

Category I:	Observed critical health effect endpoint is < the AEGL threshold effect.
Category II:	Observed critical health effect is adjusted from a LOAEL to a NOAEL using a UF, MF, or an adjustment factor, e.g. $LC_{50}/3$.
Category III:	Observed critical health effect level is adjusted from a LOAEL to a NOAEL based on unique circumstances surrounding the study in question, e.g., multiple exposures.
Category IV:	Chemicals with NAS-recommended changes in AEGL development
Category V:	Observed critical health effect endpoint appears to be > the AEGL threshold level.

Attachment 7

CATEGORY I CHEMICALS: Observed critical health effect endpoint < the AEGL threshold level.							
#	Chemical	AEG Level	Alexeeff Comment on The Critical Health Effect Endpoint for AEGL Development	LOAEL or NOAEL (Uncertainty factor used)	NAC Draft (NAC Final) [Status]	AEGL Staff Response	Author/ Reviewer
1	Chlorine	L-2	Exposure of a susceptible subject to 1 ppm for 4 hours resulted in serious asthmatic-like symptoms and pulmonary function changes (Rotman et al., 1983).	LOEL (No)	Oct-01 (Oct-01) [Proposed-FR Publication] Check status of NAS review	The endpoint for the AEGL-2, asthmatic-like critical symptoms consisting of shortness of breath and wheezing in an exercising atopic individual, is a NOAEL for irreversible or other serious, long-lasting health effects or an impairment to escape. The atopic individual voluntarily left the exposure chamber after 4 hours; he was not incapacitated. Following the exposure, the symptoms were completely reversible by the examination on the next day. Fifteen lung function tests were normal. Healthy subjects also had some changes in pulmonary function parameters, but these were asymptomatic. This represents a clear AEGL-2 NOAEL Total UF = 1; MF = N.A.	Talmage/Gephart
2	Chlorine trifluoride	L-1	"Dogs had a definite sign of irritancy within the first 45 minutes of exposure (nasal discharge); lacrimation occurred after three hours of exposure (presumably during the first day of exposure)" (p.11 of document), to 1.17 ppm. The starting point is based on a 3 hour exposure. (Horn and Weir, 1956). Note: This document was first written in 1997 and the endpoints were chosen to comply with the old definitions of AEGLs which included the phase "at or above." The document will be re-written to satify the new definitions of AEGLs. In spite of the change in definitions, the AEGL endpoints are still basically NOAELS.	LOAEL (No)	Aug-00 (Aug-00) [Interim-NAS-Comment Response Done]	The endpoint of nasal discharge in dogs during a 3-hour exposure to 1.17 ppm is a NOAEL for notable discomfort. The nose of a dog is extremely sensitive to odors and irritants and a nasal discharge in response to slight irritation is acceptable within the definition of an AEGL-1. Lacrimation, which did not occur during this time, could be considered notable discomfort. These exposures were repeated for several months with effects becoming greater with repeated exposures (Horn and Weir, 1956). Total UF = 10; MF = N.A.	Talmage/Benson

	Chlorine trifluoride	L-2	Strong irritation in two dogs exposed to 5.15 ppm for 6 hours, may be extremely uncomfortable but are reversible; however, they could possibly impair the ability to escape. (Horn and Weir, 1955).	LOEL (No)	Aug-00 (Aug-00) [Interim-NAS Comment Response Stage]	The endpoint was strong irritation as evidenced by signs of salivation, lacrimation, rhinorrhea, and blinking of the eyes in dogs exposed to a concentration of 5.15 ppm for 6 hours (Horn and Weir, 1955). These signs of irritation occurred during the six hours, but by the end of the six-hour exposure, dogs did not appear markedly affected. Therefore, the signs **do not** (wording change) impair the ability to escape. Total UF = 10; MF = N.A.	Talmage/Benson
3	Croton-aldehyde (cis and trans)	L-1	Mild eye irritation (lacrimation) in workers at 0.58 ppm during the workday. (Frannick, 1982)	LOAEL (No)	May-00 (Jan-02) [Interim-NAS Comment Response Stage]	NOAEL - Mild eye irritation is not considered notable discomfort by the AEGL-1 definitions.	Milanez/Hanson
4	Diborane	L-2	Inflammatory epithelial degeneration in the bronchioles in male ICR mice (4/10) exposed to 5 ppm for 2 hours (Nomiyama et al., 1995)	LOAEL (No)	Dec-00 (Jan-02) [Interim-NAS Comment Response Stage]	10 minutes to 8 hrs. AEGL-2 Exposure to 5 ppm for 2 days in mice resulted in inflammatory epithelial degeneration in bronchioles. The effects are reversible, would not impede escape, and are below AEGL-2 effects.	Troxel/Holler
5	1,2-Dichloro-ethylene (cis and trans)	L-2	For 10-min to 1-hour AEGLs, dizziness produced in 2 human subjects after 10-min exposure to 1000 ppm was used (Lehman and Schmidt-Kehl, 1936). For 4 and 8-hour AEGLs, narcosis in rats at 6000 ppm for a 6-hour exposure was used (Hurtt et al., 1993)	LOEL (No)	Jan-00 (June-00) [Interim-NAS Comment Response Stage]	10-, 30- minute, 1-hour Dizziness is not incapacitating and is reversible (1000 ppm). 4-, 8-hour: Although signs of narcosis as incoordination were observed at 6000 ppm in a pilot study, no clinical narcosis as incoordination was reported at 6000 ppm in the principal study. Also, clinical signs of lethergy were only reported at 12, 000 ppm in the principal study. Therefore, 6000 ppm is considered a NOAEL for AEGL-2 effects. UF = 1 for 10', 30', 1 hr.; 10 for 4 & 8 hrs. MF = 2 differential isomer toxicity	Bast/Falke

6	Ethylene oxide	L-2	Fetal growth retardation in rats manifested by a statistically significant decrease in fetal weight and non-statistical increase in the incidence of delayed ossification at 100 ppm (Snellings et al., 1982a)	LOEL (No)	Apr-00 (NAC4/2000) [Proposed Stage]	The 5 - 7% decrease in fetal body weight is below threshold for AEGL-2 (and no statistically significant increase in delayed ossification). UF = 10; MF = 1	Davidson/ Blackman
7	Ethylene-diamine	L-2	Bronchiolar edema, and light cloudy kidney swelling in rats from ~484 ppm for 6 hours. (Carpenter et al., 1948)	LOEL (No)	Aug-00 (Jan-02) [Interim-NAS Comment Response Stage]	Bronchiolar edema (a delayed effect) and kidney swelling would not impair escape and the effects were reversible. UF = 100; MF = 0	Milanez/McClanahan
8	Hydrazine	L-2	Lesions of the nasal transitional epithelium (minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, and mild apoptosis) from 1 hour exposure to 750 ppm of rats (Latendresse et al., 1995)	LOEL (No)	Mar-00 (June-00) [Interim-NAS Comment Response Stage]	Completely reversible nasal lesions would not impair escape and is considered an AEGL-2 NOAEL. UF = 30; MF = 2 sparse data base	Young/Falke
9	Hydrogen fluoride	L-1	Subthreshold concentration for inflammation of 3 ppm (0.85-2.9 ppm) for 1 hour which was without sensory irritation (Lund et al., 1997, 1998)	NOAEL? (No)	Jan-02 (Jan-02) [Interim-NAS Comment Response Stage]	NOAEL - Effects (low-sensory irritation, increase in 1% CD3 cells and in bronchial BAL) are below an AEGL-1 threshold. UF = 3; MF = N.A.	Talmage/Gephart
	Hydrogen fluoride	*L-2 (10 min)*	*NOEL (950 ppm, for 10 minutes) for lethal effects which produced lung effects in rats include small increases in myeloperoxidase and polymorphonuclear leukocytes in the BAL were observed along with histologic changes in the treachea. (Dalbey, 1996)*	*NOEL not applicable*	*Jan-02*	*NOAEL - effects (increase in myeloperoxidase and polymorphonuclear leukocytes in BAL) below AEGL-2 threshold. Also, trcheal cannulation simulated 100% mouth breathing*	*Talmage/Gephart*
	Hydrogen fluoride	L-2 30', 1,4 8 hr	Reversible irritation in dogs exposed to 243 ppm for 1 hour (Rosenholtz et al., 1963	NOEL (No)	Jan-02 (Jan-02)	Effects in dogs (a sensitive model for irritants) represents great discomfort but not expected to impair escape or result in irreversible effects. Considered an AEGL-2 NOAEL. UF = 10; MF = N.A.	Talmage/Gephart

	Hydrogen fluoride	*L-3 30', 1-, 4-, 8 hour*	*No lethal effects at 263 ppm for 1- hour axposure in mice (Wohlslager et al., 1976)*	*Estimated NOEL (N.A.)*	*Jan-02*	*NOAEL - No deaths in mice, the most sensitive species.*	Talmage/Gephart
10	Hydrogen sulfide	L-2	Minor perivascular edema and increased protein and LDH in lavage fluid in rats exposed to 200 ppm for 4 hours (Green et al., 1991; Khan et al., 1991)	LOEL (No)	Sep-00 (Sep-01) [Interim-NAS Comment Response Stage]	At 200 ppm: No adverse clinical signs or gross pathology, increased protein and LDH in lavage fluid; 200 ppm: no effect on viability of pulmonary alveolar macrophages. Two well conducted studies suggest no irreversible effects below the AEGL-2 or impairment of escape considered a NOAEL for AEGL-2 effects. UF = 10; MF = N.A.	Bast/Barbee
	Hydrogen sulfide	*L-3*	*Highest concentration (504 ppm) causing no mortality in the rats after 1-hour exposure (Mac Ewen and Vermot, 1972)*	*NOEL (No)*	*Sep-00 (Sep-00) [Interim-NAS Comment Response Stage]*	*NOAEL - 0/10 mortality* *UF = 10; MF = N.A.*	*Bast/Barbee*
11	Otto Fuel (Propylene glycol dinitrate) CAS 6423-43-4	L-2	Severe headaches in humans, and one subject reported dizziness at 0.5 ppm for a 6-hour exposure. Slight loss of equilibrium occurred after 6.25 hours. Starting point was at 6 hours. (Stewart et al., 1974)	LOEL (No)	Jan-00 (Jan-01) [Final-Ready for Publication after ORNL Review]	No inability to escape was evident in the extremely sensitive tests used to measure equilibrium (Romberg test used to measure postural equilibrium - balance standing heel to toe in a straight line with eyes closed) in human subjects during a 6-hour exposure to 0.5 ppm of otto fuel. No ability to escape was indicated from any of the effects indicated in the study. This is considered an NOAEL for AEGL-2. The NAS/COT has accepted the values generated for otto fuel. UF = 3; MF = N.A.	Talmage/Bress

12	*Phosgene*	*L-2*	*Chemical pneumonia occurred in rats exposed to 2 ppm for 1.5 hours (Gross et al., 1965)*	*LOEL (No)*	*Aug-00 (April-02)* *[Final- Ready for publication after ORNL review]*	*Chemical pneumonia - 1.5 hrs. at 2 ppm. The pneumonia develops after exposure. Clinical latency was less than or equal to 24 hours but would not impede escape . (This type of latency is inversely proportional to the dose received.)* *UF = 10; MF = N.A.*	*Bast/Bress* .
13	*Phosphine*	*L-2*	*No severe respiratory effects in rats exposed to 10 ppm phosphine for 6 hours. (Newton et al., 1993)*	*NOEL (No)*	*Dec-00 (Dec-00)* *[Interim-NAS Comment Response Stage]*	*NOAEL for AEGL-2 effects - 6 hrs. at 10 ppm red, nasal discharge.* *UF = 30; MF = N.A.*	*Bast/Falke*
14	Sulfur Mustard	L-1	An exposure of 6 mg/m^3 for 2 minutes produced a band of fine injection across exposed bulbar conjunctiva in 3 of 4 human subjects. Trace angular conjunctivitis in one of 4 subjects. Absence of irritation. (Anderson, 1942)	LOAEL (No)	Jan-00 (Sept-01) [Final-Ready for Publication after ORNL Review]	NOAEL - mild, ocular effects (mild injection to notable conjunctivis). No notable discomfort and considered an AEGL-1 NOAEL. UF =3; MF = N.A.	Young/Still
15	Tetrachloro-ethylene	L-1	106 ppm for 1 hour resulted in eye irritation in the exposed volunteers, and slight fullness in the head reported by one subject (Rowe et al., 1952)	LOAEL (No)	Dec-00 (July-01) [Interim-NAS Comment Stage]	NOAEL - 106 ppm for 1 hour resulted only in mild eye irritation. UF = 3; MF = N.A.	Troxel/Bress
16	Toluene	L-1	In humans, eye and nose irritation, headache with no significant effects on psychomotor function at 100 ppm for a 6 hour exposure (Anderson et al., 1983)	LOAEL (No)	Dec-00 (July-01) Interim-NAS Comment Stage] Note: NAS requested that all number be revised (too low).	100 ppm for 6 hrs. eye and nose irritation and headache in only 2 of 20 studies. Other studies showed that at 200 ppm there was no irritation. Toluene is not an irritant and not considered notable discomfort. NAS committee members objected strongly to these numbers and indicated they are unrealistic based on human experience. Values will be revisited at the earliest time. UF = 3; MF = N.A.	Talmage/Gephart

17	*TDI, 2,6-*	*L-2*	*Severe eye and throat irritation, lacrimation in 1 of 6 humans exposed to 0.5 ppm for 30 minutes. (Henschler et al., 1962)*	*NOEL (N.A).*	*May-00 (May-00)* *[Interim-NAS Comment Response Stage]*	*NOAEL - Humans exposed at 0.5 ppm for 30 minutes. Pronounced irritation (marked discomfort, lacrimation, nasal secretions, is reversible and would not impair escape*	*Forsyth/Barbee*
18	*TDI, 2,4-*	*L-2*	*Same as above*	*NOEL (No)*	*(May-00)*	*Same as above.*	*Forsyth/Barbee*
CATEGORY II CHEMICALS: Observed critical health effect endpoint is adjusted from a LOAEL to a NOAEL using a UF, or a MF, or an adjustment factor, e.g., $LC_{50}/3$.							
1	*Hydrazine*	*L-3*	*1-hour rat LC_{50} of 3,192 ppm (HR, 1993*	*LOEL (Yes, 3)*	*Mar-00 (June-2000)* *[Interim-NAS Comment Response Stage]*	*LOAEL adjusted to NOAEL by dividing 1 hr. LC_{50} (3,192 ppm/3 = 1064 ppm)* *UF = 30; MF = N.A./multiple species*	Young/Falke
2	Hydrogen chloride	L-2 (10 min)	RD_{50} value of 309 for mice (Barrow, 1988) was divided by 3 to produce a significant irritation level.	LOEL (No)	May-00 (Jan-02) [Interim-NAS Comment Response Stage]	LOAEL adjusted to NOAEL by dividing RD_{50} of 309 ppm by a factor of 3.to obtain a concentration causing irritation.	Bast/Hinz
	Hydrogen-chloride	L-2 [30] 1-, 4, 8 hr	Histopathology observed in rats exposed to 1300 ppm for 30 minutes included severe necrotizing rhinitis, turbinate necrosis, thrombosis of nasal submucosa vessels (nose breathers) and severe ulcerative traecheitis accompanied by necrosis and luminal ulceration (mouth breathers) (Stavert et al., 1991)	LOEL (No)	May-00 (Jan-02	30 minute, 1, 4, and 8 hr. AEGL-2 A LOAEL of 1300 ppm for 30 min. that caused severe lung and nasal effects was divided by a factor of 3. This "modifying" factor also included adjustment for the sparse data base. Therefore, a LOAEL to NOAEL adjustment was made. UF = 10 (30', 1,4 8 hr); MF = 3 sparse data base and severe effects.	Bast/Hinz
	Hydrogen chloride	*L-3*	*1-hour LC_{50} of 3,124 ppm (Wholslagel et al, 1976.; Vernot et al., 1977)*	*LOEL (Yes, 3)*	*May-00 (Jan-02)*	*LOAEL (LC_{50}) adjusted to NOAEL for AEGL-3 vis 1/3 of 1 hour LC_{50}* *UF = 10; MF = N.A.*	Bast/Hinz

3	*Hydrogen sulfide*	*L-1*	*Headache (3/10), increased airway resistance (8/10) in asthmatic humans at 2 ppm for 30 min (Jappinene et al., 1990)*	*LOAEL (Yes, 10)*	*Sep-00 (Sept-01)* *[Interim-NAS Comment Response Stage]*	*LOAEL (significannt increase in RAW 2/10) adjusted to NOAEL with a 3x MF.* *UF = 3; MF = 3 effects more severe than defined by AEGL-1; shallow dose/response curve*	*Bast/Barbee*
4	*Isobutyro-nitrile*	*L-3*	*LC_{50} of 1800 ppm for a 1-hour exposure in rats (Eastman Kodak, 1986a)*	*LOEL (Yes,3)*	*Aug-00 (Mar-01)* *[Interim-NAS Comment Response Stage]*	*LOAEL (LC_{50}) adjusted by dividing 3x to NOAEL for AEGL-3 effect.* *UF = 10; MF = N.A.*	Bast/Rodgers
5	*Methanol*	*L-3*	*Lowest calculated peak blood concentration resulting in death was 1109 mg/L (Naraqi et al., 1979)*	*LOEL (Yes, 2)*	*Feb-00 (Feb-01)* *[Interim]*	*10 minute to 8 hrs. AEGL-3 LOAEL (blood methanol level) for lethality adjusted by dividing 2x to NOAEL for AEGL-3 effect.* *UF = 3; MF = N.A.*	Griem/Falke
6	*Methyl iso-cyanate*	*L-2*	*Based on decreased fetal body weights at 2 ppm for single 3-hour exposure (Verma, 1987) and cardiac arrythmias in rats after 2-hour exposure to 3 ppm (Tepper et al., 1987)*	*LOEL (Yes, 3)*	*May-00 (May-00)* *[Interim-NAS Comment Response Stage - July NAC meeting]*	*AEGL-2 LOAEL (reduced fetal body weight and increased cardiac arrhythmias) adjusted by dividing 3x to NOAEL for AEGL-3 effects.* *UF = 30; MF = 0*	Forsyth/Koller
7	*TDI, 2-6*	*L-3*	*4-hour LC_{50} of 9.7 ppm in the mouse (Duncan et al., 1962)*	*LOEL (Yes, 3)*	*Apr-00 (May-00) [Interim -NAS Comment Response Stage - July meeting]*	*10 minute to 8 hrs. AEGL-3 LOAEL (4 hr. LC50) adjusted to NOAEL for AEGL-3 by dividing 3x adjusted factor.*	Forsyth/Barbee
CATEGORY III CHEMICALS:			**Observed critical health effect endpoint is adjusted from a LOAEL to a NOAEL based on unique circumstances surrounding the study in question, e.g., multiple exposures.**				

1	Carbon monoxide	L-2	Decrease in time to onset of angina pectoris during physical exercise at 4 % COHb pronounced from a 253 ppm exposure for 50-70 min in humans (Allred et al., 1989a,b; 1991; Sheps et al. 1990, 1991)	LOEL (No)	Feb-01 (Feb-01) [Interim]	NOAEL - At 4% COHb, the decrease in time to the ST segment change was 12.1%. Also, significant change in maximal amplitude of the ST segment change and possible reduced time to onset of angina during physical exercise of coronary disease patients with stable exertional angina for 50 - 70 minutes. This is a reversible effect that is not considered an impairmnent to escape. Note it is logically implausable to set a 1-hour AEGL-2 that is lower than the OSHA or ACGIH 8- hour values. Total UF = 1; MF = N.A.	Griem/Rodgers
2	HCFC 141b	L-2	Cardiac response on 1/10 dogs at 5200 ppm, exposed for 10 minutes, for cardiac arrhythmia (Mullin, 1977)	LOEL (No)	Jan-00 (Jan-02) [Final- Ready for Publication after ORNL review]	The response of cardiac arrythmia in 1 of 10 beagles inhaling 500 ppm HCFC-141b folllowing injection with 8 ug of exogenous epinephrine was not incapacitating and was fully reversible. As explained in the TSD this endpoint is conservative as the test is supersensitive (large dose of exogenous epinephrine - 10x endogenous levels) and the cardiac response that led to death occurred at 2- to 3- fold higher concentrations. **It should be noted that the AEGLs for this chemical, and the critical endpoints, have all been accepted by the NAS/COT.** UF =3; MF = N.A.	Talmage/Rusch
3	Hydrogen fluoride	L-3 10 min	Lethality (1/20) in orally cannulated rats exposed to 1764 ppm for 10 min (Dalby, 1996). Note: oral cannulation is said to eliminate scrubbing by the nose.	LOEL (No)	Jan-02 (Jan-02) Interim-NAS Comment Response Stage]	10 minute AEGL-3 Based on endpoint of 1/20 deaths in rats. Represents a NOAEL rather than a LOAEL since oral cannulation model is conservative compared to normal nose breathing. Additional data shows that concentrations that cause up to 80% mortality in cannulated rats results in no deaths in normal breathing rats. UF =10; MF = 0	Talmage/Gephart

4	Sulfur Mustard	L-2	An exposure of 4.5 mg/m^3 for 13.5 minutes produced irritation, soreness, widespread conjunctivitis, photophobia, and chemoses, necessitating medical treatment in 3 military volunteers. Ocular effects could be characterized as military casualties and such personnel might be ineffective for up to 7 days. Effects were severe enough to impair escape (Anderson, 1942)	LOEL (No)	Jan-00 (Sept-01) Ready for NAS Publication	Effect (ocular irritation - generalized conjunctivitis, edema, photophobia, and irritation, requiring medical treatment) at 60 mg-min/m^3. Expansion of same type of effect as in AEGL-1 would not impair escape and MF (3x) included for long term effects considered a NOAEL for AEGL-2. Note that these effects take hours to develop but may not be reversible. UF = 3; MF = 3 to accommodate uncertainties regarding the onset of potential long-term ocular or respiratory effect.	Young/Still
5	Toluene 2,4-diisocyanate	L-1	Chest tightness, eye and throat irritation, cough, rhinitis, dyspnea, and/or headache lasting for up to several hours post exposure in 15 asthmatics exposed to 0.01 ppm for 1 hour. (Baur, 1985)	LOAEL (No)	May-00 (May-00) [Interim-NAS Comment Response Stage - July meeting]	Based on use of 1 hr. exposure of asthmatics to 0.01 ppm after 1 hour exposure (and 45 minute rest) plus 0.02 ppm for another hour experienced no change in lung parameters but 5/15 reported chest tightness, rhinitis, cough, dyspnea, throat irritation and/or headache. There were no statistically significant changes in eye and throat irritation in the asthmatics tested. (OSHA PEL is 0.02 ppm; ACGIH TLV is 0.005 ppm (short term). Don't set a 1- hour AEGL-1 level that OSHA permits for 8 hours.) UF = 0; MF = 0	Forsyth/Barbee

6	TDI, 2,6-	L-1	Chest tightness, eye and throat irritation, cough, rhinitis, dyspnea, and/or headache in 15 asthmatics exposed to 0.01 ppm for 1 hour (Baur, 1985)	LOAEL (No)	Apr-00 [Interim-NAS Comment Response Stage - July meeting}	Same as above.	Forsyth/Barbee
CATEGORY IV CHEMICALS:			**Chemicals with NAS-recommended changes in AEGL development.**				
1	Allylamine	L-2	Four rats exposed to 60 ppm for 14 hours developed cardiovascular lesions including scattered myofibril fragments with loss of striation, perivascular edema, and cellular infiltration. (Guzman et al., 1961)	LOEL (No)	May-00 (Jan-02) Interim 2 [Interim-NAS Comment Response Stage]	STUDY BEING REPLACED.	Milanez/Koller
2	Dimethyl-dichloro-silane	L-2	Necrotic and swollen paws, corneal opacity, grey areas on lungs, and other effects in rats exposed to 1309 ppm for 1 hour (Dow Corning, 1997a)	LOEL (No)	May-00 (May-00) [Interim-NAS Comment Response Stage]	All surviving animals fully recovered; all effects were fully reversible. No impairment of escape indicated. A modifying factor of 3 was used to account for the sparse data base (and an implied adjustment from a LOAEL to a NOAEL). UF = 30; MF = 3 (sparse data base.)	Bast/Falke
3	Nerve Agent GB (Sarin)	L-1	Rhinorrhea, headache, tightness in chest, cramps, nausea and miosis observed in human volunteers exposed to 0.05 mg GB/m^3 for 20 minutes (Harvey, 1952) STUDY REPLACED WITH NEW ONE.	LOAEL (No)	Oct-00 (Oct-01) [Interim-NAS Comment Response Stage]	10 minute to 8 hrs. AEGL-2 Reconsideration of approach to AEGL-1 based on COT review.	Watson/Hinz

4	Nickel carbonyl REVISIT AT JUNE MEETING	L-2	Single 15-minute exposure of pregnant hamsters to 8.4 ppm on GD 4 or 5 resulted in significant increased malformations, increased proportions of litters with malformed fetuses, and serious cavity hemorrhage in offspring (Sunderman et al., 1980)	LOEL (No)	May-00 (Jan-02) [NAS-Comment Response Stage - July meeting]	(No 8-hr number generated) Weak data set. NAS returned chemical because the developmental studies were considered inadequate. Author objected to using this study in favor of estimating lethality threshold. UF = 100; MF = 0	Young/Blackman
5	Toluene BEING REVISED	L-2	Headache, nausea, incoordination, decreased reaction time in humans exposed to 200 ppm for 8 hours (Wilson, 1943). The studies by Wilson (1943) and von Oettinger et al. (1942) establish that toluene concentration at 200 or above for an 8-hour exposure produce mental confusion, incoordination, lassitude, nausea and headache in humans.	LOEL (No)	Dec-00 (July-01) [Interim-NAS Comment Response Stage] Note: NAS/COT says values are too low.	Values have been deamed too low by the NAS/COT based on human experience. New values will be assigned UF = 3; MF = N.A.	Talmage/Gephart
	Toluene *BEING REVISED*	*L-3*	*Exposure for 1-hour to 19,018 ppm in mice was the LC_{50} (Moser and Baister, 1985).*	*LOEL (Yes, 3)*	*Dec-00 (July-01)* *[NAC/Draft 4 Interim-NAS Comment Response Stage]*	*Values too low based on human experience.* *UF = 10; MF = N.A.*	Talmage/Gephart
6	1,1,1-Tri-chloro ethane	L-1	Eye irritation, slight dizziness, and a decline in perceptual acuity in humans exposed to 450 ppm for 4 hours (Salvini et al., 1971).	LOAEL (No)	Sep-99 (June-00) [Interim-NAS Comment Response Stage] Values rejected by the NAS/COT for being too low.	NOAEL - Eye irritation, slight dizziness and mental fatigue at 450 ppm for 4 hours (mild CNS effects). However, values rejected for being too low and new AEGL values will be generated. [Doesn't meet the standard of AEGL-2.] UF = 2; MF = N.A.	Talmage/ McClanahan

	1,1,1-Trichloro-ethane NEEDS REVISION	L-2	EC_{50} for ataxia in rats of 6740, 6000, 4240, and 3780 ppm for 30 minutes, 1 hour, 2 hours, and 4 hours respectively. (Mullin and Krivansk, 1982)	LOEL (No)	Sep-99 (June-00) [Interim-NAS Comment Response Stage NAS/COT says values too low.	EC50 for ataxia (loss of equilibrium) "might impede escape". These values have been rejected by the NAS/COT as being too low. Revisions required.	Talmage/ McClanahan
CATEGORY V CHEMICALS:			**Observed critical health effect endpoint appears to be >AEGL threshold level**				
1	Chloro-methyl methyl ether	L-2	Pulmonary hyperplasia, broncheotracheal squamous metaplasia in rats exposed to 1 ppm for 6 hours for 30 exposures (Drew et al., 1975)	LOEL (but effect was following 30 expos) (No)	Dec-00 (Dec-00) [Interim]	Carcinogenic agent. Effects observed immediately after **30 exposures** showed four animals with normal lungs and one animal with slight bilateral hemorrhage. Thirteen animals retained for their lifespan showed minimal mucosal effects with 2/13 with regenerative hyperplasia and 2/13 with tracheobronchial squamous metaplasia. Total UF = 10; MF = 3 tech grade	Milanez/Falke
2	Croton-aldehyde (cis and trans)	L-2	Rat impaired pulmonary function (manifest as a 20-40% reduction in carbon monoxide and ether uptake rates compared to pre-exposure value) and bronchiole lesions at 8000 ppm-min (Rinehart, 1967).	LOEL (No)	May-00 (Jan-02) [Interim-NAS Comment Response Stage]	10 minutes to 8 hrs. AEGL-2 Decreased pulmonary function and proliferative lesions of the respiratory bronchioles at 8000 ppm per minute. Lesions are seen above 8000 ppm. Seventy percent lethality seen; 20 - 40 % reduction in CO/ether uptake. UF = 100; MF = 0	Milanez/Hansen
3	Iron penta-carbonyl	L-3	10% mortality (1/10) in rats exposed to a single 6-hour exposure of 2.91 ppm (BASF, 1995)	LOEL (No)	May-00 (Jan-02) [Interim-NAS Comment Response Stage - July meeting]	See NAS comments. Author claims there is not enough data to calculate LC_{50} value. UF = 30; MF = 0	Young/Blackman
4	Methyl trichloro-silane (Also see dimethyldich lorosilane)	L-2	Ocular opacity, irritation, hunched posture, and NOEL for lethality in rats exposed to 622 ppm for 1 hour (Dow Corning, 1997a). "This level was considered to be the threshold for impairment of escape and onset of serious long-term effects."	LOEL (No)	May-00 (May-00) [Interim-NAS Comment Response Stage]	The ocular opacity seen were adjusted to account for the LOAEL to NOAEL by dividingby a factor os 3. UF = 30; MF = 3 sparse data base	Bast/Falke?

5	Propionitrile	L-2	Headache, nausea, vomiting, dizziness, confusion in a human subject exposed to 33.8 ppm for 2 hours who had to be admitted to a hospital and given an antidote. (Schoinick et al., 1993)	LOEL (No)	Aug-00 (Mar-01) [Interim-NAS Comment Response Stage]	The subject escaped after two hours because he was feeling sick, thus his ability to escape was not impaired. An uncertainty factor was included for susceptible individuals and, as further safety, a modifying factor of two was added because of the sparse data base. UF = 3; MF = 2 sparse data base	Bast/Rodgers

NOTE: Chemicals in italics were based on the NOAEL or have safety factor adjustments and are included for comparison purposes only.

Attachment 8

57028

00330

C-001

7pp

George Alexeeff <GALEXEEF@oehha.ca.gov> on 03/15/2002 07:42:05 PM

To: NCIC OPPT/DC/USEPA/US@EPA
cc: Roger Garrett/DC/USEPA/US@EPA, Paul Tobin/DC/USEPA/US@EPA, gabriele.haeffner@fobig.de, lpy@ornl.gov, MTM.van.Raaij@rivm.nl

Subject: OPPTS-00330, FRL-6815-8

Attached are comments on three AEGL documents carbon tetrachloride, chlorine dioxide and chlorine. Hard copy will be sent to follow.

George V. Alexeeff, Ph.D., D.A.B.T.
Deputy Director for Scientific Affairs
Office of Environmental Health Hazard Assessment
Cal/EPA
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Oakland phone: (510) 622-3202
Sacramento phone: (916) 322-2067

The energy challenge facing California is real. Every Californian needs to take immediate action to reduce energy consumption.

Carbon Tet Fed Reg comments-1.txt Chlorine Dioxide Fed Reg comments-1.txt Chlorine Fed Reg comments-1.txt

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March 15, 2002

Document Control Office (7407)
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Environmental Protection Agency
1200 Pennsylvania Avenue
Washington, DC 20460

Docket control # OPPTS-00330 - Carbon tetrachloride values

I would like to raise several concerns regarding carcinogenicity calculations, the AEGL-1 values and the AEGL-2 values recommended by the Acute Exposure Guideline Levels Committee (AEGL) for carbon tetrachloride.

Carcinogenicity Calculations
The carbon tetrachloride document appears to have some miscalculations in Appendix D where the cancer risks are evaluated. Page D-1 describes the cancer assessment of carbon tetrachloride. The document uses the inhalation unit risk of 1.5E-5 µg/m3 and states that this is associated with a 1 in 100,000 risk of 7 E-2 µg/m3. Online the U.S. Environmental Protection Agency (U.S. EPA) indicates the following risks (http://cfpub.epa.gov/iris):

Air Concentrations at Specified Risk Levels

Risk Level	Concentration
E-4 (1 in 10,000)	7x10-3 mg/m3
E-5 (1 in 100,000)	7x10-4 mg/m3
E-6 (1 in 1,000,000)	7x10-5 mg/m3

Thus the risk cited for 7 E-2 µg/m3 should be a 1 in a 1,000,000 risk level, not 1 in 100,000. The calculated risk for 1 x 10-4 risk is incorrect in that it provides two answers, 64 µg/m3 or 0.18 mg/m3, neither of which is correct. Instead the value should be 64 mg/m3.

The document only calculated the 1 x 10-4 risk level. On page 117 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (SOPs) it states:

"...Therefore, the Committee will continue to provide data and information on the carcinogenic properties of chemicals in the Technical Support Documents, and in instances where the appropriate data are available, develop quantitative cancer risk assessments at risk levels of 10-4, 10-5, and 10-6 in accordance wi

th the National Academy of Science (NAS) guidance (NAS, 1993a). T
he NAC/AEGL Committee will attempt to limit potential cancer risk
to 10-4 or less where there is scientifically credible data to sup
port the risk based on a single exposure. If at some future date,
substantial and convincing scientific data become available that
clearly establishes a relationship between a single, short-term in
halation exposure to a chemical and the onset of tumors that are l
ikely to occur in humans, the carcinogenic risk in the development
of the appropriate AEGL values will be considered..."

Consequently, it would appear that the calculations for risk level
s of 10-4, 10-5, and 10-6 should be added to the document. Also
, to give a more complete picture of the carcinogenicity of carbon
tetrachloride, I suggest that the following statement be added to
the Executive Summary, at the beginning of the first full paragra
ph on page 3: "U.S. EPA has classified carbon tetrachloride as a
possible human carcinogen."

Finally, I believe that the AEGL committee has discussed on numero
us occasions, without objection that the table of proposed values
include a footnote indicating the carcinogenicity of the chemical.

AEGL-1 Values
As stated in the SOPs (page 36), "therefore, in the development of
the AEGLs, the NAC/AEGL Committee selects the highest exposure le
vel from animal or human data where the effects used to define a g
iven AEGL tier are not observed." This point is reiterated in the
Chapter subheading 2.2.1 "Selection of the Highest Exposure Level
at Which the Effects that Define an AEGL are not Observed." Also
as stated on page 40, "for reasons discussed earlier in this chap
ter, the NAC/AEGL Committee generally selects the highest experime
ntal concentration that does not elicit the symptoms or effects de
fined by the AEGL tier in question. This concentration represents
the starting point for AEGL development."

Specifically the SOPs (page 42) indicate that the starting point f
or AEGL-1 development is the "highest experimental exposure withou
t an AEGL-1 effect." However, the carbon tetrachloride document a
ppears to identify the concentration producing an AEGL-1 effect, n
amely "resulting in a feeling of nervousness and slight nausea."
Thus, the document identified a lowest observed adverse effect lev
el (LOAEL), instead of a no-observed adverse effect level (NOAEL),
as the starting point. Identification of a LOAEL as the starting
point for AEGL development is inconsistent with the SOPs, the app
roach for identifying starting points of many other AEGLs, and app
ears to be inconsistent with the AEGL-1 definition.

One could address the problem by identifying an appropriate NOAEL from the study and to use it as the starting point. In this case it appears to be 76 ppm for two and one-half hours.

AEGL-2 Values
For carbon tetrachloride the document states "the AEGL-2 was also based upon human data from controlled exposure experiments in whic h subjects experienced headache, nausea and vomiting following 15-minute exposure to 1191 ppm carbon tetrachloride (Davis, 1934). I t is believed that these effects may impair escape." However, the SOPs (page 42) clearly state: "in developing AEGL-2 values, the NAC/AEGL Committee estimates a NOAEL for serious or irreversible e ffects or effects that impair escape." Consequently, the document describes these effects as AEGL-2 effects. This appears to be in consistent with the AEGL-2 definition and the SOPs. One could add ress the problem by identifying an appropriate NOAEL from the stud y and to use it as the starting point. In this case it appears to be 317 ppm for a 30-minute exposure.

Thank you for consideration of these comments. If you sho uld have any questions about the comments, please contact me at (5 10) 622-3202 or by e-mail: galexeef@oehha.ca.gov.

Sincerely,

George V. Alexeeff, Ph.D., D.A.B.T.
Deputy Director for Scientific Affairs
Office of Environmental Health
Hazard Assessment
1515 Clay Street, 16th Floor
Oakland, California 94612

March 15, 2002

Document Control Office (7407)
Office of Pollution Prevention and Toxics (OPPTS)
Environmental Protection Agency
1200 Pennsylvania Avenue
Washington, DC 20460

Docket control # OPPTS-00330 - Chlorine Dioxide values

I would like to raise a concern regarding the AEGL-1 value s recommended by the Acute Exposure Guideline Levels Committee (AE GL) for chlorine dioxide.

As stated in the SOPs (page 36), "therefore, in the development of the AEGLs, the NAC/AEGL Committee selects the highest exposure le vel from animal or human data where the effects used to define a g iven AEGL tier are not observed." This point is reiterated in the Chapter subheading 2.2.1 "Selection of the Highest Exposure Level at Which the Effects that Define an AEGL are not Observed." Also as stated on page 40, "for reasons discussed earlier in this chap ter, the NAC/AEGL Committee generally selects the highest experime ntal concentration that does not elicit the symptoms or effects de fined by the AEGL tier in question. This concentration represents the starting point for AEGL development."

Specifically as the SOPs (page 42) indicate that the starting poin t for AEGL-1 development is the "highest experimental exposure wit hout an AEGL-1 effect." However, the chlorine dioxide document ap pears to identify the concentration producing an AEGL-1 effect, na mely "slight salivation, slight lacrimation, and slight red ocular discharge in rats exposed to 3 ppm chlorine dioxide for 6 hours (DuPont, 1955)" as the starting point. In this case it does not ap pear that the document identified a no-observed adverse effect lev el (NOAEL) for this study. The effects reported are AEGL-1 effect s. Consequently, if another appropriate NOAEL cannot be identifie d from another study, an adjustment factor could be used as has be en done with a number of other chemicals. However, identification of a LOAEL as the starting point for AEGL development is inconsis tent with the SOPs, and appears to be inconsistent with the AEGL-1 definition.

Thank you for consideration of these comments. If you sho uld have any questions about the comments, please contact me at (5

10) 622-3202 or by e-mail: galexeef@oehha.ca.gov.

Sincerely,

George V. Alexeeff, Ph.D., D.A.B.T.
Deputy Director for Scientific Affairs
Office of Environmental Health
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1515 Clay Street, 16th Floor
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March 15, 2002

Document Control Office (7407)
Office of Pollution Prevention and Toxics (OPPTS)
Environmental Protection Agency
1200 Pennsylvania Avenue
Washington, DC 20460

Docket control # OPPTS-00330 - chlorine values

I would like to raise a concern regarding the AEGL-2 values recommended by the Acute Exposure Guideline Levels Committee (AEGL) for chlorine.

As stated in the SOPs (page 36), "therefore, in the development of the AEGLs, the NAC/AEGL Committee selects the highest exposure level from animal or human data where the effects used to define a given AEGL tier are not observed." This point is reiterated in the Chapter subheading 2.2.1 "Selection of the Highest Exposure Level at Which the Effects that Define an AEGL are not Observed." Also as stated on page 40, "for reasons discussed earlier in this chapter, the NAC/AEGL Committee generally selects the highest experimental concentration that does not elicit the symptoms or effects defined by the AEGL tier in question. This concentration represents the starting point for AEGL development."

The AEGL-2 definition states that it is "the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape." The SOPs indicate that this is accomplished by choosing the appropriate AEGL-2 no-observed adverse effect level (NOAEL), as the starting point.

For chorine the AEGL-2 starting point appears inconsistent with the AEGL-2 definition. The chlorine document states "...an exercising susceptible individual exhibited effects consistent with the definition of the AEGL-2." Specifically, it states that a susceptible individual experienced an asthmatic-like attack (shortness of breath and wheezing) at a concentration of 1 ppm after 4 hours of exposure (Rotman et al., 1983)." The document suggests that an asthmatic attack is an AEGL-2 response. This is consistent with discussions of the committee. However, the document uses this AEGL-2 effect as a starting point instead of using the NOAEL. Thus, the appropriate NOAEL, possibly 0.5 ppm for 4 hours, should have been used as the starting point for AEGL-2 level.

Thank you for consideration of these comments. If you should have any questions about the comments, please contact me at (510) 622-3202 or by e-mail: galexeef@oehha.ca.gov.

Sincerely,

George V. Alexeeff, Ph.D., D.A.B.T.
Deputy Director for Scientific Affairs
Office of Environmental Health Hazard Assessment
1515 Clay Street, 16th Floor
Oakland, California 94612

Attachment 9

00330

C-003

John Morawetz <JMorawetz@ICWUC.org> on 03/15/2002 02:35:12 PM

4pp

To: NCIC OPPT/DC/USEPA/US@EPA
cc: George Rusch <george.rusch@alliedsignal.com>, Po-Yung Lu <lpy@ornl.gov>, Roger Garrett/DC/USEPA/US@EPA, Paul Tobin/DC/USEPA/US@EPA

Subject: RE: Docket OPPTS-00330 Carbon tetrachloride

Docket OPPTS-00330

Enclosed are my comments on the AEGL proposed values for Carbon tetrachloride.

John S. Morawetz

(513)621-8882

CFR Carbon Tetrachloride.doc

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Washington, DC 20460

March 15, 2002

Docket control # OPPTS-00330 Carbon Tetrachloride values

I would like to raise concerns regarding the AEGL-2 and AEGL-3 values recommended by the AEGL Committee for Carbon Tetrachloride.

The 4 subjects in the Davis article, which is relied on for the AEGL-2 values, had more serious effects than stated in the current version of the TSD with three of the four subjects not staying the entire 15 minutes. As the TSD states, one subject "could not stay" and left after nine minutes however two of the other three subjects left before the end of exposure (10 and 12 minutes and all three who left had vomiting and nausea). The inability to remain in an exposure chamber for the original exposure time period has been used by the committee before to set AEGL-2 values. The 1,191 ppm exposure appears to be the appropriate starting level for the AEGL-2 determination but the LOAEL time period is 9 minutes. The committee needs to determine either a lower time period or exposure for a NOAEL.

My concerns on the AEGL-3 level are centered on the Norwood, 1951 article that describes the death of a heavy drinker 6 days after exposure to carbon tetrachloride for 15 minutes. The authors state "The conditions under which this man was exposed were duplicated to the best of our ability, and the measured concentration was 250 parts of carbon tetrachloride per million parts of air." Without a significant reason for discounting this published report, this should be the committee's starting point.

One question is the possible theoretical calculation of exposure given Norwood's detail of the amount of carbon tetrachloride used, time period of exposure, size of the room and ventilation (erroneously reported as the Norwood method in section 7.1). There are some factors that might effect a theoretical calculation of exposure. As a first cut, the calculated amount of vapor dispersed in the room volume would only occur at the end of the 15 minutes when all the carbon tet was used and evaporated. The time weighted average for the 15 minutes of exposure would therefore be an integrated function of the rising exposure levels and be approximately half of the final concentration. This, however, assumes complete mixing, even distribution and no loss of solvent from the room.

The location of the vent that supplied fresh air to the room is unknown, the location of the deceased's work to the open door that served as the exhaust from the room is unknown and the magnitude of the "slight negative gradient" to the rest of the building is unknown. In addition, this process does not account for the Molecular Weight of carbon tet (153; approximately 5 times heavier than air, which would tend to keep the vapors close to the floor and possibly the door with it's negative gradient). The fresh air, in contrast, regardless of the location of the vent, would tend to rise above the dense solvent vapors and probably be closer to the deceased's breathing zone. With all these uncertainties, the best option is to use the measured concentration as reported in the published paper.

I request that the Committee reconsider and lower the current recommended AEGL 3 levels by using the Norwood exposure value of 250 ppm for 15 minutes as a LOAEL for lethality. Alternatively, the Committee could leave the 1, 4 and 8 hour values as is but set the 10 and 30 minute values at the current 1 hour 170 ppm AEGL 3 value. The rational then would be that the human data places an upper limit of levels at lower time periods that the animal model may not fully take into account.

In addition, the description in the TSD of the Norwood article has some errors. In the initial summary in Section 2.1, it should state that there were 55 (not 51) industrial cases (51 summarized and cases 4 through 7). Of the three (rather than 7) non-industrial exposures, one (not 5) resulted in serious health effects. The second Norwood fatality described in Section 2.1 should include information stated about her drinking habits: "The patient had been a heavy user of alcoholic liquors for many years".

Table 2 lists the Norwood study as "estimated" exposure. The original study states "The conditions under which this man was exposed were duplicated to the best of our ability, and the measured concentration was 250 parts of carbon tetrachloride per million parts of air." Table 2 should list the 250 ppm with the notation "(duplicated conditions)" for the fatality.

Section 7.1 describes the Norwood exposure method as "the concentration (250 ppm) was determined based upon a reconstruction of the accident using room volume and the amount of carbon tetrachloride dispersed". Although this information is included in the article, it does not state that it used this information to calculate the 250 ppm. Rather Norwood clearly states that the level was "measured". In Section 7.3 on the derivation of the AEGL-3 level, the phrase "exposure terms are uncertain" should be explained. It also states "the information is anecdotal". This report is a case series and not anecdotal since it is published in a peer reviewed journal, has a complete medical description of a number of cases and exposure level under duplicated conditions for the reported case.

Sincerely,

John S. Morawetz

c: Larry Gregoire
Secretary Treasurer's Office
Eric Bray
Michael Sprinker
Frank Mirer, UAW
Bill Kojola, AFL-CIO
George Rusch, AEGL Chairman
Rodger Garrett, EPA
Po-Yung Lu, ORNL

Table 2 also lists the exposure for 2 individuals at 250 ppm. The conditions that were duplicated was the work the deceased did. The article states that the other two workers "continued the mopping under the same conditions" but is not clear whether they continued to work in the same room for 4 hours.

Attachment 10

CARBON TETRACHLORIDE

RESPONSE TO FEDERAL REGISTER COMMENTS

NAC/AEGL - 25
JUNE 17-19, 2002

EOHSI
Rutgers University
Piscataway, NJ

Response to FR comments on Carbon Tetrachloride - J. Morawetz

Regarding AEGL-2:
The fact that individuals could not tolerate the exposure for a full 15 minutes does not necessarily imply that there were "more serious effects". "Tolerance" in the context of the Davis report is not referring to mechanistic or metabolic-mediated tolerance but rather to a subjective decision regarding what the individual was willing to endure. If the subjects were, for some reason, unable to extract themselves from the exposure situation they would likely have suffered no more than additional nausea and vomiting; effects that are in and of themselves not actually AEGL-2 severity. In developing the AEGL-2 values, a conservative assumption was made that these effects may impair escape. In fact, such effects may actually encourage egress. For these reasons, the 15-minute exposure time was used for the basis for time scaling.

Use of the 9-minute exposure could be used, however, and would provide lower AEGL-2 values as follows:

10-minute	114 ppm
30-minute	74 ppm
1 hr	56 ppm
4 hrs	32 ppm
8 hrs	24 ppm

These values, while expectedly lower, do not appear to be unreasonable when compared to available data, and to the AEGL-1 and AEGL-3 values.

Regarding the Norwood study and AEGL-3:
Regardless of the precision of the measurements obtained during the reconstruction, it is still just that, a reconstruction. The individual in the Norwood report was highly compromised and represents an extremely sensitive individual (analogous to using moribund animals in a controlled experiment). As such, the case report by Norwood was not used as a **driver** for AEGL-3 development. It was considered inappropriate to use the response of one individual where the quantitative exposure component was derived from a reconstruction.

The alternate proposal to leave intact the 1, 4, and 8-hr AEGL-3 values (170, 99, 75 ppm, respectively) but set the 10-minute and 30-minute values equivalent to the 1-hr value (i.e., 170 ppm for all three exposure durations) is, however, justifiable. Such an approach would allow for incorporation of the Norwood report to some extent (thereby incorporating a human data element into the assessment, but not to the point of being the sole driver for all AEGL-3 values) and still allow for use of the more quantitatively definitive animal data.

Response to FR comments on Carbon Tetrachloride - G. Alexeeff

Regarding carcinogenicity calculations

The 0.64 mg/m^3 is, in fact, for the 10^{-6} risk not 10^{-4} as noted in the FR comment. The values listed at the bottom of page D-1 in the TSD are correct but refer to 10^{-6} risk levels not a 10^{-4} risk as implied. Corresponding values for lower risk levels will be added. A carcinogenicity footnote also can be incorporated in the AEGL Exec. Summary table although a carcinogenicity statement does appear in the Executive Summary and in §2.5. Application of the cancer assessment for AEGL development is, however, difficult to justify due to the fact that the unit risk was derived by route-to-route extrapolation.

Regarding AEGL-1 values

The use of 76 ppm at 2.6 hr as a NOAEL for AEGL-1 would provide the following AEGL-1 values:

10 minutes	22 ppm
30 minutes	14 ppm
1 hr	11 ppm
4 hrs	6.3 ppm
8 hrs	4.8 ppm

These are slightly less than the originally accepted values and would appear to be justified.

Regarding AEGL-2 values

Use of the suggested 317 ppm, 30-minute exposure results in the following AEGL-2 values:

10-minute	49 ppm
30-minute	32 ppm
1 hr	24 ppm
4 hrs	14 ppm
8 hrs	10 ppm

Upon comparison with human exposure information, these appear to be unrealistically low values. For example, 70-minute exposures of 6 subjects to 31-87 ppm (TWA of 49 ppm) resulted in odor detection, and transient, clinically insignificant changes in serum ions and urinary urobilinogen in 2 subjects (Stewart et al., 1961). Generally, repeated exposures of humans equivalent to the suggested AEGL-2 values result in effects below what would be considered AEGL-2 severity.

Proposed Revisions to Carbon Tetrachloride AEGLs in Response to Fed. Reg. Comments

AEGL VALUES FOR CARBON TETRACHLORIDE (ppm)						
Classification	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1	25 **22**	16 **14**	12 **11**	6.9 **6.3**	5.2 **4.8**	Nervousness and slight nausea in human subjects exposed for 30 minutes to ~~158~~ **76** ppm (Davis, 1934)
AEGL-2	140 **114**	90 **74**	68 **56**	39 **32**	30 **24**	Nausea, vomiting, headache in human subjects exposed to 1191 ppm for ~~15~~ **9** minutes (Davis, 1934)
AEGL-3	350 **170**	230 **170**	170	99	75	Lethality in rats; estimated LC_{01} (Adams et al., 1952; Dow Chemical, 1986); **human case report (Norwood et al., 1950)**

Federal Register Comment Regarding Chlorine AEGL-2:

I would like to raise a concern regarding the AEGL-2 values recommended by the Acute Exposure Guideline Levels Committee (AEGL) for chlorine.

As stated in the SOPs (page 36), "therefore, in the development of the AEGLs the NAC/AEGL Committee selects the highest exposure level from animal or human data where the effects used to define a given AEGL tier are not observed." This point is reiterated in the Chapter subheading 2.2.1 "Selection of the Highest Exposure Level at Which the Effects that Define an AEGL are Not Observed." Also as stated on page 40, "for reasons discussed earlier in this chapter, the NAC/AEGL Committee generally selects the highest experimental concentration that does not elicit the symptoms or effects defined by the AEGL tier in question. This concentration represents the starting point for AEGL development."

The AEGL-2 definition states that it is "the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape." The SOPs indicate that this is accomplished by choosing the appropriate AEGL-2 no-observed adverse effect level (NOAEL), as the starting point.

For chlorine the AEGL-2 starting point appears inconsistent with the AEGL-2 definition. The chlorine document states "...an exercising susceptible individual exhibited effects consistent with the definition of the AEGL-2." Specifically, it states that a susceptible individual experienced an asthmatic-like attack (shortness of breath and wheezing) at a concentration of 1 ppm after 4 hour of exposure (Rotman et al. 1983)." The document suggests that an asthmatic attack is an AEGL-2 response. This is inconsistent with discussions of the committee. However, the document uses this AEGL-2 effect as a starting point instead of using the NOAEL. Thus, the appropriate NOAEL, possibly 0.5 ppm for 4 hours should have been used as the starting point for AEGL-2 level.

Thank you for consideration of these comments. If you should have any questions about the comments, please contact me at (510) 622-3202 or by e-mail: galexeef@oehha.ca.gov.

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

AEGL Development Team Response to Federal Register Comment:

The chlorine document was written prior to adoption of the present SOPs. At that time the AEGL levels were defined as "..at or above.." and the endpoint used by the NAC met the definition of an AEGL-2. The chlorine document has been edited and includes the following description:

The endpoint for the AEGL-2, transient pulmonary function changes and asthmatic-like symptoms consisting of shortness of breath and wheezing in an exercising atopic individual, is a NOAEL for irreversible or other serious, long-lasting health effects or an impaired ability to escape. The atopic individual voluntarily left the exposure chamber some time after 4 hours of

exposure ("before the full 8-h exposure to 1 ppm"); he was not incapacitated. Following the exposure, the symptoms were completely reversible by the follow-up examination on the next day (15 pulmonary tests/parameters were measured). Healthy subjects also had some changes in pulmonary function parameters during an 8-hour exposure to 1 ppm, but these were asymptomatic.

In summary, the AEGL Development Team for chlorine considers the symptoms experienced by an exercising atopic individual in response to a 4-hour exposure to 1 ppm of chlorine to be a NOAEL for the AEGL-2 endpoint.

RESPONSE TO FEDERAL REGISTER COMMENT

CHLORINE DIOXIDE

NAC/AEGL-25
June 17-19, 2002

Chemical Manager: Bob Benson
ORNL Staff Scientist: Cheryl Bast

Attachment 12

One comment was submitted concerning the proposed AEGL-1 value for chlorine dioxide. The comment stated that the derivation of the AEGL-1 value started from an effect level. The comment further stated the NAC's SOP document (page 42) indicates that the starting point for AEGL-1 development is the 'highest experimental exposure without an AEGL-1 effect."

The TSD as published for comment stated:

> The AEGL-1 was based on slight salivation, slight lacrimation, and slight red ocular discharge in rats exposed to 3 ppm chlorine dioxide for 6 hours (DuPont, 1955). A total combined uncertainty factor of 10 was applied since chlorine dioxide is highly reactive and clinical signs are likely caused by a direct chemical effect on external tissues. This type of effect has no pulmonary component, and the dose to the target tissues should be identical within and between species. Therefore, there are no sensitive subgroups. A modifying factor of 2 was also applied to account for the sparse data base. Thus, the total uncertainty/modifying factor is 20. The AEGL-1 value was held constant across all time points since minor irritation is not likely to be time dependent.

The Chemical Manager and ORNL staff scientist suggest that the AEGL-1 rationale be modified to read:

> The AEGL-1 value was based on sight salivation, slight lacrimation, and slight red ocular discharge in rats exposed to 3 ppm chlorine dioxide for 6 hours (DuPont, 1955). A total uncertainty factor of 10 was applied to account for interspecies and intraspecies variability because chlorine dioxide is highly reactive and the clinical signs of irritation are likely caused by a direct chemical effect on external tissues. The exposure-response relationship for this irritation is not likely to vary greatly among species or among individuals. A modifying factor of 2 was applied to account for the fact that the observed effects exceed the definition of AEGL-1 and the sparse data base. Thus, the total uncertainty/modifying factor is 20. The AEGL-1 value was held constant across all time points because minor irritation is not likely to show a time dependent response. The resulting AEGL-1 value is considered protective because no irritation was noted in rats exposed to 0.1 ppm chlorine dioxide, 5 hours/day 10 weeks (Dalhamn, 1957) and no irritation was noted in rats exposed at 5 ppm for 15 minutes, 2 or 4 times/day for 1 month (Paulet and Desbrousses, 1974).

Historical Summary of AEGL-1 Values for Chlorine Dioxide [ppm]							
Draft/Date	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**	**UF/MF**	**Endpoint (Reference)**
Draft 1/ May, 2001	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**None**	**NOEL in rats exposed to 0.1 ppm, 5 hr/day for 10 weeks (Dalhamn, 1957)**
Draft 2/ Sept. 2001	**NR**	**NR**	**NR**	**NR**	**NR**	**NA**	**Insufficient data for derivation of AEGL-1 values**
Proposed 1/ Nov. 2001	**0.15**	**0.15**	**0.15**	**0.15**	**0.15**	**UF = 10 MF = 2 (database) *(above AEGL-1 definition)***	**Slight salivation, slight lacrimation, and slight red ocular discharge in rats exposed to 3 ppm for 6 hours (DuPont, 1955)**

Summary Table of AEGL Values for Chlorine Dioxide [ppm (mg/m^3)]								
	10-min	30-min	1-hour	4-hour	8-hour	UF/MF	Time Scaling	Endpoint (Reference)
AEGL-1	0.15 (0.41)	0.15 (0.41)	0.15 (0.41)	0.15 (0.41)	0.15 (0.41)	UF = 10 MF = 2	NA	Slight salivation, slight lacrimation, and slight red ocular discharge in rats exposed to 3 ppm for 6 hours (DuPont, 1955)
AEGL-2	1.4 (3.9)	1.4 (3.9)	1.1 (3.0)	0.69 (1.9)	0.45 (1.2)	UF = 10 MF = 2	'n'= 1 or 'n' = 3 (default)	Lacrimation, salivation, dyspnea, weakness, and pallor in rats exposed to 12 ppm for 6 hours (DuPont, 1955)
AEGL-3	3.0 (8.3)	3.0 (8.3)	2.4 (6.6)	1.5 (4.1)	0.98 (2.7)	UF = 10 MF = 2	'n'= 1 or 'n' = 3 (default)	No lethality in rats exposed to 26 ppm for 6 hr (DuPont, 1955)

Attachment 13

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C-004

Anne_LeHuray@americanchemistry.com on 03/18/2002 12:48:30 PM

Spp

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

Docket #00330

Subject: Comments re Proposed AEGL Values for Propylene Oxide 031802

Please find attached comments on EPA's proposed AEGL values for propylene oxide (CAS no. 75-56-9) published in the Feb. 15, 2002 Federal Register notice. A hard copy of the comments are being submitted to the Document Control Office via US Mail.

(See attached file: PO_AEGL_031802.pdf)

Anne P. LeHuray, Ph.D.
Manager, Propylene Oxide/Propylene Glycol Panel
American Chemistry Council
1300 Wilson Boulevard
Arlington, Virginia 22209
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March 18, 2002

Via US Mail and E-Mail

Document Control Office (7407)
Office of Pollution Prevention and Toxics (OPPT)
Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Re: National Advisory Committee for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances: Proposed AEGL Values – Propylene Oxide (CAS No. 75-56-9)

The Propylene Oxide/Propylene Glycol Panel ("Panel") of the American Chemistry Council appreciates this opportunity to comment on the October 2001 "Public Draft" of "Proposed Acute Exposure Guideline Levels (AEGLs) for Propylene Oxide (CAS No. 75-56-9)." The Panel, whose members are Huntsman Corporation, Lyondell Chemical Company and The Dow Chemical Company, has previously provided comments and participated in meetings as the AEGL values and documentation have been developed. The Panel recognizes that, in response to our earlier comments, some changes have been adopted.

While all of our prior specific recommendations on appropriate AEGL value levels have not been adopted, the Panel understands that its prior views have been previously considered and will not reiterate them here. Thus, while the Panel does not view the current AEGL values as being appropriate, it is not now seeking further revisions in those values. Rather, our comments below focus on the content of the Public Draft dated October 2001.

Appendix C

The Panel is concerned that the Public Draft and particularly Appendix C include carcinogenicity data that are not up-to-date and therefore are scientifically inaccurate and incomplete. For the reasons discussed below, two types of changes should be made. First, a brief disclaimer should be added concerning the limited purpose of Appendix C for chemicals, like propylene oxide, where carcinogenicity data do not drive the AEGL values. Second, important specific changes should be made to the calculations.

Scope of Appendix C

Where carcinogenicity test data do not drive the AEGL values, detailed analysis of cancer data should be beyond the scope of AEGL documentation which is concerned with acute

exposure. As Appendix C shows, the propylene oxide data do not suggest that short term exposures, as defined in the AEGL program, would lead to human cancer.

Importantly, EPA and other U.S. and international agencies have well-established programs to evaluate carcinogenicity data and to use the data to classify chemicals as to their carcinogenic potential. Propylene oxide has been reviewed by the European Union, by IARC, and others. In its most recent Report, NTP has classified propylene oxide as "reasonably anticipated to cause cancer." NTP, 9th Report on Carcinogens (revised 2001). Thus, we do not quarrel with conclusions concerning potential carcinogenicity of propylene oxide. We are disturbed, however, that the Public Draft may leave the impression that the carcinogenicity information in the document is up-to-date and fully articulated.

As a policy matter, the AEGL Committee should avoid becoming embroiled in detailed discussions of carcinogenicity data as such discussions detract from the AEGL Committee's mission of establishing short term acute values. Often, as is the case with propylene oxide, data concerning carcinogenicity are complex, involve multiple animal and human data sets, and require extensive consideration of mechanistic data. The AEGL Committee already has a difficult task in establishing AEGL values for the current chemicals and the additional chemicals likely to be added to the program over the next few years. To burden this process with the obligations associated with detailed reviews of carcinogenicity data is short-sighted and surely will lead to much greater controversy over issues that are not central to the mission of the AEGL program.

A better approach is to limit the scientific discussion, both in the text and Appendix C to the minimum necessary to demonstrate that the carcinogenicity data do not impact the AEGL values. It is important to acknowledge explicitly that the AEGL Committee has not extensively reviewed all of the available data bearing on carcinogenicity qualitatively and quantitatively. This is particularly true here where Appendix C is based on EPA's IRIS documentation that is woefully out-of-date. The current IRIS documentation does not consider voluminous mechanistic data, some of which are cited in the Public Draft and are erroneous in that the data do not reflect current methodology. The Draft should contain a standard caveat for materials like propylene oxide where cancer potency data do not impact the AEGL values adopted in order to put Appendix C in its appropriately limited context. We suggest adding a statement such as:

> "This Appendix was developed for the limited purpose of determining whether carcinogenicity concerns should be used in driving any AEGL values. It is based on a preliminary analysis and does not represent a comprehensive determination by the Environmental Protection Agency of carcinogenicity classification or potency factors."

Changes to Appendix C

The draft Appendix C requires several changes. None of these changes impact the Panel-supported conclusion that cancer potency should not be a factor in setting AEGL values for

propylene oxide, but EPA should not be issuing documents that are incorrect and inaccurate without the caveats described above, as they have a way of being cited out-of-context as authoritative in many different places. The corrections described below and the fact that the current propylene oxide IRIS value, the starting point for Appendix C, is quite dated are further reasons why a minimalist approach, with appropriate caveats about old data sources and lack of review and consensus, should be adopted.

We agree with the decision not to use the values based on carcinogenicity for AEGL-3 as calculated in Appendix C. Not only were the calculated time-dependent values all above the respective AEGL-3 proposed values, the negative tumor results from the Sellakumar *et al.* (1987) short term, high dose rat study are quite convincing that cancer is not the appropriate endpoint of concern for the AEGLs, no matter what excess cancer risk level is used.

An important clarification, however, is needed for the calculations presented. Appendix C uses an adjustment factor of 6: "*To adjust for uncertainties in assessing potential cancer risks for short-term exposures under the multistage model,...*" citing Crump and Howe (1984). This adjustment factor is not explicitly described in Crump and Howe (1984), but an adjustment factor of 2.8 described as being derived from Crump and Howe (1984) is found in NRC (1986), the reference cited by the Public Draft as the source of the method used for calculations performed in Appendix C. If further adjustments to the factor recommended in NRC (1986) for adjusting short-term exposures were made, this should be explained and further justified in Appendix C. The two-fold difference between the adjustment factor described by NRC (1986) and that used in Appendix C would further increase the values listed.

Several comments regarding the cancer slope factor used in the Public Draft calculations for propylene oxide are also warranted. The male mice from the NTP (1985) study that determined the cancer potency used in the calculations for Appendix C may have exceeded a maximum tolerated dose (MTD) at the high dose used (400 ppm). Mortality was significantly increased compared to controls, and the average body weight of the male mice at 400 ppm were 22% below the average body weight of control male mice. Female mice also had increased mortality at the high dose compared to controls and had mean body weights 10% lower than controls at the high dose. Male and female mice only had significant nasal tumor increases at the high dose and nasal tumor response in female mice was less than in male mice. Male and female rats demonstrated no nasal tumor increases at the doses tested, and rats did not exhibit increased mortality or body weight decreases compared to control rats. These results taken together indicate that the cancer potency currently listed in IRIS using the NTP (1985) male mouse data may be reflective of a high dose effect due to toxicity (e.g., the MTD was exceeded), thus resulting in overly conservative predictions of human risk.

In addition, the cancer potency used for the calculations in Appendix C was derived using an interspecies dose scaling factor of two-thirds body weight, the default at that time, and not the more current EPA default value of three-fourths body weight. This correction alone would decrease the cancer potency by a factor of two, and other refinements that should be made would lower the cancer potency even more. Decreases in the cancer potency would increase the values calculated in Appendix C, values that are not currently intended for setting AEGLs for propylene

oxide If, on the other hand, the current cancer potency for propylene oxide listed in IRIS was to be considered for setting future regulatory criteria, including AEGLs, an extensive re-evaluation of cancer potency for propylene oxide using more current data, approaches and refinements, especially new mechanistic data, must be completed.

Other Comments

The current draft leaves the false impression that human lethality has resulted from exposure to propylene oxide in both the tables and text. For example, the summary table for "AEGL-3 Lethality" currently reads: "Highest recorded nonlethal concentration of ...." As there are no reports of human lethality (see Draft at Section 2.1, page 2), something like the following language would be more appropriate: "No human lethality reports identified; highest documented human exposure was 1520 ppm for 171 minutes, resulting in irritation. (CMA, 1998)." A similar correction would also be appropriate for the Executive Summary, page viii, 1.18 and Section 7.3, page 39. Insertion at the beginning of those paragraphs of the following phrase would help clarify the Draft: "No reports of human lethality were identified."

Another important comment refers to page 6, last paragraph which states at line 36: "Cytogenetic studies have not yet found ...." The word "yet" should be deleted as it implies that positive results are expected, which is both speculative, and unlikely, based on the negative results in monkeys following 2-year inhalation exposures to propylene oxide for chromosomal aberrations or micronuclei, the endpoints under discussion (Lynch *et al.*, 1984).

Finally, Section 8.3 "Data Adequacy and Research Needs" should include an explicit statement that no research needs were identified. Alternatively, the Section title could be changed to "Data Adequacy" or something similar, such as the former section title "Confidence in AEGLs."

Should there be any questions or requests for further information, please contact the Panel Manager, Dr. Anne LeHuray at *anne_lehuray@americanchemistry.com* or (703) 741-5630.

Sincerely yours,

Courtney M. Price

Courtney M. Price
Vice President, CHEMSTAR

cc: Paul S. Tobin, OPPT
Propylene Oxide/Propylene Glycol Panel

Attachment 14

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March 15, 2002

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C-005

Document Control Office (7407)
Office of Pollution Prevention and Toxics (OPPTS)
EPA
1200 Pennsylvania Avenue
Washington, DC 20460

Docket control # OPPTS-00330 Propylene Oxide values

I would like to raise concerns regarding the AEGL-1 values recommended for Propylene Oxide. As with many risk assessment documents, only limited information is available to extrapolate to safe levels of exposure. If there are significant limitations in the available studies, it is imperative that adequate uncertainty factors be taken into account.

The current document relies primarily on a letter sent to the AEGL Committee by the CMA. This summarizes industrial hygiene data from 3 manufacturing facilities in 1949, 1968 and 1975. Although the CMNA has been helpful in answering questions from the committee, there are some limitations with these reports:

1) These reports are monitoring surveys that did not include any questioning of workers on the presence or absence of symptoms.

2) The sample size of the employees who reportedly have no health effects at the specified level of exposure is small.

3) This is unpublished data and the original reports are not available to the committee.

In general, an occupational health survey that summarizes the health status of a group of people should also summarize the exposure of the entire group. The usual value taken for the exposure of group is the mean. In this case, we have 5 job titles with the range and arithmetic mean for each group. It is not appropriate to start with the exposure value of the few people in the single highest exposure group who have the highest exposure values (31 ppm) if we are then summarizing the health status of the rest of the workers. In addition, these individuals are the investigators who conducted the monitoring survey, not the usually people to rely on for the presence or absence of symptoms.

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Members of the Consortium

International Chemical Workers Union Council/UFCW
United Steelworkers of America
USWA Rubber/Plastics Conference
USWA Aluminum, Brick and Glass Division
International Association of Machinists and Aerospace Workers
American Flint Glass Workers Union
Coalition of Black Trade Unionists
United Food and Commercial Workers
American Federation of Teachers
Greater Cincinnati Occupational Health Center
University of Cincinnati Department of Environmental Health

I request that the Committee reconsider and lower the current recommended AEGL-1 levels. Alternatively, the committee could start with the value of 18 ppm, the mean exposure value of the three job categories with the vast majority of the samples from employees of facility 3 (23 of 24 measurements). If the committee decides to rely on the exposure of the few individuals with the highest exposure, a modifying factor of 2 should be incorporated for the sparse data set (as done in the AEGL-3 value; only two samples for the lab personnel who did the sampling and one for an engineer at a similar exposure value). Finally, there was no investigation of the presence or absence of symptoms in this population. Instead we are relying on the lack of "mention of complaints by workers in the report" and no complaints in the workers medical files "during routine medical surveys and physical exams". The lack documentation of symptoms without a scientific or systematic investigation is an additional reason for using a modifying factor of 2.

Sincerely,

John S. Morawetz

John S. Morawetz

c: Larry Gregoire
Secretary Treasurer's Office
Eric Bray
Michael Sprinker
Frank Mirer, UAW
Bill Kojola, AFL-CIO
George Rusch, AEGL Chairman
Rodger Garrett, EPA
Po-Yung Lu, ORNL

PROPYLENE OXIDE: Federal Register Comments

Comments from John Morawetz:

AEGL-1 values based on letter sent to NAC/AEGL by the CMA. Letter summarizes industrial hygiene data. Limitations of summarized reports:

- *monitoring surveys did not include questioning of workers on the presence or absence of symptoms.*
- *sample size of employees who reportedly have no health effects at specified level of exposure is small.*
- *unpublished data and original reports are not available to the committee.*

For AEGL-1 value, the highest 8-hour TWA value of 31.8 ppm was chosen for the derivation. It is not appropriate to start with the exposure value of the few people in the single highest exposure group who have the highest exposure values (31 ppm) if we are then summarizing the health status of the rest of the workers. In addition, these individuals are the investigators who conducted the monitoring survey, not the usual people to rely on for the presence or absence of symptoms.

1

Request reconsidering and lowering the current AEGL-1:

- *could start with value of 18 ppm, the mean exposure value of the 3 job categories with vast majority of samples from employees (23 of 24 measurements)*
- *or, if NAC decides to stay with high exposure concentration, a modifying factor of 2 should be incorporated for sparse data set (as was done for AEGL-3)*

2

Response: Summary of Data Provided by CMA

Background PO concentrations were measured over three 8-hour shifts in a plant in 1975 to perform baseline routine annual monitoring (CMA, 1998a). The concentration of the samples in ambient air ranged from none detected (< 0.1 ppm) to 31.8 ppm (vol/vol). PO concentrations were also measured in the breathing zones of workers using Sipin Personal Sampler Pumps over the eight-hour work periods. Measured concentrations ranged from 13.2 to 31.8 ppm as 8-hour time weighted averages measured over the 3-day sampling period (see Table). No worker complaints were noted in the report.

Summary Results of Personal Exposure Monitoring

Job Classification	No. of People	No. of Samples	Propylene Oxide		
			Conc. Ranges (ppm)	Mean* Job Class Conc. (ppm)	
				Mean	95% UCL
Maintenance personnel	5	8	14.9 - 18.9	17.4	18.30
Laboratory personnel	2	2	30.2 - 31.8	31.0	36.05
Engineer	1	1	30.2	30.2	---
Foreman	2	4	16.1 - 23.8	20.58	24.49
Operators	6	11	13.2 - 23.3	18.69	20.31

*Calculated arithmetic mean and 95% upper confidence level for the associated job class. Job classes were identified and monitored by homogenous exposure groups rather than job titles. Source: CMA, 1998a

3

Justification of AEGL-1 in Executive Summary

Proposed AEGL-1 values for PO were based on environmental health survey in which 8-hour time weighted averages (TWA) were determined from a 3-day sampling period during which no worker complaints were noted (CMA, 1998). The highest 8-hour TWA value of 31.8 ppm was chosen for the derivation. An interspecies UF was not needed, since the data were from human exposures. An intraspecies UF of 3 was applied because the toxic effects (no complaints noted) were less severe than those defined for the AEGL-1 tier. Therefore, total UF of 3.

These values are supported by mouse data from an NTP (1985) study. Mice were the most sensitive species tested, and dyspnea was the most sensitive endpoint of toxicity following exposure to propylene oxide. Dyspnea was observed in mice exposed for 4 hours to 387 ppm propylene oxide vapor, the lowest concentration tested, but not in mice were exposed to 98.5 ppm propylene oxide vapor or less for 6 hours/day, 5 days/week for 2 weeks (NTP, 1985). Therefore, an AEGL-1 can be derived using the exposure concentration of 98.5 ppm for 6 hours (a NOEL for dyspnea). Following application of a total UF of 3 (interspecies UF of 1 because mice were the most sensitive laboratory species tested, and available data indicate that mice are equally or slightly more sensitive than humans; an intraspecies UF of 3 because the toxic effect [NOEL for dyspnea] was less severe than that defined for the AEGL-1 tier), one obtains AEGL-1 values approximately 2-fold greater than those generated using the human data.

4

Summary of Proposed AEGL Values for Propylene Oxide (ppm)						
Level	10-m	30-m	1-hr	4-hr	8-hr	Endpoint (CMA, 1998)
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 4 exposure concentrations and durations: 380 ppm for 177 minutes, 525 ppm for 121 minutes, 392 ppm for 135 minutes, 460 ppm for 116 minutes
AEGL-3	2700	1100	610	190	110	Humans: Highest recorded nonlethal concentration of 1520 ppm for 171 minutes

Comments from American Chemistry Council

Concerned that Public Draft and particularly Appendix C include carcinogenicity data that are not up-to-date and therefore are scientifically inaccurate and incomplete.

Recommendations:

- *Brief disclaimer should be added concerning the limited purpose of Appendix C for chemicals, like PO, where carcinogenicity data do not drive AEGL values. Example:*

  "This appendix was developed for the limited purpose of determining whether carcinogenicity concerns should be used in driving any AEGL values. It is based on a preliminary analysis and does not represent a comprehensive determination by the EPA of carcinogenicity classification or potency factors."

Response: This disclaimer could easily be added

- *Important clarifications/changes should be made to the calculations.*
  - *To adjust for uncertainties in assessing potential cancer risks for short-term exposures under the multistage model, a factor of 6 was used, when a factor of 2.8 is found in the reference cited by the Public Draft as the source of the method used for calculations (NRC, 1986). If a 6 is used, the increases in the adjustment factor should be explained and justified.*

Response: The SOP states that in instances in which multistage models can be used and prudence dictates conservatism, the NRC guidance suggests reducing the approximation of D by an adjustment factor of 2 to 6, depending on the number of assumed stages in the multistage model used.

- *Several comments should be included regarding the cancer slope factor.*
  - *NTP study that determined cancer potency factor may have exceeded maximum tolerated dose*
  - *cancer potency used for calculations derived using interspecies dose scaling factor ⅔ b.w. (default at that time), not the more current EPA default factor of ¾ b.w.*

Response: these comments will be added to text in Appendix C

- Other comments are editorial in nature. The three editorial comments will be incorporated into the document.

Benzene - AEGL values
NAC-AEGL 25 (june 2002)

Author: Marcel TM van Raaij
Chemical Manager: Bob Snyder
Chemical Reviewers: George Rusch, Loren Koller

rivm
National Institute for Public Health and the Environment

Research for man and environment

Benzene characteristics

- Aromatic compound, used as solvent in industry since late 1800's.
- Obtained from coal tar and crude oil, constituent of gasolines.
- Low vapor pressure, inhalation primary route of exposure
- Highly flammable, LEL is 1.4%
- Toxicity of benzene is qualitatively well characterised: primary effects CNS depression (acute) and bone marrow toxicity (chronic).
- Human carcinogen: leukemia

Benzene TSD development

- Benzene induces various effects (CNS, hemato-toxicity, leukemia, genotoxicity, developmental effects). So, all fields need to be adressed.
- "Data-rich chemical" - enormous amount of literature on chronic (occupational) exposure and leukemia / hematoxicity
- Long time spent to search for relevant literature.
- Almost no human volunteer studies (in contrast with e.g. toluene)
- Very little quantitative data on acute toxicity both in humans and animals.
- Still a feeling: Do we miss something ?

Human data - 1 (lethality)

- Pathological effects of acute lethal benzene intoxication are well known
- Only anecdotal type of information
- No actual exposure information
- Tissue levels of benzene in victims shows large variation (blood 0.9 - 120 mg/L, brain 13.8-179 mg/kg) → other mechanisms may contribute to sudden death (cardiac failure ?)
- However, no adequate human data for cardiac sensitisation
- Exposure data (occupational) available showing no lethality.

Attachment 16

Human data - 2

- A large number of data describing occupational exposure levels *(not all are in the TSD !)*
- Mostly, repeated (sub) chronic exposure
- Few actual data on acute benzene exposure
- Most studies lack a direct connection to exposure levels and effects at the individual level.
- Most concrete indications for acute toxicity effects in humans come from Gerarde 1960 (see table)
- However, no clear basis exists for table of Gerarde ?

rivm

Acute toxicity Benzene - "Table by Gerarde"

Concentration (ppm)	Duration (min)	Effect
1.5	-	Olfactory threshold
25	480	No effects, detectable in blood
50-150	300	Headache, lassitude, weariness
500	60	Symptoms of illness
1500	60	Serious symptoms
3000	30	May be tolerated up to 1 hr
7500	60	Sings of toxicity, dangerous to life
20000	5-10	Fatal within 5-10 min

rivm

Human data - 3

Occupational

- Up to about 4000 ppm in occup. settings. Recently in China still levels of up to 300-400 ppm routinely.
- Greenburg 1926b: mean exposure 70-1080 ppm (peaks up to 4140 ppm), Hematological effects, CNS effects in 9 individuals
- Greenburg 1939: three plants 11-298 ppm, 24-675 ppm, 50-1060 ppm: "dose-related" increase in symptoms (irritation, CNS)
- Kellerova 1985: mean exposure 45-145 (308) ppm (-2h sampling), EEG changes in exposed group
- Yin 1987: mean 7h TWA exp 47 ppm (max 210 ppm). SLight effects on WBC, upper airway irritation, CNS effects
- Kraut 1988: limited measurements peaks 30-300 ppm associated with unusual odors: irriation and CNS effects

rivm

Human data - 4

Volunteer studies

- Srbova 1950: volunteer metabolism study. Exp up to 110 ppm for 2h. Volunteers report no subjective symptoms.
- Metabolism studies used levels up 125 ppm (Inoue 1986, Hunter and Blair, 1972). No information on health effects.

Case studies

- Drozd & Bockowski 1967: 600 - 1500 ppm (simulation exp) intermittently for periods of 2-3,5h (2 days). CNS effects
- Midzenski 1992: Tank cleaning > 60 ppm (653-987 ppm) 1 day - 3 weeks (2.5-8h/day). No hematological effects, self reported irritation and CNS effects.

rivm

Acute Lethality - animal data

Species	Exposure levels (ppm)	Exposure duration	LC50 (ppm)	Remarks	Reference
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

rivm

Acute lethality - animal studies

- Information from animal studies suggest a steep dosis-response curve for lethality: from 0 to 100% mortality in mice occurs within a concentration range with a factor of 3; from 10 to 100% mortality in rats occurs within a factor 2.
- Delayed mortality is not major factor (Svirbely 1943)
- There seems to be a narrow time window between the occurence of deep narcosis and death.
- Light narcotic signs are rapidly reversible.

rivm

Possible Endpoints ☛ AEGL-2

- **CNS effects** (direct action, dizziness, narcosis)
- **Hematotoxicity** (circulating lymphocytes, lymphocytic proliferation, bone marrow or splenic cell counts, progenitor cells, stem cells) → these parameters might be used as early indicators for pancytopenia and leukemia
- **Chromosome aberrations**
- **Embryo/fetotoxicity**

rivm

CNS effects -1

- CNS depression is most likely caused by benzene (parent compound) itself.
- Probably depends on the level of benzene within the brain (related to its incorporation in lipid membranes)
- Effects mostly recover rapidly after cessation of exposure
- At very high exposures, some effects may be present for a few weeks after exposure.
- No quantitative C x T information on acute exposure in humans, only estimations that can be used as supporting evidence.

rivm

CNS effects -2

- Various animal studies available for CNS effects
- Some studies focussed on the occurence of clear narcosis (or time to reach narcosis)
- Some studies focussed on neurobehavioural endpoints (mainly hyper(re)activity and depressed locomotor activity
- Extrapolation of various behavioural endpoints is difficult.
- Only overt decreases of behavioral endpoints such as locomotor activity are considered relevant for AEGL-2 development.

rivm

Hematotoxicity - 1

- Hematotoxicity of benzene is characterised by decreased numbers of circulating cells, anemia, leucocytopenia, lymphocytopenia, thrombocytopenia, pancytopenia and eventually myelodysplastic syndrome (MDS) and acute myelocytic leukemia (AML).
- Hematotoxicity is probably caused by several benzene metabolites
- These metabolites are mainly formed in the liver and transported to the bone marrow (but also partly formed in bone marrow cells).
- Metabolic capacity (CYP 2E1) is limited, at high levels a lesser percentage of benzene is metabolised.

rivm

Hematotoxicity - 2

- Hematotoxicity should be splitted into
  - effects on circulating cells (WBC)
  - effects on several lines of progenitor cells (CFU-GM, CFU-E)
  - effects on the pluripotent stem cells (CFU-S)
- Effects on circulating cells and progenitor cells are reversible after discontinuing of exposure, effects on CFU-S are not !
- Generally, bone marrow toxicity and leukemia are considered to be relevant for repeated exposure. With respect to acute exposure no info for humans, limited info from animal studies.
- A single exposure has less effect than the same dose applied over several days.

rivm

Hematotoxicity - 3

- No effects on circulating cells at 10-30 ppm (repeated exp.) Decreased WBC after 6h at 1000 and 3000 ppm (Dempster 1984) but not at 100 ppm.
- Effects on CFU-GM and CFU-E at 100 ppm (repeated exp) but not at 400 ppm for 1 or 4 days (Farris 1997).
- Effects on CFU-S: decreased at 3 x 8h 5020 ppm (Uyeki, 1977), at 5 days exposures CFU-S decreased at 103 ppm but not at 10 ppm (Green 1981).

rivm

Chromosome aberrations (CA) -1

- Benzene is generally negative in various gene-mutation assays.
- Benzene is known to induced CA's and SCE's both in vitro and in vivo.
- SCE's (and CA) can be observed in workers repeatedly exposed to low levels of benzene (1-10 ppm).
- SCE's (and CA) can be induced in animals after acute inhalation exposure (4-6h) at levels of ≥ 3 ppm.
- However, SCE is not an adequate marker for future leukemia risk (Zhang 2002)

rivm

Chromosome aberrations - 2

- Benzene induced AML is probably related to some type of chromosome damage (mainly associated with chromosome 5 and 7).
- CA induced by benzene are partially reversible.
- No quantitative relation between CA and future leukemia development is known.
- CA should be considered only as a marker for future leukemia risk
- Genotoxicity is therefore not an appropriate endpoint for AEGL development of benzene.

rivm

Developmental toxicity - 1

- Epidemiological studies reporting effects on reproduction / foetal development have major shortcomings. No clear indications for effects.
- Relation parental benzene exposure and childhood leukemia is inconclusive.
- If any effects are present, the question remains if these type of effects are relevant for AEGL development.

rivm

Developmental toxicity - 2

- In "standard protocol" type of developmental studies (mainly rats) benzene induces developmental effects.
- Effects primarily characterised as developmental retardation: decreased fetal weight, decreased crown-rump length, retarded ossification, skeletal variants [at levels > 10 ppm, NOAELs <100, <50, 10, 40 ppm] Probably more related to repeated exposure.
- No consistent indications for structural irreversible effects.
- AEGL development team: developmental tox of benzene is not relevant for AEGL development.

rivm

AEGL-1 derivation

- Relevant effects: eye / airway irritation, slight CNS effects
- No adequate quantitative human data available for setting AEGL-1.
- Srbova 1950 report no subjective symptoms at 110 ppm 2h, but from other observations symptoms cannot be excluded at lower levels.
- Kraut 1988 reports signs of irritation when unusual odors are present (30-300 ppm). (Also Midzenski 1992)
- Use LOA - method to estimate threshold for odor and irritation.

rivm

Benzene NAC AEGL 25 | MTM van Raaij 21

AEGL-1 derivation

- Odor threshold: two studies 0.2 ppm and 1.1 ppm, use mean value of 0.65 ppm
- Using default k_w, the LOA is 8 ppm.
- Proposed AEGL -1 values 8 ppm for all time intervals based on the coupling of odor and signs.

rivm

Benzene NAC AEGL 25 | MTM van Raaij 22

AEGL-2 derivation

- CNS depression is the most obvious effect after acute exposure.
- No adequate human data available to develop AEGL-2 values. Only supportive information.
- Midzenki 1992: > 60 ppm (up to 653-987 ppm) CNS effects but work continued 2,5-8h/day (1 day - 3 weeks). Condition considered not to impair escape.
- Routinely occup. exposure levels may have been up to 1000 ppm.

rivm

Benzene NAC AEGL 25 | MTM van Raaij 23

AEGL-2 derivation

- Use animal neurobehavioral studies as AEGL-2 starting point.
- Clear decreases in locomotor activity are primarily considered to be relevant in terms of "impairment of escape". Hyperactivity or changes in other subtle neurobehavioral parameters are not relevant.
- Highest level without AEGL-2 effect in rats: 4000 ppm for 4h.
- In mice effects are seen at somewhat lower levels. Considered less relevant because mice have higher body load or experiments used static conditions.

rivm

Benzene NAC AEGL 25 | MTM van Raaij 24

AEGL-2 derivation

- With regard to CNS depression benzene is about equipotent to toluene (for which much more human data are available).
- AEGL-2 levels of benzene based on CNS depression should be in the same order of magnitude than those for toluene.
- No specific N value can be derived (use default values of n=3 and n=1).
- Interspecies factor of 3 (little species differences for CNS depression, higher factor does not comply with human experience).
- Intraspecies factor of 3: CNS depression does not vary by more than a factor 2-3 in the human population.

rivm

AEGL-2 derivation

- Use 4000 ppm for 4h as starting point (Molnar et al., 1986)
- Use default values of N
- Use total UF of 10 (3x3)

TABLE 8: AEGL-2 VALUES FOR BENZENE (ppm)

AEGL Level	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-2	1150	800	635	400	200
AEGL-2 Toluene	*900*	*450*	*300*	*300*	*300*

rivm

AEGL-3 derivation

- No quantitative human data available for AEGL-3, only estimations. In addition, data with exposure levels without mortality are present. Use human data as supportive evidence.
- Only two adequate LC50 values in rats (4h and 6h) and two in mice (6h and 7h). Data do not allow determination of N.
- Various studies available with exposure levels that do not show mortality in animals.

rivm

AEGL-3 derivation

Studies with single dose inhalation without any mortality

Duration	Exposure level without mortality (ppm)	Species	Ref
15 min	7332-8824	rat	Magos et al. 1990
30 min	8300	mice	Nielsen and Alarie, 1982
2 h	10,000	rat	Furnas and Hine, 1958
3h	20,000	rabbit	Kujime, 1990 (abstract)
4 h	5940	rat	Molnar et al., 1986
6 h	3000	mice	Dempster et al., 1984
6 h	7700	Rabbit + cat	Estler, 1935
6.5 h (17 days)	2000	Rat + mice	Coate, 1983
7 h	4890	mice	Svirbely et al., 1943
8 h	5020	mice	Uyeki et al., 1977

rivm

AEGL-3 derivation

- Select animal study: quality of study, species, time frame of exposure.
- Use Molnar et al., 1986 as key study (5940 ppm for 4h, NOEL for mortality).
- No substance specific N value; use default values of n=3 and n=1.
- Interspecies factor =1 (based on allometric arguments (see also toluene, higher factor would not comply with human experience)
- Intraspecies factor = 3 (mechanism is CNS-depression which does not vary more than a factor of 2-3 in the human population.

rivm

AEGL-3 derivation

- Use 5940 ppm for 4h as starting point (Molnar et al., 1986)
- N=3 or n=1
- Total UF is 3

AEGL-3 VALUES FOR BENZENE (ppm)

AEGL Level	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-3 (based on 5940 ppm 4h)	5700	4000	3100	1980	990
AEGL-3 for Toluene	7200	4200	2900	1500	1000

rivm

AEGL - summary

TABLE 10: SUMMARY/RELATIONSHIP OF PROPOSED AEGL VALUES

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
LOA			8		
AEGL-1 (Nondisabling)	8	8	8	8	8
AEGL-2 (Disabling)	1150	800	635	400	300
AEGL-3 (Lethal)	5700	4000	3100	1980	990

rivm

ACUTE EXPOSURE GUIDELINE LEVELS for HYDROGEN FLUORIDE and HYDROGEN CHLORIDE Modification of 4- and 8-hour AEGL-2 and AEGL-3

National Advisory Committee for AEGLs Meeting 25
June 17-19, 2002

ORNL Staff Scientists:
Sylvia S. Talmage (HF)
Cheryl B. Bast (HCl)

Chemical Managers:
Ernest Falke (HF)
John Hinz (HCl)

Attachment 17

MODIFICATION OF 4- AND 8-HOUR AEGL-2 AND AEGL-3 VALUES

Time scaling for both HF and HCl were based on exposure durations of ≤100 minutes.

HF: n = 2 over exposure duration of 5 minutes to 60 minutes.

HCl: n = 1 over exposure duration of 1 minute to 100 minutes.

Time scaling beyond these times may not be appropriate.

For both HF and HCl we have human data that shows that the 4- and 8-hour AEGL-2 and AEGL-3 values may be too conservative.

Proposal: First, modify HCl by setting the 4-hour value equal to half of the 1-hour value.

For both HF and HCl, Set the 8-hour AEGL-2 and -3 values equal to the respective 4-hour values.

Rationale for HCl: justified by several reasons: (1) the present 8-hour AEGL-2 of 2.7 is close to the 1.8 ppm tolerated by exercising asthmatics without adverse health effects, (2) the modified 4- and 8-hour AEGL-2 value of 11 ppm is approximately 0.03 x the RD_{50} of 309 ppm, (3) the procedure for the HCl 1-hour value is consistent with the time-scaled values for HF, and (4) repeated-exposure rat data suggest that the revised values are protective. Rats exposed to 10 ppm HCl for 6 hrs/day, 5 days/week for life exhibited only tracheal and laryngeal hyperplasia, and rats exposed to 50 ppm HCl for 6 hrs/day, 5 days/week for 90 days exhibited only mild rhinitis.

Rationale for HF: healthy adults were able to tolerate intermittent exposure to 8.1 ppm for 6 hours/day over many days with only slight irritation.

PROPOSED HYDROGEN FLUORIDE MODIFICATIONS

Classification	Exposure Duration (Values in ppm)				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	1.0	1.0	1.0	1.0	1.0
AEGL-2 (Disabling)	95	34	24	12	8.6 **12**
AEGL-3 (Lethal)	170	62	44	22	15 **22**

AEGL-1: Based on human exposure to 3 ppm; threshold for pulmonary inflammation; no changes in lung function parameters; minor irritation. UF of 3.

AEGL-2: 10-minute: 950 ppm to cannulated rats; minor irritation; UF of 10
≥30-minutes: 243ppm for 1 hour to dogs; severe irritation; UF of 10; n = 2.

AEGL-3: 10-minute: 1764 ppm for 10 minutes to cannulated rats; threshold for death; UF of 10.
≥30 minutes: 263 ppm for 1 hour; threshold for lethality; UF of 3 and MF of 2; n = 2.

Basis for modification: Healthy adult males were able to tolerate mean exposures of 1.42 to 4.74 ppm (range 0.9-8.1 ppm) for up to 50 days with only slight irritation. Effects were no more severe in two subjects who were exposed to concentrations up to 7.9 and 8.1 ppm.

PROPOSED HYDROGEN CHLORIDE MODIFICATIONS

Classification	Exposure Duration (Values in ppm)				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	1.8	1.8	1.8	1.8	1.8
AEGL-2 (Disabling)	100	43	22	5.4 **11**	2.7 **11**
AEGL-3 (Lethal)	620	210	100	26	13 **26**

AEGL-1: Based on exercising asthmatics inhaling 1.8 ppm for 45 minutes; no effects; no UF.

AEGL-2: Based on severe nasal/pulmonary histopathology in rats exposed to 1300 ppm for 30 minutes; UF of 10; MF of 3; n = 1.

AEGL-3: Based on 1/3 of 1 hour LC_{50} of 3124 ppm in rats; UF of 10; n = 1.

Basis for modification: If exercising asthmatics could tolerate 1.8 ppm for 45 minutes with no adverse health effects, "they should certainly be able to inhale HCl at 2.7 ppm for 8 hours or 5.4 ppm for 4 hours without serious, long-lasting effects or impaired ability to escape."

Attachment 18

Abbreviated
HF/HCl

Seventh Interim Report of the Subcommittee on Acute Exposure Guideline Levels

Subcommittee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

National Research Council

National Academy Press

Seventh Interim Report of the Subcommittee on Acute Exposure Guideline Levels

BACKGROUND

In 1991, the U.S. Environmental Protection Agency (EPA) and the Agency for Toxic Substances and Disease Registry (ATSDR) asked the National Research Council (NRC) to provide technical guidance for establishing community emergency exposure levels (CEELs) for extremely hazardous substances (EHSs) pursuant to the Superfund Amendments and Reauthorization Act of 1986. In response to that request, a subcommittee of the NRC Committee on Toxicology (COT) prepared a report titled *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993). That report provides step-by-step guidance for the derivation of CEELs for EHSs.

In 1995, EPA, several other federal and state agencies, and several private organizations convened an advisory committee—the National Advisory Committee on Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances (referred to as the NAC)—to develop, review, and approve AEGLs (similar to CEELs) for up to 400 EHSs. AEGLs developed by the NAC have a broad array of potential applications for federal, state, and local governments and for the private sector. AEGLs are needed for prevention and emergency response planning for potential releases of EHSs either unintentionally from accidents or as a result of terrorist activities.

THE CHARGE TO THE SUBCOMMITTEE

The NRC convened the Subcommittee on Acute Exposure Guideline Levels to review the AEGL documents approved by the NAC. The subcommittee members were selected for their expertise in toxicology, pharmacology, medicine, industrial hygiene, biostatistics, risk assessment, and risk communication.

The charge to the subcommittee is to (1) review AEGLs developed by the NAC for scientific validity, completeness, and conformance to the NRC (1993) guidelines report, (2) identify priorities for research to fill data gaps, and (3) identify guidance issues that may require modification or further development based on the toxicological database for the chemicals reviewed.

This interim report presents the subcommittee's comments concerning the draft AEGL documents for 14 chemicals: phosgene, hydrogen chloride, hydrogen fluoride, hydrogen sulfide, G nerve agents, VX, diborane, *cis*- and *trans*-crotonaldehyde, perchloromethyl mercaptan, iron pentacarbonyl, nickel carbonyl, allylamine, cyclohexylamine, and ethylenediamine.

COMMENTS ON PHOSGENE

At its February 6-8, 2002 meeting, the subcommittee reviewed the AEGL document on phosgene. The document was presented by Cheryl Bast of Oak Ridge National Laboratory. The subcommittee concluded that the revised document conforms with the *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* (NRC 2001) and that no further modifications to the document are required.

COMMENTS ON HYDROGEN CHLORIDE

At its February 6-8 2002 meeting, the subcommittee reviewed the revised AEGL document on hydrogen chloride (HCl). The document was presented by Cheryl Bast of Oak Ridge National Laboratory. The subcommittee recommends that the following revisions be made.

Comments

Compare and contrast the HCl documentation and literature cited in the NRC (2002) report titled *Review of Submarine Escape Action Levels for Selected Chemicals* to the draft AEGL document. Specifically, the proposed AEGLs should be considered in light of the NRC (2002) conclusion: "The subcommittee believes that for irritant gases, the concentration of the gases is more important than the exposure duration for determining toxicity" (page 3).

Page ii, lines 30-33: The data on exercising asthmatics should be used to justify an intraspecies UF of 3.

Page 2, lines 21-24: Is reactive airways dysfunction syndrome (RADs) a clinically or scientifically recognized condition? If so, provide reference to literature sources to justify that statement.

Page 2, lines 37-40: Delete this unsubstantiated information apparently taken from an old textbook.

Page 6, lines 22-23: Delete the studies by Darmer et al. (1974), Wohlslagel et al. (1976), and Higgins et al. (1972). The results of those investigations are discussed in detail later in the report.

Page 13, lines 8 and 9: Delete "dissolves in the nasal passages" and replace with "solubilizes in mucus present in the nasal passages."

Page 15, lines 35-37: It is stated here that "baboons exposed to up to 17,000 parts per million (ppm) exhibited increases in respiratory frequency." It should be stated that "baboons

inhaling 500, 5,000, or 10,000 ppm exhibited concentration-dependent increases in respiratory frequency."

Page 15, lines 39-41: Some explanation of the species difference in the susceptibility of mice and rats to HCl should be included. The same phenomenon has been documented in the case of hydrogen fluoride (HF), and the HF document mentions that mice may have a greater nasal scrubbing capacity. Has this been established? If so, insert references to the peer-reviewed literature to substantiate that statement. The higher respiratory rate of the mouse should result in greater disposition of HF in the nasal passages and deeper pulmonary-tract penetration of the chemical. It would be worthwhile to consider including here the paragraph (page 35, lines 39-45, and page 36, lines 1 and 2) from the HF document. That paragraph from the HF documentation contrasts breathing patterns of rodents (obligate nose breathers) and humans.

Page 17, 34-41: It should be recognized that exercise will increase HF uptake and exacerbate irritation. Thus, these asthmatic human subjects should be considered a sensitive subpopulation.

Page 19, lines 1-26: It is difficult to understand the magnitude of the total UF and how it was derived. There is no mention of the modifying factor (MF).

Page 19, lines 15-17 and lines 23-26: It is stated that confidence in time scaling for HCl is good and that ten Berge et al. (1986) calculated an *n* value of 1 for HCl. The 4- and 8-hour (h) AEGL-2 values derived with this approach are inconsistent with the empirical data. If exercising asthmatic subjects can inhale HCl at 1.8 ppm for 45 minutes (min) without any adverse health effects, they should certainly be able to inhale HCl at 2.7 ppm for 8 h or 5.4 ppm for 4 h without serious, long-lasting effects or impaired ability to escape. Therefore, the 4- and 8-h AEGL-2 values should be changed.

Page 21, line 10: The sentence that starts with "A number of factors argue ..." should begin a new paragraph. The logic is hard to follow in Section 7.3, because there is so much information on different subjects.

Page 21, lines 25-34: As with the AEGL-2 values, use of the $C^1 \times t = k$ equation by the NAC resulted in unrealistically low AEGL-3 values for 4 to 8 h. The 13 ppm and 26 ppm concentrations proposed by the NAC are inconsistent with the AEGL-3 definition and are not likely to cause any changes more severe than moderate sensory irritation in some individuals.

Page 25, lines 34-39: Why are the two papers by Bond and coworkers listed as "Cited in IARC, 1992"? The original literature should be consulted and cited. The Machle et al. (1942) lethality study with rabbits and guinea pigs should be included.

Major concern is focused around the rationale for using the least sensitive rodent for developing AEGL values. The most sensitive rodent was the mouse, and the rat was the least sensitive. As the text is written, it seems that the justification was that although the rat is the

least sensitive rodent, the rat is more sensitive than humans to inhaled HCl. Is this reference correct, and, if so, what specific peer-reviewed publications support that conclusion?

It is not clear why the authors used one-third of the LC_{50} value to establish AEGL-3 values.

It appears that the NAC failed to consider a MF of 3, which is generally used per the SOP for a sparse database.

COMMENTS ON HYDROGEN FLUORIDE

At its February 6-8, 2002 meeting, the subcommittee reviewed the revised AEGL document on hydrogen fluoride. The document was presented by Sylvia Talmage of Oak Ridge National Laboratory. The subcommittee recommends that the following revisions be made in the document.

Comments

Page 5, line 1: The title of this section should be "Executive Summary" rather than "Summary."

Page 6, line 1: Insert the following after the sentence that ends "and coughing (Rosenhaltz et al., 1963)": "This value is one-fourth of the rat LC_{50} value in the same study. Rats exposed to a similar concentration (291 ppm) developed moderate eye and nasal irritation. The next higher concentration (489 ppm for 1 h) resulted in respiratory distress and severe eye and nasal irritation in the rat, signs more severe than those ascribed to AEGL-2. The moderate eye and nasal irritation observed in dogs at 243 ppm was considered the threshold for impaired ability to escape."

Page 6, line 8: The following sentence should be added at the end of the paragraph: It should be noted that the resulting 30-min AEGL-2 value of 34 ppm is similar to the 32 ppm concentration that was tolerated for only several minutes by human subjects in the study by Machle et al. (1934).

Page 9, lines 10 and 11: The order of the concentrations of hydrogen fluoride (HF) listed in parts per million should be revised to correspond with the respective concentrations presented in milligram per liter.

Page 30, lines 40-46: LC_{50} studies demonstrate that mice are 2- to 4-fold more susceptible to HF-induced pulmonary damage and lethality than rats. This species difference is tentatively attributed to differences in nasal scrubbing capacity. Are there data relevant to species differences in scrubbing capacity? If so, those references should be cited in the discussion. The species difference in LC_{50} values may be due largely to the greater respiratory rate of the mouse. Are there comparative studies of the relative pulmonary

deposition of HF or similar water-soluble compounds in humans and rodents that could serve as reference material?

Page 34, line 10: It is noted here that the NRC (1991) concluded that the mouse may not be a good model for humans exposed to respiratory irritants. This is apparently at odds with the RD_{50} database and its correlations to workplace air standards (e.g., Am. Ind. Hyg. Assoc. J. 54(9):488-544, 1993), therefore, a brief summary of the NRC rationale for that statement should be added.

Page 35, lines 4-6: Persons who are exercising should experience greater HF deposition and pulmonary irritation than persons at rest. Individuals involved in emergency situations are likely to be under duress and engaged in physical activity; therefore some consideration of emergency response personnel and those attempting to escape as a susceptible subpopulation might be appropriate.

Page 36, lines 23-25: Were the volunteers in the study by Lund et al. (1999) exercising throughout their 1-h HF exposures? The subjects in the 1997 study by Lund et al. rested for the first 45 min and exercised during the last 15 min of their 1-h exposures. Clarify the protocols utilized in the Lund (1999) investigation.

Page 36, lines 27-30: Were the workers described in these four studies asymptomatic?

Page 39, lines 42 and 43: This sentence should be revised to be consistent with the recommended additions at the top of page 6 of the Executive Summary.

Page 39, lines 44 and 45: The use of the equation $C^2 \times t = k$ to scale from 1 to 8 h yields 4- and 8-h AEGL-2 values that are inconsistent with the AEGL-2 definition. Subjects in the studies by Largent (1960, 1961) were exposed to approximately 8 ppm for 6 h daily for up to 50 days (d). The eye, nose, and skin irritation that they experienced was far from disabling. HF is very rapidly absorbed and should therefore not accumulate in the mucus membranes under such conditions. The intensity of eye and nasal irritation associated with exposure to a moderate concentration of a direct ocular and upper respiratory tract irritant, however, will increase somewhat at moderate vapor levels. Therefore, if the $c \times t$ relationship is applied as contrast to a ceiling value (NRC 2002), consideration should be given to proposing the 4- and 8-h AEGL-2 values that are only marginally lower than the 1-h AEGL-2 values.

Page 41, line 23: "Disabling, irreversible effects or inability to escape" is the definition of AEGL-2, not AEGL-3.

Page 41, lines 26 and 27: Judging from the data in Tables 3 and 6, the mouse is approximately 3 to 10 times more sensitive to HF acute lethality than the rat.

Page 41, lines 31 and 32: The use of the same time-scaling equation yields values that are far too low at the 4- and 8-h time points. However, there are no controlled lethality data for exposures longer than 1 h. This necessitates caution. Also, deep-lung irritant effects

(e.g., pulmonary edema) can become more pronounced with time at relatively high vapor concentrations. Nevertheless, comparisons of the proposed AEGL values with the empirical experience should be performed. For example, two human subjects were exposed 6 h daily to concentrations of 8 ppm for 25 or 50 d without apparent ill effects (Largent 1960, 1961). No deaths occurred in groups of four male and female rhesus monkeys inhaling 690 ppm for 1 h (MacEwen and Vernot 1970). These comparisons dictate revision of the proposed values to conform to the SOP definitions of the respective AEGLs.

Page 43, lines 34 and 35: Remove the latter part of the sentence that refers to secondary sources that state that 50 ppm exposure for a 30- to 60-min period was lethal. It should be noted that the National Institute for Occupational Safety and Health (NIOSH) immediately dangerous to life and health (IDLH) value was based on eye, nasal, and airway irritation seen in animals (Machle et al. 1934) and in humans (Largent 1961). The other concern is the obvious difference between the 30-min AEGL-3 value (62 ppm) and the existing IDLH value (30 ppm). It seems that the only justification was that the IDLH value was derived from the studies of Largent (1961) and Machle et al. (1934 (page 43, lines 34-35), which was apparently based on reported irritation of eyes, nose, and airways, and (unidentified) secondary sources that cited that 50 ppm was lethal for a 30- to 60-min exposure. What studies were those? The established IDLH value and those "secondary sources," stating that 50 ppm was lethal for 30 min, require more complete justification.

COMMENTS ON HYDROGEN SULFIDE

At its February 6-8, 2002 meeting, the subcommittee reviewed the revised AEGL document on hydrogen sulfide (H_2S). The document was presented by Cheryl Bast of Oak Ridge National Laboratory. The subcommittee recommends that the following revisions be made in the document.

General Comments

Compare and contrast the H_2S documentation and literature cited in the NRC (2002) report titled *Review of Submarine Escape Action Levels for Selected Airborne Chemicals* to the draft AEGL document. Specifically, the proposed AEGL values should be reconsidered in light of the NRC (2002) conclusion: "The subcommittee believes that for irritant gases the concentration of the gases is more important than the exposure duration for determining toxicity (NRC 2002, page 3).

On the basis of arguments presented on page 21, line 26, and page 22, lines 1-3, the derivation of AEGL-1 is inconsistent with the Standing Operating Procedures (SOP) manual. A 30% incidence of headache complaints is not inconsistent with the AEGL-1 definition: "the effects are not disabling and are transient and reversible upon cessation of exposure." The use of an "extra" 3-fold UF "because adult asthmatics may not be more sensitive than healthy individuals to headache" has no plausible physiological basis. The rationale for the use of an additional 3- fold UF because the "end point (headache) is more severe than the end points

Summary of Current AEGL Values for Tetrachloroethylene (ppm)						
Level	10-m	30-m	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1	50	50	35	18	12	Mild eye irritation in 6 subjects exposed to 106 ppm for 1 hr (Rowe et al., 1952)
AEGL-2	230	230	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) (Goldberg et al., 1964) *
AEGL-3	690	690	490	240	170	Highest conc. with no deaths: 2450 in mice and 2445 ppm in rats for 4 hrs (Friberg et al., 1953; NTP, 1986)

* 10- and 30-min AEGL-2 value set equal to 1-h value of 230 ppm because human study demonstrated exposure to 600 ppm for 10 min caused significant effects (eye and nose irritation, dizziness, tightness and numbing about mouth, some loss of inhibitions, motor coordination required great effort; Rowe et al., 1952). After applying an UF of 3, AEGL values based upon this study are consistent with the 1-h AEGL-2 value of 230 ppm.

Time scaling using an n = 2 derived by ten Berge, 1986.

1

COT Comments for Tetrachlorotheylene

AEGL-1

- *Inappropriate exposure level (i.e., 100 ppm) used as starting point. Exposure to approximately 100 ppm (Stewart et al. 1961b; Rowe et al. 1952; Stewart et al. 1970; Stewart et al. 1981) consistently resulted in mild irritation of ocular and nasal mucus membranes in some subjects. The AEGL-1 is defined as the airborne concentration above which persons could experience notable discomfort or irritation. Subjects exposed to approximately 475 ppm for approximately 2 hr reported modest eye irritation, tightness in frontal nasal sinuses, and increased nasal secretions (Carpenter 1937). These symptoms seem more consistent with notable discomfort. Rowe et al. (1952) observed only slight eye irritation in volunteers inhaling 100 ppm. Nasal irritation and more pronounced eye irritation were seen at 200 ppm by Rowe et al. (1952) and Stewart et al. (1961).* ***In light of the foregoing, 200 ppm would appear to be a more appropriate starting point.***

- *Odor and irritation are related to local concentration. Therefore, duration-dependent adjustment (or the use of Haber's rule) for such effects is inappropriate.*

2

Response for AEGL-1

- Agree that the values should not have been scaled across time because the endpoint is that of irritation

- If keep the same key study and endpoint, then the values would be 35 ppm across time

- With regard to key study, this study was the one reporting the lowest exposure producing irritant effects. Mild irritation was reported in 5 subjects exposed to 106 ppm for 1 hour. **COT recommends going with more notable discomfort reported at concentration of 200 ppm, which would result in values of 70 ppm across time**

3

AEGL-2

- *It is probably best to use 1,150 ppm (the no-effect level for ataxia of rats in the study by Goldberg et al. (1964)) as the basis for derivation of the AEGL-2 value.* ***An interspecies UF is not warranted due to the greater systemic dose of an inhaled VOC received by a rat (versus a human).*** *The intraspecies UF of 3 is appropriate.* ***Use of $C^n \times t = k$ equation to scale across time is inappropriate. As described below, this generic approach is not appropriate for VOCs.***

AEGL-3

- ***The ten Berge (1986) equation is not valid for scaling across time with VOCs.*** *PCE is rapidly absorbed from the lungs and reaches near steady-state, or equilibrium, in the blood (and brain) within 1-2 hr or less (Stewart et al. 1961b). Thereafter, the blood and brain PCE concentrations and the level of CNS depression increase asymptotically (i.e., very slightly) for the duration of the exposure. Thus, the AEGL-3 values for longer exposures will not diminish significantly.*

4

Response for AEGL-2 and -3:

- If decrease interspecies UF to 1, then total UF of 3. See Table for AEGL-2 and 3 values

- With regards to the comment about time-scaling, with this particular chemical the data demonstrate that it is indeed appropriate. The value of n=2 is obtained from ten Berge, who used the rat mortality data from Rowe et al (1952). Clearly for the mortality data, the response varied with time and concentration.

  Additionally, the statement COT makes about Perc reaching near steady-state within 1-2 hr or less (Stewart et al. 1961b) does not appear to be true. Although the Stewart et al. (1961b) study did reach this conclusion, other studies indicate that this is not the case. Studies that measured the amount of Perc in exhaled air of humans during exposures up to 8-hours long found the Perc concentrations continued to rise throughout the exposures. Another study that measured Perc concentrations in the brain and blood of rats exposed to 200 ppm for up to 6 hours found that equilibrium had not yet been reached.

Therefore, it appears appropriate to scale across time with n=2.

Summary of AEGL Values for Tetrachloroethylene (ppm)					
10-m	**30-m**	**1-h**	**4-h**	**8-h**	**Comment**
AEGl-1					
50	*50*	*35*	*18*	*12*	*Currently proposed (start with 106 ppm for 1 h; UF=3; scale across time)*
35	35	35	35	35	Flatline because irritant effect (at a minimum, this needs to be done)
70	70	70	70	70	COT: start with 200 ppm; UF=3; flatline
AEGL-2					
230	*230*	*230*	*120*	*81*	*Currently proposed (UF = 10); 10 min, 30 min and 1-h set equal because 600 ppm for 10 min caused significant effects*
770	770	770	400	270	COT: UF = 3 (keep 10 min, 30 min, and 1-hr equal to one another based on effects seen at 600 ppm for 1 hr
1100	1100	770	400	270	COT: UF = 3; 10 min equal to 30 min because 4 hr exposure
400	400	400	400	400	COT: UF = 3 and flatline
AEGL-3					
690	*690*	*490*	*240*	*170*	*Currently proposed*
2300	2300	1600	800	570	COT: UF = 3
800	800	800	800	800	COT: UF = 3 and flatline

To keep AEGL values in context of the exisiting data, here are some experimental data from metabolism and elimination studies in humans. While some of these studies did not address subjective symptoms, they do show that exposure to 200 ppm for 8 hours is not disabling. The studies (with the exposure concentrations and durations) are as follows:

Fernandez et al. (1976: 23 males and 1 female exposed to 100 ppm for 1, 2, 4, or 8 hours; 150 ppm for 1, 4, 6, or 8 hours; 200 ppm for 2, 4, 8 hours)
Jang et al. (1997: 6 male Caucasians and 6 male Orientals exposed to 50 ppm for 6 hours)
Monster et al. (1979: 6 healthy male workers ages 27-34 exposed for 4 hours to 72 ppm at rest, 144 ppm at rest, and 142 ppm at rest combined with work load)

These were also summarized in human nonlethal toxicity section:

Stewart et al. (1981: 10 male workers and 11 females exposed for 1, 3, or 7.5 hours daily to 50 to 150 ppm for up to 4 weeks - minimal effects)
Stewart et al. (1961b: groups of six, healthy male workers ages 30-59 exposed to 194 ppm for 187 minutes, 194 ppm for 83 minutes, or 101 ppm for 183 minutes - irritation reported)

Attachment 20

NICKEL CARBONYL

REVISIT OF AEGL-2
IN RESPONSE TO COT/AEGL

NAC/AEGL - 25
JUNE 17-19, 2002

EOHSI
Rutgers University
Piscataway, NJ

Summary of Interim AEGL Values For Nickel Carbonyl [ppm]						
Classification	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	not recommended
AEGL-2 (Disabling)	~~0.096~~ **0.15**	~~0.042~~ **0.11**	~~0.021~~ **0.053**	~~0.0053~~ **0.013**	~~NA~~ **0.0026**	~~developmental toxicity in hamsters; gestational exposure (15 minutes, 8.4 ppm)~~ **3-fold reduction of AEGL-3 values**
AEGL-3 (Lethal)	0.46	0.32	0.16	0.040	~~NA~~	estimated lethality threshold (LC_{01} of 3.17 ppm); mouse lethality data (Kincaid et al., 1953)

NR: Not recommended. Numeric values for AEGL-1 are not recommended because the lack of available data. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

Summary of Interim AEGL Values For Nickel Carbonyl [ppm]						
Classification	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	not recommended
AEGL-2 (Disabling)	~~0.096~~ **0.13**	~~0.042~~ **0.056**	~~0.021~~ **0.028**	~~0.0053~~ **0.007**	~~NA~~ **0.0035**	~~developmental toxicity in hamsters; gestational exposure (15 minutes, 8.4 ppm)~~ **NOAEL (11.2 ppm, 15-min. on gestation Day 8) for eye malformations in rats (Sunderman et al., 1979)**
AEGL-3 (Lethal)	0.46	0.32	0.16	0.040	~~NA~~	estimated lethality threshold (LC_{01} of 3.17 ppm); mouse lethality data (Kincaid et al., 1953)

NR: Not recommended. Numeric values for AEGL-1 are not recommended because the lack of available data. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

CURRENT INTERIM AEGL-2 VALUES

- COT/AEGL found the basis for the interim AEGL-2 values to be unacceptable

  - developmental toxicity endpoint in compromised dams is inappropriate

- very limited data regarding nickel carbonyl-induced effects consistent with AEGL-2 definition

- caution regarding extrapolation of nickel-induced teratogenic effects in animals to possible effects in the work place (Warner, 1979)

ALTERNATE AEGL-2

- no AEGL-2 values
- 3-fold reduction of AEGL-3 values
- NOAEL for developmental toxicity in rats (Sunderman et al., 1979)

ALTERNATE AEGL-2

- initial TSD draft recommended no AEGL-2 values due to insufficient data

ALTERNATE AEGL-2

- 3-fold reduction of AEGL-3 values as estimate of AEGL-2

  - precedent for 3-fold reduction of AEGL-3 as estimate of AEGL-2
    - AEGL-2 values for iron pentacarbonyl developed by 3-fold reduction of AEGL-3 values
    - AEGL-2 for monomethylhydrazine (NRC, 2000)
    - accepted procedure in SOP/AEGL (NRC, 2001)

  - 3-fold reduction of AEGL-3; justifiable ?
    - occupational exposure data showed lung function and EEG effects (not life-threatening) in workers following long-term exposure to 0.0009 - 0.07 ppm (Shi et al., 1986; 1994)
    - human experience suggests that long-term exposure to levels similar to AEGL-2 were without serious, irreversible effect

ALTERNATE AEGL-2

- developmental toxicity in rats (Sunderman et al., 1979)

  - absence of eye malformations; 11.2 ppm, 15 min, gestation Day 8
  - increased incidences ($p<0.001$) of eye malformations at 22.4 and 42 ppm, 15-min, gestation Day 8
  - total UF of 100 (10 x 10)

- developmental endpoint; justifiable ?

  - caution regarding extrapolation of nickel-induced teratogenic effects in animals to possible effects in the work place (Warner, 1979)

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Sunderman, F.W., Jr., Alpist, P.R., Mitchell, J.M., et al., 1979. Eye malformations in rats: Induction by prenatal exposure to nickel carbonyl. Science 203: 550-553.

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Summary of Proposed AEGL Values For Iron Pentacarbonyl [ppm (mg/m^3)]						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended; insufficient data
AEGL-2 (Disabling)	1.2 (9.6)	0.40 (3.2)	0.19 (1.5)	0.050 (0.40)	**0.024 (0.19)**	Based upon a three-fold reduction in the AEGL-3 values
AEGL-3 (Lethal)	3.5 (28)	1.2 (9.6)	0.58 (4.6)	0.15 (1.2)	**0.073 (0.59)**	Estimated lethality threshold in rats (6-hr exposure to 2.91 ppm) (BASF, 1995). $n = 1$; UF=30 (10 for interspecies variability, 3 for individual variability)

NR: Not recommended. Numeric values for AEGL-1 are not recommended because (1) the lack of available data, and (2) an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

8-hour AEGL values extrapolated using $C^1 \times t = k$; where $(2.91 \text{ ppm})^1 \times 6 \text{ hrs} = 17.46$ ppmhr

Attachment 22

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR ALLYLAMINE

(CAS Reg. No. 107-11-9)

$$H_2C{=}C{-}CH_2{-}NH_2$$

DRAFT – ***Responses to February 2002 COT Comments on Allylamine***

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The major comments addressed were as follows:

Incorporate new allylamine mechanistic studies (post-1994). For example, Conklin et al. (2001) provided evidence of a two-step mechanism of cardiotoxicity: (1) metabolism of AA to acrolein and hydrogen peroxide (H_2O_2) by semicarbazide-sensitive amine oxidase (SSAO) in the coronary arteries; and (2) the induction of vasospasm of coronary arteries by those metabolites.

- **This new mechanistic information is reflected in the rewritten Section 4.2., Mechanism of Toxicity.**

Give more emphasis to and greater description of information indicating that AA can be cardiotoxic in most mammals.

- **Section 4.2., Species Variability was rewritten.**

Discuss information about human subpopulations (diabetics, patients with congestive heart failure and/or uremia) that may be more susceptible due to their increased serum SSAO activity or less susceptible [e.g. persons prescribed monoamine oxidase inhibitors].

- **Potentially susceptible subpopulations are discussed in the rewritten Section 4.4.2. Less susceptible persons were not discussed (no information; not directly relevant for AEGL derivation).**

Why was a sub-NOAEL conc. (i.e., 0.2 ppm) adopted as AEGL-1? The AEGL-1 should probably be ~1 ppm, in view of the threshold for irritation of 2.5 ppm in the more sensitive human subjects of Hine (1960).

- **The AEGL-1 was re-derived using human 5-minute exposure study where 2.5 ppm (lowest conc tested) caused slight to moderate eye and nose irritation and pulmonary discomfort in 21-54% of volunteers. Applied a UF of 10 because the threshold for sensory irritation was not established and exposure was for only 5 minutes. An AEGL-1 of 1 ppm is not appropriate because it is similar to the 8-hour AEGL-2.**

For AEGL-2, an ***intraspecies*** UF of 10 is appropriate due to lack of information about variability in vascular SSAO activity and possible sensitive subpopulations.

COT previously recommended an ***interspecies*** UF of 3 (total UF=30), which yields AEGL-2 values only slightly lower than AEGL-3 values. An interspecies UF of 10 (total UF=100), yields AEGL-2 values lower than the 5-ppm "ceiling" value recommended for occupational exposure by Guzman et al. (1961). An interspecies UF of 5 (total UF=50) is recommended because considerable detail is known about the mode of action and it appears to be the same in all mammalian species (including humans) that have been tested.

- **The AEGL-2 values were re-derived using an interspecies UF of 5 and an intraspecies UF of 10. Additionally, AEGL-2 values were derived using a different exposure scenario in the same study, one that was a threshold for heart lesions (previously used scenario where heart lesions were induced).**

Summary of AEGL Values for Allylamine [ppm (m/mg^3)]						
Classification	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Non-disabling)	0.25 (0.58)	0.25 (0.58)	0.25 (0.58)	0.25 (0.58)	0.25 (0.58)	Mild irritation or discomfort (Hine et al., 1960)
AEGL-2 (Disabling)	6.1 (14)	6.1 (14)	4.1 (9.5)	1.8 (4.2)	1.2 (2.8)	Threshold for rat heart lesions (Guzman et al., 1961)
AEGL-3 (Lethal)	146 (341)	40 (94)	18 (42)	3.5 (8.1)	2.3 (5.4)	Lethality threshold in rats (Hine et al., 1960)

Uncertainty factors (UF) used for derivation of Allylamine AEGLs
AEGL-1: Total UF=10 ***Interspecies UF***: not applicable ***Intraspecies UF***: **10**: threshold for sensory irritation not established, exposure was for only 5 minutes. Supported by occupational study where exposure to 0.2 ppm for up to 4 hours did not elicit worker complaints.
AEGL-2: Total UF=50 ***Interspecies UF***: **5**: Variability is not likely sufficient to warrant a default of 10 because the mechanism of toxicity is similar among several mammalian species and humans, but cardiotoxicity from inhalation exposure *in vivo* was only shown in rats. UF of 3 results in concs near the threshold for lethality from pulmonary lesions at 4 and 8 hrs. ***Intraspecies UF***: **10**: There were no studies evaluating the variability of the cardiotoxic response among humans, and there are several potentially sensitive subpopulations (persons with congestive heart failure and/or diabetes).
AEGL-3: Total UF=30 ***Interspecies UF***: **10**: Due to lack studies with AEGL-3 endpoints in species other than rats; uncertainty if pulmonary toxicity is most sensitive endpoint. ***Intraspecies UF***: **3**: Threshold for lethality due to direct destruction of lung tissue is not likely to vary greatly among humans.

ALLYL ALCOHOL - April 2002 Meeting

- Discussed COT proposed changes:
  Because available data do not clearly indicate the extent to which the AEGL-3 value should exceed the AEGL-2 value, the subcommittee recommends that the AEGL-3 and AEGL-2 values be identical.

- The primary reason for this suggestion was because of problems with scaling AEGL values across time

  - **AEGL-2:** Default of n = 1,3. 10-min value set equal to 30-min value because extrapolating from 7-h exposure duration.

  - **AEGL-3:** If go with default of n=1,3, the 4-h AEGL-3 value approaches 4-h AEGL-2 (5.0 vs. 4.8 ppm) and the 8-h AEGL-3 is below the 8-h AEGL-2 (2.5 vs. 3.5 ppm). Therefore, an n=3 was used to extrapolate from longer to shorter durations, and an n=2 was selected for shorter to longer duration extrapolations

- It was suggested by NAC that available data be used to generate a value for *n* for scaling across time

1

- Empirical derivation of *n* based on data from Dunlap et al., 1956

  - rat 1-, 4- and 8-hour LC_{50} values of 1060, 165, and 76 ppm, respectively

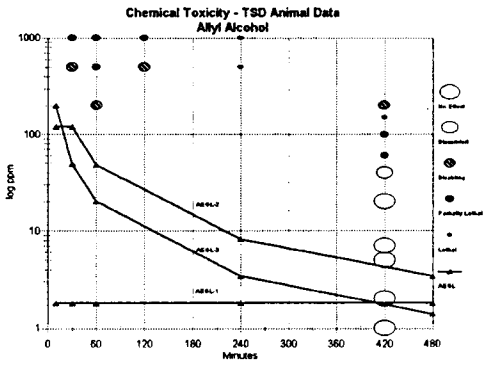
  - $n = 0.78$

This was discussed the first time allyl alcohol was presented to NAC. It initially was decided not to use this value because the LC_{50} values were based on target concentrations. Although authors stated that actual concentrations ranged from 15-25% of nominal, the actual measured concentrations were not given.

2

Values based upon scaling across time using the empirically derived value of 0.78 for *n*:

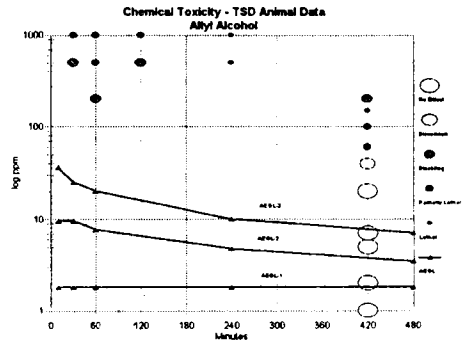
Level	10-m	30-m	1-hr	4-hr	8-hr
AEGL-1	1.8	1.8	1.8	1.8	1.8
AEGL-2	120	120	48	8.2	3.4
AEGL-3	200	49	20	3.4	1.4



3

Values based upon default *n* values to scale across time (currently approved values)

Level	10-m	30-m	1-hr	4-hr	8-hr	Endpoint (Reference)
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	Reversible irritation in rats exposed to 40 ppm for 7 h for 60 exp. (increased lung wt observed at necropsy)
AEGL-3	36	25	20	10	7.1	Highest conc. causing no mortality in mice, rabbits, and rats: 200 ppm for 1 h



4

Other considerations: Study by Dunlap et al., 1958

- Groups of 5-7 human volunteers exposed to allyl alcohol for 5 minutes
- Volunteers exposed to 25 ppm for 5 min reported severe eye irritation

Summary of Sensory Response to Allyl Alcohol During 5-Minute Exposure [a]							
Conc. (ppm)	No. Subjects	Olfactory Recognition [b]		Eye Irritation [b]		Nose Irritation [b]	
		Any Response	≥ Moderate	Any Response	≥ Moderate	Any Response	≥ Moderate
0.78	6	5	1	0	0	2	0
6.25	6	5	2	1	0	3	1
12.5	7	6	1	1	0	7	4
25.0	5	3	1	5	5 [c]	5	5

[b] The numbers listed in the "Any Response" column are for the number of volunteers showing any response at all; the "≥ Moderate" column represents those listing responses greater than "slight".
[c] Response graded as severe

CONCLUSIONS

- n value of 0.78 produces AEGL values that are inconsistent with each other and with existing empirical data (human 5-minute exposure values)
- Leaves few choices
  - ***Stick with the values as currently proposed***
    (COT has issue with this because of the problem with time-scaling; need convoluted justification of n value for AEGL-3 values)
  - ***Do not derive AEGL-2 value***
    (not recommended - these values serve as a baseline: they are based on a multiple exposure scenario in which rats exposed for 40 ppm for 7 hrs/d exhibited reversible signs of irritation.)
  - ***Do not derive AEGL-3 value***
    (these values are based on data from a 1951 study in which the only information recorded was mortality; no information on controls, method of exposure, analytical verification of conc., or period of observation following exposure).

Appendix A

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

April 9-11, 2002

Final Meeting-24 Highlights

U.S. Department of Transportation
DOT Headquarters/Nassif Building, Rooms 6200-6204
400 7th Street, S.W., Washington, D. C.

INTRODUCTION

George Rusch, NAC/AEGL Chair, opened the meeting with brief remarks and along with AEGL Program Director, Roger Garrett, welcomed the committee members and guests. Thanks were expressed to George Cushmac for continued hosting of the NAC/AEGL meeting at the Department of Transportation. Roger Garrett briefly discussed his health situation and offered his continued commitment to the AEGL Program.

George Rusch made the following administrative announcements:

- The current emphasis of the AEGL Program is to work closely with NAS/COT and publish as many TSDs as possible in 2002. Therefore, we are seeing many recycled TSDs in this meeting instead of new TSDs.
- To facilitate the process of meeting highlights preparation, the Chemical Manager along with the ORNL scientist, will capture the essence of the discussions and forward the results to Po-Yung Lu in two weeks. Po-Yung can then integrate the information and distribute the highlights to NAC/AEGL members in a timely manner.

Bob Snyder inquired about the accessibility of the meeting recording tapes. These are available upon request through Paul Tobin.

The highlights of NAC/AEGL-23 held December 3-5, 2001, in San Antonio were reviewed; two minor revisions will be made. They were : "There was discussion on the appropriateness of product presentations to the committee and the limitations on short term detection tubes." and " Revisions were made to the discussion and vote on methanol." A motion was made by John Hinz and seconded by David Belluck to accept the aforementioned draft meeting highlights. The motion passed unanimously. The revised highlights of NAC/AEGL-23 are attached (Appendix

A). The highlights of the NAC/AEGL-24 meeting are presented below along with the meeting agenda (Attachment 1) and the attendee list (Attachment 2). Ballots were taken during the meeting and are incorporated into the appropriate chemical specific section as Appendices.

Publication Status/TSDs Review by NAS/COT (Feb. 2002)

George Rusch reported to NAC/AEGL that the preparation of volume three of TSD documents is under way and publication by the NRC should take place in summer. This volume will include HFC-134a, HCFC- 141b, Otto Fuel, HCN and Phosgene. He also summarized the status of Interim TSDs submitted to NAS for review. An impressive number of TSDs, a total of 17, were reviewed by the NAS/COT AEGL subcommittee during the February 6-8, 2002, meeting at Irvine, California. These chemicals are listed in Attachment 3. The NAS formal report on these chemicals will be available in early May. In addition, George Rusch provided the NAC/AEGL with a list of TSDs that are available for presentation to the COT Subcommittee at the July and October 2002 meetings (Attachment 4).

In a separate presentation, George Rusch reported on the status of the G-Nerve agent (GA, GB, GD, and GF) and VX AEGLs which were presented to the COT Subcommittee at the February 2002 meeting (Attachment 5). In order to expedite the review of these compounds, the TSD authors were asked to submit their responses to the COT Subcommittee concerns prior to publication of the COT's formal report. The TSD's responses were provided to the COT Subcommittee on March 15, 2002 and are currently under review.

Upcoming Conference Event Pertinent to AEGL Program

Bob Snyder announced an upcoming conference jointly sponsored by UMDNJ-Robert Wood Johnson Medical School and Rutgers University. The conference, entitled "Preparing for Biological & Chemical Terrorism: A New Jersey Perspective," will be held on June 6-7, 2002 at the Environmental and Occupational Health Sciences Institute, Piscataway, NJ. The conference will discuss some of the "lessons learned" as well as the current research on biological and chemical terrorism. It will be a synthesis of public health, basic research and emergency preparedness issues. Bob welcomed and encouraged all NAC/AEGL members and guests to attend since several AEGL features will be discussed during the conference. Conference brochures were distributed (Attachment 6).

REVIEW OF PRIORITY CHEMICALS FOR 10-Minutes AEGL VALUES

AMMONIA
CAS Reg. No. 7664-41-7

Chemical Manager: Larry Gephart, Exxonmobil
Staff Scientist: Kowetha Davidson, ORNL

A discussion on derivation of 10-minute values was initiated by Larry Gephart, noting that the TSD is SOP compliant. Kowetha Davidson presented the proposed 10- minute AEGL values for ammonia (Attachment 7). The same data and approach used to derive the 5-and 30-minute values, and 1-, 4-, and 8-hour values was recommended to derive the 10-minute values. Following the discussion, NAC/AEGL decided to use irritancy rather than odor as the primary endpoint for the AEGL-1. The 10-minute AEGL-1 value, 25 ppm, was made equal to the other proposed AEGL-1 values. The 10-minute values for AEGL-2, 270 ppm, and AEGL-3, 2700 ppm, were time-scaled using a calculated value of n = 2. A motion to accept the values was made by Loren Koller and seconded by Ernest Falke. Each level was voted on separately. AEGL-1 (YES:22; NO:0; Abstain:0); AEGL-2 (YES:21; NO:2; Abstain:0); AEGL-3 (YES:23; NO:0; Abstain:0) (Appendix B).

FLUORINE
CAS Reg. No. 7782-41-4

Chemical Manager: Ernie Falke, EPA
Staff Scientist: Sylvia Talmage, ORNL

The data base on fluorine was reviewed by Sylvia Talmage prior to establishing 10-minute values (Attachment 8). In response to the suggestion by the COT Subcommittee that accommodation to irritant gases occurs at low concentrations, the AEGL-1 values for fluorine were all set equal. The 15-minute no-effect exposure of human subjects to a concentration of 10 ppm was divided by an intraspecies uncertainty factor of 3 and a modifying factor of 2 (based on a limited data base). The resulting value of 1.7 ppm was applied across all AEGL-1 exposure durations. The 10-minute AEGL-2 and AEGL-3 values were both time-scaled from the previously-approved values. Because the previously-approved time-scaled 8-hour values for the AEGL-2 and AEGL-3 appeared low in light of the human experience and because the 8-hour AEGL-2 value conflicted with the 8-hour AEGL-1 value, the 8-hour values were set equal to the respective 4-hour values. An AEGL category graph developed by Ernie Falke demonstrated the appropriateness of setting the 8-hour values equal to the 4-hour values. It was moved by Mark McClanahan and seconded by Loren Koller to accept the revised values. Separate votes were taken for the 10-minute values and for the AEGL-2 and AEGL-3 8-hour values: AEGL-1, 2, & 3 for 10-minutes values (YES: 21; NO:3; Abstain:2); AEGL-2 for 8 hours (YES:21; NO:0; Abstain:3); AEGL-3 for 8-hours (YES:21; NO:0; Abstain:3) (Appendix C). The NAC-approved values appear below:

SUMMARY OF AEGL VALUES FOR FLUORINE (ppm)						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL–1	1.7	1.7	1.7	1.7	1.7	No sensory irritation - human
AEGL–2	20	11	5.0	2.3	2.3	Mild lung congestion - mouse

AEGL–3	36	19	13	5.7	5.7	Severe lung congestion - mouse

NITROGEN DIOXIDE
CAS Reg. No. 10102-44-0
&
NITRIC ACID
CAS Reg. No. 7697-37-2

Chemical Manager: Loren Koller, OSU (retired)
Staff Scientist: Carol Forsyth, ORNL

Loren Koller led the discussion on development of 10-minutes AEGLs as outlined in Attachment 9. The NAC/AEGL questioned the information used for development of the nitric acid AEGL-2 [Diem (1907), cited in Henschler (1991)] in that the exposure involved a single human subject. Furthermore, the information was from a secondary source. Mark Ruijten commented that the study by Gray et al. (1954), selected for the AEGL-3 value of nitric acid, has problems with the reporting as well as the interpretation of the data. Mark indicated that the exposure was to a mixture but that the results are reported as nitrogen dioxide. The NAC/AEGL directed the TSD Development Team to reexamine the Gray manuscript (Attachment 10) to confirm his comments. If the data cannot be used, another study should be selected for development of AEGL-3 values.

There were also some questions about the Henschler et al. (l960) data used for the AEGL-2 and the Henry et al. (1969) paper used for the nitrogen dioxide AEGL-3. Again, the TSD Development Team was directed to confirm the quality of the data and reevaluate the available data for deriving AEGLs. Tom Sobotka agreed to search for FDA information on nitrogen dioxide (nitric oxide) for inclusion in the TSD development. The entire TSD of nitric acid and nitrogen dioxide should be reevaluated at a later time.

REVISION OF PRIORITY CHEMICALS

ETHYLENIMINE
CAS Reg. No. 151-56-4
&
PROPYLENIMINE
CAS Reg. No. 75-55-8

Chemical Manager: Mark McClanahan, CDC
Staff Scientist: Kowetha Davidson, ORNL

The NAS/COT/AEGL Subcommittee requested the NAC/AEGL to consider deriving AEGL-1 values for these chemicals. At the December 2001 meeting Mark McClanahan presented AEGL-1 values based on dividing the AEGL-2 values by two. This factor was the average for the ratio of AEGL-3 divided by AEGL-2 for the time 10-, 30- and 60-minutes as these were the only

AEGL-1 values proposed. Values for 4- and 8-hours would be below the odor detection threshold. At the December meeting NAC/AEGL members raised the question about the AEGL ratios for similar chemicals. A check of the chemicals the NAC/AEGL has approved showed the committee had evaluated no other imines and had approved only three amines. The AEGL ratios from these three amines provided no useful insight. Between the December 2001 meeting and the April 2002 meeting Mark McClanahan compiled the AEGL-3/AEGL-2 and AEGL2/AEGL-1 ratios for all the chemicals approved by the NAC/AEGL (List compiled by Paul Tobin dated January 18, 2001.) Mark presented the results of the ratio analysis in the following table. The results show that for the 8-hour data the ratio of the geometric means for the two ratios, AEGL-3/AEGL-2 and AEGL-2/AEGL-1 for the approved chemicals is one. This ratio for the 30-minute data is 2.2.

RATIO AEGL-2 TO AEGL-1				
time	number of chemicals	geometric mean	multiplicative standard deviation	range
30-minute	40	8.85	3.70	1.50 to 1066.67
8-hour	40	3.61	3.05	1.30 to 566.67
RATIO AEGL-3 TO AEGL-2				
30-minute	72	3.97	1.94	1.67 to 36.40
8-hour	73	3.62	2.00	1.33 to 40.77
RATIO OF AEGL-1/AEGL-2 TO AEGL-3/AEGL2				
30-minute	NA	2.2	NA	NA
8-hour	NA	1.0	NA	NA

Mark presented proposed AEGL-1 values for 10- 30- and 60-minute of 11, 3.3, and 1.5 ppm respectively (Attachment 11). The basis for these was the Carpenter et al. (1948) study in guinea pigs. Animals exposed to 25 ppm for 3 hours experienced extreme respiratory difficulty while animals exposed to 10 ppm for 4 hours did not. The 10 ppm, 4-hour exposure was the basis for the AEGL-2 derivation as a no-effect level for AEGL-2 type symptoms. To estimate the threshold for AEGL-1 effects (notable discomfort, irritation, or certain asymptomatic, non-sensory effects) a factor of 3 was used to adjust to the less severe effects defining level one. The NAC/AEGL has occasionally derived AEGL-2 values by dividing AEGL-3 values by 3, however, it did not believe the available data warranted development of AEGL-1 values for ethylenimine. Because the AEGL values for propylenimine are based on its chemical similarity and relative acute toxicity (one-fifth) to ethylenimine, the NAC/AEGL also chose not to develop AEGL-1 values for it.

George Rusch, Chair, will take the result from NAC/AEGL discussion not to develop AEGL-1 values for ethylenimine and propylenimine to the next NAS/COT/AEGL meeting in July.

METHYL MERCAPTAN

CAS Reg. No. 74-93-1

Chemical Manager: Doan Hansen, BNL
Staff Scientist: Cheryl Bast, ORNL

Doan Hansen pointed out that methyl mercaptan is one of the older chemicals on the first AEGL priority working list. Because originally there had not been agreement on the role that odor should play in setting AEGL-1, it had been difficult to finalize the AEGL values. The document had been tabled at that time, pending development of the SOP.

Cheryl Bast lead the discussion of new data that potentially affected existing AEGL-2 and -3 levels (Attachment 12). The new data resulted in new AEGL-2 and -3 values as shown below. The Committee was about to address AEGL-1, with no new data, and with presentation and discussion of the odor Level of Annoyance (LOA) concept still to take place at the next meeting. However, rather than engage in an unproductive discussion, the results of which might be changed after the LOA discussion, the Committee decided to table methyl mercaptan for one or two more meetings. It is hoped that consensus will be more easily reached on AEGL-1 at that time.

AEGL-2 values were based on shallow breathing and hypoactivity in mice exposed to 258 ppm methyl mercaptan for 6 hours (Elf Atcohem, 1996). An intraspecies uncertainty factor of 3 was applied and is considered sufficient due to the steepness of the lethal response curve which implies limited individual variability. An interspecies uncertainty factor of 3 was also applied. Although an interspecies uncertainty factor of 10 might normally be applied due to limited data, AEGL-2 values calculated utilizing a total UF of 30 would yield values that are inconsistent with the total data base. Temporal scaling was performed using the default values of n=3 when extrapolating to shorter time points (30-minutes, 1-hour, and 4-hours) and n = 1 (8-hours) when extrapolating to longer time points using the $c^n \times t = k$ equation. The 30-minute AEGL-2 value was also be adopted as the 10-minute AEGL-2 value due to the added uncertainty of extrapolating from a 6-hour time point to 10-minutes. It was moved by Ernest Falke and seconded by Bob Benson to adopt the proposed AEGL-2 values. The values were accepted: (YES:19; NO:2; Abstain:0) (Appendix D).

AEGL-3 values were based on the LC_{01} (430 ppm) for rats exposed for four hours (Tansy et al., 1981). An intraspecies uncertainty factor of 3 was applied and is considered sufficient due to the steepness of the lethal response curve. An interspecies uncertainty factor of 3 was also applied. Although an interspecies uncertainty factor of 10 might normally be applied due to limited data, AEGL-3 values calculated utilizing a total UF of 30 would yield values that are inconsistent with the total data base. Temporal scaling was performed using n=3 when extrapolating to shorter time points (30-minutes, 1-hour, and 4-hours) and n = 1 (8-hours) when extrapolating to longer time points using the $c^n \times t = k$ equation. A motion to accept the AEGL-3 values was made by Steve Barbee and seconded by Nancy Kim (YES:21; NO:1; Abstain:1) (Appendix D).

Summary of Proposed AEGL Values for Methyl Mercaptan [ppm]						
Classification	**10-minutes**	**30-minutes**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1	_	_	_	_	_	TABLED
AEGL-2	59	59	47	30	19	Shallow breathing and hypoactivity in mice (Elf Atochem, 1996)
AEGL-3	120	86	68	43	22	LC_{01} in rats (Tansy et al., 1981)

PHOSPHORUS TRICHLORIDE
CAS Reg. No. 7719-12-2

Chemical Manager: Tom Hornshaw, IEPA
Staff Scientist: Bob Young, ORNL

Bob Young presented a re-visit of the AEGLs for phosphorus trichloride (PCl3), for which the NAC/AEGL has previously accepted Proposed AEGL-3 values (Attachment 13). This re-visit was prompted by the submission of an unpublished study conducted by Hazelton Laboratories that suggested that the proposed AEGL-3 values may be too low.

Bob presented an overview of the Hazelton study, in which rats were exposed to 0, 0.5, 3.4, and 11.0 ppm (analytical concentrations) for 6 hr/d, 5 d/wk, for 4 weeks. This study reported no deaths or treatment-related clinical signs, hematological or clinical chemistry changes, or effects on body or organ weights. The only adverse effects reported were from histopathological findings of respiratory (mainly nasal) lesions. The NOAEL and LOAEL for these lesions were 3.4 and 11.0 ppm, respectively.

Based on these new study results, Bob suggested that the current AEGL-3 values (1.1, 1.1, 0.88, 0.56, and 0.28 ppm for 10 min, 30 min, 60 min, 4 hr, and 8 hr, respectively) may be too low since the Hazelton study rats survived 4 week exposures to 11 ppm. He also suggested that the Hazelton study might be used as the basis for developing the AEGLs 1 and 2. Regarding an approach for adjusting the current AEGL-3 values, Bob suggested that the new data could support a reduction in the interspecies uncertainty factor used with the guinea pig LC_{50} from 10 to 3, since it appears that the guinea pig is more sensitive than rats; this is supported by occupational reports (albeit of relatively poor quality) that workers exposed to 14-27 ppm for 2-6 hours experienced only irritation (Sassi, 1953). Regarding an approach for the AEGLs-1 and 2, he suggested that the Hazelton study NOAEL and LOAEL could be the basis for developing these values, although the data are from a repeated dose study.

To begin the discussion, it was noted that the rat nose more efficiently protects the lungs than the guinea pig nose, which may account for the disparity in the rat and guinea pig results. It was

asked if the AEGL values for hydrogen chloride could provide help in deriving new values for PCl3, since 3 molecules of HCl are generated from the rapid reaction of PCl3 with water. Since the AEGL-3 values for HCl are about 2 orders of magnitude greater than the current PCl3 AEGL-3 values, and phosphoric, phosphonic, and pyrophosphonic acids and significant heat of dissociation are also generated in the reaction with water, it was decided that comparison to HCl AEGLs would not be beneficial. It was then suggested that the occupational data from Sassi (1953) might be used as the basis for the AEGLs-1 and 2, but Bob reminded the NAC/AEGL that these data are taken from an abstract of an article, which is all that is available to the Committee. As a result, it was decided that the Sassi study could be no more than supporting information for AEGL development.

After further discussion, it was suggested that the rat 4-hr LC_{50} of 104.3 ppm (Weeks et al., 1964) could be used as the basis for the AEGL-3 values, using one-third of this concentration as the threshold for lethality, inter- and intraspecies uncertainty factors of 3, and the default values of n. The intraspecies UF of 3 is unchanged from the current AEGL-3 values. It was argued that an interspecies UF of 3, instead of the current value of 10, is supportable because the guinea pig is not a good model for deep lung irritants, and the occupational data suggest that humans can survive exposures to concentrations similar to those that only cause nasal lesions in rats upon repeated exposure. A motion for AEGL-3 values of 7.0, 7.0, 5.6, 3.5, and 1.8 ppm for the 5 AEGL time periods was made by Larry Gephart and seconded by John Hinz. The motion passed (YES:20; NO:1; Abstain:0)(Appendix E).

It was then argued that the LOAEL of 11.0 ppm from the Hazelton study could be the basis for the AEGLs-2, being the highest dose not causing AEGL-2 effects, and the NOAEL of 3.4 ppm could be the basis for the AEGLs-1, being the highest dose not causing AEGL-1 effects. Inter- and intraspecies uncertainty factors of 3 were again suggested, using the same reasoning as for the AEGLs-3, and the occupational data were cited as supportive of the appropriateness of using the Hazelton study for developing the AEGLs-1 and 2. Using the default values of n, AEGL-2 values of 2.5, 2.5, 2.0, 1.3, and 0.83 ppm for the 5 AEGL time periods were proposed by Bob Benson and seconded by Richard Thomas. The motion passed (YES:21; NO:0; Abstain:0). A motion to accept AEGL-1 values of 0.78, 0.78, 0.62, 0.39, and 0.26 ppm was made by Bob Benson and seconded by Mark McClanahan. The motion passed (YES:13; NO:5; Abstain:3).

SUMMARY OF AEGL VALUES FOR PHOSPHORUS TRICHLORIDE (ppm)

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint
AEGL–1	0.78	0.78	0.62	0.39	0.26	NOAEL for nasal lesions - rat
AEGL–2	2.5	2.5	2.0	1.3	0.83	LOAEL for nasal lesions - rat
AEGL–3	7.0	7.0	5.6	3.5	1.8	One-third of 4-hour LC50 - rat

RESPONSES TO *FEDERAL REGISTER* COMMENTS ON THE PROPOSED AEGL VALUES

(A). Comments from the *Federal Register Notice* of May 2, 2001, on the proposed AEGL values for acrylic acid were received and discussed. The NAC/AEGL deliberation of these chemicals are briefly summarized as the following:

ACRYLIC ACID

Comments were received from the Basic Acrylic Monomer Manufacturers, Inc. (BAMM) regarding the proposed AEGL-1, -2 and -3 values; the comments addressed the selection of end points, the selection of key studies, and the time scaling and completeness of the considered data by the NAC/AEGL. Initial discussion took place in September, 2001 (NAC/AEGL-22). At that time, Clay Frederick, Rohm and Haas Company, indicated that a recent report would be made available for NAC/AEGL evaluation. Two reports were subsequently distributed to NAC/AEGL by BAMM via Elizabeth Hunt (dated November 9 and December 31, 2001) prior to the April (NAC/AEGL-24) meeting.

This is a continuation of the discussion of acrylic acid from NAC/AEGL-22 which focused the discussion on the new information provided by BAMM. Tipton Tyler, Health Studies Management & Consulting, presented comments on acrylic acid to the NAC/AEGL on behalf of BAMM (Attachment 14). BAMM asked the committee to consider basing the AEGL-1 on irritation rather than odor. They felt that value(s) between 5 and 10 ppm would be justified if irritancy rather than the odor threshold was used as the critical end-point. BAMM felt odor was not an appropriate end-point for acrylic acid as the chemical is "data rich" and concentrations that produce direct effects on the nasal mucosa of rodents and primates have been well established. BAMM asked the Committee to consider basing the AEGL-2 value on impairment of avoidance of escape and felt that values between 60 and 75 ppm were justified on the basis of involuntary eye closure in rabbits. Finally, BAMM expressed concern over the low values selected by the Committee for AEGL-3 (51 ppm to 470 ppm for times ranging from 8 hours to 10 minutes). BAMM felt the large gap between the Committees proposed values and lethal levels in laboratory animals (up to 2000 ppm for 4 hours without lethality) could compromise the credibility of the AEGL-3. A lack of credibility in the AEGL values could possibly lead to their being ignored in life-threatening situations.

Dr. Gundert-Remy also presented the AEGL Development Team's responses to these issues and concerns (the detailed responses from the acrylic acid TSD Development Team are found in Attachment 15). The AEGL Development Team explained its view that AEGL values cannot be derived directly from existing workplace exposure limits or other limit or guideline values, because these values are derived for other purposes, subpopulations, exposure times and exposure frequencies and are derived using methodologies different from the AEGLs Standing Operating Procedures. Workplace monitoring and health surveillance data may, in principle, be used in the AEGL derivation, however, evaluation of the data provided by BAMM was difficult because the medical examination was not performed in correlation with exposure measurement, which was

seen as critical for slight irritative effects. Moreover, the exposure data of BAMM and BASF indicated that for most of the time actual workplace concentrations are far below the limit values. The NAC/AEGL committee decided to change the endpoint for the AEGL-1 derivation from the odor threshold to irritation without changing the actual AEGL-1 values. Acceptance of the present AEGL-1 values with a change of endpoint was shown by a unanimous show of hands (Appendix F).

With regard to AEGL-2, the AEGL Development Team considered a level of 75 ppm as an adequate threshold for an AEGL-2 effect because at higher concentrations, clinical effects occurred in animals (tearing and blepharospasm) that could impair the ability to escape, and because olfactory tissue destruction which increases with the exposure concentration is increasingly likely to result in permanent damage of the olfactory epithelium. The available animal data clearly demonstrate that the degree of olfactory epithelium damage increases with increasing exposure time and, thus, argue against using the same exposure concentration as the AEGL-2 value for all relevant periods of time. The AEGL Development Team suggested incorporation of the monkey study into the TSD. This study, together with the histopathological analysis was considered an adequate basis for a further reduction of the interspecies factor to 1. At the same time, this study strengthens the rationale for reduction of the default interspecies factor. For the AEGL-2 derivation, the monkey study will be used as an additional key study. The motion to accept the revised AEGL-2 values was made by Bob Snyder and seconded by Steve Barbee. The motion passed (YES:17; NO:4; Abstain:0) (Appendix F).

With regard to AEGL-3, the aerosol data from the study of Hagan and Emmons (1988) were considered a better basis for the derivation of AEGL-3 values because, in contrast to the vapor exposure part of the study, three different exposure times were used providing information on the time-dose-response relationship. Also, this study used a considerable higher number of animals. The monkey study on histopathological effects on the nasal mucosa was not considered an adequate rationale for a further reduction of the interspecies uncertainty factor. The AEGL Development Team referred to the AEGL Standing Operating Procedures for more information on the derivation of the exponent for time scaling. The Committee found no compelling reasons or data to change the values or rationale for the AEGL-3 at this time. It was moved by George Rodgers and seconded by Dave Belluck to keep the present AEGL-3 values. The motion passed (YES:20; NO:0; Abstain:1) (Appendix F).

Further more, a motion made by Steve Barbee and seconded by Ernest Falke, the acrylic acid values were raised to Interim status (YES:21; NO:0; Abstain:1 or 0) (Appendix F). The new AEGL-2 values appear below.

SUMMARY OF AEGL-2 VALUES FOR ACRYLIC ACID (ppm)						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL–2	68	68	46	21	14	Threshold for clinical effects and permanent olfactory epithelium damage

(B). No comments from the *Federal Register Notice* of February 15, 2002, on the proposed AEGL values for boron trifluoride, HFE-7100, and uranium hexafluoride were received. Therefore, these chemicals were elevated to Interim status as indicated below.

BORON TRIFLUORIDE

No comments were received from the *Federal Register Notices* of February 15, 2002. A motion to move the chemical from proposed to interim status was made by Mark McClanahan and seconded by Richard Thomas. The motion was approved unanimously by the NAC/AEGL (Appendix G).

HFE-7100

No comments were received from the *Federal Register Notices* of February 15, 2002. A motion to move the chemical from proposed to interim status was made by Mark McClanahan and seconded by Richard Thomas. The motion was approved unanimously by the NAC/AEGL (Appendix H).

URANIUM HEXAFLUORIDE

No comments were received from the *Federal Register Notices* of February 15, 2002. A motion to move the chemical from proposed to interim status was made by Mark McClanahan and seconded by Richard Thomas. The motion was approved unanimously by the NAC/AEGL (Appendix I).

REVIEW OF PRIORITY CHEMICALS FOR AEGL VALUES

TRICHLOROETHYLENE
CAS Reg. No. 79-01-6

Chemical Manager: Bill Bress, ASTHO
Staff Scientist: Marcel van Raaij, RIVM

Marcel van Raaij discussed the available toxicity data on trichloroethylene (TCE) (Attachment 16). The data base includes controlled human studies, human metabolism studies, narcosis information, and rat neurobehavioral studies. Marcel suggested a "weight of evidence" approach to development of AEGL-1 values. The AEGL-1 was based on a 2-hour NOAEL of 300 ppm for neurobehavioral effects in a study with humans volunteers (Vernon and Ferguson 1969); additional studies with human volunteers were cited as supporting data. For extrapolation across time a human PBPK model supplied by Boyes et al. (2002) was used. An intraspecies uncertainty factor of 3 was used because the mechanism of action for general CNS depression is not expected

to vary greatly among individuals. It was moved by Bill Bress and seconded by John Hinz to accept the proposed numbers. The motion passed (YES:24; NO:0; Abstain:1) (Appendix J). The AEGL-2 was based on effects seen at 1000 ppm for 2 hours in the study by Vernon and Ferguson (1969). These effects included dizziness, light-headedness and lethargy. These effects were considered to be below a level for an AEGL-2 endpoint, i.e., the highest level not showing any AEGL-2 effects. For extrapolation across the various time periods, the human PBPK model of Boyes et al. (2002) was used. For inter-individual variation among humans an intraspecies factor of 3 was used (the mechanism of action for general CNS depression is not expected to vary greatly among individuals. It was moved by Bob Benson and seconded by John Hinz to accept the proposed values (YES:17/18; NO:7; Abstain:0) (Appendix J).

The 30-minute to 8 hour AEGL-3 values were based on a NOAEL for mortality in mice of 4600 ppm for 4 hours. An uncertainty factor of 3 was applied. A value of 1.5 was used for time scaling (n) based on a rat mortality study of Adams et al. (1951). The 10-minute number was kept at a maximal level of 10,000 ppm based on the experience with trichloroethylene as an anesthetic agent. At concentrations above 10,00 ppm, cardiac arrhythmias may occur in humans (Orth and Gillespie, 1945; Pembleton, 1974). It was moved by Robert Snyder and seconded by Richard Thomas to accept the values (YES:19; NO:5; Abstain:0) (Appendix J).

SUMMARY OF AEGL VALUES FOR TRICHLOROETHYLENE (ppm)						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL–1	260	180	130	84	77	NOAEL for neuro-behavioral effects in humans
AEGL–2	960	620	450	270	240	Neurobehavioral effects in humans
AEGL–3	10,000	6100	3800	1500	970	Cardiac sensitization; threshold for lethality-mouse

RESPONSE TO NAS/COT/AEGL COMMENTS

TOLUENE
CAS Reg. No. 108-88-3

Chemical Manager: Larry Gephart, Exxonmobil
Staff Scientist: Sylvia Talmage, ORNL

Sylvia Talmage distributed the COT Subcommittee's review comments on the toluene AEGLs. The COT Subcommittee felt that, based on extensive human data, the toluene AEGL values were unrealistic. New values were proposed (Attachment 16), but the NAC suggested that further research into the data available for modeling, particularly for the longer-term AEGL-2 values, be

pursued. It was suggested that a comparison could be made between the AEGL-2 values modeled for the xylenes and AEGL-2 values for toluene.

ALLYL ALCOHOL
CAS Reg. No. 107-18-6

Chemical Manager: Mark McClanahan, CDC
Staff Scientist: Claudia Troxel, ORNL

The NAS/COT Committee reviewed the allyl alcohol document during its August 2001 meeting and made the following recommendation:

> *Because available data do not clearly indicate the extent to which the AEGL-3 value should exceed the AEGL-2 value, the subcommittee recommends that the AEGL-3 and AEGL-2 values be identical.*

Mark McClanahan summarized the AEGL values approved by the NAC/AEGL at the October 2000 meeting for allyl alcohol (Attachment 18). The basis for the AEGL-2 values was a 7-hour exposure repeated 60 times in which 10 rats/group experienced reversible lung irritation at 40 ppm. Time scaling for AEGL-2 used an n of 3 going to shorter times and an n of 1 going to longer times. AEGL-3 values were based on a one page summary from Union Carbide (1951) in which no rats exposed to 200 ppm for 1-hour died and was taken as the threshold for lethality. Time scaling for AEGL-3 values use an n of 3 going to short times and an n of 2 going to longer times. The use of an n of 2 was necessary to avoid producing AEGL-3 values essentially equal with the AEGL-2 value for 4-hours and smaller than the AEGL-2 value at 8-hours.

The revised TSD provided the following as support for the suggestion of setting AEGL-3 values equal to the AEGL-2 values:

- Study used for AEGL-3 is very weak - database does not provide good background for assessing acute lethal concentrations. Really is no clear indication of how much AEGL-3 value should exceed AEGL-2 value. Conversely, decent support for the AEGL-2 value, which is the level for "action."

- Would eliminate the inconsistency observed during the time scaling of the AEGL-2 and AEGL-3 values.

Thus, the proposed values for allyl alcohol, modified according to the suggestion by the NAS/COT are presented in the following table.

SUMMARY OF PROPOSED AEGL VALUES FOR ALLYL ALCOHOL (ppm)					
Level	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
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	9.6	9.6	7.7	4.8	3.5

The NAC/AEGL disagreed with the idea of making AEGL-2 and AEGL-3 values equal. Ernest Falke suggested that data from Table 3, "Summary of Acute Lethal Inhalation Data in Laboratory Animals," are available to calculate an n value for time scaling rather than using the default value. Thus, NAC/AEGL directed the TSD Development Team to use all available data to set a value for n and recycle the TSD.

FURAN
CAS Reg. No. 110-00-9

Chemical Manager: George Rodgers, AAPCC
Staff Scientist: Claudia Troxel, ORNL

George Rodgers presented the status of furan as follows (Attachment 19). At its August 2001 meeting the COT reviewed the AEGL TSD on furan. Claudia Troxel presented the document at that time. The COT Subcommittee made many specific comments about the TSD. Most of these were editorial and have been addressed by Claudia. The one issue needing NAC discussion relates to the total uncertainty factor used to calculate the AEGL-2 and AEGL-3 values. We have never proposed AEGL-1 values because of the total lack of usable data. The furan database contains only one study suitable for derivation of AEGL-2 or-3 values. This study was done in rats by Terrill et al. in 1989. Groups of 10 rats (5 male and 5 female) were exposed for 1 hour to three different concentrations of furan. Surviving animals were sacrificed 14 days after exposure. No animals died at the two lower concentrations and 9/10 died at the highest concentration. A 1-hour LC_{50} was calculated to be 3466 ppm. In our initial consideration of furan, interspecies and intraspecies uncertainty factors of 10 and 3, respectively, were used. An additional modifying factor of 3 was used for a total uncertainty factor of 100. The COT has suggested a higher modifying factor because of the extremely poor data set. After discussion the NAC voted to change the modifying factor to 5 for a total uncertainty factor of 150. The values appear below. A motion to accept the revised values was made by Tom Hornshaw and seconded by George Rodgers. The vote was (YES:13; NO:5; Abstain:1) (Appendix K)

SUMMARY OF AEGL VALUES FOR FURAN (ppm)						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL–1	NR	NR	NR	NR	NR	Insufficient data
AEGL–2	12	8.5	6.8	1.7	0.85	Threshold for adverse effects - rat
AEGL–3	35	24	19	4.8	2.4	Threshold for lethality - rat

NR = Not recommended.

REVIEW OF CHEMICALS WITH ISSUES FROM

PREVIOUS MEETINGS

Sylvia Talmage presented the chronology on development of AEGL values for HCN and the studies used as "weight of evidence" for development of the AEGL-1 (Attachment 20). As of January, 2002, The HCN AEGL values/TSD have been accepted as final by NAS/COT. John Morawetz brought up points of disagreement with the description and use of some of the studies and values used for AEGL-1 development (Attachment 21). George Rodgers, the Chemical Manager, also disagreed with a statement taken from a NIOSH document. In order to resolve these issues, George Rodgers will rewrite the justification for the AEGL-1.

In addition, John Morawetz also passed out a handout that he prepared on the issues of AEGL applications to occupational settings (Appendix 22).

SECOND AEGL CHEMICAL PRIORITY LIST

Paul Tobin distributed the draft second AEGL chemical priority list to NAC/AEGL (Attachment 23). In addition, he described briefly how the priority list was put together from inputs provided by the participating agencies and interested stake holders. This list comprised 137 high priority and 236 low priority chemicals for AEGL development. He also explained the value of a chemical classes approach for AEGL development. Any comments on the draft priority list should be addressed to Paul Tobin.

Administrative Matters

1. George Alexeeff would like to discuss the inconsistency in endpoints used in development of AEGL values. This subject will be addressed at the June meeting.
2. John Morawetz handed out a memo in which he discussed the application of AEGL values to the occupational setting. The memo calls for a clear distinction to be made between occupational guidelines such as ACGIH and OSHA and AEGLs (Attachment 22).

The next meeting, NAC/AEGL-25, has been set for June 17-19, 2002, in Piscataway, N.J. (Rutgers University, hosted by Bob Snyder). More information about the lodging will be provided soon by Po-Yung Lu. The tentative NAC/AEGL-26 meeting is proposed for September 10-12, 2002, in Washington, D.C.

The meeting highlights were prepared by Po-Yung Lu and Sylvia Talmage, Oak Ridge National Laboratory, with input from the respective chemical managers.

LIST OF ATTACHMENTS

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

Attachment 1. NAC/AEGL-24 meeting agenda
Attachment 2. NAC/AEGL-24 attendee list
Attachment 3. TSDs reviewed at February NAS/COT/AEGL meeting
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PROPOSED → INTERIM

NAC/AEGL Meeting 25: June 17-19,2002

Chemical: CARBON TETRACHLORIDE **CAS Reg. No.:** 56-23-5

NAC Member	AEGL 1	AEGL 2	AEGL 3	AEGL 3 ‡	NAC Member	AEGL 1	AEGL 2	AEGL 3	AEGL 3 ‡
George Alexeeff	N	P	Y N	Y	Nancy Kim	Y	Y	Y N	Y
Steven Barbee	Y	Y	Y Y	N	Loren Koller	Y	Y	Y Y	N
Lynn Beasley	A	A	A A	A	Glenn Leach	A	A	A A	A
David Belluck	Y	Y	Y Y	N	Mark McClanahan	Y	Y	Y Y	N
Robert Benson	Y	Y	Y P	Y	John Morawetz	A	Y	N N	Y
Jonathan Borak	A	A	A A	A	Richard Niemeier	Y	Y	Y Y	P
William Bress	Y	Y	Y P	Y	Marinelle Payton	A	A	A A	A
George Cushmac	Y	Y	Y Y	N	Zarena Post	A	A	A A	A
Al Dietz	A	A	A A	A	George Rodgers	Y	Y	N N	Y
Ernest Falke	Y	Y	Y N	Y	George Rusch, Chair	Y	Y	Y P	Y
Larry Gephart	Y	Y	Y Y	P	Robert Snyder	Y	Y	Y Y	N
John Hinz	Y	N	Y Y	N	Thomas Sobotka	A	A	A A	A
Jim Holler	Y	Y	Y N	Y	Kenneth Still	A	A	A A	A
Thomas Hornshaw	Y	Y	Y N	Y	Richard Thomas	A	A	A	A
Doan Hansen	A	A	A		TALLY	17/19	17/18	9/16	10/17

16/18

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1 *	25 ,( )	16 ,( )	12 ,( )	6.9 ,( )	5.2 ,( )
AEGL 2	114 ,( )	74 ,( )	56 ,( )	32 ,( )	24 ,( )
AEGL 3 ‡	350 ‡ 230 ,( )	230 ,( )	170 ,( )	99 ,( )	75 ,( )

* REAFFIRM PROPOSED AEGL VALUES POST PUBLIC COMMENT (ER) 2/15/2002

AEGL-3 ☆ 350 230 170 99 75

AEGL 1 Motion: Snyder **Second:** Hinz

AEGL 2 Motion: Falke **Second:** McClanahan

AEGL 3 Motion: Hinz ‡ Rodgers **Second:** Koller ‡ Benson

→ ☆ HORNSHAW NIEMEIER

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/18/02

→ AEGL-3 MTIM THAT CARRIED

RAISE TO INTERIM (RUSCH / BRESS) → UNANIMOUS

* PROPOSED → INTERIM

NAC/AEGL Meeting 25: June 17-19,2002

Chemical: CHLORINE **CAS Reg. No.:** 7782-50-5

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff				Nancy Kim			
Steven Barbee				Loren Koller			
Lynn Beasley	A	A	A	Glenn Leach			
David Belluck				Mark McClanahan			
Robert Benson				John Morawetz			
Jonathan Borak	A	A	A	Richard Niemeier			
William Bress				Marinelle Payton			
George Cushmac				Zarena Post	A	A	A
Al Dietz				George Rodgers			
Ernest Falke				George Rusch, Chair			
Larry Gephart				Robert Snyder			
John Hinz				Thomas Sobotka	A	A	A
Jim Holler				Kenneth Still	A	A	A
Thomas Hornshaw				Richard Thomas			
Doan Hansen	A	A	A	TALLY			

* UNANIMOUS BY SHOW OF HANDS

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )

AEGL 1 Motion: McClanahan **Second:** Hinz

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

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

Approved by Chair: [signature] **DFO:** [signature] **Date:** 6/18/02

Proposed → Interim

NAC/AEGL Meeting 25: June 17-19,2002

Chemical: CHLORINE DIOXIDE **CAS Reg. No.:** 10049-04-4

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff				Nancy Kim			
Steven Barbee				Loren Koller			
Lynn Beasley	A	A	A	Glenn Leach			
David Belluck				Mark McClanahan			
Robert Benson				John Morawetz			
Jonathan Borak	A	A	A	Richard Niemeier			
William Bress				Marinelle Payton			
George Cushmac				Zarena Post	A	A	A
Al Dietz				George Rodgers			
Ernest Falke				George Rusch, Chair			
Larry Gephart				Robert Snyder			
John Hinz				Thomas Sobotka	A	A	A
Jim Holler				Kenneth Still	A	A	A
Thomas Hornshaw				Richard Thomas			
Doan Hansen	A	A	A	TALLY			

Raise to Interim - (REVISE EXPLANATION -) UNANIMOUS (2/15/00 FR)

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

AEGL 1 Motion: McClanahan **Second:** Hinz

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

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

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/17/02

☆ PROPOSED → INTERIM

Appendix E

NAC/AEGL Meeting 25: June 17-19,2002

Chemical: PROPYLENE OXIDE **CAS Reg. No.:** 75-56-9

NAC Member	AEGL 1	AEGL 2 ☆	AEGL 3 ☆	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	*N ‡N			Nancy Kim	P Y		
Steven Barbee	Y Y			Loren Koller	Y Y		
Lynn Beasley	A A	A	A	Glenn Leach	A A	A	A
David Belluck	A Y			Mark McClanahan	Y Y		
Robert Benson	P Y			John Morawetz	N N		
Jonathan Borak	A A	A	A	Richard Niemeier	N N		
William Bress	N N			Marinelle Payton	A A	A	A
George Cushmac	Y Y			Zarena Post	A A	A	A
Al Dietz	A A	A	A	George Rodgers	N N		
Ernest Falke	Y Y			George Rusch, Chair	Y Y		
Larry Gephart	Y Y			Robert Snyder	P Y		
John Hinz	Y Y			Thomas Sobotka	A	A	A
Jim Holler	Y Y			Kenneth Still	A	A	A
Thomas Hornshaw	P Y			Richard Thomas	A	A	A
Doan Hansen	A	A	A	TALLY	9/14 14/19		

☆ Proposed → Interim UNANIMOUS

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1 *‡	110 ,( )	110 ,( )	60 ,( )	19 ,( )	11 ,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

*REAFFIRM AEGL-1 + ELEVATE TO INTERIM
‡RE-VOTE ON MOTION

AEGL 1 Motion: Barbee **Second:** Koller

AEGL 2 Motion: ☆ Rodgers **Second:** McClanahan

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

Approved by Chair: [signature] **DFO:** [signature] **Date:** 6/18/02

NAC/AEGL Meeting 25: June 17-19,2002

Chemical: HYDROGEN FLUORIDE **CAS Reg. No.:** 7664-39-3

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff		N	Y	Nancy Kim	A	A	A
Steven Barbee		Y	Y	Loren Koller		Y	Y
Lynn Beasley	A	A	A	Glenn Leach	A	A	A
David Belluck		Y	Y	Mark McClanahan		Y	Y
Robert Benson		Y	Y	John Morawetz		N	Y
Jonathan Borak	A	A	A	Richard Niemeier		N	Y
William Bress		Y	Y	Marinelle Payton	A	A	A
George Cushmac		Y	Y	Zarena Post	A	A	A
Al Dietz	A	A	A	George Rodgers		P	P
Ernest Falke		Y	Y	George Rusch, Chair		Y	Y
Larry Gephart		Y	Y	Robert Snyder		Y	Y
John Hinz		Y	Y	Thomas Sobotka	A	A	A
Jim Holler		Y	Y	Kenneth Still	A	A	A
Thomas Hornshaw		Y	Y	Richard Thomas	A	A	A
Doan Hansen	A	A	A	TALLY		14/17	17/17

MODIFICATION FOLLOWING NAS PEER REVIEW COMMENTS

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	12 ,( )
AEGL 3	,( )	,( )	,( )	,( )	22 ,( )

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

AEGL 2 Motion: HINZ **Second:** HINZ

AEGL 3 Motion: FALKE **Second:** FALKE

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/17/02

NAC/AEGL Meeting 25: June 17-19,2002

Chemical: HYDROGEN CHLORIDE **CAS Reg. No.:** 7647-01-0

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

MODIFICATION FOLLOWING NAS PEER REVIEW COMMENTS

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	11 ,( )	11 ,( )
AEGL 3	,( )	,( )	,( )	,( )	26 ,( )

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

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

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

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/17/02

NAC/AEGL Meeting 25: June 17-19,2002

Chemical: TETRACHLOROETHYLENE **CAS Reg. No.:** 127-18-4

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	N		N	Nancy Kim	A		A
Steven Barbee	Y		Y	Loren Koller	Y		Y
Lynn Beasley	A	A	A	Glenn Leach	A		A
David Belluck	Y		Y	Mark McClanahan	Y		Y
Robert Benson	Y		N	John Morawetz	N		N
Jonathan Borak	A	A	A	Richard Niemeier	Y		Y
William Bress	Y		Y	Marinelle Payton	A		A
George Cushmac	Y		Y	Zarena Post	A	A	A
Al Dietz	A		A	George Rodgers	Y		P
Ernest Falke	Y		N	George Rusch, Chair	Y		Y
Larry Gephart	Y		Y	Robert Snyder	Y		Y
John Hinz	P		P	Thomas Sobotka	A	A	A
Jim Holler	Y		Y	Kenneth Still	A	A	A
Thomas Hornshaw	Y		Y	Richard Thomas	A		A
Doan Hansen	A	A	A	TALLY	15/16		12/16

Revisit post NAS peer review comments.

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	35 ,( )	35 ,( )	35 ,( )	35 ,( )	35 ,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	1600 ,( )	1600 ,( )	1200 ,( )	580 ,( )	410 ,( )

AEGL 1 Motion: Snyder **Second:** McClanahan

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

AEGL 3 Motion: Snyder **Second:** McClanahan

Approved by Chair: [signature] **DFO:** Paula Tolin **Date:** 6/17/02

NAC/AEGL Meeting 25: June 17-19,2002

Chemical: Nickel Carbonyl **CAS Reg. No.:** 13463-39-3

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

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR ,( )	NR ,( )	NR ,( )	NR ,( )	NR ,( )
AEGL 2	0.13 ,( )	0.056 ,( )	0.028 ,( )	0.0070 ( )	0.0035 ,( )
AEGL 3	,( )	,( )	,( )	,( )	0.020 ,( )

NR: NOT RECOMMENDED. NUMERIC VALUES FOR AEGL-1 ARE NOT RECOMMENDED BECAUSE (1) THE LACK OF AVAILABLE DATA, & (2) AN INADEQUATE MARGIN OF SAFETY EXISTS BETWEEN THE DERIVED AEGL-1 & -2. ABSENCE OF an AEGL-1 does not imply the absence of adverse effects.

AEGL 1 **Motion:** Falke **Second:** NIEMEIER Exposure below the AEGL-2 is within

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

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

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/18/02

NAC/AEGL Meeting 25: June 17-19,2002

Chemical: Iron pentacarbonyl **CAS Reg. No.:** 13463-40-6

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff				Nancy Kim			
Steven Barbee				Loren Koller			
Lynn Beasley	A	A	A	Glenn Leach			
David Belluck				Mark McClanahan			
Robert Benson				John Morawetz			
Jonathan Borak	A	A	A	Richard Niemeier			
William Bress				Marinelle Payton			
George Cushmac				Zarena Post	A	A	A
Al Dietz				George Rodgers			
Ernest Falke				George Rusch, Chair			
Larry Gephart				Robert Snyder			
John Hinz				Thomas Sobotka	A	A	A
Jim Holler				Kenneth Still	A	A	A
Thomas Hornshaw				Richard Thomas			
Doan Hansen	A	A	A	TALLY			

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	0.024 ,( )
AEGL 3	,( )	,( )	,( )	,( )	0.073 ,( )

Unanimous to adopt 4 + 8 hr. Values.

AEGL 1 Motion: McClanahan **Second:** Niemeier

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

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

Approved by Chair: [signature] **DFO:** [signature] **Date:** 6/18/02

NAC/AEGL Meeting 25: June 17-19,2002

Chemical: Allyl amine **CAS Reg. No.:** 107-11-9

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

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.42, ( )	0.42, ( )	0.42, ( )	0.42, ( )	0.42, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )

AEGL 1 Motion: Benson **Second:** McClanahan

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

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

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/19/02

NAC/AEGL Meeting 25: June 17-19,2002

Chemical: ALLYL ALCOHOL **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	Nancy Kim	Y	Y	N
Steven Barbee	Y	Y	Y	Loren Koller	Y	P	Y
Lynn Beasley	A	A	A	Glenn Leach	A	A	Y
David Belluck	Y	Y	Y	Mark McClanahan	Y	Y	Y
Robert Benson	Y	Y	Y	John Morawetz	A	A	A
Jonathan Borak	A	A	A	Richard Niemeier	Y	Y	Y
William Bress	Y	Y	Y	Marinelle Payton	A	A	A
George Cushmac	Y	~~A~~ Y	Y	Zarena Post	A	A	A
Al Dietz	A	A	A	George Rodgers	Y	Y	Y
Ernest Falke	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Larry Gephart	Y	Y	Y	Robert Snyder	A	A	A
John Hinz	Y	Y	Y	Thomas Sobotka	A	A	A
Jim Holler	Y	Y	Y	Kenneth Still	A	A	A
Thomas Hornshaw	Y	Y	Y	Richard Thomas	A	A	A
Doan Hansen	A	A	A	TALLY	16/16	15/15	16/16

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	2.1 ,( )	2.1 ,( )	2.1 ,( )	2.1 ,( )	2.1 ,( )
AEGL 2	4.2 ,( )	4.2 ,( )	4.2 ,( )	4.2 ,( )	4.2 ,( )
AEGL 3	130 ,( )	130 ,( )	67 ,( )	17 ,( )	8.3 ,( )

AEGL 1 Motion: Hinz **Second:** Belluck

AEGL 2 Motion: Benson **Second:** Koller

AEGL 3 Motion: Barbee **Second:** Hinz

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 6/19/02