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

September 9-11, 2002

Final Meeting-26 Highlights

US EPA
1201 Constitution Ave N.W., Rm 1117, Washington, DC 20460

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.

Roger Garrett reported on the July NRC/Committee on Toxicology/AEGL Subcommittee (COT/AEGL) meeting. The COT/AEGL is pleased with the quality of the documents and intends to more rapidly facilitate both the publication of their interim report and approval of AEGL values. Roger then commented on the issue raised by John Morawetz regarding a disclaimer for the use of AEGLs in workplace situations. Roger pointed out that the NAC/AEGL committee should not emphasize when the AEGL values should or should not be used. This is a decision for the various stakeholders (i.e. risk management; not the purview of this science-based committee). It is not likely for the NAC/AEGL to be able to define or predict all scenarios that may be amenable to the use of AEGL values. This issue will be part of the larger NAC/AEGL process development. Roger noted that the key committee members interested in this issue will meet for lunch on this date to strategize how to handle this.

As a follow-up to the NAC/AEGL-25 meeting, Susan Ripple, American Chemistry Council liaison to NAC/AEGL, submitted four studies on carbon tetrachloride (Attachment 1) by providing paper copies of the studies referred to during the NAC/AEGL-25 meeting. George Alexeeff noted that for the AEGL-1, a LOAEL was used instead of the NOAEL (as per the SOP) and the write-up should include the justification for this in the TSD. John Morawetz sent his comments to Po-Yung Lu prior to the meeting. He requested that all votes, including those that failed to pass values, be included in the record. A motion was made by Mark McClanahan and seconded by Richard Thomas to accept the draft meeting highlights with the above-noted changes. The motion passed unanimously by voice vote. Nancy Kim requested that the revised highlights be distributed to the NAC/AEGL members.

The revised highlights of NAC/AEGL-25 are attached (Appendix A) and have been distributed to NAC/AEGL. The highlights of the NAC/AEGL-26 meeting are presented below along with the meeting agenda (Attachment 2) and the attendee list (Attachment 3). The subject categories of the highlights do not necessarily follow the order listed in the NAC/AEGL-26 agenda.

TECHNICAL ISSUE DISCUSSIONS

AEGL-1 Characterization and LOA/Odor Issues:

1. Review of Characterization of AEGL-1 by Richard Thomas

Richard Thomas gave an overview of the history (Attachment 4) and role of relevant limits including pre-1990 Emergency Exposure Limits developed or approved by the National Research Council (NRC) in cooperation with other agencies. These included 1961 Air Force-NRC/COT Emergency Tolerance Limits or ETLs; 1964 AIHA-NRC/COT Emergency Exposure Limits or EELs, which in the early 1980s became Emergency Exposure Guidance Levels or EEGLs; Ceiling Exposure Limits (CELs) for non-emergency use which became Ceiling Exposure Guidance Levels (CEGLs); and, in 1986, Short-term Public Emergency Guidance Limits (SPEGLs). In contrast to some other guidelines, SPEGLs take sensitive populations into consideration. Richard pointed out that the CEGL-1 covers the level of odor detectability as defined by smell, taste, sight or sensations (mild sensory irritation). The ERPG-1 also considers objectionable odor, whereas with the AEGL-1, odor has been inconsistently used. In general, development of emergency planning guidance level-1 has often been referred to as a level of detection or notification. Odor has been addressed differently by various groups.

2. Application of Level of Odor Annoyance (LOA) to AEGL-1 by Marc Ruijten ("Annoyance" was changed to "Awareness" as the meeting progressed)

Marc Ruijten outlined briefly the application of AEGL values in aspects of prevention and mitigation; preparedness; and response in emergency situations (Attachment 5). He then explained why odor should be considered as an AEGL-1 endpoint. Marc pointed out that odor should be used as an AEGL-1 endpoint because it fits the definition of an AEGL-1. Furthermore, the public may associate odor with toxicity which, in the absence of information, can lead to hyper-vigilance and arousal, resulting in a cascade of autonomic symptoms, including altered respiration (often to minimize odor perception), increases in heart rate, feelings of dizziness or throat or chest tightness. These very same effects that are generated out of the individual's concern are then perceived as and attributed to a direct physiological effect of the chemical exposure, unless information to the contrary is provided from a trusted source.

Marc then presented information about the science of odor detection. Four major attributes are used to characterize the sensory perception of odorants: detectability, intensity, hedonic tone, and odor quality. He presented information about the methodology for obtaining standardized responses from small populations of individuals (odor panels) for these four odor attributes. Test subjects are selected by their response to the reference material, *n*-butanol. For test chemicals, an OT_{50} is used. OT_{50} is defined as the point where the probability of odor detection is 50% of the odor panel. He noted that olfactory responses of individuals in the general population vary with age, gender and health status, smoking behavior, personality, and educational background;

training may contribute in some degree to the ability to assess an odor. Marc also presented results of odor tests in which bias was presented prior to testing. In these cases panel members with positive information about the chemical to which they were exposed reported far fewer specific somatic symptoms than did panel members who were uninformed or who were negatively biased prior to exposure. The frequency of symptoms reported by the latter two groups was very similar.

Annoyance is the complex of human reactions that occurs as a result of exposure to an ambient stressor that, once perceived, causes negative cognitive appraisal that requires a degree of coping. Any unusual odor not common to the normal "odor landscape" will have the potential to cause awareness in individuals, the probability that this happens increases with odor concentration. A distinct odor may go unnoticed, but a strong odor will probably be detected. The question is at what level odor awareness becomes significant in emergency response. Marc described a stepwise procedure to derive a Level of significant Odor Awareness (LOA). This is a change in terminology from the LOA (Level of Annoyance) used during previous discussions of odor. This procedure applies the current knowledge and data available, and makes a best estimate for whatever knowledge or data are lacking, much like what has been done for other endpoints.

1. Determine or obtain the odor detection threshold.

2. Determine or derive the concentration range where a distinct to strong odor is perceived.
For example the concentration that leads to perception of a distinct odor (I=3) equals 11.8 x OT_{50}.
A concentration of 31.7 x OT_{50} leads to perception of a strong odor (I=4). This means that 12-32 odor units generate distinct to strong odor perception in laboratory conditions.

3. Correct for field circumstances (distraction, peak exposure).
Adjustment for distraction and peak exposure lead to a correction factor of 4 / 3 = 1.33 from laboratory to time-weighed average field conditions. It follows that 16-42 odor units will lead to a distinct–strong odor perception by the general population under field conditions.

4. Select and apply the Level of significant Odor Awareness (LOA).

Marc finished the discussion by suggesting that the NAC/AEGL address the following questions and statements. Is LOA a valid endpoint for the AEGL-1? If acceptable, decide on an intensity level (distinct vs strong) and application methodology. If odor is not an acceptable endpoint, develop a LOA reference level in addition to the AEGL-1.

3. Critique of LOA approach by Pamela Dalton (Monell Chemical Senses Center, Philadelphia, PA)

Awareness of the presence of unknown or unwanted odors in the environment can elicit vigilance, concern and a variety of stress-mediated somatic responses. This observation is supported by the experiences of emergency response personnel as well as evidence from field and controlled laboratory studies. For some chemicals, these effects will occur at levels that are well below currently proposed AEGL-1 values and may result in a public request for information or action at

exposure concentrations for which emergency response agencies have little or no information to provide. Given this concern, it was proposed to develop a "Level of Odor Awareness" (LOA) for each chemical that could be used as the basis for the AEGL-1 level, provided that such a value was lower than the concentrations at which other health-based effects might occur.

There is an important need to provide information about odor to emergency responders, as in most cases, the odor of a chemical will be the first warning of exposure and will frequently generate some level of concern among the public. Thus, there is ample reason to develop a method to determine concentrations of chemicals that will lead to odor awareness. However, there are caveats to the methods proposed for developing a LOA based on odor detection threshold data without empirical verification of such values, and more importantly, there are significant reasons to be concerned about the use of such information as the basis for a health-based guideline such as AEGL-1. It seems appropriate to ask that some validation of these proposed values (either field-based or laboratory-based) for a subset of chemicals be performed in order to ensure their empirical relevance for emergency response.

A concern of greater importance, however, relates to the application of such values as a basis for AEGL-1 levels. For example, at a concentration above the level of significant odor awareness, the frequency of adverse effects and complaints will begin to rise. However, it should be noted that the effects associated with 'odor awareness' represent indirect or 'stress-mediated' effects of chemical exposure. With increasing concentrations, however, a threshold will be crossed whereupon individuals may begin to experience direct or 'biologically-based' effects of chemical exposure. Provided these latter effects are transient, reversible upon cessation of exposure and non-incapacitating, they fulfill the criteria as appropriate endpoints for AEGL-1 levels, as defined. If, however, the threshold for AEGL-1 levels is reduced to the level of odor awareness, all stress- and biologically-mediated effects that occur below AEGL-2 would be subsumed into one category of response. If so, the category of AEGL-1 would span a fairly wide concentration range, from a level that elicited perceived risk from odor awareness to levels that directly elicited biologically-based adverse responses. Basing AEGL-1 values on psychogenic and/or stress-mediated responses introduces discontinuity between AEGL-1 basis and other AEGL levels. A LOA-based AEGL-1 would represent the threshold for the perception of toxicity, whereas the AEGL-2 and 3 values would represent the threshold for potential and actual toxicity. Thus, while there are compelling reasons to develop and provide 'odor awareness' values to emergency responders for their use in chemical emission management, there are equally important reasons that such values not be used as the basis for AEGL-1 levels.

4. NAC/AEGL Committee Discussion

The discussion took several paths, raising both questions and uses for the AEGL-1. Are we shifting the AEGL-1 definition again? We must make a decision to use odor or health based values for AEGL-1. How are AEGL-1 values to be used? Jim Holler pointed out that AEGL values are used in various scenarios, for example, AEGL-1 is used in public notification where the chemical is detected but no adverse health effects should occur. Others, including Jonathan Borak, suggested that AEGL-1 values be assigned subcategories, e.g, a and b designations with an

explanation as to whether this is a warning/detection or a health based property. The NAC/AEGL needs to consider risk communication and give serious thoughts to the users.

Glenn Leach and John Hinz considered that the U.S. Army and U.S. Air Force could produce "Fact Sheets: on all relevant AEGL chemicals of concern to them. Richard Neimeier noted there are already numerous agencies producing fact sheets: CDC, ATSDR, Counter Terrorism Response (over 500 chemicals), plus those with medical details, etc. There is an emergency response data base that could be "hot-linked" to the values. Finally, George Rusch raised the question, "How do we foster the use of AEGL values?" Suggestions from the NAC/AEGL included formal meeting with the stakeholders, such as Bob Snyder's workshop at Rutgers. The NAC/AEGL could also use the Homeland Security training as a medium. In addition, George Rusch asked for volunteers to form a subcommittee to address this question, including the LOA-AEGL-1 relationship and report back at the December meeting; he also suggested bringing the issue up with the COT/AEGL. A second "Fact Sheet"subcommittee was identified to address the initial requests from the DoD representatives to consider the desirability of developing short summaries of the AEGL values and the toxic properties associated with over exposure.

Concerning the LOA, the NAC/AEGL decided not to use the Level of significant Odor Awareness at either Intensity level 3 (16 x OT_{50}) or 4 (42 x OT_{50}) to establish AEGL-1 values. However, the committee voted to provide the LOA value using Intensity level 3 for all chemicals for which an OT_{50} or an acceptable estimate is available because this is useful information for the emergency responders. The motion was made by Mark McClanahan and seconded by Richard Neimeier. The motion carried. (YES: 20; NO: 1; Abstain: 0) (Appendix B).

AEGL Ratios Approach
Tom Hornshaw

Tom Hornshaw presented the results of an analysis he conducted of the ratios between the AEGL-3 and AEGL-2 and between the AEGL-2 and AEGL-1 values developed for all chemicals as of June 2002 (Attachment 6). This analysis was a follow-up to an earlier review conducted by Mark McClanahan, who attempted to determine a default divisor for extrapolating from a higher-level AEGL to the next lower-level AEGL when toxicological data are insufficient to derive the lower-level AEGLs. Mark found that both comparisons resulted in average ratios for all AEGL time periods slightly greater than 3. Tom's review differed from Mark's, however, in that he deleted certain values from the data sets whereas Mark calculated ratios for all chemicals having both AEGL values. Tom tried to eliminate all values that were not derived from toxicological data specific to a particular AEGL level and exposure time for a chemical, deleting all values that were flat-lined, derived as one-third of a higher level AEGL, or derived from potency relative to another chemical. This resulted in ratio data sets of 59 for the AEGL-3 to AEGL-2 comparison and 19 for the AEGL-2 to AEGL-1 comparison for the 84 chemicals available. These data sets were then subjected to routine statistical analyses. For the AEGL-3 to AEGL-2 comparisons, the mean ratio for all time periods was slightly greater than 5 (range 5.13-5.34) and the median was greater than 3 (range 3.05-3.67). None of the data sets were found to be normally or log normally

distributed, therefore 95th percentiles were determined nonparametrically, with values from 13.7 for the 30-minute ratios (range 1.46-36.4) to 18.7 for the 8-hour ratios (range 1.16-40.8). In contrast, the AEGL-2 to AEGL-1 ratio statistics were higher for all measures, with the means ranging from 12.3 (8-hour ratios) to 25.5 (10-minute ratios), the medians ranging from 3.19 (8-hour ratios) to 4.13 (10-minute ratios), and the 95th percentiles (also determined nonparametrically) ranging from 27.1 (8-hour ratios) to 113.6 (10-minute ratios).

Tom then discussed some of the highlights of the review. All data sets were skewed, and box plots of the data sets revealed three main outliers for the AEGL-3 to AEGL-2 ratios and one extreme outlier for the AEGL-2 to AEGL-1 ratios. For the AEGL-3 to AEGL-2 comparisons, the outliers were bromine (ratios for all time periods greater than 35), Otto Fuel (2 ratios greater than 32), and sulfur mustard (3 ratios greater than 20.5); the outlier for the AEGL-2 to AEGL-1 comparisons was hydrogen sulfide (all ratios greater than 160). A review of the toxicological data for these outliers revealed that in all cases the higher-level AEGL was derived from animal data and the lower-level AEGL from human data, and the human endpoints were all neuropsychological and/or subjective in nature (headache, nausea, irritation, odor, etc.). Tom suggested that this implies that for certain chemicals there will be toxicological endpoints in humans that will not be predictable from the animal toxicity database. He also suggested that if the Committee wishes to be protective of these types of human endpoints when extrapolating AEGL values from higher-level AEGLs, this analysis points to an extrapolation divisor greater than the value of 3 used in the past. He finished his presentation with four recommendations: if a default divisor is adopted for AEGL-3 to AEGL-2 extrapolations, this value should be at least 19 (greater than all of the 95th percentiles determined for the 5 time periods); no default divisor is appropriate at this time for 10-minute AEGL-2 to AEGL-1 extrapolations (too much uncertainty with only 8 comparisons available); if a default divisor is adopted for the other time periods for AEGL-2 to AEGL-1 extrapolations, this value should be at least 28 (greater than all of the 95th percentiles determined for these 4 time periods); and no extrapolation from AEGL-3 to AEGL-1 is appropriate (too much uncertainty). Some discussion of the results occurred, with the NAC/AEGL generally concurring that, for some chemicals, animal data will be insufficient to predict neuropsychological endpoints in humans. There was not general agreement, however, that a default divisor for extrapolation to lower-level AEGLs when toxicological data are sparse or lacking for that level is appropriate at this time.

Acute Toxicity Threshold for Land Use Planning
Annick Pichard

Annick Pichard made a presentation based on the final report of the Ministry of Ecology and sustainable Development, prepared by National Institute for the Industrial Environment and Risks (INERIS). This is a consensus report on French procedure to set an acute toxicity threshold in the context of controlling urban development or land-use planning. She used vinyl chloride as an example to set the toxicity threshold values because it had not been previously examined for its acute toxicity as it is a carcinogenic chemical for humans chronically exposed at low concentrations. She also noted that the acute toxicity values are established in a regulatory

context (European Seveso II Directive 1996). There is a five-step procedure involved in establishing the acute toxicity values: (1) review official Temporary Exposure Emergency Limits of Vinyl chloride; (2) conduct a toxicity literature review of vinyl chloride for humans and animals; (3) analyze lethal and non-lethal toxicity data; and (4) establish the acute toxicity values. The report adopted the following acute toxicity values as summarized in the table:

(1). Lethal Effects Thresholds

Time (minutes)	Concentration	
	mg/m^3	ppm
1	1,561,167	603,000
10	608,415	235,000
20	455,664	176,000
30	385,761	149,000
60	289,968	112,000

(2). Irreversible Effects Threshold: Not established.

The Health Canada Existing Substances Program - Relevance to AEGLs

Bettie Meek

Under the *Canadian Environmental Protection Act* (*CEPA*), which was first enacted in 1988, Health Canada assesses the potential risks to public health posed by existing substances. As required by the legislation, detailed health and environmental assessments have been completed within the mandated time frames for a total of 69 entries on the first (PSL1) and second (PSL2) Priority Substances Lists.

The mandate of the program has recently been expanded, as a result of renewal of the legislation. In addition to the continuing requirement to establish and assess lists of Priority Substances, *CEPA '99* requires that the Ministers of Health and Environment complete **"**categorization" of all of the 23,000 substances on the Domestic Substances List by September 2006, with subsequent screening and full assessment, where warranted. This iterative approach to priority setting for risk management for all existing substances in Canada is precedent setting internationally.

Robust proposals for categorization of substances with respect to potential impact on human health have been developed and a pilot phase to conduct screening assessments for 123 substances. The nature of approach to and progress on these initiatives will be reviewed, with particular emphasis on relevance and potential for interface in the development of AEGLs.

The potential relevance of guidance on the use of kinetic and dynamic data to replace default values in quantitative extrapolations for inter-species differences and human variability in dose response assessment developed in a project of the International Programme on Chemical Safety (IPCS) initiative on *Harmonisation of Approaches to the Assessment of Risk from Exposure to Chemicals* will also be addressed.

REVIEW AND RESOLUTION OF COT/AEGL COMMENTS

Nerve agents (GA, GB, GD, GF, and VX)
CAS Reg. No. GA: 77-81-6; GB: 107-44-8; GD: 96-64-0, GF:329-99-7, and VX: 50782-69-9.

Chemical Managers: John Hinz for G-agents, DoD/AF
Glenn Leach for VX, DoD/Army
Staff Scientist: Annetta Watson, ORNL

As planned at NAC/AEGL-25, the Nerve Agent Development Team updated the NAC/AEGL on its responses to, and clarified the commentary received from, the COT/AEGL peer review of the nerve agent TSD as expressed in the COT/AEGL *7th Interim Report*. John Hinz, Chemical Manager for G-agents, outlined the agenda for the Committee's consideration (Attachment 7). Glenn Leach, Chemical Manager for VX, reviewed the chronology and history of the development of the nerve agent TSDs while reminding the NAC/AEGL of its long effort to complete these risk assessments (Attachment 8).

Following these introductory remarks, Annetta Watson presented information detailing the Development Team's response to COT/AEGL comments for nerve agents in their 7th Interim Report, as well as their 10th meeting (Woods Hole, July 2002) (Attachment 9). A significant recommendation by the COT/AEGL was that, since the G-agents and VX share a common mechanism of action, these two TSDs be merged into one, large, nerve agent document with redundancies eliminated. A key issue for the nerve agent VX was the value of the Relative Potency (RP) factor used for deriving AEGL values for VX based on toxicity information for GB. The COT/AEGL agreed with the RP approach and concept, but they believed that basing the RP on historical rabbit miosis data by Callaway and Dirnhuber (1971) was limited by analytical capabilities of the time, and might not be the best comparison for estimating human toxicity. The COT/AEGL instead recommended that the Development Team and the NAC/AEGL committee investigate the possibility of basing the RP on existing human data. The COT/AEGL further recommended no change in the existing modifying factor (MF) of 3 for nerve agent VX. Annetta Watson presented data from two studies by Grob and Harvey (1958) and Sidell and Groff (1974), which compared the ability of GB and VX to inhibit red blood cell acetylcholinesterase activity in human volunteers. These studies indicated that VX was approximately 4 times more toxic than GB; thus, a RP of 4 was proposed for derivation of AEGLs for VX. This issue was discussed at length, and incorporated the technical analysis summarized in the Development Team's White Paper, "Considering AEGL Significance of Non-Cholinergic Mechanisms," sent to all members of the NAC/AEGL prior to the 26th meeting (Attachment 10). The application of a RP of 4, with

a MF of 3, was approved by the NAC/AEGL for use in developing all final AEGL values for agent VX from available toxicity data for agent GB. The motion was made by Loren Koller, seconded by John Hinz, and approved by the NAC/AEGL [YES: 13; NO: 3; Abstain: 5] (Appendix C). The approved AEGL values are summarized below.

Agent GA (Tabun) (ppm) [mg/m^3]

	10 min	30 min	60 min	4 hr	8 hr
AEGL 1	0.0010 [0.0069]	0.00060 [0.0040]	0.00042 [0.0028]	0.00021 [0.0014]	0.00015 [0.0010]
AEGL 2	0.013 [0.087]	0.0075 [0.050]	0.0053 [0.035]	0.0026 [0.017]	0.0020 [0.013]
AEGL 3	0.11 [0.76]	0.057 [0.38]	0.039 [0.26]	0.021 [0.14]	0.015 [0.10]

Agent GB (Sarin) (ppm) [mg/m^3]

	10 min	30 min	60 min	4 hr	8 hr
AEGL 1	0.0012 [0.0069]	0.00068 [0.0040]	0.00048 [0.0028]	0.00024 [0.0014]	0.00017 [0.0010]
AEGL 2	0.015 [0.087]	0.0085 [0.050]	0.0060 [0.035]	0.0029 [0.017]	0.0022 [0.013]
AEGL 3	0.064 [0.38]	0.032 [0.19]	0.022 [0.13]	0.012 [0.070]	0.0087 [0.051]

Agent GD (Soman) (ppm) [mg/m^3]

	10 min	30 min	60 min	4 hr	8 hr
AEGL 1	0.00046 [0.0035]	0.00026 [0.0020]	0.00018 [0.0014]	0.000091 [0.00070]	0.000065 [0.00050]
AEGL 2	0.0057 [0.044]	0.0033 [0.025]	0.0022 [0.018]	0.0012 [0.0085]	0.00085 [0.0065]
AEGL 3	0.049 [0.38]	0.025 [0.19]	0.017 [0.13]	0.0091 [0.070]	0.0066 [0.051]

Agent GF (ppm) [mg/m^3]

	10 min	30 min	60 min	4 hr	8 hr
AEGL 1	0.00049 [0.0035]	0.00028 [0.0020]	0.00020 [0.0014]	0.00010 [0.00070]	0.000070 [0.00050]
AEGL 2	0.0062 [0.044]	0.0035 [0.025]	0.0024 [0.018]	0.0013 [0.0085]	0.00091 [0.0065]
AEGL 3	0.053 [0.38]	0.027 [0.19]	0.018 [0.13]	0.0098 [0.070]	0.0071 [0.051]

Agent VX (ppm)[mg/m^3]

	10 min	30 min	60 min	4 hr	8 hr
AEGL 1	0.000052 [0.00057]	0.000030 [0.00033]	0.000016 [0.00017]	0.0000091[0.00010]	0.0000065 [0.000071]
AEGL 2	0.00065 [0.0072]	0.00038 [0.0042]	0.00027 [0.0029]	0.00014 [0.0015]	0.000095 [0.0010]
AEGL 3	0.0027 [0.029]	0.0014 [0.015]	0.00091 [0.010]	0.00048 [0.0052]	0.00035 [0.0038]

Boron Trifluoride
CAS Reg. No. 353-42-4

Chemical Manager: George Rusch, Honeywell
Staff Scientist: Claudia Troxel, ORNL

The discussion was tabled because Honeywell may consider conducting a no-effect level irritation study in responding to COT/AEGL review comments. However, George Aleexeff indicated that we may have the needed data in the TSD to develop AEGL-1 values for BF3.

Chlorine
CAS Reg. No. 7782-50-5

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

Sylvia Talmage reported on the preliminary comments from the COT/AEGL regarding chlorine (Attachment 11). These comments included the fact that the 8-hour AEGL-1 of 0.5 ppm and the 8-hour AEGL-2 of 0.71 ppm are basically the same number. The NAC/AEGL discussed the possibility of raising the 8-hour AEGL-2 to 1.0 ppm (based on the same study with an atopic individual) and lowering all AEGL-1 concentrations to 0.4 ppm (based on a study with asthmatic subjects). It was decided that, at this time, the NAC/AEGL will retain the present AEGL values and wait for the final COT/AEGL interim report. George Rodgers and George Alexeeff were asked to help draft a response to the COT/AEGL upon receipt of final comments.

HFE-7100
CAS Reg. No. 163702-07-6

Chemical Manager: George Rusch, Honeywell
Staff Scientist: Sylvia Talmage, ORNL

Sylvia Talmage reviewed the issues raised by the COT/AEGL regarding HFE-7100 (Attachment 12). The COT/AEGL decided that (1) there was no data for, and therefore no justification for, development of AEGL-1 values, (2) the cardiac sensitization study with beagles was not relevant to the AEGL-2, but tremors in dogs in the absence of the cardiac sensitization test might be considered an AEGL-2, and (3) the sparse lethality data for AEGL-3 would indicate that the AEGL-3 could be based on the highest non-lethal concentration with a ">" sign as a prefix. COT/AEGL also questioned the appropriateness of the interspecies uncertainty factor of 1, even when combined with a modifying factor of 2 (to account for the lack of human data). The majority of well-conducted studies available for HFE-7100 involve repeated exposures which the COT/AEGL did not consider relevant to acute exposures. Following discussion of the two acute studies and the five well-conducted repeat-exposure studies for HFE-7100, the NAC/AEGL agreed with the TSD staff scientist and Chemical Manager that data were available to develop

values for all AEGL classifications and that the present values should be retained. The ORNL staff scientist was asked to rewrite the basis for the AEGL-2, using a NOAEL for tremors in dogs in the absence of exogenous epinephrine (cardiac sensitization test).

Allylamine
CAS Reg. No. 107-11-9

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

A brief review of the issues raised by COT/AEGL and concerns of NAC/AEGL from NAC/AEGL-25 was presented by Chemical Manager, Loren Koller (Attachment 13). This is a continued discussion session since AEGL-1 values were approved as 0.42 ppm for all exposure time periods at NAC/AEGL-25.

The AEGL-2 values for 10-, 30-, and 60-minutes were set at 3.3 ppm. The concentration of 10 ppm was considered as the threshold for severe irritation for humans who were exposed to 2.5, 5.0, 10, or 14 ppm allylamine (Hine et al 1960). An UF of 3 was applied to account for human variability. For the 4- and 8-hour AEGL-2 values, rat data were used (Guzman et al 1961). Rats exposed to 40 ppm for 16 hours exhibited early cellular cardiovascular effects, which was considered the NOAEL. An n=1.7 was calculated from the cardiovascular data. An UF of 5 was applied rather than an UF of 3 for extrapolating cardiac toxicity between animals and humans because an UF of 3 would yield values approaching lethality from pulmonary lesions observed following exposure for 4-8 hours. An intraspecies UF of 10 was applied because the cardiotoxic response to allylamine among humans is undefined, and several sensitive populations could exist (diabetics, congestive heart failure). Thus, the AEGL-2 values for 4 and 8 hours are derived as1.8 and 1.2 ppm, respectively. A motion was made by Mark McClanahan and seconded by Richard Thomas to accept the above values. The motion passed unanimously [YES: 19; NO: 0; Abstain: 0](Appendix D).

The AEGL-3 values for 1, 4, and 8 hours were obtained using the respective LC_{01} values while the 10-minute and 30-minute AEGL values were derived from the 1 hour LC_{01} using the lethality threshold study in rats (Hine at al 1960). An n=0.85 was calculated from the LC_{50} data based on the same study. A total UF of 30 was applied: a UF of 10 for interspecies variability because of the lack of other species tested and a UF of 3 for human variability based on the steep dose-response curve. A motion was made to accept AEGL-3 values of 150 ppm (10 minutes), 40 ppm (30 minutes), 18 ppm (60 minutes), 3.5 ppm (4 hours), and 2.3 ppm (8 hours) by Richard Thomas and seconded by John Hinz. The motion passed unanimously [YES:19; NO: 0; Abstain: 0] (Appendix D).

Methyl Mercaptan
CAS Reg. No. 74-93-1

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

The discussion on the methyl mercaptan AEGL-1 was led by Cheryl Bast who noted that there were no data consistent with the definition of AEGL-1 available for this chemical (Attachment 14). In the absence of health effects data to develop AEGL-1 values, there was considerable discussion on use of a LOA. However, it was moved by Jonathan Borak and seconded by Ernie Falke to not adopt AEGL-1 values (and not use a LOA as an AEGL-1). The motion passed [YES: 15; NO: 6; Abstain: 0] (Appendix E). Further discussion centered on the use of the LOA as an informational number. An intensity level of 3 and the threshold at which 50% of the population would notice a distinct odor were used as defining factors. It was moved by Ernie Falke and seconded by Richard Thomas to append a LOA, defined as a Level of Odor Awareness of 0.0019 ppm (for any time period) to the TSD. The motion passed [YES: 17; NO: 3; Abstain: 1] (Appendix E). Marc Ruijten will provide information on how the LOA was developed and a table that illustrates the number of people effected at each level of discomfort. The NAC/AEGL decided that a table on LOA development will be added to the back of the TSD and the LOA will appear as a footnote to the summary table.

Perchloromethylmercaptan
CAS Reg. No. 594-42-3

Chemical Manager: Zarena Post, Texas
Staff Scientist: Claudia Troxel, ORNL

COT/AEGL comments on the perchloromethylmercaptan (PCMM) TSD were presented by Chemical Manager, Zarena Post (Attachment 15). Specifically, COT's disapproval of the subchronic study by Knapp & Thomassen (1987) as the basis for AEGLs 1 and 2 was noted. An alternate proposal of values was presented using the1987 Knapp et al. study (abstract only) and applying a modifying factor of 2 to account for the poor database, using 0.079 and 0.575 ppm as starting points for AEGLs 1 and 2, respectively. Total uncertainty factors of 10 and 30 were applied to the AEGL-1 and -2 values, respectively. Although this is still a repeated-exposure study, rats received only 10 exposures, rather than 70-72. Also, the health effects endpoints noted in this study were more appropriate for AEGLs 1 and 2 than the interstitial pneumonia noted in the subchronic study. A motion was made by Bob Snyder and seconded by Zarena Post to accept the proposed values for AEGL-1 of 0.015, 0.015, 0.012, 0.0074, 0.0049 ppm and for AEGL-2 of 0.044, 0.044, 0.035, 0.022, and 0.014 ppm, both for 10 minutes, 30 minutes, 1hour, 4 hours, and 8 hours, respectively. The motion was approved [YES: 19; NO: 2; Abstain: 0] (Appendix F).

Later, Richard Neimeier asked if we were going to develop a LOA for PCMM. It was agreed that the Committee would ask Marc Ruijten to do so.

Hydrogen Sulfide
CAS Reg. No. 7783-06-4

Chemical Manager: Steve Barbee, Arch Chemicals, Inc.
Staff Scientist: Cheryl Bast, ORNL

Cheryl provided the long history of the development of AEGL values by the NAC/AEGL and the review comments by the COT/AEGL (Attachment 16). The COT/AEGL did not accept the AEGL-1 values derived by the NAC/AEGL, citing the use of the equivalent of two separate intraspecies uncertainty factors and disagreeing with the endpoint of headache as a LOAEL for the AEGL-1. The COT/AEGL considered the response of headache in two asthmatic individuals in one study and no headache in a study with 100 healthy individuals, a NOAEL. Cheryl provided two options suggested by the COT/AEGL: use of a single intraspecies UF of 3 or use of a single UF of 1. It was moved by Richard Thomas and seconded by Glenn Leach to use the single intraspecies UF of 3. The motion failed: [YES: 12; NO: 7; Abstain: 2] (Appendix G). It was then moved by John Hinz and seconded by Richard Niemeier to use the intraspecies UF of 1. This motion also failed to pass (YES: 10; NO: 10; Abstain: 1)(Appendix G). At this point the discussion was deferred. The following day, the NAC/AEGL was reminded of the importance of developing values for emergency situations. It was moved by Mark McClanahan and seconded by Loren Koller to develop values using the intraspecies UF of 3 (values of 0.75, 0.60, 0.51, 0.36, and 0.33 ppm for the 10-minute through 8-hour exposure durations; $n = 4.4$) and add the weight of evidence approach suggested by the COT/AEGL. This time the motion passed [YES: 16; NO: 3; Abstain: 0](Appendix G).

In addition, the NAC/AEGL considered the LOA presented by Cheryl and developed using the methodology provided by Marc Ruijten. The LOA for an intensity of 3 is 0.01 ppm. It was moved by George Alexeeff and seconded by George Rodgers to append the LOA of 0.01 ppm to the TSD summary table. The motion passed unanimously by voice vote (Appendix G). It was also pointed out that the SOPs need to be modified to include development of LOAs.

REVIEW OF PRIORITY CHEMICALS FOR AEGL VALUES

Vinyl Chloride
CAS Reg. No. 75-01-4

Chemical Manager: Bob Benson, US EPA
Staff Scientist: Fritz Kalberalh, Germany

The discussion was led by Fritz Kalberlah. He briefly described the general information on and metabolism of vinyl chloride and later focused on data relevant to AEGL development (Attachment 17). Significant comments on the AEGL-1 levels included expanding the discussion of occupational exposure in Suciu et al. (1975) and to use Lester et al. (1975) as supporting information. The data from Lester et al. (1975) may also serve as justification to derive the 10-

minute value by time scaling rather than to adopt the 30-minute value. For time extrapolation from the 3.5-hour exposure, the default exponents for time extrapolation were used (n=3 for shorter exposure periods and n=1 for longer exposure periods) because of the unknown mechanism of action responsible for the observed headaches; this mechanism of action may be different from that responsible for the CNS effects observed at higher doses. It was moved by Bob Benson and seconded by Rick Neimeier to accept the AEGL-1 values as proposed in the draft TSD (8 hours: 70 ppm; 4 hours: 140 ppm; 1 hour: 250 ppm; 30 minutes: 310 ppm; 10 minutes: 310 ppm), with the exception that the 10 minute value is 450 ppm. The motion passed [YES: 13; NO: 4 ; Abstain: 1] (Appendix H). After some discussion of the AEGL-2 values based on the CNS effects, it was moved by John Hinz and seconded by Bob Benson to accept the values proposed in the TSD (8 hours: 820 ppm; 4 hours: 820 ppm; 1 hour: 1,200 ppm; 30 minutes: 1,600 ppm; 10 minutes: 2,800 ppm). The motion passed [YES:12 ; NO: 6; Abstain: 0] (Appendix H). After some discussion of the AEGL-3 values based on the cardiac sensitization effects, it was moved by Mark McClanahan and seconded by John Hinz to accept the values proposed in the TSD (8 hours: 3,400 ppm; 4 hours: 3,400 ppm; 1 hour: 4,800 ppm; 30 minutes: 6,800 ppm; 10 minutes: 12,000 ppm). The motion passed [YES: 16 ; NO: 0; Abstain: 2] (Appendix H). It should be stated that cardiac sensitization and lethality effects occur at levels that also are linked to high flammability (between 4 to 22%). The detailed discussion on Appendix C: cancer assessment was deferred until the December meeting. Bob Benson, Chemical Manager, agreed to make modifications to the Appendix in the draft TSD to discuss more clearly issues regarding childhood sensitivity and issues relating to the non-linear production of the active intermediate believed responsible for the development of liver tumors.

Carbon Disulfide
CAS Reg. No. 75-15-0

Chemical Manager: George Rodgers, AAPCC
Staff Scientist: Jens-Uwe Voss, Germany

The first draft of the TSD on carbon disulfide (CS_2) was introduced by Jens-Uwe Voss (Attachment 18). Values for AEGLs-1, 2, and 3 at 10 minutes and 30 minutes and at 1, 4, and 8 hours were suggested. Reported odor thresholds are 0.016-0.42 ppm, but no data were available to allow the derivation of a LOA.

The AEGL-1 was based on a controlled human study in which an 8-hour exposure to 20 ppm CS_2 in the presence of alcohol (about 0.75 ‰ blood alcohol) caused an increase in the acetaldehyde concentration in blood but no other subjective or objective signs of intoxication (Freundt et al., 1976b as referenced in the TSD). The observed increase in blood acetaldehyde is explained by an inhibition of the enzyme acetaldehyde dehydrogenase (AlDH). Other chemicals known to inhibit AlDH (e.g. disulfiram, antabuse) are known to cause symptoms (such as flush, hypotension, tachycardia and headaches) in the presence of alcohol. AlDH is a polymorphic enzyme and although the effect of carbon disulfide was not sufficient in the controlled study, population subgroups (esp. Asians) with a low-activity AlDH may be more susceptible to an inhibition of the enzyme. Therefore, an intraspecies factor of 10 was used. A motion was made by Ernie Falke

and seconded by George Rodgers to accept the proposed AEGL-1 values of 5.0 ppm for 10 and 30-minutes and 4.0, 2.5, and 2.0 ppm for 1, 4, and 8 hours, respectively. The motion passed [YES: 13; NO: 1; Abstain: 2] (Appendix I).

The originally proposed AEGL-3 was based on effects observed at about 2000 ppm within 1 hour in a controlled human study on two healthy male volunteers (Lehmann, 1894). These effects included difficulty to perform tasks, anxiety, nausea, progressing dizziness, and the feeling of a marked central paralysis during exposure; after exposure, staggered gait, strong dazed feeling, sudden salivation, increased pulse, vomiting and feeling ill for up to two days were recorded. After a lengthy discussion, it was felt that the study should be used to present supportive evidence and the AEGL-3 be derived from animal data. George Rusch proposed to derive the AEGL-3 from a study on rats in which a 4 hours exposure caused no deaths at 3000 ppm (but death of all six animals at 3500 ppm). Currently, this study is only available from secondary literature and it was noted that the original study is necessary to check the acceptability of the data. A total uncertainty factor of 10 was used (3 each for interspecies and intraspecies variability, because the mechanism of action is not expected to vary greatly between species or among individuals, respectively). A motion was made by John Hinz and seconded by Bill Bress to accept the proposed values. The motion passed [YES: 13; NO: 2; Abstain: 0] (Appendix H).

The proposed AEGL-2 values were also based on the data from the Lehmann study. Exposure to about 500 ppm for 3 hours and 50 minutes caused effects on the CNS with dizziness, anxiety, persisting headaches, temporary impairment of reading ability and lacrimation and cough attacks. These effects were considered to represent the threshold for an impaired ability to escape. An intraspecies uncertainty factor of three was used since the observed CNS-effects are not expected to vary greatly among individuals. Time-scaling to all time points from 30 minutes to 8 hours was performed using a factor of n=3 since use of the default factor of n=1 for extrapolation to longer time periods was considered to be contradicted by data from controlled human studies.

Alternatively, a derivation was presented based on the inhibition of an avoidance response in rats in a neurobehavioral study of Goldberg (1964): 4-hour exposure, with a NOAEL of 1000 ppm and a LOAEL of 2000 ppm. Both alternatives and a further suggestion (derivation based on findings in reproductive toxicity studies, esp. Tabacova et al. (1978) with exposure to 16-64 ppm, 4 hours/day, for 21 days throughout gestation) brought into the discussion by George Alexeeff could only briefly be discussed because of a lack of time. A motion was made by George Rodgers and seconded by Robert Benson to accept the 10 minutes to 4 hours values as originally proposed (10 and 30 minutes: 330 ppm; 1 hour: 260 ppm; 4 hours: 170 ppm) and to derive the 8-hour value with the default factor of n=1 for extrapolation to longer time periods (8 hours: 83 ppm). The motion did not pass [YES: 9; NO: 6; Abstain: 0] (Appendix I). Further discussion regarding the AEGL-2 will be continued in March 2003.

Summary of AEGL Values For Carbon Disulfide [ppm]						
Classification	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	5	5	4	2.5	2	Increase in blood acetaldehyde in humans with moderate intake of alcohol (Freundt et al. 1976b)
AEGL-2 (Disabling)	to be derived	to be derived	to be derived	to be derived	to be derived	
AEGL-3 (Lethal)	600	600	480	300	150	Lethality in rats after 4 hours (0/6 at 3000 ppm; 6/6 at 3500 ppm)

Methylene Chloride
CAS Reg. No. 75-09-2

Chemical Manager: Bob Benson, US EPA
Staff Scientist: Peter Bos, RIVM, The Netherlands

The discussion of the TSD was led by Peter Bos (Attachment 19). The NAC/AEGL indicated that the document needed additional work before voting on AEGL values. The significant changes requested included condensing the document to focus more attention on studies used to derive the AEGL values, providing additional description and validation of the PBPK modeling used to derive the AEGL values, adding additional discussion to the mechanism of action section on the CNS effect and those effects caused by the production of HbCO, and adding additional information on the variability in response expected in humans based on the existing GST-polymorphism. One NAC/AEGL member suggested that the author give more consideration to the data of Putz et al. 1979 for deriving AEGL-1 values.

Administrative Matters

The next meeting, NAC/AEGL-27, has been set for December 9-11, 2002, in Washington, D.C. OSHA will be hosting the meeting. More information about the lodging will be provided soon by Po-Yung Lu. The tentative NAC/AEGL-28 meeting is proposed for March 12-14, 2003 in conjunction with SOT and pending on EPA off-site meeting approval.

The meeting highlights were prepared by Po-Yung Lu and Sylvia Talmage, Oak Ridge National Laboratory, with input from the respective Chemical Managers, authors, and other contributors.

LIST OF ATTACHMENTS

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

Attachment 1. American Chemistry Council data submission to AEGL Program for CCl4 AEGLs development
Attachment 2. NAC/AEGL-26 meeting agenda
Attachment 3. NAC/AEGL-26 attendee list
Attachment 4. History of AEGL-1 characterization
Attachment 5. Guidance for the application of odor in emergency response
Attachment 6. Ratios approach for AEGL development
Attachment 7. G-agent & VX TSDs-clarifying NRC/COT Commentary, Finalizing the TSDs
Attachment 8. History of Nerve Agents TSDs Development
Attachment 9. Response to Comments from 7th Interim Report of COT/AEGL
Attachment 10. White paper: Considering AEGL Significance of Non-Cholinergic Mechanisms
Attachment 11. Data Analysis and Response to COT/AEGL Comments of Chlorine
Attachment 12. Data Analysis and Response to COT/AEGL Comments of HFE-7100
Attachment 13. Data Analysis of Allylamine
Attachment 14. Data Analysis of Methyl Mercaptan
Attachment 15. Data Analysis of Perchloromethylmercaptan
Attachment 16. Data Analysis of Hydrogen Sulfide
Attachment 17. Data Analysis Vinyl Chloride
Attachment 18. Data Analysis of Carbon Disulfide
Attachment 19. Data Analysis of Methylene Chloride

LIST OF APPENDICES

Appendix A. Revised meeting highlights of NAC/AEGL-25 (sent to NAC/AEGL on 10/17/2002 by e-mail).
Appendix B. Ballot for Approval the concept of LOA
Appendix C. Ballot for Nerve Agents
Appendix D. Ballot for Allylamine
Appendix E. Ballot for Methylmercaptan
Appendix F. Ballot for Perchloromethylmercaptan
Appendix G. Ballot for Hydrogen Sulfide
Appendix H. Ballot for Vinyl Chloride
Appendix I. Ballot for Carbon Disulfide

September 9, 2002

Attachment 1

VIA EMAIL & AEGL MEETING DISTRIBUTION (9/10/2002)

OPPT Document Control Office (DCO)
EPA East Building
Room 6428
1201 Constitution Avenue
Washington, DC

Re: National Advisory Committee for Acute Exposure Guideline Levels
For Hazardous Substances; Worker Exposure Data to Carbon Tetrachloride

Dear Sir or Madam:

The American Chemistry Council (ACC) is pleased to submit human exposure data in response to the request of the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL) for consideration in the development of AEGL values for carbon tetrachloride. These data are provided for the sole purpose of developing community emergency response values.

Thank you for your request for worker exposure data and consideration of our comments. Should you have any questions regarding this letter or the attached exposure information, please contact the American Chemistry Council.

Sincerely,

Susan Ripple

Susan Ripple

ACC-AEGL Liaison
Occupational Health Committee
989-636-5572 (office)
989-205-5072 (mobile)
989-638-9975 (fax)

Attachment: "Human Exposure to Carbon Tetrachloride"

Human Exposure to Carbon Tetrachloride

USE OF CCl_4 AS A PAINT THINNER IN A WAREHOUSE FACILITY

Carbon tetrachloride had been used for sometime as thinner for paint used to paint barrels in a warehouse of an industrial facility. The employee doing the spraying operation raised the question as to the hazard involved from the breathing of CCl_4, however the worker denied having symptoms related to the workplace when interviewed by the safety officer.

Air samples were taken in the worker's breathing zone on May 24th and June 22nd, 1948 during the task of painting barrels. The results of these assessments are shown in the following table:

Table 1.

Sample Date	Length of Sample Time	Volume of Sample	CCl_4 Concentration
5-24-48	20.5 min	29.9 L	181 ppm
5-24-48	10 min	14.6 L	72 ppm
6-22-48	10 min	11.1 L	42 ppm
6-22-48	10 min	11.1 L	156 ppm
6-22-48	10 min	11.1 L	120 ppm
6-22-48	13 min	14.43 L	123 ppm

The concentrations shown in Table 1 were at the maximum amounts that could be tolerated for a 4-hour period without probable effect on the individual. Two reasons why workers doing this task had not complained of illness in the past:

1. The job was done in a large room that allows good general ventilation.
2. The carbon tetrachloride fumes are heavier than air and were likely directed to the floor by the nature of the spraying.

Concentrations of carbon tetrachloride in this assessment were at levels where any increase might have resulted in an excessive exposure, and since spray painting without specific provision for removal of fumes could easily result, this operation was placed in a ventilated booth.

WORKER EXPOSURE TO CARBON TETRACHLORIDE RESULTING IN FATALITY

An employee working in a manufacturing facility in November of 1951 became ill after exposure to carbon tetrachloride and subsequently died. This employee ran tests in a facility where the potential hazards were limited to chlorine, hydrogen, caustic and brine. The employee's non-routine task on the day of exposure to CCl_4 was to clean a porcelain pothead. The pothead was separated from the body of the pot by heating the two. The affected employee then sat down on a box with the warm pothead in front of him, and proceeded to clean the pothead using carbon tetrachloride in an open bucket with rags soaked with the CCl_4. His co-worker stated that the pothead was still warm enough that the use of cool CCl_4 on the warm porcelain probably accounted for a crack which was later found. The cleaning task lasted about 2 hours and his co-worker estimated that the employee's breathing zone was about 1.5 – 2 feet from the source of the vapors.

The affected employee went home sick before the end of the shift 3 days after exposure and did not return to work again. The employee died 11 days after his exposure to the CCl_4 during pothead cleaning.

Although the job was performed out of doors, there is no documentation of the weather conditions during the task. It is not possible to say what the potential exposure concentrations of CCl_4 vapors may have been, however the report attributes the death of the employee to CCl_4 exposure which was consistent with the kidney and liver damage reported at autopsy.

CARBON TETRACHLORIDE EXPOSURES AT A PRODUCTION FACILITY

An industrial hygiene exposure assessment performed in 1944 of an acetylating and crystallizing operation, found all exposures of the operators to carbon tetrachloride vapor within satisfactory limits except at cleaning of the crystallizing filters. However, during the period covered in this report, two mechanics and several recovery operators complained of nausea and vomiting. The CCl_4 exposures of the mechanics was not assessed in this report because the nature of their tasks required repeated vapor exposures during repairs of leaks and repacking shafts, but were unplanned events. According to the exposure report, the complaints (nausea and vomiting) of the mechanics and recovery operators could have been due to excessive vapor exposure while cleaning the filters and also to heavy exposures that resulted from spills and from release of the safety valve on the recovery still.

Exposures to area concentrations of CCl_4 vapor were greater than 100 ppm when manholes were opened in the process and during the recrystallizing filter operations. Whenever manholes were left open, area vapor concentrations of several hundred parts per million (ppm) occurred above and close to the manhole. It was apparent that the experienced workmen avoided these peak exposures to a great extent by standing a few feet away from the manholes where concentrations measured were less than 100 ppm. The filter operator was exposed to area concentrations of CCl_4 vapor greater than 100 ppm only if he willfully stood over an open manhole.

During regular operation of the CCl_4 recovery still, the recovery operator had no excessive exposure to CCl_4 vapor (< 100 ppm). On two occasions, excessive exposures undoubtedly occurred when a storage tank was run over and when the pressure safety on the still released. This operator regularly received exposures that were considered to be excessive (not defined in the report) when he cleaned out the crystallizing filters.

Although many area measurements are reported within this report are were well within acceptable vapor concentrations (< 100 ppm) at that time (1944), those area concentrations of interest by the AEGL Committee for determination of the AEGL-3 levels are:

Location – Operation	CCl_4 Vapor Concentration in ppm by Volume
Catwalk beside drier, cleaning filters	2,570; 1260; 850; 650; 520; 356; 255; 220; 205; 148; 127; 120; 119; 110
At filter, dropping batch	420; 59; 53; 49; 46; 45; 35; 15
At filter, open manhole	312
Manhole – "Bringing up to Level"	263; 114; 85; 29
Manhole – Open manhole, sampling, etc.	2024; 564; 90

As a result of the health complaints and the measured area vapor concentrations in this operation, work was halted until proper ventilation, exhaust systems, work practices, and respiratory protection was put in place.

CARBON TETRACHLORIDE AREA CONCENTRATIONS

Area CCl_4 concentrations were assessed in 1946 during several operations at a production facility. There were no worker health complaints noted in the exposure assessment report.

Area concentrations of CCl_4 vapor ranged from 5.3 ppm to 608 ppm during these operations. Concentrations exceeding 100 ppm (the exposure limit for the production company in 1946) were found only in the vicinity of operations involving the "wheel", the drying oven, and the tray-loading table. One sample of room air contained 103 ppm two hours after the wheeling operation had started. The area CCl_4 vapor concentration to which the operator was exposed ranged from 151 to 192 ppm except for one 35 ppm concentration at the very beginning of the operation, and the air concentration dropped rapidly after the end of the wheeling operation. Although these concentrations were taken as area samples, "the sampling absorber was held as close as possible to the breathing level of the operator while he moved from the wheel to the tray-loading table and oven." The following table summarizes CCl_4 concentrations found during this evaluation:

Date	Location	Concentrations CCL_4 in ppm by Volume
2-20-46	Room Air (before operations began; cold day and all doors closed)	7
2-20-46	Wheeling	35
2-20-46	Wheeling	186
2-20-46	Wheeling	192
2-20-46	Tray	608
2-20-46	Room air at end of operations	103
3-1-46	Wheeling	151
3-1-46	Drying oven	162
3-1-46	At drying trays	41.4
3-1-46	Room air (south end)	10.5
3-1-46	Room air (north end)	6.3
3-1-46	Room air (south end 3 hours later)	5.3
3-1-46	Drying oven (3 hours later)	5.4

As a result of the initial survey on February 20, 1946, personnel were placed in proper respiratory protection for the duration of installation of proper exhaust ventilation and increasing air changes in the facility. The second round of area CCL_4 sampling yielded lower concentrations, indicative of proper ventilation installations.

National Advisory Committee for
Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-26
September 10-12, 2002

Attachment 2

US EPA
1201 Constitution Ave N.W., Rm 1117, Washington, DC
Metro Subway Federal Triangle Station (Orange and Blue lines)

AGENDA

Tuesday, September 10, 2002

10:00 a.m.	Introductory remarks and approval of NAC/AEGL-25 Highlights (George Rusch, Roger Garrett, and Paul Tobin)
10:10	COT/AEGL meeting report (Roger Garrett and George Rusch)
10:15	AEGL-1 characterization and LOA/odor issues (Marc Ruijten)
	* Review of characterization of AEGL-1 (Richard Thomas)
	* Presentation with examples of LOA approach (Marc Ruijten)
	* Critique of LOA approach (Pam Dalton)
	* Committee discussion
12:15 p.m.	Lunch
1:15	* Methylmercaptan AEGL-1 development (Doan Hansen/Cheryl Bast)
1:45	* Wrap up Odor AEGL-1 issues
2:00	Review and resolution of COT/AEGL comments: Hydrogen sulfide (Steven Barbee/Cheryl Bast)
3:00	Break
3:15	Review and resolution of COT/AEGL comments: BF3, Chlorine and HFE-7100
4:30	Review and resolution of COT/AEGL comments: G-agents and VX (John Hinz, Glenn Leach/Annetta Watson)
5:30	Review and resolution of COT/AEGL comments: Perchloromethylmercaptan (Zarena Post/Claudia Troxel)
6:00	Adjourn for the day

Wednesday, September 11, 2002

8:00 a.m.	Review of Chlorine trifluoride: AEGL-1 and related issues (Bob Benson/Sylvia Talmage)
8:10	Review and resolution of COT/AEGL comments: Allylamine (Loren Koller/Sylvia Milanez)
8:30	Review of Vinyl Chloride (Bob Benson/Fritz Kalberlah)
10:00	Break
10:15	Review of Vinyl Chloride (continued)
10:45	Vinyl chloride: French approach to determine acute toxicity threshold for land use planning (Annick Pichard))
11:15	Review of Dimethyldichlorosilane, Methyltrichlorosilane, and Trimethylchlorosilane (Ernie Falke/Cheryl Bast)
12:15 p.m.	Lunch
1:15	Review of Carbon Disulfide (George Rodgers/ Jens-Uwe Voss)
3:00	Break
3:15	Review of Methylene Chloride (Bob Benson/Peter Bos)
5:15	Administrative matter
5:30	Adjourn for the day

Thursday, September 12, 2002

8:00 a.m.	The Health Canada Existing Substances Program - Relevance to AEGLs (Bettie Meek)
8:30	Review and resolution of COT/AEGL comments: Toluene (Larry Gephart/Sylvia Talmage)
9:45	Review of 1,4-Dioxane (Jim Holler/Peter Griem)
10:15	Break
10:30	Review of 1,4-Dioxane (continued)
11:30	Summary of status critical health effects starting points for AEGL determination (George Alexeeff and Roger Garrett)
12:00 noon	Adjourn meeting

Attachment 3

NAC/AEGL Meeting-26

September 10-12, 2002
Washington, D.C.

Name	Affiliation	Phone No.
Po-Zung Su	ORNL	(865)574-7587
Cheryl Bast	ORNL	865-574-7581
Robert Young	ORNL	865 574-4573
Jens Voss	Tox-Consult.	+49 7631 798477
George Rodgers	Univ. of Louisville (AAPCC)	502-852-3721
GEORGE CUSHMAC	USDOT	202-366-4493
Robert Snyder	EOHI/Rutgers	732-445-3720/0201
Suzanne Arm	OSHA	202-693-2280
JONATHAN BUCAK	ACOEM	203-777-6611
Nancy Kim	NYS Health Dept	518 402-7511
TOM HORNSHAW	ILL EPA	217-785-0832
Robert Benson	EPA Region 8	303-312-7070
John Morawetz	ICWUC	513-621-8882
George Alexeeff	Cal/EPA	510-622-3202

Richard Thomas, Intrinet, Ltd 703-734-1454

URSULA GUNDERT-REMY	BgVV	+49-30-8412-3300
Paul Tolin	EPA	202 564-8557
G. RUSCH		
R. GARRETT		
Ernest V. Falke	EPA	202 564-7646
Marc Ruijten	RIVM, Netherlands	+31 80 27 44 566
Peter Bos	RIVM, Netherlands	+31 30 27 43 932
Paul Janssen	RIVM, Netherlands	+31 20 27 43 331
John Hinz	USAF	(210) 536-6136
GLENN LEACH	U.S. ARMY	410-436-2176
Dean Hansen	BNL/USDOE	631 344-7535 dhansen@BNL.gov
FRITZ KALBERLAH	FOBIG/Germany	+49 7613 8608-11
William BRESS	ASTHO VA DOH	802-863-7598
LOREN KOLLER	Environmental Health & Toxicology	541 745-5731
Jim Holler	ATSDR	404-498-0701
MARK A McCLANAHAN	CDC	770-458-2258
Lesley Tolan	EPA	202 564 7669

Sylvia Talmage	ORNL	865-576-7758
Susan Ripple	Dow Chemical - ACC liaison	989 859-1166
Rick Niemeier	CDC/NIOSH	(513) 533-8388
CARL MACKERER	C&C, consulting in Toxicology	609-737-9688
George Woodall	API	(202) 682-8067
Edward Faeder	SRF Envtl + Hum Hlth Risk	909-860-8282
Blair Gardner	Jackson & Kelly	(304) 340-1146
RICHARD Bannick	Ineris France	(33) 3 [illegible] 3344 6513
Pat Phibbs	BNA	202 452 4106
Robert Meeks	Dow Corning	989-496-8629
Reo Menning	SEHSC	703 904 4322
Wendy Koch	EPA/OSA	960 429 0038
Thomas Sobotka	FDA/CFSAN	301 827-8459
David Morgott	Eastman Kodak Co.	585 588-3704
Paul Dugard	HSIA	202-775-0232
Ray David	Eastman Kodak Co	585-588-4763 raymond.david@kodak.com
Kulbir Baker	National Research Council	202-334-2633

Pre-1990

- In 1961, COT met to consider a request from the U.S. Air Force to recommend short-term exposure limits for several jet propellants. These new limits were called, "Emergency Tolerance Limits."
- In 1964, AIHA-Toxicology Committee and the NRC-COT drew up a set of guidelines for emergency exposure limits. They were called, "Emergency Exposure Limits" or "EELs."

Attachment 4

Pre-1990

- NRC Continues the Development of Emergency Exposure Levels.
  - In the early 1980s, EEL's became EEGL's (Emergency Exposure Guidance Levels)
  - In the 1980's, Short-Term Public Emergency Guidance Levels or SPEGL's were developed.
  - Other non-emergency levels such as CEL's (becoming CEGL's) were also developed.

SPEGL

"The SPEGL (previously known as short-term public emergency limit, or SPEL) is defined as a suitable concentration for unpredicted, single, short-term, emergency exposure of the general public. In contrast to the EEGL, the SPEGL takes into account the wide range of susceptibility of the general public. This includes sensitive populations—such as children, the aged, and persons with serious debilitating diseases. Effects of exposure on the fetus and on reproductive capacity of both men and women should also be considered." (NRC, 1986)

Setting Emergency Exposure Limits

CEELs – NRC/NAS, 1993

"CEEL-1 refers to the concentration of an airborne substance (such as a gas, vapor, or aerosol) below which direct toxic effects are unlikely to lead to discomfort in the exposed population, but above which discomfort becomes increasing common – for example, eye and nose irritation or headaches (the description of CEEL values for a chemical must specify the symptoms to be expected)." (NRC, 1993)

Table 1 Characteristics of CEEL's 1-3 (CEEL-1 Only)

"Detectability

Exposed persons might complain, inquire, or express anxiety, but exposure, if perceived at all, will be perceived only by smell, taste, or sight or by sensations (mild sensory irritation) that do not persist after exposure ceases. There are no direct effects of exposure on health." (NRC, 1993, p12)

ERPG-1 (AIHA - ERP COMMITTEE)

"The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 hour without experiencing more than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.."

(Emergency Response Planning Guidelines, AIHA, 2002)

AGEL (NAC/AEGL Committee)

"AEGL-1 is the airborne concentration (expressed as ppm or $mg/m^{3)}$ of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asympatomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure."

"It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be sensitive or susceptible."

Below the AEGL-1

"Airborne concentrations below the AEGL-1 represents exposure levels that could produce mild and progressively increasing odor, taste, and sensory irritation, or certain asympatomatic, non-sensory effects."

Development of Emergency Guidelines

- Level 1 has often been referred to as a level of detection or notification.
- Odor has been addressed differently in different recommendations.
  - CEEL's and ERPG's often use odor in developing recommendations.
  - AEGL's have used odor at times, but not consistently.

Marc Ruijten

Attachment 5

Marc Ruijten, Centrum voor Gezondheidsonderzoek bij Rampen (CGOR)

Guidance for the application of odor in emergency response

rivm
Rijksinstituut voor Volksgezondheid en Milieu

Onderzoek in dienst van mens en milieu

The odor discussion

- WHY
  - Consider application of odor as an AEGL-1 endpoint
- HOW
  - Definition of odor and psychophysics
  - Proposed methodology for odor derived AEGL-1
  - Odor methodology AEGL-1 fits in the AEGL SOP
- CHOICE to accept odor as AEGL-1 endpoint, or not
  - And face the consequences

Mechanics of the odor discussion

- Presentations
  - Marc Ruijten – development of odor methodology
  - Pamela Dalton – critique of proposed methodology
- Discussion
- Resolution – recommendation

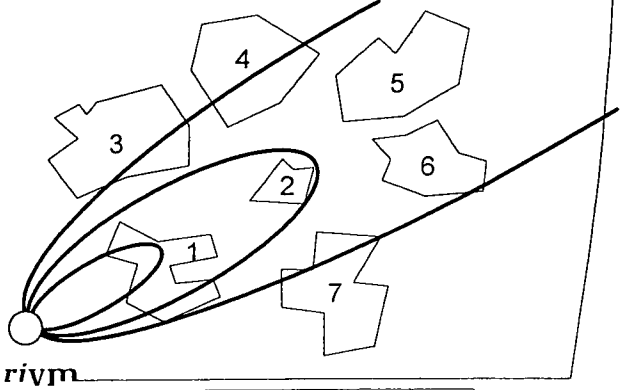
Application of AEGL values

- Prevention and mitigation
  - Land-use planning
  - Tunnel safety guidelines
- Preparedness
  - Scenario development for medical emergency capacity planning
  - Prediction of types of chemical injuries
- Response
  - Rapid assessment scale of emergency response
  - Rapid assessment of dangerous area (responders)
  - Multiple effect zones

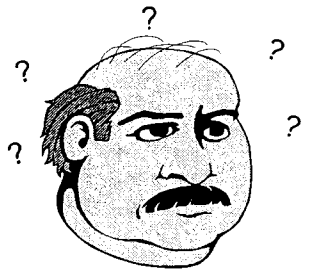
WHY consider odor as AEGL-1 endpoint

- Odor fits in AEGL-1 definition
- Application of AEGL values
  - Main application AEGL-1 is in emergency response.
- Odor awareness and emergency response
  - Exposed public associates odor with toxicity.
  - Risk communication requires information about what does happen, not what doesn't.
  - Notification can modulate appraisal & behavior.
  - Emergency response community requests odor based AEGL-1 values.
- ***Needed: a concentration to predict 'telephone zone' / public response zone***

Rapid health risk assessment



Incident managers



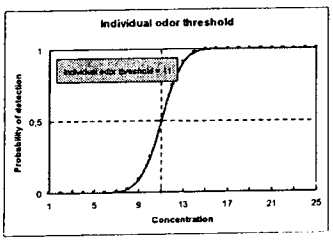
Incident managers are like mushrooms:
they are kept in the dark
and they are fed horseshit.

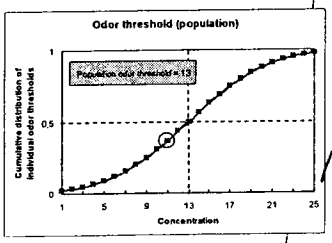
Psychophysiological dimensions of odor

- Sensory testing:
  - A precise, formal and structured methodology
  - To assess the response of a human population
  - Similar concepts for all sensory modalities (virbotactile perception, sound, vision and odor)
- Odor has 4 dimensions
  - Detectability
  - Intensity
  - Quality
  - Hedonic tone

Detectability - 1

- Odor threshold – 2 steps
  - Individual odor threshold
  - Group odor threshold concentration: 50% of panelists in olfactometry respond to the presented stimulus





50% respond

Detectability - 2

- Odor threshold does not allow an evaluation of significant odor awareness by itself
- Problems with former odor testing methodology
  - Instrument calibration, testing conditions, flow rate
  - Panel size is insufficient to compensate for biological variability in the population.
    - Inter-individual variability - GSD ~ 4
    - Intra-individual variability < factor 2
- Standardization: NVN 2820 (NL), EN13725 (CEN - Europe), DR 99306 (Australia)

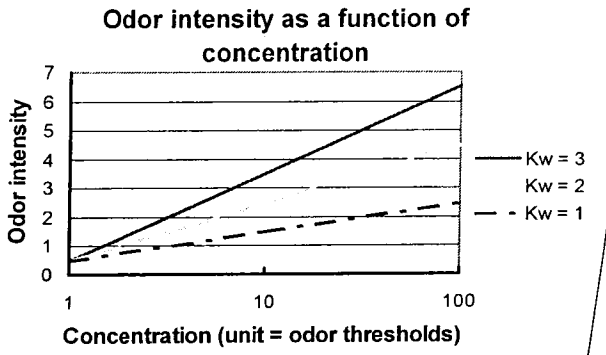
Detectability - 3

- Standards (NVN 2820, CEN 13725, DR99306)
  - Standardization through selection of test subjects with respect to the response to a reference material (*n*-butanol)
  - Assumes that sensitivity for *n*-butanol predicts sensitivity to other odorants
    - This assumption may not be correct
    - However, variability between standardized odor thresholds is far less than without standardization (table annex 3)
- Allows definition of performance criteria for odor laboratories for bias and precision

Intensity

- Supra-threshold phenomenon
- $I = k_w * \log (C / C_0) + 0.5$
  - Intensity measured on 7-point ordinal scale
    - I = 3 distinct odor
    - I = 4 strong odor
  - Weber-Fechner coefficient k_w
    - Slope factor – increase intensity / concentration unit
    - Standard methodology VDI 3882
    - Slope factor is less variable between individuals than sensitivity near the odor threshold
  - C_0 is odor threshold

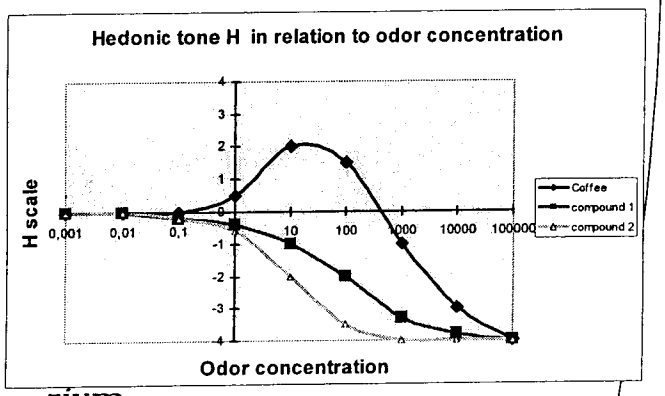
Intensity



Hedonic tone - 1

- Category judgment of relative pleasantness (H)
- Measured on a 9-point ordinal scale (VDI 3882)
  - +4 very pleasant
  - 0 neutral / no odor
  - -2 moderately unpleasant

Hedonic tone - 2



Odor quality

- Qualitative attribute, descriptive
  - Fruity
  - Fishy
  - Hay
- ASTM 'Atlas of Odor Profiles'
  - 146 descriptors
  - For 160 chemicals
  - With a large panel of 120-140 individuals
- Change of odor quality over concentration range
  - H_2S: rotten eggs – sweet – odorless

Field considerations

Factors affecting the odor detection threshold (Amo83)

Factor	Odor threshold compared to average 40-yr old male
Average woman	0.8
18-yr male	0.5
62-yr male	2
Smoking during test	4
Chewing during test	4
Head cold, nasal allergy	4
Undirected test	**4**

Information bias

Health symptoms (each group n=30) after 20 minutes exposure to 800 ppm acetone (Dalton 1999).

Symptom %	Information bias presented		
	Positive	Negative	Neutral
Troat irritation	4.4	8.7	8.6
Eye iritation	2.4	4.7	4.6
Nasal Irritation	6.1	13.0	14.4
Lightheadedness	5.4	8.5	12.6
Headache	2.4	4.9	5.1
Nausea	1.9	2.6	5.2
Drowsiness	3.0	7.0	5.6

LOA development

- Apply current knowledge
- Best estimate for missing knowledge or data
- Four steps
  - Determine or obtain the chemical's odor detection threshold
  - Determine or derive the concentration range where the odor is perceived to be distinct – strong
  - Adjust for field circumstances
  - Select and apply the Level of significant Odor Awareness

Step 1: Odor detection threshold

- **Level 1**: threshold determined re EN 13725
- **Level 2**: threshold from source which includes an odor threshold for *n*-butanol. Allows correction, eg:
  - Styrene = 30 ppb and *n*-butanol = 50 ppb
  - $C_{o,\,stand}$ = 30 * (40 / 50) = 24 ppb
- **Level 3**: thresholds from compilations with quality critique, but without internal standard
  - Nearly all bias is towards higher odor thresholds
  - Use lowest accepted odor threshold

Step 2: Intensity

- Calculate Weber-Fechner coefficient from intensity curve (VDI 3882).
  - If no Weber-Fechner coefficient k_w is available, a Stevens' coefficient n can be converted to k_w as follows: $= k_s * 1.10731 * 7^n - 0.055365$
- Value of k_w varies between 0.78 and 3.5 approx.
  - In absence of a chemical-specific value, the median value of k_w = 2.33 is proposed.
- An odor uncommon to the 'odor landscape' at an intensity of ≥ 3 has potential to cause odor annoyance:
  - Distinct (I = 3) will be perceived at 11.8 * OT_{50}
  - Strong (I = 4) odor will be perceived at 31.7 * OT_{50}
  - In the laboratory!!

Step 3: adjust for field conditions

- Undirected test conditions *raise* the odor threshold by a factor of 4.
- Odor detection, perception and appraisal takes 1 breath of approx. 5 seconds
  - Odor awareness does not require constant exposure above the criterion.
  - Peak exposure levels, the height and the frequency of occurrence of peaks determine the perception of odor.
  - The preliminary consensus for an appropriate peak-to-mean ratio not too close to the source is 3.
  - The TWA exposure level should be *lowered* to allow just a certain number of peaks to exceed the criterion.
  - This procedure takes care of time extrapolation ('flatline')
- Total adjustment = 4 / 3 = 1.33

Step 4: select and apply LOA

- Choose an LOA level:
  - Distinct or strong odor
  - In absence of data, the LOA defaults to:
    Distinct odor level (I = 3) → 11.8 * 1.33 = 16 * OT_{50}
    Strong odor level (I = 4) → 31.7 * 1.33 = 42 * OT_{50}
- Determine which AEGL-1 endpoint produces the lowest AEGL-1 values.
- Use the numbers derived from this endpoint to develop AEGL-1 values
- For a sneak preview of the results: cf. table in annex 4 of the document

Summary

- At 'Level of significant Odor Awareness', the public's response to a release dictates an emergency response
  - Often to provide information (but that's risk *management*)
  - Our customers need odor-based AEGL-1 values
- Odor testing methodology is as precise as any of the other human toxicological methodologies
- Odor intensity is as subjective as slight irritation
- A procedure has been proposed that:
  - Allows the reproducible development of a 'Level of significant Odor Awareness' as *one possible* AEGL-1 endpoint
  - Resolves inevitable data gaps
  - Allows application of biased results of 'old' odor testing methodology

Core issues

- Determine if LOA is a valid endpoint for AEGL-1
- Decide on level of intensity
  - Distinct odor level (I = 3) = 16 * OT_{50}
  - Strong odor level (I = 4) = 42 * OT_{50}
- If odor is acceptable:
  - Decide on applicable methodology: as proposed or with changes
- If odor is not acceptable:
  - Re-evaluate all existing AEGL-1 values based on odor
  - Developed separate LOA reference level?

End of presentation

Discussion please

Tom Hornshaw

Attachment 6

AEGL RATIOS APPROACH

- EVALUATE RATIOS OF AEGL-3 TO -2 & AEGL-2 TO -1 FOR ALL TIME PERIODS WHERE VALUES EXIST

- DELETE ALL VALUES FLAT-LINED FROM NEXT TIME PERIOD — all isotants ??

- DELETE ALL VALUES DERIVED AS 1/3 OF HIGHER AEGL

- DELETE ALL VALUES BASED ON POTENCY RELATIVE TO ANOTHER CHEMICAL

- VALUES AVAILABLE FOR 59 CHEMICALS FOR AEGL-3/2 RATIOS AND 19 AEGL-2/1 RATIOS

- STATISTICAL EXAMINATION OF ALL DATA SETS

AEGL-3:AEGL-2 RATIOS

10-MINUTE RATIOS

- N = 32
- MEAN = 5.34 +/- 6.66
- MEDIAN = 3.05
- RANGE = 1.55 – 34.55
- 95th PERCENTILE = 16.58

30-MINUTE RATIOS

- N = 57
- MEAN = 5.13 +/- 5.34
- MEDIAN = 3.65
- RANGE = 1.46 – 36.36
- 95th PERCENTILE = 13.71

60-MINUTE RATIOS

- N = 59
- MEAN = 5.19 +/- 5.49
- MEDIAN = 3.67
- RANGE = 1.45 – 35.42
- 95th PERCENTILE = 14.14

AEGL-3:AEGL-2 RATIOS (CONT'D)

4-HOUR RATIOS

- N = 56
- MEAN = 5.23 +/- 6.52
- MEDIAN = 3.17
- RANGE = 1.43 – 34.62
- 95^{th} PERCENTILE = 16.91

8-HOUR RATIOS

- N = 52
- MEAN = 5.28 +/- 7.34
- MEDIAN = 3.16
- RANGE = 1.16 – 40.77
- 95^{th} PERCENTILE = 18.69

AEGL-2:AEGL-1 RATIOS

10-MINUTE RATIOS

- N = 8
- MEAN = 25.51 +/- 57.72
- MEDIAN = 4.13
- RANGE = 1.50 – 168.0
- 95^{th} PERCENTILE = 113.6

30-MINUTE RATIOS

- N = 19
- MEAN = 12.91 +/- 35.75
- MEDIAN = 4.00
- RANGE = 1.50 – 160.0
- 95^{th} PERCENTILE = 27.25

60-MINUTE RATIOS

- N = 19
- MEAN = 13.05 +/- 36.85
- MEDIAN = 3.55
- RANGE = 1.50 – 164.7
- 95^{th} PERCENTILE = 27.72

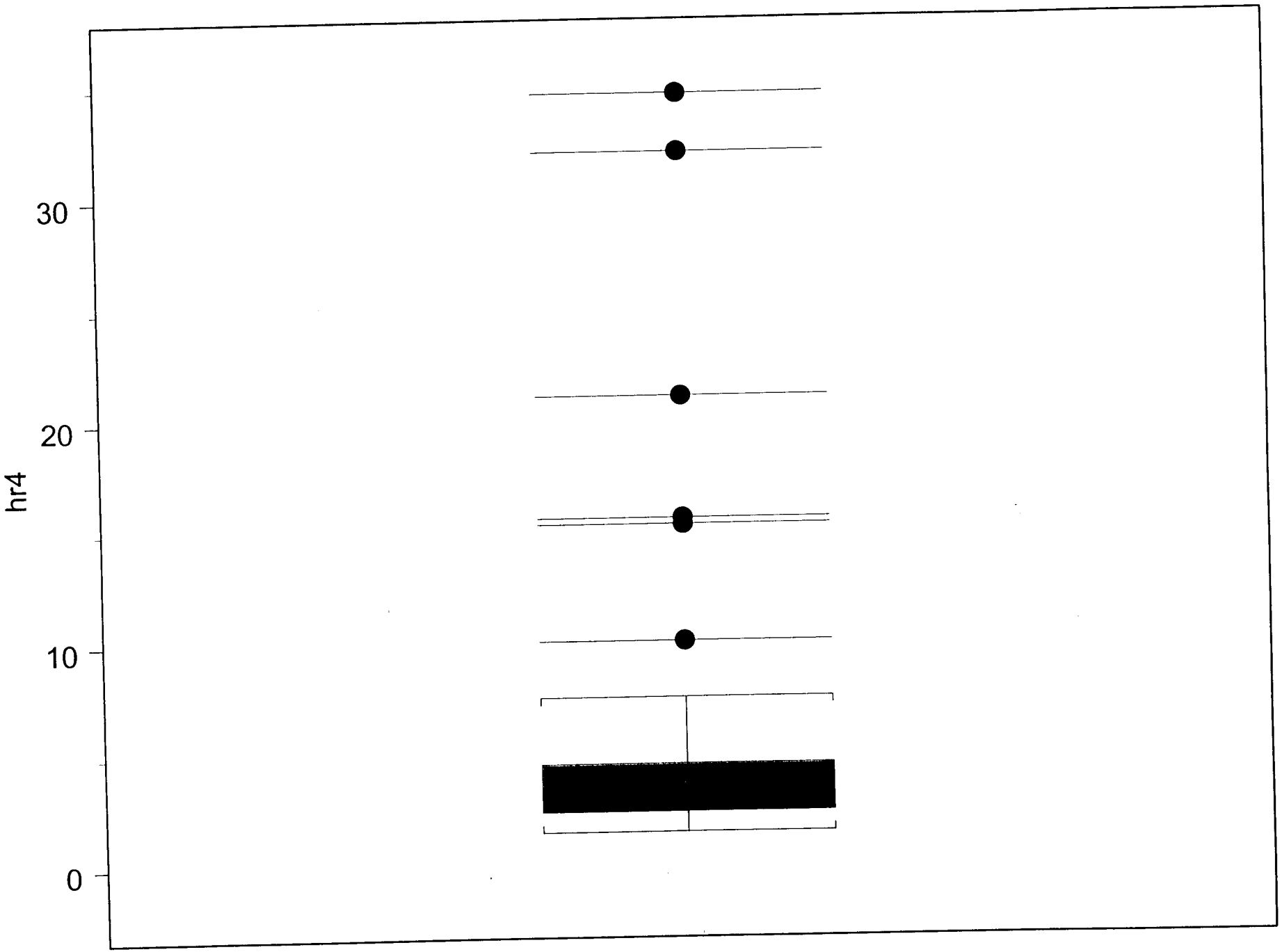
AEGL-2:AEGL-1 RATIOS (CONT'D)

4-HOUR RATIOS

- N = 19
- MEAN = 12.91 +/- 37.35
- MEDIAN = 3.28
- RANGE = 1.46 – 166.7
- 95^{th} PERCENTILE = 27.54

8-HOUR RATIOS

- N = 19
- MEAN = 12.31 +/- 34.59
- MEDIAN = 3.19
- RANGE = 1.50 – 154.5
- 95^{th} PERCENTILE = 27.10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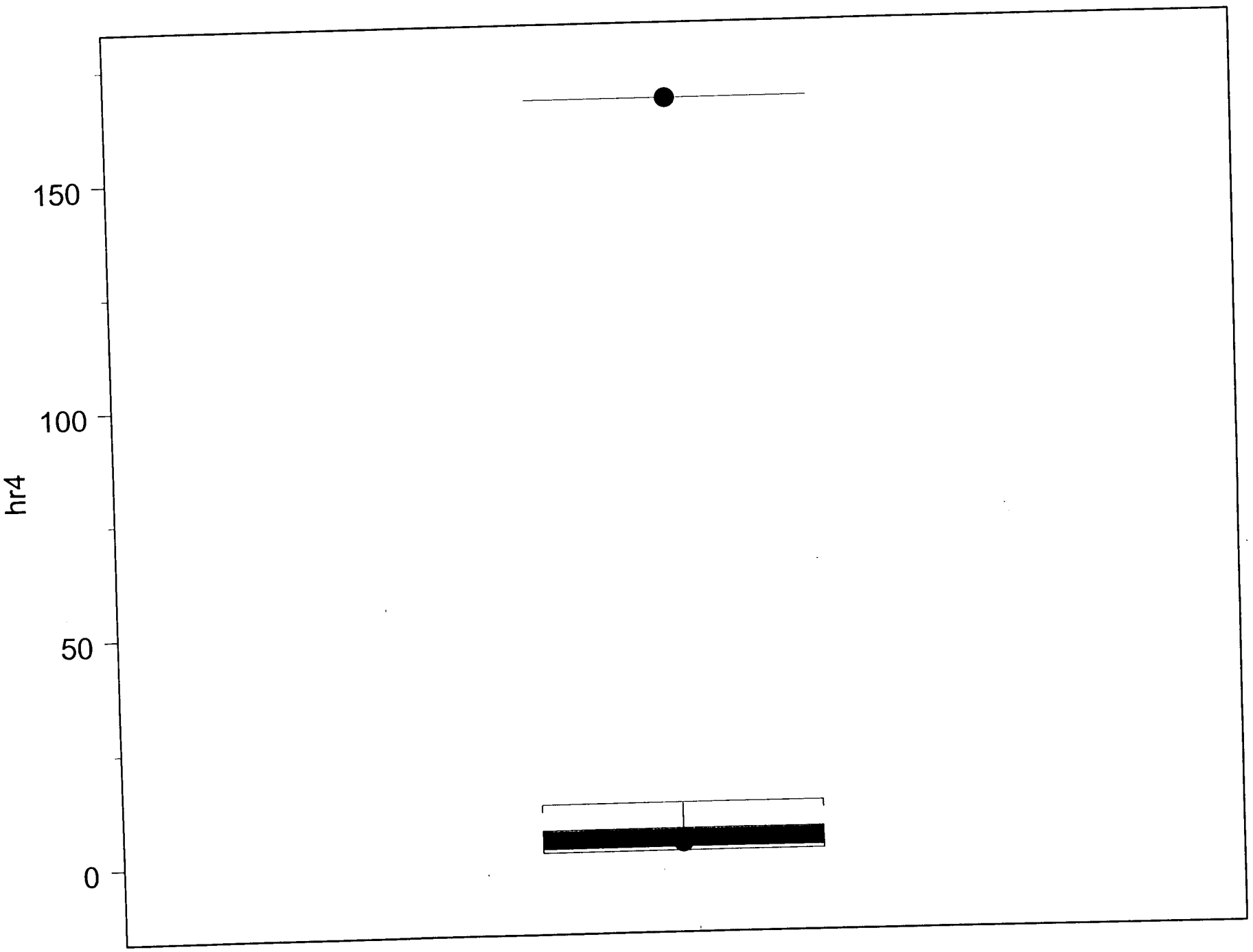
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HIGHLIGHTS

- ALL DATA SETS SKEWED, NEITHER NORMAL NOR LOGNORMAL
- RANGE OF MEDIANS = 3.05 – 4.13
- AEGL-3:AEGL-2 OUTLIERS = BROMINE (ALL RATIOS 35+), OTTO FUEL (4&8 HR RATIOS = 32.0 & 40.8), SULFUR MUSTARD (60 MIN – 8 HR RATIOS 20.5+)
- AEGL-2:AEGL-1 OUTLIER = H2S (ALL RATIOS 160+)
- ALL OUTLIERS = ANIMAL DATA FOR HIGHER AEGL & HUMAN DATA FOR LOWER AEGL

RECOMMENDATIONS

- DEFAULT AEGL-3:AEGL-2 DIVISOR FOR ALL TIMES = 19

- NO DEFAULT AEGL-2:AEGL-1 DIVISOR FOR 10 MINUTES

- DEFAULT AEGL-2:AEGL-1 DIVISOR FOR OTHER TIMES = 28

- DO NOT EXTRAPOLATE FROM AEGL-3 TO AEGL-1

G-AGENT & VX TSDs
- Clarifying NRC/COT Commentary, Finalizing the TSDs -

Glenn Leach – U. S. Army
John Hinz – U.S. Air Force
Annetta Watson – Oak Ridge Nat'l Labs

NAC-AEGL #26 (10/12Sep02)

AGENDA

- Glenn Leach: chronology and history of nerve agent AEGL development – or, how we finally got here!

G-Agents

- Annetta Watson: review/resolution of principal COT concerns regarding G-agent TSD, per COT's *7th Interim Report*
- AEGL Committee: discussion and vote finalizing G-agent TSD

VX

- Annetta Watson: review/resolution of principal COT concerns regarding VX TSD, per COT's *7th Interim Report*
- AEGL Committee: discussion and vote finalizing VX TSD

Attachment 8

BRIEF CHRONOLOGY OF NERVE AGENT AEGL EVALUATION

Autumn, 1999

- Nerve agents (and sulfur mustard) initially proposed/formally added to AEGL list of priority chemicals

December 1999

- Background brief to NAC membership on emergency planning need for agent AEGLs; and nerve agent chemical, physical and toxicological properties. At NAC/AEGL-16 (6-8 Dec 1999).

July 2000

- Draft nerve agent TSDs sent to NAC membership early in the month; formal presentation of AEGL estimations at NAC/AEGL-18 (26-28 Jul 2000)
- NAC decision postponed to NAC-19 to allow greater opportunity for NAC membership review

October 2000

- Draft AEGL values examined, and converted to "Proposed " status on votes taken at NAC-19 (23-25 Oct 2000)

May 2001

- Proposed values published in 66 FR 21940-21964 (2 May 2001)

June 2001

- Development Team responses to FR comments presented to NAC membership. AEGL values converted from "Proposed" to "Interim" status on votes taken at NAC-21 (11-13 June 2001)

December 2001

- Updated TSD files (including benchmark dose analysis prepared at NAC request), and written "Summary of progress since NAC-21" provided to COT Subcommittee on AEGLs

February 2002

- Formal presentation of Interim values and logic to COT Subcommittee on AEGLs at Beckman Center, Irvine, CA (6-8 Feb 2002); COT Subcommittee Meeting #9

May 2002

- Publication of *Seventh Interim Report of the Subcommittee on AEGLs*

May/June 2002

- Development Team composed and transmitted to COT Subcommittee both Summary and Detailed responses to *Seventh Interim Report*

July 2002

- Formal presentation of Development Team response to *Seventh Interim Report* comments before COT Subcommittee at Jonsson Center, Woods Hole, MA. All COT Subcommittee concerns resolved; "the scientific analysis of the COT Subcommittee supports all adjustments made by the Development Team" in response to the *Seventh Interim Report* and COT Subcommittee guidance provided at Woods Hole. (COT Subcommittee Meeting #10)

NERVE AGENTS (GA, GB, GD, GF, VX) AEGLs (CAS Nos. 77-81-6, 107-44-8, 96-64-0, 329-99-7, and 50782-69-9)

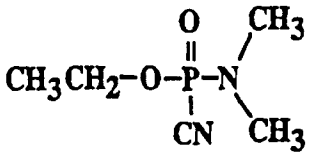
RESPONSE TO COMMENTS FROM 7TH INTERIM REPORT of the SUBCOMMITTEE ON ACUTE EXPOSURE GUIDELINE LEVELS COMMITTEE ON TOXICOLOGY

NAC/AEGL-26
USEPA; 2101 Constitution Ave, Rm 1117
Sep 10-12, 2002

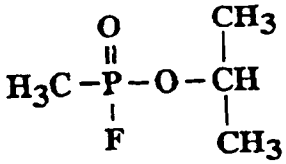
G-series Nerve Agents: Identification

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

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

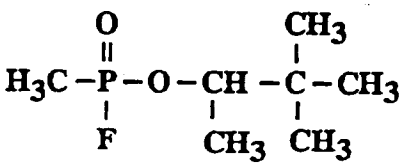


- Agent GB; sarin; Isopropyl methylphosphono-fluoridate; $C_4H_{10}FO_2P$; CAS No. 107-44-8; contains fluoride; chemical terrorist use in Japan (Matsumoto, 1994; Tokyo, 1995). Sizable US stockpile inventory, toxicity data.

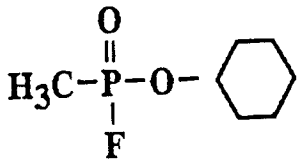


G-series Nerve Agents: Identification (cont'd)

- Agent GD; soman; Pinacolyl methylphosphonofluoridate; $C_7H_{16}FO_2P$; CAS No. 96-64-0; contains fluoride; not in US stockpile

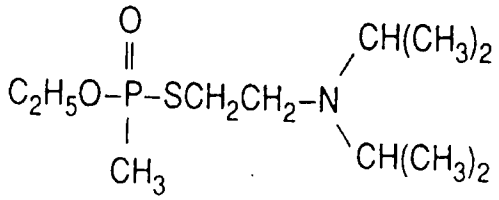


- Agent GF; *O*-cyclohexylmethylfluorophosphonate; $C_7H_{14}FO_2P$; CAS No. 329-99-7; contains fluoride; currently considered of little strategic interest (thought to have been manufactured in Iraq during Persian Gulf War); not in US stockpile. Included for completeness.



Nerve Agent VX: Identification

- Organophosphate ester derivative of phosphonic acid containing a sulfur substituent group; $C_{11}H_{25}NO_2PS$, O-ethyl-S-(diisopropylaminoethyl) methyl phosphonothiolate; CAS No. 50782-69-9



- Persistent, "terrain denial" compound with deliberately formulated low volatility (considered "2000 times less volatile than nerve agent GB"); oily liquid in normal state

- Principal differences from G-agents are physical (low volatility) and chemical (sulfur substituent group)

NOTE: All these nerve agents are clinically considered anticholinesterase compounds, are successfully treated with the same antidotes, and exhibit same endpoints

- Principal between-agent effect differences are consequence of agent-specific potencies

Principal COT Subcommittee Concerns

- Selection of critical study for developing agent GB AEGL-1 estimates

- Value of "n" for agent GB time scaling

- Relative potency determination for GB: VX

These issues were the subject of Nerve Agent Development Team Responses to the COT Subcommittee on AEGLs *Seventh Interim Report* ("Detailed Response.." of 30 May 02, "Summary Response..." of 3 Jun 02). COT Subcommittee concurred with all other points of the TSD analyses.

Critical Study Selection for GB AEGL-1

Interim: human volunteers in exposure chambers; threshold miosis, rhinorrhea (3/14), headache (2/14), eye pain (2/14), tightness in chest (1/14), cramps (1/14), nausea (1/14), at 0.05 mg/m^3 for 20 min (Harvey 1952; Johns 1952)

7th Interim Report: Harvey study "very old;" analytical techniques for air concentration determination questioned

Development Team Response: Substitute recent lab animal data for GB vapor miosis EC_{50}. Of the two recent data sets not previously available (marmosets; van Helden et al 2002; rats, Mioduszewski et al 2002b), Development Team recommends Mioduszewski et al (2002b) miosis EC_{50} as most robust:

- 283 rats (142 F, 141 M) exposed WB in dynamic flow chamber to GB range of 0.0100 to 0.0620 mg/m^3 and for 3 exposure durations (10, 60, 240 min) of AEGL significance
- With controls and range-finding, N = 423 rats
- V. credible documentation for GB vapor generation/meas.
- EC_{50} for females (susceptible gender at 10, 240 min)
- no significant change in monitored blood RBC-ChE, BuChE, CaE from baseline; no other clinical signs
- Local and direct effect to ChE controlling pupillary muscles of eye; well-defined animal endpoint supported by human and non-human primate (marmoset) miosis and subjective effects data; transient/reversible/non-disabling; appropriate endpoint for AEGL-1

Miosis EC_{50}

Definition (Mioduszewski et al 2002b): Post-exposure pupil diameter 50% or less of pre-exposure pupil diameter in 50% of exposed population; measured at 30 minutes post-exposure.

Potential Implications for General Public:

- In bright daylight, or under bright lights, 50% reduction in pupil diameter would result in greater visual acuity among some members of the affected population, and no marked reduction in visual acuity for the majority of the affected population.
- In twilight or dim light conditions, 50% reduction in pupil diameter in some persons would result in reduced visual acuity and less-than-optimal performance of tasks requiring
  - operation of vehicular controls
  - monitoring or tracking on computer screens
  - reading of fine text
  - shifts in focus between near and far fields
- For individuals with central cataracts, effects at all light levels would likely be more pronounced

Human Evidence of Harvey (1952) and Johns(1952):

- see Tables 5-6 in G-agent TSD
- Reduction in pupil diameter of ~50% associated with headache, feeling of chest tightness, rhinorrhea

Miosis EC_{50} (cont'd)

During Tokyo Subway Incident (March 1995):

- Terrorist release of agent GB in occupied commuter subway cars
- Persons experiencing ≥50% pupil diameter reduction from vapor exposure to agent GB were able to self-rescue and render aid to others

Critical Study Selection for GB AEGL-1 (cont'd)

TABLE 19. AEGL-1 Estimates for Nerve Agent GB

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); COT PREFERRED STUDY**
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., 2002. 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 (14-17 May, 2001). Research and Technology Organisation (RTO) Meeting Proceedings 75, Operational Medical Issues in Chemical and Biological Defense [RTO-MP-075, AC/323 (HFM-060) TP/37] held in Estoril, Portugal, 14-17 May 2001. North Atlantic Treaty Organisation, BP 25, 7 Rue Ancelle, F-92201 Neuilly-sur-Seine CEDEX, France [5 hour exposures]

[c] Mioduszewski R et al., 2002b. Low-level sarin vapor exposure in rats: Effect of exposure concentration and duration on pupil size. ECBC-TR-235. Edgewood Research Development and Engineering Center, U.S. Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD. (May, 2002) [10 min, 60 min, and 240 min exposures]

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; this position is supported by the miosis data, and the AEGL Nerve Agent Development Team concurs); intraspecies UF = 10 (adjustment for possible susceptible individuals); $\sum UF = 10$

Remarkable concordance in AEGL-1 estimates across species

Critical Study Selection for GB AEGL-1 (cont'd)

Development Team Recommendation: Existing Interim values for AEGL-1 are representative and protective, and can be retained. Consider Mioduszewski et al (2002b) as the new critical study, with van Helden et al (2002; marmosets), Harvey (1952; human), and Johns (1952; human) as secondary and supportive studies.

- Weight-of-evidence analysis indicates concordance/corroboration across species, with little to no change from present Interim values required

COT Subcommittee Guidance: Accept retention of existing Interim values and inclusion of Mioduszewski et al (2002b) as the new critical study, with secondary studies treated as above.

Value of "n" for Agent GB Time Scaling

Interim: "n" = 2, obtained from regression plot of female SD rat LC_{01} (n = 1.92, r^2 = 0.995; Mioduszewski et al 2000a,b, 2001, 2002a)

7th Interim Report: Question application of "n" derived for lethality endpoint to estimations of non-lethal endpoints

Development Team Response:

- Recently published data from Mioduszewski et al (2002b; "Low-level sarin exposure in rats; effect of exposure concentration and duration on pupil size") subjected to regression analysis; "n" = 2.00, r^2 = 0.4335
- Concordance on "n" for lethal and non-lethal endpoints
- Graphical analysis of plots resulting from "n" = 1, vs. "n" = 3 with human and animal experimental data; plots drawn for "n" = 2 most reflective of human and animal database.

Development Team Recommendation: "n" = 2 for time scaling for all AEGL endpoints

- Concordance on "n" = 2 obtained from two recent and well-conducted studies on female (susceptible gender) SD rats for lethal (LC_{01}) and non-lethal endpoints (miosis only; no other signs).

COT Subcommittee Guidance: Accept "n" = 2 for all scaling

Summary of COT Review and Guidance for G-Agents

- ✓ ACCEPTED ALL NAC/AEGL G-Agent AEGL values and logic

- ✓ Recommends selection of recently published Mioduszewski et al (2002b) evaluation of rat miosis as critical study for developing agent GB AEGL-1 estimates

    - ✓ treat earlier human studies and recent marmoset studies as secondary and supportive.
    - ✓ retain existing AEGL-1 Interim values, which are considered representative and protective

- ✓ Concur with value of "n" for agent GB time scaling derived from lethality data, and additionally supported by recent non-lethality (miosis) data

Development Team concurs with COT Subcommittee guidance

NOTE: Redline/strikeout draft nerve agent TSDs prepared with above COT Subcommittee guidance and Development Team concurrence; transmitted to NAC membership in early August 02.

Relative Potency Determination for GB: VX

Interim: Relative potency (RP) of GB: VX = 12.0, from comparison of 90% miosis in rabbits receiving direct vapor exposure to the eye (Callaway and Dirnhuber, 1971; rounded from ratio = 11.8)

- coupled with MF = 3 (for VX data base limitations)
- combined RP x MF = 12 x 3 = 36

7th Interim Report: Agreement on MF; Differing opinions on RP;

- RP = 12 for some AEGL values but not AEGL-3
- RP = 5-7 for AEGL-3
- RP = 10, RP = 10-12

Development Team Response: Beckman Center advice from COT was to reconsider available experimental data to evaluate option of developing a RP based on human data, regardless of exposure route. With removal of flawed and nonverifiable data sets (e.g., Bramwell et al 1963):

- GB: VX = 4.3 ($RBC\text{-}ChE_{50}$; oral exposure studies of Grob and Harvey 1958, Sidell and Groff 1974)
- GB: VX = 2.7 ($RBC\text{-}ChE_{50}$; intra-arterial/intravenous exposure studies of Grob and Harvey 1958, Sidell and Groff 1974)

Relative Potency Determination for GB: VX (cont'd)

Development Team Recommendation: ChE_{50} endpoint is part of the response continuum to cholinesterase inhibitors; it is thus consistent to apply an RP ratio derived from relative data such as ChE_{50} for estimating all AEGL values. Agent exposure (oral and IV/IA) concentrations and observed endpoint (ChE_{50}) in the human exposure studies of Grob and Harvey (1958) and Sidell and Groff (1974) are well-characterized and known with precision.

For RP derivation from human data set, recommend remove flawed data (Bramwell et al 1963) from consideration. Of remaining data from well-conducted human studies, recommend application of more protective ratio derived from oral exposures (RP = 4.0, rounded) for all AEGL levels (coupled with MF = 3 for all AEGL estimates). Callaway and Dirnhuber (1971) supports potency VX > GB. Improvements to TSD analysis:

- remove questionable determination of RP resulting from 1970-era analytical limitations to vapor concentration measurements; C&D (1971) not reasonable study for accurate determination of time-specific agent concentrations.
- address what is now considered "semi-subjective" measurement technique for % miosis; what was appropriate for 1970's has been superseded
- address lack of reported miosis incidence data in Callaway and Dirnhuber (1971)

Relative Potency Determination for GB: VX (cont'd)

Improvements to TSD analysis (cont'd)

- does not give the Callaway and Dirnhuber (1971) results more precision and accuracy than are warranted
- considers Callaway and Dirnhuber (1971) as a secondary and supportive study for concept that VX is more potent than GB

COT Subcommittee Guidance: Apply RP ratio = 4 derived from well-conducted human studies as an appropriate estimate of GB: VX relative potency for all VX AEGL determinations. The MF = 3 (for database limitations) is retained.

- combined RP x MF = 4 x 3 = 12

Adjustment Factors Considered in Estimation of AEGL values for VX

	AEGL-1	AEGL-2	AEGL-3
Interim (66FR 21940; 2/5/2001)			
RP	12	12	12
MF	3	3	3
Interspp. UF	1	1	3
Intraspp. UF	10	10	10
Composite	*360*	*360*	*1200*
COT Guidance			
RP	4	4	4
MF	3	3	3
Interspp. UF	1	1	3
Intraspp. UF	10	10	10
Composite	*120*	*120*	*400*

Summary of COT Review and Guidance for Agent VX

- ✓ Concurred with general Relative Potency concept and approach, and MF of 3

- ✓ Recommends application of RP ratio = 4 derived from well-conducted human studies as an appropriate estimate of GB: VX relative potency for all VX AEGL determinations.

    - ✓ Retain the MF = 3 (for database limitations)
    - ✓ Combined RP x MF = 4 x 3 = 12

Development Team concurs with COT Subcommittee guidance.

NOTE: Redline/strikeout draft nerve agent TSDs prepared with above COT Subcommittee guidance and Development Team concurrence; transmitted to NAC membership in early August 02.

White Paper: Considering AEGL Significance of Non-Cholinergic Mechanisms
Nerve Agent AEGL Development Team
6 September 2002

The Nerve Agent AEGL Development Team wishes to take this opportunity to respond to the message transmitted to all of you during the afternoon of 5 Sep by NAC member Dr. Robert Snyder regarding the relative potency analyses documented in the Nerve Agent Technical Support Documents and previously sent for consideration to the NAC membership in early August. As is customary at meetings of the National Advisory Committee, the Development Team for nerve agent AEGLs had intended to summarize for you at NAC/AEGL-26 next week the COT Subcommittee review and recommendations, as documented in the *Seventh Interim Report of the COT Subcommittee On Acute Exposure Guideline Levels* (May 2002) and provided as COT Subcommittee guidance. One of the principal changes recommended by the COT Subcommittee on AEGLs - **not** the Army, as indicated in Dr. Snyder's message - is that of the relative potency between agents GB and VX.

Given that the issue has been brought to your attention by Dr. Snyder's communication in advance of the NAC/AEGL-26, we summarize for you below the main points raised and the guidance received from the COT Subcommittee, as well as the Nerve Agent AEGL Development Team evaluation of Dr. Snyder's concerns. These points will also be discussed during the regularly scheduled time for these compounds on the NAC/AEGL-26 agenda.

RELATIVE POTENCY DETERMINATION FOR GB: VX

NAC Interim AEGL values for Agent VX: Were developed on the basis of a relative potency (RP) of GB:VX = 12.0, from comparison of reported 90% miosis in rabbits receiving direct vapor exposure to the eye (Callaway and Dirnhuber, 1971; rounded from GB:VX ratio = 11.8)

- coupled with MF = 3 for limitations in VX data base
- composite adjustment of: RP x MF = 12 x 3 = 36

7th Interim Report of COT Subcommittee: Expressed differing opinions on this point;

- RP = 12 for some AEGL values but not for AEGL-3
- RP = 5-7 for AEGL-3
- RP = 10, RP = 10-12

Advice from COT was to reconsider available experimental data to evaluate the option of developing a RP based on human data, regardless of exposure route.

Development Team Response to COT: On the recommendations of the COT, the Development Team considered available human experimental data for all available exposure routes. With removal of flawed and nonverifiable data sets (e.g., Bramwell et al 1963):

- GB: VX = 4.3 (RBC-ChE_{50}; oral exposure studies of Grob and Harvey 1958, Sidell and Groff 1974)

- GB: VX = 2.7 (RBC-ChE_{50}; intra-arterial/intravenous exposure studies of Grob and Harvey 1958, Sidell and Groff 1974)
- no change in Uncertainty Factors

Development Team Recommendation: ChE_{50} endpoint is part of the response continuum to cholinesterase inhibitors; it is thus consistent to apply an RP ratio derived from relative data such as ChE_{50} for estimating all AEGL values. Agent exposure (oral and IV/IA) concentrations and observed endpoint (ChE_{50}) in the human exposure studies of Grob and Harvey (1958) and Sidell and Groff (1974) are well-characterized and known with precision (See Table 8 of VX TSD).

With removal of flawed data (Bramwell et al 1963), consideration of remaining data from well-conducted human studies, and with COT-recommended focus on human data only, the Development Team recommended application of the more protective ratio derived from oral exposures studies (RP = 4.0, rounded) for all AEGL levels (coupled with MF = 3 for all AEGL estimates). Callaway and Dirnhuber (1971) still supports potency VX > GB. Resulting improvements to TSD analysis include:

- removal of questionable determination of RP resulting from 1970-era analytical limitations to vapor concentration measurements; Callaway and Dirnhuber (1971) is not a reasonable study for accurate determination of time-specific agent concentrations.
- addresses what is now considered "semi-subjective" measurement technique for % miosis; what was appropriate for 1970's has been superseded by more accurate and quantitative methods
- addresses lack of reported miosis incidence data in Callaway and Dirnhuber (1971)
- does not give the Callaway and Dirnhuber (1971) results more precision and accuracy than are warranted
- considers Callaway and Dirnhuber (1971) as a secondary and supportive study regarding the concept that VX is more potent than GB

COT Subcommittee Guidance, July 2002: Incorporate RP ratio = 4 derived from well-conducted human studies as an appropriate estimate of GB: VX relative potency for all VX AEGL determinations. The MF = 3 (for database limitations) is retained.

- Composite adjustment, prior to application of UFs, is RP x MF = 4 x 3 = 12
- No change in Uncertainty Factors

AEGL SIGNIFICANCE OF NON-CHOLINERGIC MECHANISMS

Brief Statement of Dr. Snyder's Concern: Observed response of nicotinic receptors, effects on GABAnergic synaptic transmission in brain, and related neurophysiological changes in individual mammalian cells and cell cultures as complimentary mechanism of lethality has raised a concern for Dr. Snyder regarding the incorporation of adequate amounts of uncertainty in the estimation of AEGL-3 values for agent VX. The source for these observations is the extensive neurophysiological literature generated by the research lab of Edson X. Albuquerque, Univ. Of

MD School of Medical Pharmacology and Experimental Therapy, Baltimore, MD. Dr. Snyder states that he "would oppose any change in the relative potency factor" from the Interim estimated RP= 12 for AEGL-3.

Neurophysiological citations provided by Dr. Snyder are listed in the Bibliography section of this White Paper.

Examination of Reference Dose Report published by National Academy Press (referenced by Dr. Snyder, 5 Sep 2002)

Dr. Snyder quotes the text of the published report prepared by the COT "Subcommittee on Chronic Reference Doses for Selected Chemical Warfare Agents" that he chaired. The Subcommittee's report (*Review of the U.S. Army's Health Risk Assessments for Oral Exposure to Six Chemical-Warfare Agents*) was published by the National Academy Press in 1999. Dr. Edson Albuquerque was a member of the Panel, as was Dr. Mohamed Abou-Donia, Dr. Barry Wilson, and other investigators. The technical analyses for chemical warfare agent reference doses reviewed in this 1999 COT subcommittee report was prepared by most of the same ORNL staff as have prepared the nerve agent TSDs.

The Subcommittee report was later published in the open literature as:

Bakshi, KS, SNJ Pang and R Snyder (eds) 2000. "Review of the U.S. Army's Health Risk Assessments for Oral Exposure to Six Chemical Warfare Agents" *J. Toxicol. Environ. Health* vol 59 (5-6) 281-526.

Pages from this latter open literature and peer-reviewed publication are quoted when Dr. Snyder points out text identifying the presence of non-cholinergic actions for organophosphates. The nerve agent Technical Support Documents also include these points (see Sects. 4.2 of both the G-agent and VX TSDs).

The COT Subcommittee on Chronic Reference Doses dealt with the issue of non-cholinergic actions in performing risk assessments and has documented their position in both the report published by the National Academy Press in 1999 and the *Journal of Toxicology and Environmental Health* article edited by Bakshi, Pang and Snyder (2000) as cited above.

We quote from Bakshi, Pang and Snyder (2000) below, and from the chapter "Evaluation of the Army's Interim Reference Dose for VX":

pp. 333 and 334—"The subcommittee notes that ChE inhibition is typically considered a biomarker of exposure to organophosphate agents rather than an adverse effect. However, it is generally agreed that inhibition of RBC and plasma ChE contributes to the overall hazard identification of ChE-inhibiting agents. The U.S. Environmental Protection Agency (EPA) has used ChE inhibition to establish RfDs for several organophosphate pesticides such as malathion (USEPA 1992) and ethion (USEPA 1989). The subcommittee agrees with ORNL that ChE inhibition is a valid endpoint on which to base the RfD for VX but recommends that data on ChE inhibition be taken from the human study...."

p. 334--"The subcommittee considered other possible critical endpoints, notably neurotoxicity, associated with VX exposure. Organophosphate compounds like VX might act directly on nerve cell receptors or, by inhibiting neural AChE, interfere with neuromuscular transmission and produce delayed onset subjunctional muscle damage. VX at concentrations of 10 pM has been shown to depress gabanergic transmission in the central nervous system (Rocha et al 1998), and this could have profound implications for **behavioral** effects in laboratory animals and humans." (Development Team emphasis).

still on p. 334--"Provided that appropriate assays were used, the subcommittee finds no reason at this time to alter the practice of using RBC ChE or plasma ChE inhibition as the critical toxicity endpoint and agrees with ORNL that such inhibition is the best available critical noncancer endpoint on which to base the calculation of the RfD for VX."

from the same chapter on VX, p. 337--"The subcommittee believes that data from human studies should be used to derive the RfD whenever possible..."

With regard to Dr. Snyder's concerns on variability in results of various cholinesterase assays, we further quote from Bakshi, Pang and Snyder (2000) and Appendix G "Inhibition of Cholinesterases and an Evaluation of the Methods Used to Measure Cholinesterase Activity":

pp. 525-526–"A case can be made that the critical studies on GA, GB, GD and VX were not optimal...The subcommittee believes, however, that the critical studies are probably sufficiently reliable to permit their use in deriving RfDs. One reason is that the absolute values of the enzyme activities might not be as important as the relative inhibitions because it is the highest dose at which an inhibition can be detected that is important."

Development Team Summary Response:

- non-cholinergic effects are already identified in TSD sections 4.2 "Mechanism of Toxicity"
- the very excellent literature from EX Albuquerque's lab does not elucidate how these electrophysiological alterations in rat hippocampal neurons relate to the integrative endpoint of whole-body lethality, or allow qualitative/quantitative between-agent comparisons directly relevant to lethality
- at present, there is an undefined dose conversion of nM-induced amplitude change in post-synaptic currents recorded in rat hippocampal neurons exposed to nerve agent solutions to integrative effects such as multi-system failure and death
- the neurophysiological citations document results largely obtained from single cells in isolation from whole organs and systems

Development Team Findings: Nerve agent AEGL Technical Support Documents have followed the published procedures and logic as documented by the COT Subcommittee on Chronic Reference Doses for Selected Chemical-Warfare Agents chaired by Dr. Snyder. The RP for GB: VX now employs human data and RBC-ChE_{50} by "appropriate assays" measuring the relative ChE change from baseline, also in keeping with the logic of the COT Subcommittee on Chronic Reference Doses for Selected Chemical-Warfare Agents. This logic has been published in both by the National Academy Press (1999) and in the peer-

reviewed *Journal of Toxicology and Environmental Health* (2000). As a consequence, the Development Team and COT Subcommittee on AEGLs are maintaining consistency with known practice in developing risk assessment analyses from experimental data on nerve agents. It is appropriate to follow this approach until such time as the field of neurophysiological research attains the level of completeness and maturity necessary to apply experimental results to prediction of whole-organism responses such as lethality.

Development Team Recommendations: Expand Technical Support Document treatment of non-cholinergic effects in Sect. 4.2 "Mechanism of Toxicity" to include the 2002 and other recent literature from EX Albuquerque's lab and identified for us by Dr. Snyder. Expand Sect. 8.3 "Data Adequacy and Research Needs" to include recommendations for additional research comparing and contrasting non-cholinergic effects of agents GB and VX, and how these results relate to whole-system responses such as lethality.

THE ROLE OF HYDROLYZING ENZYMES

With regard to Dr. Snyder's concerns regarding other hydrolyzing esterases in the liver and blood, it should be noted that the COT Subcommittee on AEGLs had also requested expanded treatment of carboxylesterase amount, affinity, and inhibitor resistant activity in the Technical Support Document has been composed to address this COT recommendation, and is included as redline text in the TSDs provided to the NAC membership in early August (e.g., see new text in Section 4.0 "Special Consideration"). This point is included in the presentation material already prepared for delivery to NAC/AEGL-26.

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EXECUTIVE SUMMARY - CHLORINE

Chlorine is a greenish-yellow, highly reactive halogen gas with a pungent, suffocating odor. The vapor is heavier than air and will form a cloud in the vicinity of a spill. Like other halogens, chlorine does not occur in the elemental state in nature; it rapidly combines with both inorganic and organic substances. Chlorine is used in the manufacture of a wide variety of chemicals, as a bleaching agent in industry and household products, and as a biocide in water and waste treatment plants.

Chlorine is an irritant to the eyes and respiratory tract; reaction with moist surfaces produces hydrochloric and hypochlorous acids. Its irritant properties have been studied in human volunteers and its acute inhalation toxicity has been studied in several laboratory animal species. The data from the human and laboratory animal studies were sufficient for development of three AEGLs for five time periods (i.e., 10 and 30 minutes and 1, 4, and 8 hours). Regression analysis of human data on nuisance irritation responses (itching or burning of the eyes, nose, or throat) for exposure durations of 30-120 minutes and during exposures to 0-2 ppm of chlorine determined that the relationship between concentration and time is approximately $C^2 \times t = k$ (ten Berge and Vis van Heemst, 1983).

The AEGL-1 was based on the observation that exposure of adult human volunteers, including an atopic individual with allergic rhinitis, to 0.5 ppm for 4 hours produced no sensory irritation but did result in transient changes in some pulmonary function parameters for the atopic individual (Rotman et al., 1983). During the exposure, the subjects were undergoing light exercise on a treadmill or step test that increased the heart rate to 100 beats/minute. Because both sexes were tested, subjects were undergoing light exercise, making them more vulnerable to sensory irritation, and an exercising susceptible individual did not exhibit adverse effects, no uncertainty factor to account for differences in human sensitivity was applied. The intraspecies uncertainty factor of 1 is supported by another study in which a concentration of 0.4 ppm for 1 hour produced no statistically significant responses in airflow or resistance in individuals with airway hyperreactivity/asthma (D'Alessandro et al. 1996). The intraspecies uncertainty factor of 1 is further supported by the fact that pediatric asthmatics do not appear to be more responsive to irritants than adult asthmatics (Avital et al. 1991). Asthmatics have been identified as the most susceptible when exposed to irritant gases. Chlorine is a highly irritating and corrosive gas that reacts directly with the tissues of the respiratory tract with no pharmacokinetic component involved in toxicity; therefore, effects are not expected to vary greatly among other susceptible, non-asthmatic populations. Because the 0.5 ppm concentration appeared to be a threshold concentration for more severe effects in susceptible individuals regardless of the exposure duration, the 0.5 ppm concentration was applied across all AEGL-1 exposure durations. The 0.5 ppm concentration was considered appropriate for the 8-hour AEGL-1 because effects were not increased in the atopic individual following a second 4-hour exposure to 0.5 ppm on the same day.

The AEGL-2 values were based on the same study in which healthy human subjects experienced

some sensory irritation and transient changes in pulmonary function measurements and 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 susceptible individual remained in the exposure chamber for the full 4 hours before the symptoms occurred. Therefore, when considering the first 4 hours of exposure, this concentration was a no-effect level in a susceptible individual. The symptoms of shortness of breath and wheezing occurred some time after 4 hours but before the end of the 8-hour exposure. The symptoms were fully reversible and did not impair the ability of the individual to leave the chamber (escape). Because both sexes were tested, subjects were undergoing light exercise during the exposures, making them more vulnerable to sensory irritation, and an exercising susceptible individual exhibited effects that did not impede escape for the 4-hour exposure duration (consistent with the definition of the AEGL-2), no uncertainty factor to account for differences in human sensitivity was applied. The intraspecies uncertainty factor of 1 is supported by another study in which a concentration of 1.0 ppm for 1 hour resulted in significant changes in pulmonary function parameters for all five tested individuals who had a history of airway hyperreactivity or asthma; two of the five subjects experienced undefined respiratory symptoms following exposure (D'Alessandro et al. 1996). Chlorine is a highly irritating and corrosive gas that reacts directly with the tissues of the respiratory tract with no pharmacokinetic component involved in toxicity; therefore, effects are not expected to vary greatly among other susceptible, non-asthmatic populations. Although concentration is more important than exposure duration for inducing asthmatic symptoms, time-scaling was considered appropriate for the AEGL-2 as the AEGL-2 is defined as the threshold for irreversible effects which in the case of irritants generally involves tissue damage. Although the endpoint used in this case, wheezing that was accompanied by a significant increase in airways resistance, has a different mechanism of action than that of direct tissue damage, it is assumed that some biomarkers of tissue irritation would be present in the airways and lungs at the AEGL-2. For the shorter exposure durations, the AEGL-2 was time-scaled from the 4-hour 1 ppm concentration using the relationship, $C^2 \times t = k$. The scaling factor was based on regression analyses of concentrations and exposure durations that attained nuisance levels of irritation in human subjects. The 10-minute value was set equal to the 30-minute value in order to not exceed the highest exposure of 4.0 ppm in controlled human studies. The 8-hour value was set equal to the 4-hour value as the symptoms experienced after 4 hours of exposure were fully reversible.

In the absence of human data, the AEGL-3 values were based on animal lethality data. The mouse was not chosen as an appropriate model for lethality because mice often showed delayed deaths which several authors attributed to bronchopneumonia. Because the mouse was shown to be more sensitive to chlorine than the dog and rat and because the mouse does not provide an appropriate basis for quantitatively predicting mortality in humans, a value below that resulting in no deaths in the rat (213 and 322 ppm in two studies) and above that resulting in no deaths in the mouse (150 ppm) for a period of 1 hour was chosen (MacEwen and Vernot, 1972; Zwart and Woutersen, 1988). The AEGL-3 values were derived from a 1-hour concentration of 200 ppm. This value was divided by a total uncertainty factor of 10: 3 to extrapolate from rats to humans (interspecies values for the same endpoint differed by a factor of approximately 2 within each of

several studies), and by an uncertainty factor of 3 to account for differences in human sensitivity. The susceptibility of asthmatics relative to healthy subjects when considering lethality is unknown, but the data from two studies with human subjects showed that doubling a no-effect concentration for irritation and bronchial constriction resulted in potentially serious effects in the asthmatics but not in the normal individuals. Time-scaling was considered appropriate for the AEGL-3 because tissue damage is involved (data in animal studies clearly indicate that time scaling is appropriate when lung damage is involved). The AEGL-3 values for the other exposure times were calculated based on the $C^2 \times t = k$ relationship which was derived based on the endpoint of irritation from a study with humans.

The calculated values are listed in the table below.

SUMMARY OF AEGL VALUES FOR CHLORINE [ppm (mg/m^3)]						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**
AEGL-1[a]	0.5 (1.5)	0.5 (1.5)	0.5 (1.5)	0.5 (1.5)	0.5[b] (1.5)	Symptomless, transient changes in pulmonary function parameters in atopic individual (Rotman et al., 1983) and in asthmatic individuals at 0.4 ppm (D'Alessandro et al., 1996)
AEGL-2	2.8 (8.1)	2.8 (8.1)	2.0 (5.8)	1.0 (2.9)	0.7 (2.0) **1.0** **(2.9)**	No symptoms in healthy individuals; respiratory symptoms in atopic and asthmatic individuals (Rotman et al., 1983; D'Alessandro et al., 1996)
AEGL-3	50 (145)	28 (81)	20 (58)	10 (29)	7.1 (21)	Threshold for lethality in the rat (MacEwen and Vernot, 1972; Zwart and Woutersen, 1988)

[a]The distinctive, pungent odor of chlorine will be noticeable to most individuals at this concentration.
[b]Because effects were not increased following an interrupted 8-hour exposure of an atopic individual to 0.5 ppm, the 8-hour AEGL-1 was set equal to 0.5 ppm.

Attachment 12

ACUTE EXPOSURE GUIDELINE LEVELS
for HFE-7100
Modification of AEGL Values

National Advisory Committee for AEGLs Meeting 26
September 10-12, 2002

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
George Rusch

Summary of animal toxicity data for HFE-7100

Concentration (ppm)	Exposure Duration	Species	Effect	Reference
214,000	several 20-minute sessions at lower concentrations	rat	convulsions, death of 3 of 4 rats; not anesthetic	Eger 1998
100,000	4 hours	rat	no deaths; few signs	3M Company 1995
89,300 48,900 18,800 10,000	5 minutes 5 minutes 5 minutes 5 minutes	dog	slightly agitated, head tremors, stiff limbs no signs described no signs described no signs described	Kenny et al. 1996
30,000 15,056 7538 4629	gd 6-19, 6 hours/day	rat	slight stress of dams as indicated by slightly reduced body weights in dams at two higher concentrations; no visceral or skeletal malformations of fetuses	Huntingdon Life Sciences 1996b
28,881 9283 2935 1489	4 weeks: 6 hours/day, 5 days/week	rat	no clinical signs at any exposure; minimal, reversible hepatocellular hypertrophy in some animals at two higher exposures; no toxicologically significant effects; not neurotoxic	Coombs et al. 1996a
15,159 7533 4550 1502	13 weeks: 6 hours/day, 5 days/week	rat	no clinical signs at any exposure; no toxicologically significant effects; reversible hepatocyte hypertrophy at high concentration; not neurotoxic	Coombs et al. 1996b

gd = gestation days

HFE-7100

Cardiac Response to Administration of Epinephrine in Dogs[a]	
Concentration (ppm)	**Effects**
10,000	Struggling and slight salivation in 1 of 6 dogs; no cardiac response in any of 6 dogs.
18,800	Deep, slow breathing (1/6), forelimbs cold to touch (1/6), struggling (1/6), licking of lips when mask removed (2/6), salivation (2/6)[b]; no cardiac response in any of six dogs.
48,900	Several of the following signs in all 6 dogs: trembling, tremors, arched back, rigid legs, licking lips when mask removed, restlessness, forepaws or ears and neck cold to touch; no cardiac response in any of 6 dogs.
89,300	Restlessness, forepaws and ears cold, front legs rigid, tremors, arched back, excessive salvation; no cardiac response (only one dog tested)

[a] The described effects follow administration of epinephrine at doses of 1-12 µg/kg; epinephrine was administered 5 minutes after the start of exposure.

[b]These effects were generally observed in different dogs.

Data from Kenny et al. 1996.

Summary of AEGL Values for HFE-7100 [ppm (mg/m^3)]						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1 Nondisabling	2500 (25,550) **NR**[a]	2500 (25,550) **NR**	2500 (25,550) **NR**	2500 (25,550) **NR**	2500 (25,550) **NR**	Reversible organ weight changes, repeated exposures, rat (Coombs et al. 1996b)
AEGL–2 Disabling	8200 (84,000) **4900**	8200 (84,000) **4900**	8200 (84,000) **4900**	8200 (84,000) **4900**	8200 (84,000) **4900**	Clinical signs, cardiac sensitization test, dog (Kenny et al. 1996) **NOAEL for clinical signs - dog (Kenney et al. 1996)**
AEGL–3 Lethal	15,000 (150,000) **NR**[b]	15,000 (150,000) **NR**	15,000 (150,000) **NR**	15,000 (150,000) **NR**	15,000 (150,000) **NR**	Severe clinical signs, cardiac sensitization test, dog (Kenney et al. 1996)

[a]Not Recommended. Numeric values for AEGL-1 are not recommended as data that meet the definition of an AEGL-1 are not available. Repeated exposures of rats to 30,000 ppm did not result in toxicologically significant effects.

[b]Not Recommended. Numeric values for AEGL-3 are not recommended as data that meet the definition of an AEGL-3 are not available. The lethal value for rats was >100,000 ppm and <214,000 ppm.

PROPOSED HFE-7100 MODIFICATIONS

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	4900 ppm	4900 ppm	4900 ppm	4900 ppm	4900 ppm
AEGL-2 (Disabling)	8900 ppm	8900 ppm	8900 ppm	8900 ppm	8900 ppm
AEGL-3 (Lethal)	>10,000 ppm	>10,000 ppm	>10,000 ppm	>10,000 ppm	>10,000 ppm

AEGL-1: Based on no signs in dogs exposed for 5 minutes.
Alternative: 30,000 ppm/10 = 3000 ppm (but, this is a repeated no-effect exposure)
AEGL-2: Based on severe, reversible signs of stress in dogs exposed for 5 minutes.
AEGL-3: Based on no deaths in rats exposed to 100,000 ppm for 4 hours.

AEGLs for ALLYLAMINE

NAC-26 (September 10-12, 2002)

DRAFT 3, Second Edition – Continuation from NAC-25

ORNL Staff Scientist:	**Chemical Manager:**
Sylvia Milanez	Loren Koller
Chemical Reviewers: Mark McClanahan, Ernest Falke	

- An Executive Summary for allylamine was presented to NAC-25 (6/2002) which incorporated February 2002 COT comments. NAC-25 developed alternative values for AEGL-1, as shown below *(AEGL values presented to NAC-25 are in italics).* A discussion was begun on the AEGL-2 and AEGL-3 values, leading to new AEGL-2 values developed post- NAC-25. AEGL-3 is unchanged.

Summary of AEGL Values for Allylamine [ppm (m/mg^3)]

Classification	10-mine	30-mine	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1	0.42	0.42	0.42	0.42	0.42	Mild human irritation or discomfort (Hine et al., 1960)
[NAC-25]	*[0.25]*	*[0.25]*	*[0.25]*	*[0.25]*	*[0.25]*	
AEGL-2	3.3	3.3	3.3	1.8	1.2	Threshold for severe human irritation (≤ 1 hr; Hine et al., 1960) and heart lesions in rats (≥ 4 hrs; Guzman et al., '61)
[NAC-25]	*[6.1]*	*[6.1]*	*[4.1]*	*[1.8]*	*[1.2]*	
AEGL-3	~~146~~ 150	40	18	3.5	2.3	Lethality threshold in rats (Hine et al., 1960)

AEGL-1

- Based on young adult volunteer study. Exposure for 5 min to 2.5, 5, or 10 ppm, or briefly to 14 ppm (10-14/concentration; sex not specified; Hine et al., 1960). Graded sensory responses for eye irritation, nose irritation, pulmonary discomfort, CNS effects, and olfactory cognition on 5-point scale (1=absent; 2=slight; 3=moderate; 4=severe; 5=extreme or intolerable).

- 14 ppm was intolerable; exposure terminated almost immediately and sensory responses not graded.

- Odor detection, slight or moderate eye and nose irritation, and pulmonary discomfort were reported in all groups (2.5-10 ppm), incidence generally increasing with concentration. AEGL-1 based on 2.5 ppm.

- Same AEGL-1 value used for 10 min. to 8 hrs because mild irritant effects do not generally vary greatly with time. Intraspecies UF=3 applied for human variability. MF=2 applied because exposure was only 5 min and no tested conc. elicited only slight irritation; "moderate" irritation may exceed AEGL-1. Supported by occupational study indicating exposure to 0.2 ppm allylamine ≤4 hrs was no-effect level for workers (Shell Oil Co., 1992).

Attachment 13

AEGL-2

- 10, 30, and 60-min AEGL-2 based on same study as AEGL-1(Hine et al., 1960). 10 ppm considered threshold for "extreme or intolerable" irritation, seen at 14 ppm. Same AEGL-2 value used for 10- 60 min. because irritation from exposure for 5 min to 10 ppm (slight or moderate eye and nose irritation and pulmonary discomfort; severe olfactory cognition) was not expected to increase beyond scope of AEGL-2. Intraspecies UF=3 for human variability, yielding AEGL-2 values of 3.3 ppm for 10-60 minutes.

- Exposure to 3.3 ppm for 4 or 8-hrs, however, was predicted to cause cardiovascular toxicity based on a rat study (myofibril fragment damage, perivascular edema, and cellular infiltration; Guzman et al., 1961). In this study, exposure to 40 ppm for 16 hrs was threshold for cardiovascular lesions. AEGL-2 values of 1.8 and 1.2 ppm were derived for 4 and 8 hrs using $C^n \times t = k$, where n = 1.7 (calculated from this study cardiotox. data).

- An interspecies UF=5 was applied (similar mechanism of toxicity among mammalian species and humans, but 3 yields values approaching threshold for lethality from pulmonary lesions for 4-8 hours). The intraspecies UF=10 because variability of cardiotoxic response to allylamine among humans is undefined, and several potentially sensitive populations exist (diabetics, persons with congestive heart failure).

AEGL-3

- Derived from rat LC_{50} study where exposures were for 1, 4, or 8 hours (Hine et al., 1960). Rats that died had stomachs distended with air, fluid-filled lungs, alveolar hemorrhage, and pulmonary edema. The threshold for lethality, as represented by LC_{01} values calculated using probit analysis, was the AEGL-3 endpoint.

- The 1-hr, 4-hr, and 8-hr AEGLs were obtained using the respective LC_{01} values. The 10-min and 30-min AEGLs were derived from 1-hr LC_{01} using $C^n \times t = k$, where n = 0.85 was calculated from this study LC_{50} data. Total UF=30: 10 for interspecies variability (lack of acute toxicity studies from other species with AEGL-3 level endpoints) and 3 for human variability (steep dose-response indicates threshold for lethality due to direct destruction of lung tissue is not likely to vary greatly among humans).

- Similar AEGL-3 values were obtained from other rat studies that used fewer animals and exposure levels.

Perchloromethyl Mercaptan

Summary of Currently Proposed AEGL Values for PMM (ppm)						
Level	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1	0.018	0.018	0.014	0.0090	0.0060	NOAEL of 0.079 ppm for 6 hr/d, 5 d/wk for 70-72 exposure days; UF = 10 (Knapp and Thomassen, 1987)
AEGL-2	0.044	0.044	0.035	0.022	0.015	Exposure-related mild to minimal focal subacute interstitial pneumonia and slightly increased lung weights in rats exposed to 0.58 ppm for 6 h/d, 5 d/wk for 70-72 days; UF = 30 (Knapp and Thomassen, 1987)
AEGL-3	0.54	0.38	0.30	0.075	0.038	No mortality in rats exposed to 9 ppm for 1 hour; UF = 30 (Stauffer Chemical Co., 1971)

COT COMMENTS

Major COT comments are provided at the back of the handout for your review. A summary of the comments relevant to the NAC are as follows:

COT has expressed reservations about the use of the subchronic study as the basis for PMM AEGL derivations:

- The AEGL-1 is based on a NOAEL from a study in which rats were exposed to PMM for 6 hr/d, 5 d/wk for 70-72 exposure days, with an UF = 10.
- AEGL-2 was based on exposure-related mild to minimal focal subacute interstitial pneumonia and slightly increased lung weights in rats exposed to 0.58 ppm for 6 h/d, 5 d/wk for 70-72 days, with an UF = 30.

Specifically, COT has asked if it really is the NAC's intent to base AEGL values on prevention of opportunistic pulmonary infection following a single exposure to an irritant rather than being associated with direct irritant properties of the material.

COT also recommends that the NAC should consider including a modifying factor to account for the poor data quality.

Attachment 14

Other alternatives to the current AEGL derivations (based on more acute-driven endpoints, incorporate COT's suggestion to add MF, and result in almost the same values).

AEGL-1

Use the Knapp et al., 1987 study:

- 0.13 ppm for 6 h/day, 5 d/wk for 2 wks resulted in mild nasal epithelial changes only.
- Gage (1970) study reported that twenty, 6-hour exposures to 0.5 ppm resulted in no signs of toxicity or organ abnormalities

Add MF of 2 for poor database - end up with 0.065 ppm as the starting point, which is almost same as currently proposed starting point of 0.079 ppm based on NOAEL from subchronic exposure study.

AEGL-2

Use the Knapp et al., 1987 study:

- 1.15 ppm for 6 h/day, 5 d/wk for 2 wks caused: haircoat stains, labored breathing, tremors, reduced bw gain; increased lung weights, pulmonary edema, mucous secretions, mild nasal epithelial changes. All rats survived.
- Supported by Gage (1970) study in which 4 rats exposed to 2 ppm for twenty, 6-hour exposures: resulted in initial respiratory difficulty; postmortem revealed pulmonary congestion (again, all rats survived).

Effects more consistent with definition of AEGL-2. Add MF of 2 for poor database - end up with 0.575 ppm as starting point. Same as currently proposed starting point (0.58 ppm for 6 h/d, 5 d/wk for 70 exposures) , but now based upon more substantial health effects, and although is a repeated-exposure study, it is not a subchronic study

AEGL-3

MF not as critical for the AEGL-3 level. Vernot and Stauffer reported almost identical rat 1-hr LC_{50} values.

Summary of Alternative AEGL Values for PMM (ppm)						
Level	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1	0.015	0.015	0.012	0.0074	0.0049	0.13 ppm for 6 h/d, 5 d/wk for 2 wks resulted in mild nasal epithelial changes; UF = 10; MF 2 (Knapp et al., 1987)
AEGL-2	0.044	0.044	0.035	0.022	0.014	1.15 ppm for 6 h/d, 5 d/wk for 2 wks caused haircoat stains, labored breathing, tremors, reduced b.w. gain, increased lung wts, mucous secretions, mild nasal epithelial changes; UF = 30; MF 2 (Knapp et al., 1987)
AEGL-3	0.54	0.38	0.30	0.075	0.038	No mortality in rats exposed to 9 ppm for 1 hour; UF = 30 (Stauffer Chemical Co., 1971)
	0.27	0.19	0.15	0.038	0.019	with additional MF of 2

Additional information for your reference:

COT Comments

The toxicity database for this chemical is weak. The derived AEGL values rely on unpublished papers and an abstract. The document dismisses other available published studies as inadequate for reasons such as "the purity of the chemical was not determined" (page 4), chemical was mixed with acetone (page 6), and the lack of verification of chamber concentrations (page 6). These arguments are not very convincing because as the papers relied upon for AEGL derivations have their own very substantial limitations as well. It would be best to discuss the overall lack of quality in all of the available studies and to make an argument for why the studies chosen were most appropriate. ***The NAC should consider including a modifying factor to account for the poor data quality.***

It appears that the repellent, suffocating, unbearable, acrid odor of this material (Section 5.1, sentence 3) and the notorious irritation associated with mercaptans could serve as an objective basis for the AEGL-1. Instead, the proposed AEGL-1 is based on a rat 72-d subchronic, repeated-exposure inhalation study rather than a more appropriate acute, single-exposure study with durations relevant to the 1-8 h AEGL derivations. From the AEGL-1 derivation, the end point of concern is "minimal interstitial pneumonia," which developed after 70-72 ppm, 5 d/wk, 6 h/d exposure. Pneumonia did not claim any of these animals during the exposures, and the only signs were "increased sneezing." Could rat deaths from pneumonia even be possible after a single 6-h acute inhalation exposure at 0.014-0.58 ppm? Rat pneumonia after repeated exposures is consistent with observations in dogs and guinea pigs (Section 3.2.2), but it appears that the AEGL-1 values are actually based on prevention of opportunistic pulmonary infections following exposure to PMM rather than being associated with direct irritant properties of the material.

To dismiss the use of a subchronic study to calculate the AEGL-1 because it is "inherently conservative" (Section 5.3) borders on the bureaucratic. Explain and justify the biological basis for scaling results from 432 h of exposure to a 10 min AEGL? It appears that the NAC was unable to locate the original full text of the acute range-finding report, was reluctant to base an AEGL upon only an abstract, was impressed with Stauffer's GLP record-keeping, and therefore could not recommend an AEGL based on the rodent subchronic empirical NOAEL without an additional UF. The arguments on these points lack credibility.

It is important that the reader be appraised of the magnitude and intensity of mercaptan odor and ocular and upper respiratory tract irritation (if any) at the proposed AEGL values. Specifically, the AEGL documentation should be of sufficient clarity to address the inevitable situation wherein residents, visitors, or workers are exposed to and recognize the odor of PMM; can hazardous-materials planners and emergency responders anticipate adverse health effects on the lung at AEGLs 1 and 2 derived on the basis of systemic toxicity (ES, paragraph 3)? This is important, because the proposed values are more than 10 times less than promulgated federal PELs, and the current TLVs are based on avoidance of objectionable irritation—not on avoidance of secondary respiratory infections after repeated daily exposures over a prolonged period. ***Should the NAC adopt the position that prevention of opportunistic pulmonary infection following a single exposure to an irritant is the proper public health end point for mercaptans and other irritants, that should be stated.***

Summary of existing data.

Vernot et al., 1977

Groups of 5 M or 5 F Sprague-Dawley (SD) rats

1-hour LC_{50} - M: 11 ppm
Fe: 16 ppm

Notes: no other information provided

Stauffer, 1971

Groups of 5 M and 5 F SD rats
Exposed to 9, 18, 124, 382, 822, and 2342 ppm for 1 hour

9 ppm: no deaths
18 ppm: 7/10 died by 24 hours post-exposure
124+ ppm - all rats died

1-hour LC_{50} - 13 ppm

All exposed animals exhibited eye and mucosa irritation within five minutes after exposure, and dyspnea, gasping, and "acute depression" were also observed.

Post mortem of animals that died revealed pulmonary edema, heart and liver congestion, and inflammation of the pericardial and peritoneal membranes and upper gastrointestinal tract.

Notes: Not known if analytical or measured concentrations. The Stauffer report is just a summary of experiment.

LC_{50} consistent with Vernot.

Gage (1970)

100 ppm for 1 hour: 4/4 rats died. Severe respiratory difficulty. Post mortem revealed pulmonary edema
10 ppm for 6 hour: 3/4 rats died. Lethargy and respiratory difficulty. Post mortem revealed pulmonary edema
2 ppm for twenty, 6-hour exposures: all 4 rats survived. Initial respiratory difficulty. Post mortem revealed pulmonary congestion
0.5 ppm for twenty, 6-hour exposures: 4 M and 4 F rats all survived; no signs of toxicity; all organs normal

Notes: Initially discounted this study because: lack of information on the purity of the chemical, mixing of the chemical with acetone for exposure purposes, and no analytical verification of chamber concentrations. However, have reconsidered. Stauffer also did not report analytical verification of chamber concentration, and inhalation of acetone with PMM should not be issue (summary of only inhalation study with acetone provided at end of this document).

Knapp et al., 1987

Groups of 15 M and F SD rats exposed to 0, 0.02, 0.13, 1.15 ppm for 6 h/d, 5 d/wk, for 2 wks

1.15 ppm: Clinical signs of haircoat stains, labored breathing, tremors, reduced bw gain
Postmortem: increased lung weights, pulmonary edema, increased mucous secretions, mild nasal epithelial changes
Microscopic examination: alveolitis, interstitial fibroplasia, and perivascular edema
0.13 ppm: Postmortem: mild nasal epithelial changes

Notes: This was an abstract. No additional information available.

Knapp and Thomassen, 1987

Groups of 18 SD rats exposed to 0, 0.014, 0.079, 0.580 ppm for 6 h/d, 5 d/wk for total of 70-72 exposures

0.580 ppm: Clinical signs: increased salivation in males and increased sneezing in males and females starting (number of observations/day of first observation for the 0, 0.014, 0.079, 0.580 ppm groups: sneezing in males: 0/0, 0/0, 0/0, 5/59, respectively; salivation in males: 7/49, 8/31, 5/26, and 12/18, respectively; sneezing in females: 0/0, 0/0, 2/59, 3/59, respectively)
Time-related decrease in absolute bw in females starting at week 1 (-6 to -12% of controls); total bw gain 64% of controls
Postmortem: Increased absolute lung wt and lung wt relative to bw and brain wt in males (+9%, +16% and +10%, respectively) and increased lung wt relative to bw in females (+15%) as compared with controls
Mucus in trachea of 2/18 males and 4/18 females.
Microscopic examination: acute inflammation and hypertrophy, and/or hyperplasia of respiratory nasal epithelium in males and females. Residues of purulent or serum exudate noted in all males and 13/18 females in the 0.580 ppm group. Only exposure-related pulmonary lesion was mild to minimal focal subacute interstitial pneumonia in 5 males and 1 female.

0.079 ppm: Microscopic examination: residues of purulent or serum exudate noted in 1 male and 1 female.

Notes: Currently, AEGL-1 is based on the 0.079 concentration (NOAEL), and the AEGL-2 is based on the 0.58 ppm concentration (exposure-related mild to minimal focal subacute interstitial pneumonia and slightly increased lung weights in rats).

Study addressing inhalation toxicity of acetone in rats.

Bruckner, J.V. and Peterson, R.G. 1981. Evaluation of toluene and acetone inhalant abuse. II. Model development and toxicology. Toxicol. Appl. Pharmacol. 61:302-312.

Male Sprague-Dawley rats were exposed to 19,000 ppm acetone for 3 hr/day, 5 d/week, for 8 weeks (Bruckner and Peterson, 1981a). Body weight gains of the treated animals were slightly less than air exposed controls, however, statistical significance was not reached at any time. Kidney weights of the treated animals were significantly ($p \leq 0.01$) less than the controls after 4 weeks, but were similar to controls after 8 weeks of exposure. Serum SGOT activities were slightly elevated (not significant) in treated animals at weeks 2, 4, and 8, however, LDH activity and BUN and liver triglyceride levels were not affected at any time during the study. No microscopic lesions were observed in the liver, brain, heart, and kidneys of acetone exposed animals. Females were not included and no other concentrations of acetone were tested.

Perchloromethyl Mercaptan

Summary of Currently Proposed AEGL Values for PMM (ppm)						
Level	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1	0.018	0.018	0.014	0.0090	0.0060	NOAEL of 0.079 ppm for 6 hr/d, 5 d/wk for 70-72 exposure days; UF = 10 (Knapp and Thomassen, 1987)
AEGL-2	0.044	0.044	0.035	0.022	0.015	Exposure-related mild to minimal focal subacute interstitial pneumonia and slightly increased lung weights in rats exposed to 0.58 ppm for 6 h/d, 5 d/wk for 70-72 days; UF = 30 (Knapp and Thomassen, 1987)
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1

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2

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Add MF of 2 for poor database - end up with 0.065 ppm as the starting point, which is almost same as currently proposed starting point of 0.079 ppm based on NOAEL from subchronic exposure study.

3

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- 1.15 ppm for 6 h/day, 5 d/wk for 2 wks caused: haircoat stains, labored breathing, tremors, reduced bw gain; increased lung weights, pulmonary edema, mucous secretions, mild nasal epithelial changes. All rats survived.
- Supported by Gage (1970) study in which 4 rats exposed to 2 ppm for twenty, 6-hour exposures: resulted in initial respiratory difficulty; postmortem revealed pulmonary congestion (again, all rats survived).

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AEGL-3

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4

Summary of Alternative AEGL Values for PMM (ppm)						
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AEGL-2	0.044	0.044	0.035	0.022	0.014	1.15 ppm for 6 h/d, 5 d/wk for 2 wks caused haircoat stains, labored breathing, tremors, reduced b.w. gain, increased lung wts, mucous secretions, mild nasal epithelial changes; UF = 30; MF 2 (Knapp et al., 1987)
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It appears that the repellent, suffocating, unbearable, acrid odor of this material (Section 5.1, sentence 3) and the notorious irritation associated with mercaptans could serve as an objective basis for the AEGL-1. Instead, the proposed AEGL-1 is based on a rat 72-d subchronic, repeated-exposure inhalation study rather than a more appropriate acute, single-exposure study with durations relevant to the 1-8 h AEGL derivations. From the AEGL-1 derivation, the end point of concern is "minimal interstitial pneumonia," which developed after 70-72 ppm, 5 d/wk, 6 h/d exposure. Pneumonia did not claim any of these animals during the exposures, and the only signs were "increased sneezing." Could rat deaths from pneumonia even be possible after a single 6-h acute inhalation exposure at 0.014-0.58 ppm? Rat pneumonia after repeated exposures is consistent with observations in dogs and guinea pigs (Section 3.2.2), but it appears that the AEGL-1 values are actually based on prevention of opportunistic pulmonary infections following exposure to PMM rather than being associated with direct irritant properties of the material.

To dismiss the use of a subchronic study to calculate the AEGL-1 because it is "inherently conservative" (Section 5.3) borders on the bureaucratic. Explain and justify the biological basis for scaling results from 432 h of exposure to a 10 min AEGL? It appears that the NAC was unable to locate the original full text of the acute range-finding report, was reluctant to base an AEGL upon only an abstract, was impressed with Stauffer's GLP record-keeping, and therefore could not recommend an AEGL based on the rodent subchronic empirical NOAEL without an additional UF. The arguments on these points lack credibility.

It is important that the reader be appraised of the magnitude and intensity of mercaptan odor and ocular and upper respiratory tract irritation (if any) at the proposed AEGL values. Specifically, the AEGL documentation should be of sufficient clarity to address the inevitable situation wherein residents, visitors, or workers are exposed to and recognize the odor of PMM; can hazardous-materials planners and emergency responders anticipate adverse health effects on the lung at AEGLs 1 and 2 derived on the basis of systemic toxicity (ES, paragraph 3)? This is important, because the proposed values are more than 10 times less than promulgated federal PELs, and the current TLVs are based on avoidance of objectionable irritation—not on avoidance of secondary respiratory infections after repeated daily exposures over a prolonged period. ***Should the NAC adopt the position that prevention of opportunistic pulmonary infection following a single exposure to an irritant is the proper public health end point for mercaptans and other irritants, that should be stated.***

Summary of existing data.

Vernot et al., 1977

Groups of 5 M or 5 F Sprague-Dawley (SD) rats

1-hour LC_{50} - M: 11 ppm
Fe: 16 ppm

Notes: no other information provided

Stauffer, 1971

Groups of 5 M and 5 F SD rats
Exposed to 9, 18, 124, 382, 822, and 2342 ppm for 1 hour

9 ppm: no deaths
18 ppm: 7/10 died by 24 hours post-exposure
124+ ppm - all rats died

1-hour LC_{50} - 13 ppm

All exposed animals exhibited eye and mucosa irritation within five minutes after exposure, and dyspnea, gasping, and "acute depression" were also observed.

Post mortem of animals that died revealed pulmonary edema, heart and liver congestion, and inflammation of the pericardial and peritoneal membranes and upper gastrointestinal tract.

Notes: Not known if analytical or measured concentrations. The Stauffer report is just a summary of experiment.

LC_{50} consistent with Vernot.

Gage (1970)

100 ppm for 1 hour: 4/4 rats died. Severe respiratory difficulty. Post mortem revealed pulmonary edema
10 ppm for 6 hour: 3/4 rats died. Lethargy and respiratory difficulty. Post mortem revealed pulmonary edema
2 ppm for twenty, 6-hour exposures: all 4 rats survived. Initial respiratory difficulty. Post mortem revealed pulmonary congestion
0.5 ppm for twenty, 6-hour exposures: 4 M and 4 F rats all survived; no signs of toxicity; all organs normal

Notes: Initially discounted this study because: lack of information on the purity of the chemical, mixing of the chemical with acetone for exposure purposes, and no analytical verification of chamber concentrations. However, have reconsidered. Stauffer also did not report analytical verification of chamber concentration, and inhalation of acetone with PMM should not be issue (summary of only inhalation study with acetone provided at end of this document).

Knapp et al., 1987

Groups of 15 M and F SD rats exposed to 0, 0.02, 0.13, 1.15 ppm for 6 h/d, 5 d/wk, for 2 wks

1.15 ppm: Clinical signs of haircoat stains, labored breathing, tremors, reduced bw gain
Postmortem: increased lung weights, pulmonary edema, increased mucous secretions, mild nasal epithelial changes
Microscopic examination: alveolitis, interstitial fibroplasia, and perivascular edema
0.13 ppm: Postmortem: mild nasal epithelial changes

Notes: This was an abstract. No additional information available.

Knapp and Thomassen, 1987

Groups of 18 SD rats exposed to 0, 0.014, 0.079, 0.580 ppm for 6 h/d, 5 d/wk for total of 70-72 exposures

0.580 ppm: Clinical signs: increased salivation in males and increased sneezing in males and females starting (number of observations/day of first observation for the 0, 0.014, 0.079, 0.580 ppm groups: sneezing in males: 0/0, 0/0, 0/0, 5/59, respectively; salivation in males: 7/49, 8/31, 5/26, and 12/18, respectively; sneezing in females: 0/0, 0/0, 2/59, 3/59, respectively)
Time-related decrease in absolute bw in females starting at week 1 (-6 to -12% of controls); total bw gain 64% of controls
Postmortem: Increased absolute lung wt and lung wt relative to bw and brain wt in males (+9%, +16% and +10%, respectively) and increased lung wt relative to bw in females (+15%) as compared with controls
Mucus in trachea of 2/18 males and 4/18 females.
Microscopic examination: acute inflammation and hypertrophy, and/or hyperplasia of respiratory nasal epithelium in males and females. Residues of purulent or serum exudate noted in all males and 13/18 females in the 0.580 ppm group. Only exposure-related pulmonary lesion was mild to minimal focal subacute interstitial pneumonia in 5 males and 1 female.

0.079 ppm: Microscopic examination: residues of purulent or serum exudate noted in 1 male and 1 female.

Notes: Currently, AEGL-1 is based on the 0.079 concentration (NOAEL), and the AEGL-2 is based on the 0.58 ppm concentration (exposure-related mild to minimal focal subacute interstitial pneumonia and slightly increased lung weights in rats).

Study addressing inhalation toxicity of acetone in rats.

Bruckner, J.V. and Peterson, R.G. 1981. Evaluation of toluene and acetone inhalant abuse. II. Model development and toxicology. Toxicol. Appl. Pharmacol. 61:302-312.

Male Sprague-Dawley rats were exposed to 19,000 ppm acetone for 3 hr/day, 5 d/week, for 8 weeks (Bruckner and Peterson, 1981a). Body weight gains of the treated animals were slightly less than air exposed controls, however, statistical significance was not reached at any time. Kidney weights of the treated animals were significantly ($p \leq 0.01$) less than the controls after 4 weeks, but were similar to controls after 8 weeks of exposure. Serum SGOT activities were slightly elevated (not significant) in treated animals at weeks 2, 4, and 8, however, LDH activity and BUN and liver triglyceride levels were not affected at any time during the study. No microscopic lesions were observed in the liver, brain, heart, and kidneys of acetone exposed animals. Females were not included and no other concentrations of acetone were tested.

ACUTE EXPOSURE GUIDELINES FOR HYDROGEN SULFIDE DERIVATION SUMMARY

AEGL-1 VALUES				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
0.26 ppm	**0.20 ppm**	**0.17 ppm**	**0.13 ppm**	**0.11 ppm**

Key Reference: Jappinen, P., Vilkka, V., Marttila, O., et al. 1990. Exposure to hydrogen sulfide and respiratory function. Br. J. Ind. Med. 47: 824-828.

Test Species/Strain/Number: Human/10 asthmatics

Exposure Route/Concentrations/Durations: Inhalation/2 ppm /30 minutes

Effects: Odor and pharyngeal dryness at the beginning of exposure; Headache (3/10); increased Raw (significant in 2/10) with no accompanying clinical signs or lung function effects

Endpoint/Concentration/Rationale: headache/2 ppm

Uncertainty Factors/Rationale:
Interspecies = 1: subjects were human
Intraspecies = 3: asthmatics not necessarily more sensitive than healthy individuals to headache induction, especially in the absence of any pulmonary function effects)

Modifying Factor: 3: for the wide variability in response after exposure to hydrogen sulfide for effects defined by AEGL-1. This is evidenced by the shallow concentration-response at the relatively low concentrations responsible for AEGL-1 effects (a rather broad change in exposure duration may allow for a relatively small change in response).

Animal to Human Dosimetric Adjustment: NA

Time Scaling: $C^n \times t = k$ where n = 4.4, value derived from rat lethality data ranging from 10 minutes to 6 hours. Data point used for AEGL-1 derivation was 30 min. Other time points were based on extrapolation.

Data quality and research needs: These values are supported by the fact that no adverse effects were observed in healthy humans exposed to 5 ppm hydrogen sulfide for 30 minutes or 10 ppm for 15 minutes while exercising to exhaustion (Bhambhani and Singh, 1991; Bhambhani et al., 1994, 1996a, 1996b). Using these concentrations and applying an uncertainty factor of 10 for sensitive human subpopulations, the following AEGL-1 values would be obtained: 0.64 ppm, 0.50, ppm, 0.43 ppm, 0.31 ppm, and 0.26 ppm for the 10-min, 30-min, 1-, 4-, and 8-hour time points, respectively, for the 5 ppm exposure for 30-minutes; and 1.1 ppm, 0.85, ppm, 0.73 ppm, 0.53 ppm, and 0.45 ppm for the 10-min, 30-min, 1-, 4-, and 8-hour time points, respectively, for the 10 ppm exposure for 15-minutes These values suggest that the proposed AEGL-1 values are protective.

AEGL-2 VALUES				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
41 ppm	**32 ppm**	**27 ppm**	**20 ppm**	**17 ppm**

Key References: (1) Green, F.H.Y., Schurch, S., DeSanctis, G.T., et al. 1991. Effects of hydrogen sulfide exposure on surface properties of lung surfactant. J. Appl. Physiol. 70: 1943-1949.; (2) Khan, A.A., Yong, S., Prior, M.G. et al., 1991. Cytotoxic effects of hydrogen sulfide on pulmonary alveolar macrophages in rats. J. Toxicol. Env. Health. 33: 57-64.

Test Species/Strain/Number: (1) Rat/Fischer 344/6 males; (2) Rat/Fischer 344/6 males

Exposure Route/Concentrations/Durations:
(1) Inhalation/ 0, 200, or 300 ppm/ 4 hours;
(2) Inhalation/ 0, 50, 200, or 400 ppm/ 4 hours

Effects:
(1) 200 ppm: No adverse clinical signs or gross lung pathology, increased protein and LDH in Lavage fluid; 300 ppm: Clinical signs during exposure, increased protein and LDH in Lavage fluid, lung atelectasis and edema.
(2) 50 and 200 ppm: no effect on viability of pulmonary alveolar macrophages; 300 ppm: decreased viability of Pulmonary alveolar macrophages. (200 ppm for 4 hours was determinant for AEGL-2)

Endpoint/Concentration/Rationale: (1) No-effect-level for gross lung pathology, minor perivascular edema, increased protein and LDH in lung lavage fluid. (2) No-effect-level for pulmonary alveolar macrophage viability/ 200 ppm

Uncertainty Factors/Rationale:
Interspecies = 3: rat and mouse data suggest little interspecies variability
Intraspecies = 3: The intraspecies uncertainty factor of 3 is considered sufficient because application of the default uncertainty factor of 10 would result in a total uncertainty factor of 30 which would yield AEGL-2 values inconsistent with the total database. AEGL-2 values derived with a total uncertainty factor of 30 would be 14 ppm for 10-minutes, 11 ppm for 30-minutes, 9.0 ppm for 1-hr, 6.7 ppm for 4-hours, and 5.7 ppm for 8-hours, values essentially identical to or below the 10 ppm concentration causing no effects in humans exercising to exhaustion (Bhambhani and Singh, 1991; Bhambhani et al., 1994, 1996a, 1996b, 1997).
Total UF = 10. The total adjustment is 10 because the factors of 3 each represent a logarithmic mean (3.16) of 10; therefore, 3.16 x 3.16 = 10.

Modifying Factor: NA

Animal to Human Dosimetric Adjustment: NA

Time Scaling: $C^n \times t = k$ where n = 4.4, value derived from rat lethality data ranging from 10 minutes to 6 hours. Data point used for AEGL-2 derivation was 4 hours. Other time points were based on extrapolation.

Data quality and research needs: Two well-conducted studies in rats support one another.

AEGL-3 VALUES				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
76 ppm	**59 ppm**	**50 ppm**	**37 ppm**	**31 ppm**

Key Reference: MacEwen, J.D. and Vernot, E.H. 1972. Toxic Hazards Research Unit Annual Report. Aerospace Medical Research Laboratory, Air Force Systems Command, Wright-Patterson Air Force Base, Ohio. Report No. ARML-TR-72-62. Pp. 66-69.

Test Species/Strain/Sex/Number: Sprague-Dawley rats/ 10 males/ concentration

Exposure Route/Concentrations/Durations: Rats/Inhalation: 400, 504, 635, or 800 ppm/1 hour
(Highest concentration causing no death in rats after a 1 hr-exposure (504 ppm) was determinant for AEGL-3)

Endpoint/Concentration/Rationale: Highest concentration causing no death in rats after a 1 hr-exposure/ 504 ppm/ threshold for death for 1 hour exposure in rats

Effects:

Concentration	Mortality
400 ppm	0/10
504 ppm	0/10
635 ppm	1/10
800 ppm	9/10

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies = 3: rat and mouse data suggest little interspecies variability
Intraspecies = The intraspecies uncertainty factor of 3 is considered sufficient because application of the default uncertainty factor of 10 would result in a total uncertainty factor of 30 which would yield AEGL-3 values inconsistent with the total database. AEGL-3 values derived with a total uncertainty factor of 30 would be 25 ppm for 10-minutes, 20 ppm for 30-minutes, 17 ppm for 1-hr, 12 ppm for 4-hours, and 10 ppm for 8-hours, values equal to or less than two-fold the concentration causing no effects in humans exercising to exhaustion (Bhambhani and Singh, 1991; Bhambhani et al., 1994, 1996a, 1996b, 1997). Effects consistent with the definition of AEGL-3 would be unlikely to occur at such concentrations.
Total UF = 10. The total adjustment is 10 because the factors of 3 each represent a logarithmic mean (3.16) of 10; therefore, 3.16 x 3.16 = 10.

Modifying Factor: NA

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^n \times t = k$ where n = 4.4, value derived from rat lethality data ranging from 10 minutes to 6 hours. Data point used for AEGL-3 derivation was 1 hour. Other time points were based on extrapolation.

Data Quality and Research Needs: Well-conducted study with appropriate endpoint for AEGL-3.

Acute Exposure Guideline Levels (AEGLs)

for

Vinyl chloride

(CAS Reg. No. 75-01-4)

$H_2C=CHCl$

NAC/AEGL Meeting 26, 10-12 September 2002, Washington, D.C.

FoBiG Scientist:
Ulrike Schuhmacher-Wolz / Fritz Kalberlah

Chemical Manager in German Toxicological Expert Group:
Wolfram Thiemann

Industry Reviewer for German Toxicological Expert Group:
Jürgen Pauluhn

Chemical Manager:
Robert Benson

METABOLISM

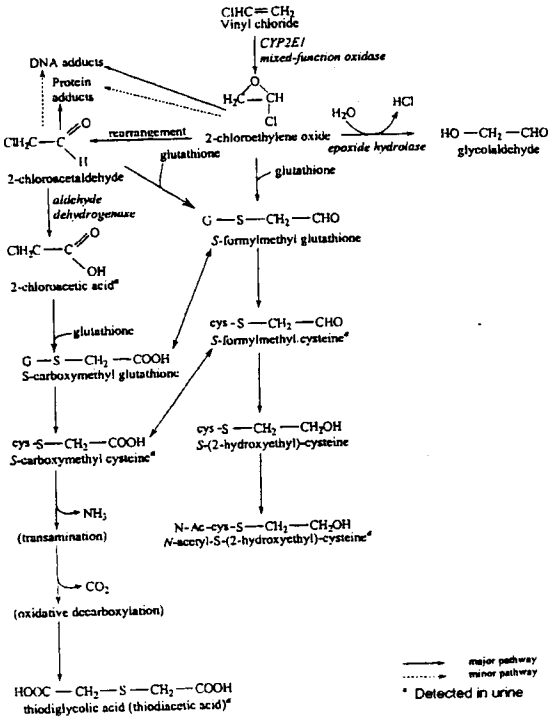


Fig 2. Proposed metabolic pathways for vinyl chloride (Plugge & Safe, 1977; Guengerich et al., 1979; Bolt et al., 1980; adapted from ATSDR, 1997).

Source: WHO, 1999

VINYL CHLORIDE

Attachment 17

PROPERTIES

- colorless flammable gas
- heavier than air
- high volatility
- decomposes to carbon dioxide and hydrogen chloride

PRODUCTION

- hydrochlorination of acetylene
- thermal cracking of 1,2-dichloroethane

USES

- mainly polymerized to PVC (PVC is used e.g. as packaging materials, building materials, electric appliances, medical care equipment)
- production of 1,1,1-trichloroethane and other chlorinated solvents

TOXICITY MECHANISMS AND CONCERNS

- poor warning properties (odor?, irritation?, headaches)
- acute toxicity only in high concentrations
- anesthetic and CNS effects after short term exposure
- cardiac sensitization and liver toxicity after short term exposure
- human carcinogen (liver angiosarcomas), carcinogenic in animals (mouse lung, rat liver) after short term exposure, in vivo: genotoxic, DNA-adducts, liver foci in low concentrations, especially in young animals

DATA RELEVANT TO AEGL-1

HUMAN

- **odor** threshold of **10 - 20 ppm** (Hori et al., 1972)
- odor detection at **261 ppm**, rapidly getting used (Baretta et al., 1969)
- average odor threshold of **3,000 ppm** (Amoore and Hautala, 1983)
- fairly pleasant odor at **25,000 ppm** for 3 min (Patty et al., 1930)
- **irritating** effects (lesions of the eyes) at very high, close to lethal concentrations (Danziger et al., 1960)
- secondary citations of unconfirmed studies (1000 ppm, 60 min.) **fatigue, visual disturbances** (Schottek, 1969; Lefaux, 1966)
- Baretta et al. (1969): experimental study; 4-6 volunteers

  491 ppm for 3.5 or 7.5 hours

  mild headache, some dryness of the eyes and nose in two subjects, odor after 5 minutes of exposure no longer detectable
- headache in workers chronically exposed to VC described by several authors (exposure concentration and duration not given in most cases) (Lilis et al., 1975; Suciu et al., 1975; EPA, 1987)
- **no effects** in human volunteers: **5 min., 8,000 ppm** (Lester et al.,1963)

ANIMAL

- Prodan et al. (1975): inhalation exposure of mice, rats, guinea pigs and rabbits

  42,900 ppm to 280,000 ppm for 2 hours

  lacrimation shortly after onset of exposure, lethal even at lowest conc.

- Mastromatteo et al. (1960): inhalation exposure of mice, rats and guinea pigs

  100,000 to 300,000 ppm for 30 minutes

  irritation occurred immediately after onset of exposure in rats and mice;

  400,000 ppm for 30 minutes

  irritating to guinea pigs

→ poor warning properties of VC

AEGL-1

→ odor detection or irritation are not suitable for the derivation of AEGL-1 values

→ endpoint: mild headache

Keystudy: Baretta et al., 1969

Endpoint: mild headache in humans at 491 ppm for 3.5h, assumed AEGL-1-NOAEL

Scaling: $C^n \times t = k$ with default n=3 for shorter exposure periods and n=1 for longer exposure periods (10 min value = 30 min value); default due to unknown mechanism

Total uncertainty factor: 3

Intraspecies: 3

A reduced factor was used because of the small interindividual differences in kinetics and nature of observed effect (headaches)

→ carcinogenic effects may not be excluded at AEGL-1 level

AEGL-1 VALUES FOR VINYL CHLORIDE

AEGL Level	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	~~310 ppm~~ 450 (800 mg/m³)	310 ppm (800 mg/m³)	250 ppm (650 mg/m³)	140 ppm (360 mg/m³)	70 ppm (180 mg/m³)

DATA RELEVANT TO AEGL-2

HUMAN

- Lester et al. (1963): inhalation exposure of 6 volunteers

  16,000 ppm for 5 min

  slight prenarcotic effects (dizziness, reeling, swimming head, nausea, dulling of visual and auditory cues) **in 5/6 subjects**

  12,000 ppm for 5 min

  1 person: reeling, swimming head; 1 person: unsure, „somewhat dizzy" in the middle of exposure; **4 persons no effects** including 1 person, who reported effects at 8,000 ppm

  8,000 ppm for 5 min

  1 person: "slightly heady" (same effect reported after sham exposure, no effect reported after 12,000 ppm by this volunteer); **5/6 persons: no effects**

- Patty et al. (1930): inhalation exposure of 2 persons

  25,000 ppm for 3 minutes

  dizziness, slight disorientation, burning sensation in the feet, headache persisted for 30 min after end of exposure

ANIMAL

- Patty et al. (1930): inhalation exposure of guinea pigs

  25,000 ppm for 5 min

  motor ataxia, unsteadiness on feet; animals were unconscious after 90 min.

- Clark & Tinston (1982): CNS-effects in rats after inhalation

  38,000 ppm for 10 min (EC_{50})

  Tremors of the limbs (range: 29,000-50,000 ppm) **added to proof**

- Clark & Tinston (1973, 1982): cardiac sensitization of dogs

  50,000 ppm - 71,000 ppm for 5 min (EC_{50})

  after injection of epinephrine (5 µg/kg , last 10 sec of 5 min exposure)

- Jaeger et al. (1974): single inhalation exposure of rats,

  100,000 ppm (LOAEL)- 50,000 ppm for 6 h (NOAEL)

  histopathological liver changes (vacuolization)

- Tátrai and Ungváry (1981): inhalation exposure of mice,

  1,500 ppm for 2 h

  stasis of blood flow, decreasing enzyme activities in the liver, subcellular liver damage in mice, shock liver after 24 h exposure;

1,500 ppm for 24 h

no histopathological changes or clinical effects in rats and rabbits.

Repeated exposure:

- Ungváry et al. (1978): developmental toxicity in rats

  1,500 ppm, day 1-9 or 8-14 of pregnancy (24h/d)

  increased absolute and relative liver weights in maternal rats, increased number of resorbed fetuses (day 1-9).

- John et al. (1977; 1981): developmental toxicity in rats

  2,500 ppm, day 6-15 of pregnancy (7 h/d)

  increased absolute and relative liver weights in maternal rats, no effects on fetuses; NOAEL 500 ppm.

- Thorton et al. (2002): developmental toxicity in rats

  1,100 ppm, day 6-19 of pregnancy (6 h/d)

  No effects on embryo-fetal development

- Thorton et al. (2002): developmental toxicity in rats, 2 generations

  100 ppm, up to 13 weeks (6 h/d)

  F_1-Generation increased hepatocellular alterations

AEGL-2

Keystudy: Lester et al. (1963)

Endpoint: prenarcotic effects, NOAEL 12,000 ppm for 5 min (effects at this concentration are below the AEGL-2 level)

Scaling: $C^n \times t = k$ with n = 2 for longer exposure periods up to equilibrium after 2 hours; from 2h to 8h no increase in effect size (2h AEGL-2 = 4h AEGL-2 = 8h AEGL-2)

Based on the dose-response curves in mice, and guinea pigs regarding prenarcotic effects values for n between 1.4 and 2.6 have been calculated for less than equilibrium durations (Mastromatteo et al.,1960)

Total uncertainty factor: 3

Intraspecies: **3**

Effects due to VC; only small differences regarding kinetics

→ supported by EC50-data (CNS-effects in rats at 38,000 ppm, 10 min, UF: 14) (Clark & Tinston, 1982)

AEGL-2 VALUES FOR VINYL CHLORIDE *					
AEGL Level	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-2	2,800 ppm (7,300 mg/m³)	1,600 ppm (4,100 mg/m³)	1,200 ppm (3,100 mg/m³)	820 ppm (2,100 mg/m³)	820 ppm (2,100 mg/m³)

* Carcinogenic effects were not considered

DATA RELEVANT TO AEGL-3

HUMAN

- Only two cases of accidental death reported, exposure concentration and time unknown (Danziger, 1960)
- Schaumann (1934): **70,000-100,000 ppm** - full narcosis (no experimental data for confirmation), no time to onset reported

ANIMAL

- Prodan et al. (1975): inhalation exposure for 2 h

  LC_{50} values:

mice	117,500 ppm
rats	150,000 ppm
rabbits	240,000 ppm
guinea pigs	240,000 ppm

  LC_{00} values:

mice	100,000 ppm (2 h, Prodan et al., 1975)
rats	100,000 ppm (8 h, Lester et al., 1963)
	200,000 ppm (0,5 h, Mastromatteo et al., 1960)
rabbits	200,000 ppm (2 h, Prodan et al., 1975)
guinea pigs	100,000 ppm (6 h, Patty et al., 1930)
	200,000 ppm (2 h, Prodan et al., 1975)

- Clark & Tinston (1977, 1982): inhalation study, beagle dogs

  50,000-71,000 ppm (EC50)

  cardiac sensitization; 5 min. exposure, last 10 sec. Bolus injection of 5 µg/kg epinephrine, further injection 10 min. after exposure. Confirmed in mice, monkeys in higher concentrations (Aviado & Belej, 1974; Belej et al., 1974).

AEGL-3

Keystudy: Clark & Tinston, 1973

Endpoint: EC_{50} for 5 minutes in dogs: 50,000 ppm (no lethality)

Scaling: $C^n \times t = k$ with $n = 2$ for longer exposure periods up to equilibrium after 2 hours; from 2h to 8h no increase in effect size (2h AEGL-3 = 4h AEGL-3 = 8h AEGL-3)

Based on the dose-response curves in mice, and guinea pigs regarding prenarcotic effects occuring immediately before lethality (muscular incoordination, side position and unconsciousness) values for n between 1.4 and 2.6 have been calculated for less than equilibrium durations (Mastromatteo et al.,1960)

Total uncertainty factor: 3

Interspecies: 1

Sensitive animal experiment with high challenge concentrations of epinephrine

Intraspecies: 3

Only small interindividual differences in kinetics are expected

→ supported by lethality data (mice) (Prodan et al., 1975)

AEGL-3 VALUES FOR VINYL CHLORIDE					
AEGL Level	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-3	12,000 ppm (31,000 mg/m³)	6,800 ppm (18,000 mg/m³)	4,800 ppm (12,000 mg/m³)	3,400 ppm (8,800 mg/m³)	3,400 ppm (8,800 mg/m³)

TUMORS IN EXPERIMENTAL ANIMALS AFTER SHORT TERM EXPOSURE TO VC

- **Tatrai and Ungvary, 1981**

  mice, single 12h exposure, 1,500ppm: hepatocellular adenoma

- **Hehir et al., 1981**

  mice, single 1 hour exposure, 5,000 - 50,000 ppm: dose-related pulmonary adenoma and carcinoma

- **Suzuki, 1981**

  mice, 4 weeks, 600 ppm: hepatic hemangioasarcoma, observed 56 weeks after expos.

- **Rats, Maltoni et al., 1981 (experiments BT 14 and BT 1)**

Administered concentration (ppm)	Angiosarcoma	Hepatoma
4 hours/day, 5 days/week for **5 weeks** starting **at day 1**		
6,000 10,000	20/42 (48%) 18/44 (41%)	20/42 (48%) 20/44 (45%)
4 hours/day, 5 days/week for **5 weeks** starting **at age 13 weeks**		
6,000 10,000	4/120 (3%) 4/120 (3%)	2/120 (2%) 0/120 (-)

- **Neonate Rats, Froment et al., 1994, exposure for, 500 ppm, 8h/d, 6d/w, 33 days**

	Angiosarcoma (Liver)	Hepatocarcinoma
	15/44	8/44
Mutations	GC->AT transition, codon 13;AT->CG transversion at codon 36 in N-*ras* gene	AT->TA transitions, second base of codon 61 of Ha-*ras* gene
	GC->AT transition, codon 13, same in human ASL; N^2,3-ethenoguanine (εG), 1,N^6-etheno-adenine (εA) adducts identified after VC exposure	1,N^6-ethenoadenine (εA) adducts identified after VC exposure

- **Rats, Drew et al., 1983, 100 ppm**

Month exposed	Angiosarcoma (Liver)	Hepatocarcinoma incl. neoplastic nodules
0	1/112 (0.9%)	5/112 (4.5%)
0-6	4/76 (5.3%)	18/75 (24%)
0-24	19/55 (34.7%)	15/55 (27%)
18-24	0/53 (-)	5/53 (9%)

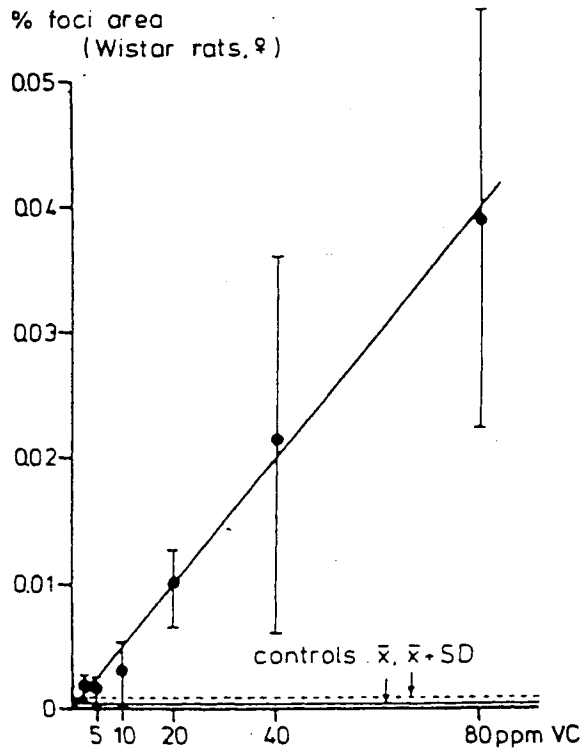
Hepatocellular foci in exp. animals after short term exposure

- **Laib et al. ,1985b, rat liver foci bioassay, 2000 ppm, 8h/d, ATPase deficient foci examination at age of 4 month**

postnatal day	0-5	1-11	21-49	90-160	control
no.foci /cm²	=control*	5 (m, f)*	2.9±2.5 (f), 0.8±0.7 (m)	=control *	0.13±0.14

* no exact figures reported; m=male, f=female

- **Laib et al., 1985a, fat liver foci bioassay, 2.5-80 ppm, 8h/d, 5d/w, 3 weeks, newborn rats, examination after 10 weeks without treatment**



DNA-ADDUCTS AFTER SHORT TERM EXPOSURE TO VC

- Adult rats, 250 ppm, single exposure, 5 hours: 23 pmol/ 100 mg liver wet weight, 0.35 pmol d-guanosine alkylation product (Bolt et al., 1980)
- Adult rats, 45 ppm, single exposure, 6 hours (Watson et al., 1991):

VC-inhalation (ppm)	0	1	10	45	100	600
7-(2'-oxoethyl)guanine (OEG) [adducts/ nucleotides]		0.026/10^6	0.28/10^6	1.28/10^6		
1,N^6-ethenoadenine (εA)				≈1/10^8		
3,N^4-ethenocytosine (εC)				≈1/10^8		
N^2,3-ethenoguanine (εG)*				≈1/10^8		
for comparison (Swenberg et al.,1999):						
εG- Background (rat)	0.9/10^7					
εG, 5 days			2/10^7		6.8/10^7	
εG, 20 days			5.3/10^7		2.3/10^6	
εG, 4h/d, 5d, immed. after exposure						3.8/10^6
εG, 4h/d, 5d, 14 days after exposure						4.7/10^7
εG- Background (human)	6/10^8 - 7/10^7					

* estimated (εG) from ratio ≈ 1/100 OEG/ εG in other VC experiments

→ **Adducts ratio neonate: adult**

Swenberg et al., 1999 (OEG), 600 ppm, 5d, 4h/d, rat	Swenberg et al., 1999 (ε G), 600 ppm, 5d, 4h/d, rat	Ciroussel et al., 1990 (ε dAdo/ dAdo), 500 ppm, 2 weeks, 7h/d, rat	Ciroussel et al., 1990 (ε dCyd/ dCyd), 500 ppm, 2 weeks, 7h/d, rat
162/43 ≈ 3.8	1.81/0.47 ≈ 3.9	1.3/0.19 ≈ 6.8	4.92/0.8 ≈ 6.15

→ ethenobases were shown to possess miscoding properties (Barbin, 2000)

→ ethenobases generate mainly base pair substitution mutations (Barbin, 2000)

→ ethenobases assumed to be initiating lesions in carcinogenesis (Barbin, 2000)

→ high correlation between DNA-adducts formation (ε G) and incidence of haemangiosarcoma in mice after exposure to vinyl fluoride (Swenberg et al., 1999)

AEGL-2 (BASED ON DNA-ADDUCTS)

Key study: Watson et al.,1991; Swenberg et al., 1999; Barbin, 2000

Toxicity endpoint: DNA-adducts; background adduct levels at single 45 ppm exposure of rats is taken as AEGL-2-NOAEL (6 hours)

Uncertainty/ modifying factors: Combined uncertainty factor of 10

1 for interspecies variability

10 for intraspecies variability

Time Scaling: $C^3 \times t = k$ for extrapolation to 4-hour, 1-hour, and 30-minute;

$k = (45\ ppm)^3 \times 360\ min = 3{,}2 \times 10E{+}7\ ppm^3\ min$

$C^1 \times t = k$ for extrapolation to 8-hours;

$k = 45\ ppm \times 360\ min = 16{,}200\ ppm^1\ min$

10-minute AEGL-2 = 30-minute AEGL-2

AEGL-2 VALUES FOR VINYL CHLORIDE					
AEGL Level	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-2 (CNS)	2,800 ppm	1,600 ppm	1,200 ppm	820 ppm	820 ppm
alternate AEGL-2 (based on DNA-adducts)*	10 ppm	10 ppm	8.2 ppm	5.1 ppm	3.4 ppm

* AEGL-1 has to be withdrawn

CARCINOGENIC RISK AFTER SINGLE EXPOSURE TO VC

Calculation A:

unit risk for continuous lifetime exposure: 8.8×10^{-6} per $\mu g/m^3$ (EPA/IRIS)

dose at risk 1 : 10,000: $11.36\ \mu g/m^3$

70 years -> 24h: $11.36\ \mu g/m^3 \times 25{,}600\ d =$ $291\ mg/m^3$

default multistage factor (SOP) /6 = $48.5\ mg/m^3$ (19 ppm)

30 min	1h	4h	8h	24h
900 ppm	450 ppm	110 ppm	56 ppm	19 ppm

For 10^{-5} and 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold and 100-fold, respectively.

Calculation B:

unit risk for exposure early life: 4.4×10^{-6} per $\mu g/m^3$

(to 10 years of age; EPA/IRIS)

dose at risk 1 : 10,000: $22.73\ \mu g/m^3$

10 years -> 24 h = $22.73\ \mu g/m^3 \times 3{,}657 =$ $83.1\ mg/m^3$

default multistage factor (SOP) /6 = $13.85\ mg/m^3$ (5.35 ppm)

30 min	1h	4h	8h	24h
260 ppm	130 ppm	32 ppm	16 ppm	5.4 ppm

For 10^{-5} and 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold and 100-fold, respectively.

- EPA: unit risk should not be used above $10\ mg/m^3$

AEGL-VALUES FOR VINYL CHLORIDE [ppm]

	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1(Baretta et al., UF:3; n=3,1; 10 min=30 min)	310	310	250	140	70
AEGL-2 (Lester et al.,UF:3; n=2 to 2h; 2h=4h=8h)	2,800	1,600	1,200	820	820
AEGL-3 (Clark & Tinston; UF:3; n=2 to 2h; 2h=4h=8h)	12,000	6,800	4,800	3,400	3,400
AEGL-2b (Jaeger et al. (liver)), UF:300; n=3: 30,60, 120,480 min; n=1: 8h; 10 min=30min.	380	380	300	190	120
AEGL-2c (Watson et al., (DNA)), UF:3; n=3: 30,60, 120,480 min; n=1: 8h; 10 min=30min.	10	10	8.2	5.1	3.4
AEGL-2d (unit risk, calc. B) early life=10 years	--	260	130	32	16

TIME SCALING: ESTIMATION OF STEADY STATE CONDITIONS (VC)

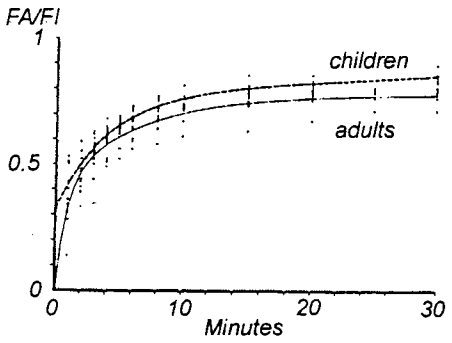
- lethality occurs as consequence of narcotic effects
- narcotic effects and cardiac sensitization are solely concentration dependent (not time dependent), when equilibrium has been reached
- the time to set up equilibrium between air and blood (brain) mainly depends on the blood/air-partition coefficient (1.2 for VC; 1.4 for isoflurane)
- human data on isofluran indicate that equilibrium of atmospheric VC and blood and brain will be achieved after ≈ 2 h
- supported by simple estimation of time to steady state in lower concentrations:

  t 1/2 x 5

  VC halftime (human): 20.5 minutes (Buchter, 1979)

  20.5 x 5 = 102.5 minutes

→ **steady state concentration of VC in blood and brain is assumed to occur at about 2 hours, used for effects which are solely concentration dependent (CNS-effects, lethality, cardiac sensitization) from 2h to 8h**



Time course of isoflurane uptake in children and adults: exspiratory (FA) versus inspiratory (FI) isoflurane concentrationen (adapted from Fitzal et al., 1985)

Source: Fiserova-Bergerova and Holaday, 1979

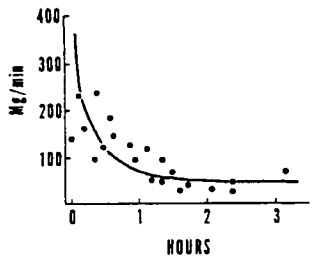


FIG. 2. Uptake of isoflurane. The uptake rate (mg/min) is plotted against time after the start of anesthesia. The points are the uptake rates measured in five patients. The line is the uptake curve calculated by Eq. (3) for an alveolar concentration of 75 mg/l.

TIME SCALING FOR LESS THAN STEADY STATE CONDITIONS

(10 min.-120 min.)

- ***Data from Mastromatteo et al. on CNS-effects, 1-30 minutes, were used for regression analysis***

example:

Unconsciousness

The time after which unconsciousness was observed in mice after exposure to 100,000, 200,000 or 300,000 ppm VC was 25 min, 10 min, and 5 min, respectively:

Time min	Concentration ppm	Log time	Log Concentration
5	300,000	0.699	5.477
10	200,000	1	5.301
25	100,000	1.398	5

The time after which unconsciousness was observed in guinea pigs after exposure to 100,000, 200, 000, 300,000, and 400,000 ppm VC was 30 min, 10 min, 5 min and 5 min, respectively:

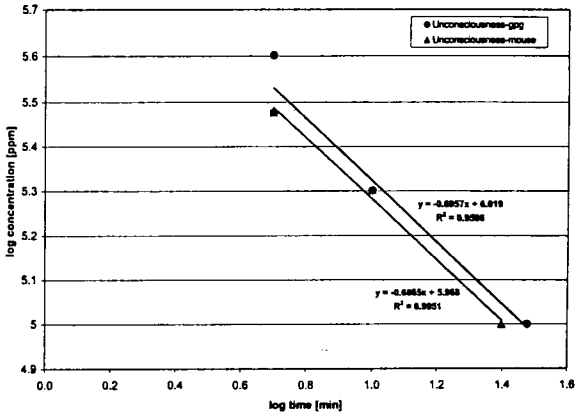
Time min	Concentration ppm	Log time	Log Concentration
5	400,000	0.699	5.602
5	300,000	0.699	5.477
10	200,000	1	5.301
30	100,000	1.477	5

AEGL-2 (ALTERNATE OPTION, BASED ON HEPATOTOXIC EFFECTS)

Key study:	Jaeger et al.,1974
Toxicity endpoint:	Centrilobular hepatocellular vacuolization and increased activity of Alanine-alpha-ketoglutarate transaminase (AKT) after single 6h exposure of rats to 100,000 ppm. No effects on liver seen at 50,000 ppm
Uncertainty/ modifying factors:	Combined uncertainty factor of 300 3 for interspecies variability 10 for intraspecies variability (CYP 2E1 variability) 10 modifying factor (severity of endpoint; much lower LOAEL after repeated exposure)
Time Scaling:	$C^3 \times t = k$ for extrapolation to 4-hour, 2-hour, 1-hour, and 30-minute; $k = (50{,}000 \text{ ppm})^3 \times 360 \text{ min} = 4.5 \times 10E{+}16 \text{ ppm}^3 \text{ min}$ $C^1 \times t = k$ for extrapolation to 8-hours; $k = (50{,}000 \text{ ppm}) \times 360 \text{ min} = 18 \times 10E{+}6 \text{ ppm}^1 \text{ min}$ 10-minute AEGL-2 = 30-minute AEGL-2

AEGL-2 VALUES FOR VINYL CHLORIDE *					
AEGL Level	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-2 (CNS)	2,800 ppm	1,600 ppm	1,200 ppm	820 ppm	820 ppm
alternate AEGL-2 (liver + modifying factor)**	380 ppm	380 ppm	300 ppm	190 ppm	120 ppm

* Carcinogenic effects were not considered ; ** AEGL-1 has to be withdrawn

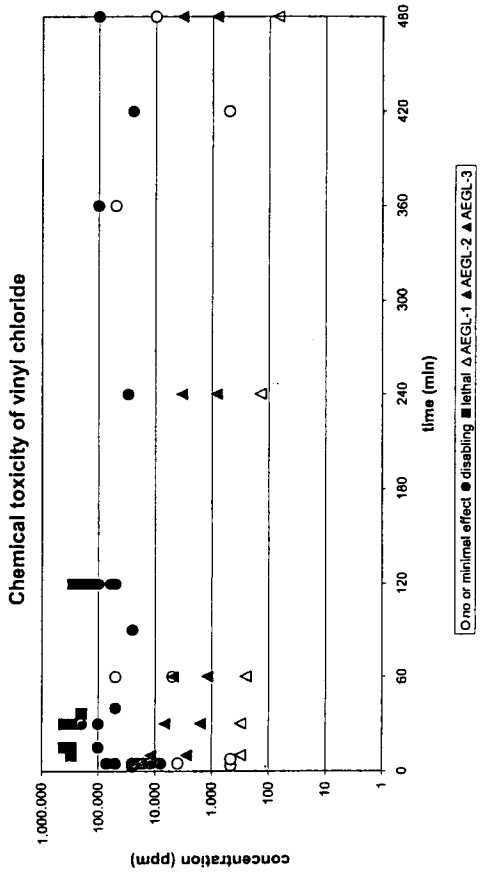


REGRESSION ANALYSIS OF THE LOG-LOG TRANSFORMED CONCENTRATION-TIME CURVE REGARDING UNCONSCIOUSNESS IN MICE AND GUINEA-PIGS (DATA FROM MASTROMATTEO ET AL., 1960)

- The slope of the regression line was -0.6865 and -0.6957 in mice and guinea pigs, respectively, corresponding to a value of 1.46 and 1.44 for n.
- similar analysis was performed on other CNS -endpoints (muscular incoordination, side position)
- **Three different endpoints, 2 species: mice, guinea pigs**

  n range 1.44 to 2.6 (1.44; 1.46; 1.8; 2.0; 2.1; 2.6; arithmetic mean: 1.9 +/- 0.4)

  → **n=2**



Attachment 18

Acute Exposure Guideline Levels (AEGLs)

for

Carbon Disulfide (CS_2)

(CAS Reg. No. 75-15-0)

S=C=S

NAC/AEGL-26

September 10-12, 2002

US EPA, Washington, DC

Scientists (Toxicological Consultants):

Jens-Uwe Voss/Gerhard Rosner

Chemical Manager USA:

(George Rodgers)

Chemical Manager in German Expert Group:

Horst Hollander

Chemical Reviewer for German Expert Group:

Helmut Greim/Rüdiger Bartsch

CS_2 Properties

- liquid, colorless when pure, normally faint yellow,
- odor chloroform-like when pure, normally foul smelling (decaying radish),
- high vapor pressure, low flash point, low autoignition temperature, wide range of explosive limits in air:
  → fire and explosion hazard.

Production

- direct (endothermic) reaction of sulfur vapors with glowing coal,
- nowadays mostly by reaction of methane with sulfur.

Use

- mainly in viscose process,
- for production of CCl_4, as solvent, for biocides.

Toxicity mechanism and concerns

- acute toxicity:
  - neurotoxic effects,
  - alterations of liver metabolism, inhibition of biotransformation reactions,
- chronic toxicity:
  - neurotoxic effects (behavioral disorders, polyneuropathy),
  - increased risk of cardiac infarction (arteriosclerosis and/or direct cardiotoxicity?).

Data relevant to AEGL-1

Humans

- Leonardos et al. (1969): 4 trained volunteers

  0.21 ppm: Odor recognition threshold

- Freundt et al. (1976b); Freundt & Lieberwirth (1974a):

  4 healthy males/group (0, 20, 40, 80 ppm) with controlled alcohol intake (0.7 ‰), controlled dynamic chamber exposure, measured concentrations:

  ≥ 20 ppm, 8 h: increase in blood acetaldehyde (1.5 - 2 x control), no signs of "antabuse syndrome"

- Münchinger (1958): brief summary only,

  occupational exposure, 100 workers; mean CS_2 concentration 1.6 – 11.2 ppm (peaks not reported); about two thirds of workers complained (among other symptoms) of alcohol intolerance

- Mack et al. (1974):

  4 healthy males/group (10, 20, 40, 80 ppm), controlled dynamic chamber exposure:

  ≥ 10 ppm, 6 h: Inhibition of oxidative biotransformation (oxidative N-demethylation of amidopyrine)

- Freundt & Lieberwirth (1974b):

  4 healthy males/group (20, 40, 80 ppm) with/without controlled alcohol intake, controlled dynamic chamber exposure:

  ≥20 ppm, 8 h: no changes of serum parameters indicative of liver damage.

Data relevant to AEGL-1

Animals

- Freundt et al. (1976b):

  Ethanol-treated rats (4-6/group; 20 or 400 ppm),

  Dynamic chamber exposure, measured concentrations

  ≥ 20 ppm, 8 h: ~ 30 % increase in blood acetaldehyde

- Freundt & Kürzinger (1975), Kürzinger & Freundt (1969), Freundt et al. (1976a); Freundt & Kuttner (1969); Freundt & Dreher (1969):

  Rats

  Dynamic chamber exposure, measured concentrations

  ≥ 20 ppm, 8 h: alterations of hepatic energy metabolism (decrease of liver glycogen, increase of inorganic phosphate, increased oxygen consumption ex vivo), inhibition of xenobiotic phase I biotransformation; no signs of liver damage.

AEGL-1

Key study: Freundt et al. (1976b)

Endpoint: Increase in blood acetaldehyde (1.5 – 2 x control) in humans, no signs of "antabuse syndrome at exposure to 20 ppm for 8 h

Scaling: $C^n \times t = k$ with default of n=3 for shorter periods of time; $AEGL_{10\ min} = AEGL_{30\ min}$ (default for derivation from 8-h-studies and no supporting studies using shorter experiods)

Total uncertainty factor: 10

Intraspecies: 10

The observed increased of blood acetaldehyde levels in normal subjects was not sufficient to cause an "antabuse syndrome". However, population groups (Asian, American Indian) with "low activity" acetaldehyde dehydrogenase (ALDH2(2)) are very sensitive to an "antabuse syndrome" following alcohol intake and could experience reactions or reactions to alcohol (vasodilation with e.g. face flush, pulsating headache, sweating, nausea, hypotension) may be aggravated by exposure to CS_2.

AEGL-1 Values for Carbon Disulfide				
10 minutes	30 minutes	1 hour	4 hours	8 hours
5.0 ppm (16 mg/m³)	5.0 ppm (16 mg/m³)	4.0 ppm (12 mg/m³)	2.5 ppm (7.8 mg/m³)	2.0 ppm (6.2 mg/m³)

Remark: AEGL-1 is above odor recognition threshold (0.21 ppm; Leonardos et al., 1979) but well below levels reported to cause "moderate odor annoyance" (180-240 ppm; Lehmann, 1894).

Data relevant to AEGL-2

Humans

- Lehmann (1894):

  2 male students, controlled static chamber exposure, CS_2 concentrations monitored at about 30 minute intervals, overall concentration range 180 - > 3000 ppm (see Table 2 of TSD draft)

  500 ppm, 4 h: dizziness, lacrymation, burning eyes, temporary impairment of reading ability, cough attacks, increased pulse rate, paleness, cold sweat.

- Freundt et al. (1974); Freundt & Lieberwirth (1974b); Mack et al. (1974):

  up to 80 ppm: no objective or subjective symptoms noted

- Demus (1964): toxikokinetic study with 10 persons

  up to 96 ppm, 8 h; 143 ppm, 5 h: neither symptoms reported nor absence of symptoms explicitly stated; but it may reasonble assumed that severe effects would not have been tolerated in a kinetic study

Data relevant to AEGL-2

Animals

- Weiss et al. (1979) **600 ppm, 2 h**:	1 Squirrel monkey behavioral alterations (altered response to aversive electric shock, elevated aversive threshold indicating anesthetic/analgesic effect)
- Du Pont (1966) **3000 ppm, 4 h**	6 rats tachypnea, ptosis, hyperexcitability, incoordination, gasping
Goldberg et al. (1964) **2000 ppm, 4 h**	8-10 rats behavioral alterations (inhibition of pole climbing as conditioned avoidance response in 50 % of rats);
1000 ppm, 4 h	no effect after one exposure
- Tarkowski & Sobczak (1971) **800 ppm, 18 h**	7 rats severe narcosis, reduced cardiac/respiratory rate
- Tarkowski & Cremer (1972) **800 ppm, 15 h**	6 rats ataxia, tremor, occasional convulsions
- Tarkowski et al. (1980) **770 ppm, 12 h**	7 rats no visible signs of toxicity reported
- Battig & Grandjean (1964) **800 ppm, 4 h**	6 rats drowsiness shortly after begin of exposure
- Wilmarth et al. (1993) **600 ppm, 10 h**	6 rats narcotic-like stupor
- Kivisto et al. (1979) **500 ppm, 6 h**	14 rats reduced activity level, not strongly irritating or prenarcotic

AEGL-2

Key study: Lehmann (1894)

Endpoint: acute neurotoxic effects on CNS and irritation in humans at/after exposure to 500 ppm for 3 h 50 min (4 h).

Scaling: $C^n \times t = k$ with default of n=3 for shorter and longer periods of time (since extrapolation with default of n=1 for longer periods of time seems not to be supported by human data)

Total uncertainty factor: 3

Intraspecies: 3

Because the threshold for acute neurotoxic effects on the CNS is not expected to vary much in humans

AEGL-2 Values for Carbon Disulfide				
10 minutes	30 minutes	1 hour	4 hours	8 hours
330 ppm (1040 mg/m³)	330 ppm (1040 mg/m³)	260 ppm (820 mg/m³)	170 ppm (520 mg/m³)	130 ppm (410 mg/m³)

Note: Calculation with n = 1 (default) for 8 hours 83 ppm (260 mg/m³)

Data relevant to AEGL-3

Humans

- Lehmann (1894):

  2 male students, controlled static chamber exposure, CS_2 concentrations monitored at about 30 minute intervals, overall concentration range 180 - > 3000 ppm (see Table 2 on page 7-8 of TSD draft)

  2000 ppm, 1 h: nausea, dizziness, mental capabilities highly impaired, feeling of marked cerebral paralysis, vomiting after exposure.

- Vigliani (1954):

  reported effects of occupational exposure to CS_2 in viscose rayon factory (during and after World War II)

  320 – 640 ppm, 4-5 h/d caused severe neurotoxicity and other effects within 2 months, but

  no deaths were reported following acute exposure.

Data relevant to AEGL-3

ACUTE LETHAL INHALATION DATA IN ANIMALS

Spec.	Exposure time	Conc. (ppm)	Effect/remarks	Reference
Rat	2 h	8025	LC_{50} (no details reported)	Izmerov et al., 1982
	4 h	3500	6/6 died	Du Pont, 1966
	4 h	3000	0/6 died	
	4 h	2000	0/(8-10) died after one exposure	Goldberg et al., 1964
	2 h	1500	0/12 died	Savolainen and Järvisalo, 1977
Mouse	2 h	3210	LC_{50} (no details reported)	Izmerov et al., 1982
	30 min	4500	"average lethal concentration", 17/30 died	Kuljak et al., 1974
	6 h	800	No death after one exposure	Lewis et al., 1999
	1 h	220	LC_{50} (???)	Gibson and Roberts, 1972
Rabbit	6 h 15 min	3220	narcosis at the end; death after 7 d	Flury and Zernik, 1931b
	6 h	3000	4/6 died, 2/6 moribund and euthanized after exposure	PAI, 1991
Cat	48 min	36000	convulsions, narcosis, died after 0.5 d	Lehmann and Flury, 1938
	2 h 15 min	6450	convulsions, narcosis; death after 1 d	Flury and Zernik, 1931b
	4 h 15 min	3220	Convulsions, narcosis, death after 1 d	

AEGL-3

Key study: Lehmann (1894)

Endpoint: Progressing acute neurotoxic effects on CNS with beginning of marked cerebral paralysis, vomiting at/after exposure to 2000 ppm for 1 h.

Scaling: $C^n \times t = k$ with default of n=3 for shorter time and longer periods of time (since extrapolation with default of n=1 for 4 hours and 8 hours is not supported by human data and leads to overly conservative estimates)

Total uncertainty factor: 3

Intraspecies: 3

Because the threshold for acute neurotoxic effects on the CNS is not expected to vary much in humans.

AEGL-3 Values for Carbon Disulfide

10 minutes	30 minutes	1 hour	4 hours	8 hours
840 ppm (2620 mg/m³)	840 ppm (2620 mg/m³)	670 ppm (2080 mg/m³)	420 ppm (1310 mg/m³)	330 ppm (1040 mg/m³)

Note: Calculation with n = 1 (default) for 4 hours and for 8 hours: 170 ppm (520 mg/m³); 83 ppm (260 mg/m³)

- Both values would be identical with AEGL-2-values derived with n = 1;
- the 8-h-value is not supported by data from controlled human studies (no lethality at 80 ppm)

AEGL-2 and AEGL-3 for longer time periods were derived by extrapolation using the equation $C^3 \times t = k$ since

- scaling to longer time periods using the default value of n = 1 for $C^1 \times t = k$ leads to overly conservative values;
- experimental data indicate that the effects are more dependent on concentration than on time;
- animal experiments with longer time periods of acute exposure (10 to 18 h) show that time has some influence on the development of acute neurotoxic effects; therefore,
- using a constant value ("flatlining") for longer time periods is not justified;
- data are not sufficient to derive a substance specific value for n, therefore,
- the value of n = 3 which is the default value for scaling to shorter time periods is used for extrapolation to 8 h as a conservative estimate which is in line with available information.

Overview of presented AEGL

	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	5.0 ppm	5.0 ppm	4.0 ppm	2.5 ppm	2.0 ppm
AEGL-2	330 ppm	330 ppm	260 ppm	170 ppm	130 ppm
AEGL-3	840 ppm	840 ppm	670 ppm	420 ppm	330 ppm

AEGL-2 – Alternative Derivation I, Animal Studies

Key studies: Goldberg et al. (1964)

Endpoint: Neurotoxicity (behavioral alterations in rats)

LOAEL: 2000 ppm, 4 h
(reduced avoidance response)

NOEL: 1000 ppm, 4h

Scaling: $C^n \times t = k$, extrapolation with n=3 for shorter time periods (default) and also n=3 for longer time periods (see above).

Total uncertainty factor: 10

Interspecies: 3

Because data do not indicate much variability in acute neurotoxic effects between species

Intraspecies: 3

Because threshold for acute neurotoxic effects is not expected to vary much in humans

AEGL-3 Values for Carbon Disulfide				
10 minutes	30 minutes	1 hour	4 hours	8 hours
200 ppm (620 mg/m³)	200 ppm (620 mg/m³)	160 ppm (490 mg/m³)	100 ppm (310 mg/m³)	80 ppm (250 mg/m³)

Note:

Calculation with n = 1 (default) for 8 hours 50 ppm (160 mg/m³)

AEGL-3 – Alternative Derivation I, Animal Studies

Key studies: Du Pont (1966) (only summary available)
PAI (1991) (only summary available)
Goldberg et al. (1964)

Endpoint: Lethality in rats and rabbits

3500 ppm, 4 h: 6/6 rats died
3000 ppm, 4 h: 0/6 rats died
3000 ppm, 6 h: 4/6 rabbits died, 2/6 moribund
2000 ppm, 4 h: 0/(8-10) rats died

Indicating steep dose-response for lethality.

NOEL: 2000 ppm, 4h

Scaling: $C^n \times t = k$, extrapolation with n=3 for shorter time periods (default) and also n=3 for longer time periods (see above)

Total uncertainty factor: 10

Interspecies: 3

Because data do not indicate much variability in acute neurotoxic effects between species

Intraspecies: 3

Because threshold for acute neurotoxic effects is not expected to vary much in humans

AEGL-3 Values for Carbon Disulfide				
10 minutes	30 minutes	1 hour	4 hours	8 hours
400 ppm (1250 mg/m³)	400 ppm (1250 mg/m³)	320 ppm (990 mg/m³)	200 ppm (620 mg/m³)	160 ppm (490 mg/m³)

Note: Calculation with n = 1 (default) for 8 hours 100 ppm (310 mg/m³)

AEGL-2 – Alternative Derivation II, Animal Studies

Key studies: Goldberg et al. (1964)

Endpoint: Neurotoxicity (behavioral alterations in rats)

LOAEL: 2000 ppm, 4 h
(reduced avoidance response)

NOEL: 1000 ppm, 4h

Scaling: $C^n \times t = k$, extrapolation with n=3 for shorter time periods (default) and also n=3 for longer time periods (see above).

Total uncertainty factor: 6

Interspecies: 2

Because data do not indicate much variability in acute neurotoxic effects between species

Intraspecies: 3

Because threshold for acute neurotoxic effects is not expected to vary much in humans

AEGL-3 Values for Carbon Disulfide

10 minutes	30 minutes	1 hour	4 hours	8 hours
330 ppm (1040 mg/m³)	330 ppm (1040 mg/m³)	260 ppm (820 mg/m³)	170 ppm (520 mg/m³)	130 ppm (410 mg/m³)

Note:

Calculation with n = 1 (default) for 8 hours 83 ppm (260 mg/m³)

Values identical to those obtained from human data

AEGL-3 – Alternative Derivation II, Animal Studies

Key studies: Du Pont (1966) (only summary available)
PAI (1991) (only summary available)
Goldberg et al. (1964)

Endpoint: Lethality in rats and rabbits

3500 ppm, 4 h: 6/6 rats died
3000 ppm, 4 h: 0/6 rats died
3000 ppm, 6 h: 4/6 rabbits died, 2/6 moribund
2000 ppm, 4 h: 0/(8-10) rats died

Indicating steep dose-response for lethality.

NOEL: 2000 ppm, 4h

Scaling: $C^n \times t = k$, extrapolation with n=3 for shorter time periods (default) and also n=3 for longer time periods (see above).

Total uncertainty factor: 6

Interspecies: 2

Because data do not indicate much variability in acute neurotoxic effects between species

Intraspecies: 3

Because threshold for acute neurotoxic effects is not expected to vary much in humans

AEGL-3 Values for Carbon Disulfide

10 minutes	30 minutes	1 hour	4 hours	8 hours
670 ppm (2080 mg/m³)	670 ppm (2080 mg/m³)	530 ppm (1650 mg/m³)	330 ppm (1040 mg/m³)	260 ppm (820 mg/m³)

Note: Calculation with n = 1 (default) for 8 hours 170 ppm (520 mg/m³)

Peter Bos
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Attachment 19

Metabolism

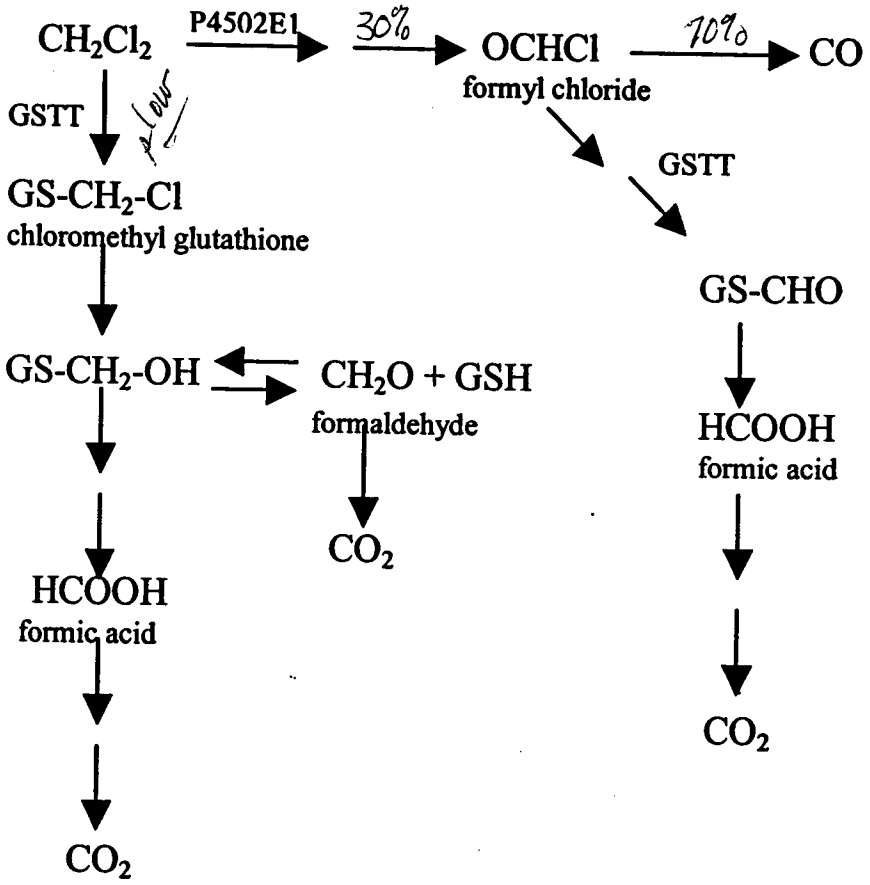


Figure 1. Biotransformation scheme of DCM (modified after Gargas et al., 1986).

rivm

AEGL-1: Human data

- Stewart et al (1972)
  - 1-h exposure to 515 ppm (n=8)
    no complaints
  - 1-h exposure to 514 ppm, 1-h exposure to 868 ppm (n=3)
    light-headedness and altered VER during the second hour
  - 2-h exposure to 986 ppm (n=3)
    no eye, nose, or throat irritation
    light-headedness (2/3); difficulties to enunciate (1/3) after 1 h;
    altered VER
- Starting point for AEGL-1: 1-h exposure to 514 ppm

AEGL-2: Animal data

Table 4. Summary of relevant nonlethal inhalation data in laboratory animals (emphasis on one-day exposure)

Species	Concentration (ppm)	Exposure time	Effect
Monkey (n=2)	9464	6 h	Side laying after 4 h
Dog (n=6)	9464	6 h	Excitement within min, arousal
Rat (n=5)	1000	24 h	Depression of REM-sleep during exposure
Rat (n=?)	1980	4 h	EC_{30} for shortening of tonic extension of the hindlimbs/ lengthening of latency of extension
Rats (n=21)	4760	6 h	No signs of narcosis
Rats (n=5)	5000	1.5 h	Decreased running activity
Rat (n=6)	9000	10 min	EC_{50} for ataxia
Rats (n=16)	9464	6 h	Signs of narcosis within 30 min, side lying after 4 h
Rats (n=20)	10,000	6h/d,7d/w,90 d	No clinical, hematological, histopathological changes
Rat (n=20)	11,200	2 h	Increasing CNS-effects, incl. narcosis
Rat (n=9)	15,000	519 s	Hind limb paralysis
Mouse (n=?)	3980	2 h	EC_{30} for shortening of tonic extension of the hindlimbs/ lengthening of latency of extension
Mouse (n=10)	4000	6 h	Hyperactive followed by subdued appearance, decreased liver weight, lung effects (damaged Clara cells)
Mouse (n=20)	13,500	50 min	First animal with anesthesia
Guinea pig (n=5)	5000	6 h	No CNS-effects, increased hepatic triglyceride level
Guinea pig (n=10)	5200	6 h	Increased hepatic and serum triglycerides
Rabbit (n=4)	4760	7h/d,5d/w,6m	No signs of narcosis, no histopathological effects

AEGL-2: Starting points

- CNS-effects
  - 230 min to 751 ppm as a conservative NOAEL *(Winneke, 1974)*
  - related to CNS concentration in the brain

- COHb-related effects
  - no data for DCM
  - compliance with TSD for carbon monoxide

    (maximal COHb of 4% based on a reduced time until onset of angina during physical exertion in patients with coronary heart disease)

AEGL-3: Human data

- No adequate data on mortality related to CNS-depression

- Compliance with TSD for carbon monoxide
  - no life-threatening symptoms at 40-56% COHb in healthy subjects
  - intraspecies UF of 3 used at corresponding CO concentrations
  - final AEGL-3 CO concentrations in air correspond to approximately 15% COHb

AEGL-3: Animal data, single exposure

Table 6. Summary of the highest non-lethal and lowest lethal data in laboratory animals

Species	Exposure Time	Non-lethality data		Lethality data	
		Concentration (ppm)	Effect	Concentration (ppm)	Effect
Single exposures					
Rat, male	1 h	15,100	0/12	--	--
Rat, unknown sex	2 h	11,200	0/20	--	--
Rat, male	4 h	10,000	0/4	15,000	1/4
Rat, male	4 h	11,000[a]	0/6	14,000[b]	2/6
Rat, male	4 h 4 h 4 h	16,500	0/5	15,500 16,800	1/5 1/5
Rat, female	4 h	17,250	0/5	18,500	1/5
Mouse	20 min	10,000	0/10	20,000	2/10
Mouse	82 min	17,360	0/3	--	--
Mouse, male	4 h	16,948	0/5	17,175	4/5
Mouse, female	4 h	16,948	0/5	17,175	3/5
Mouse	7 h	12,795	0/20	15,293	2/20
Rabbit	20 min	11,520	0/4	--	--
Guinea pig	6 h	5000	0/5	8700	3/20

a) mean concentration, range: 9300-17,000 ppm
b) mean concentration, range: 12,000-16,000 ppm

AEGL-2 derivation

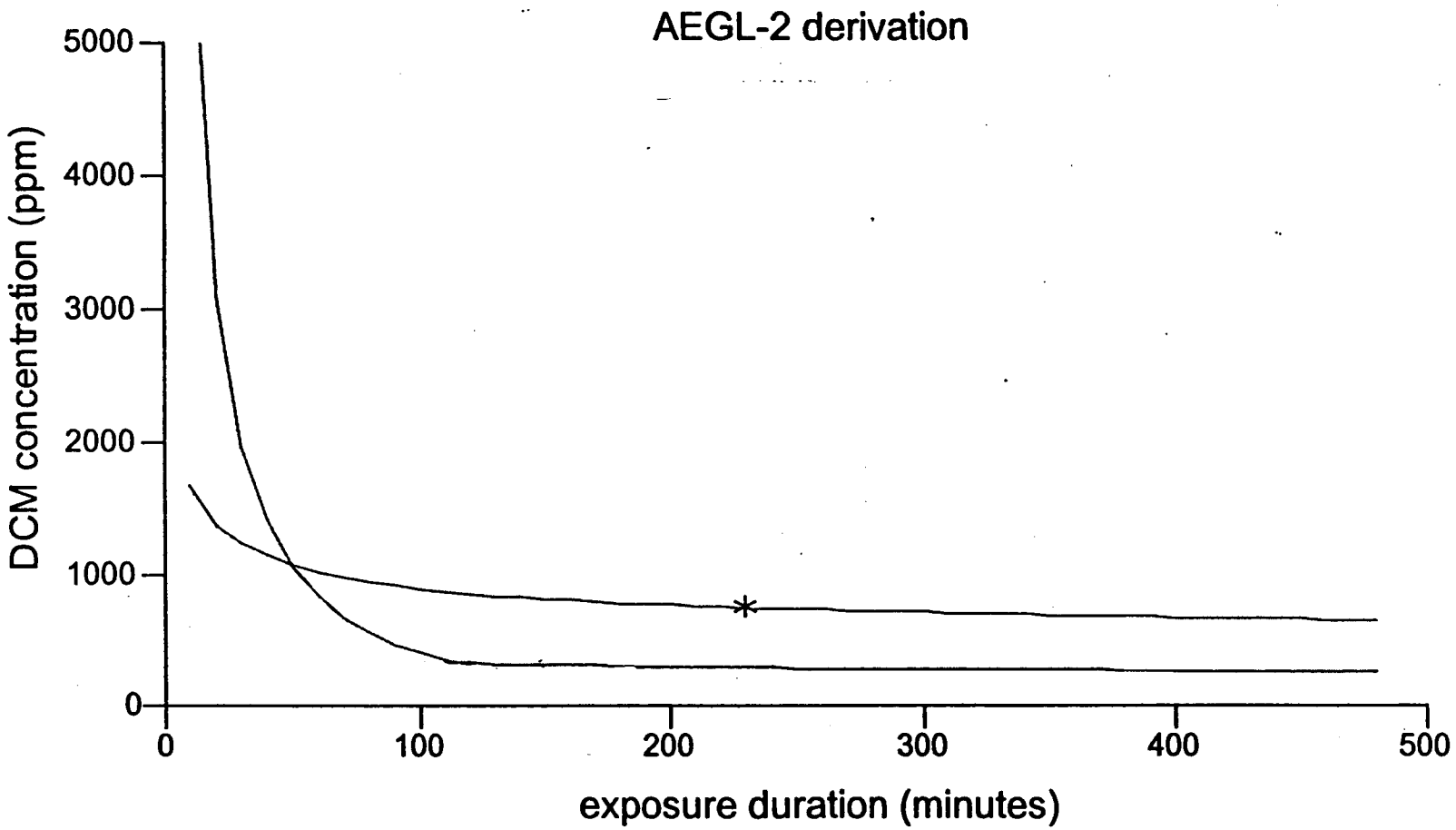
- CNS-effects
  - Starting point: NOAEL at 230 min exposure to 751 ppm *(Winneke, 1974)*
  - DCM concentration in brain: 11.6 µg/ml
  - no interspecies UF
  - intraspecies UF = 1

    effects studied are sub AEGL-2 effects

    mechanism of action will not vary greatly between individuals

    intraspecies UF >1 will lead to unrealistic AEGL-2 values for CNS effects
- COHb level
  - 4% in compliance with AEGL-2 for carbon monoxide

rivm


AEGL-2 derivation
DCM concentration (ppm)
5000
4000
3000
2000
1000
0
0
100
200
300
400
500
exposure duration (minutes)

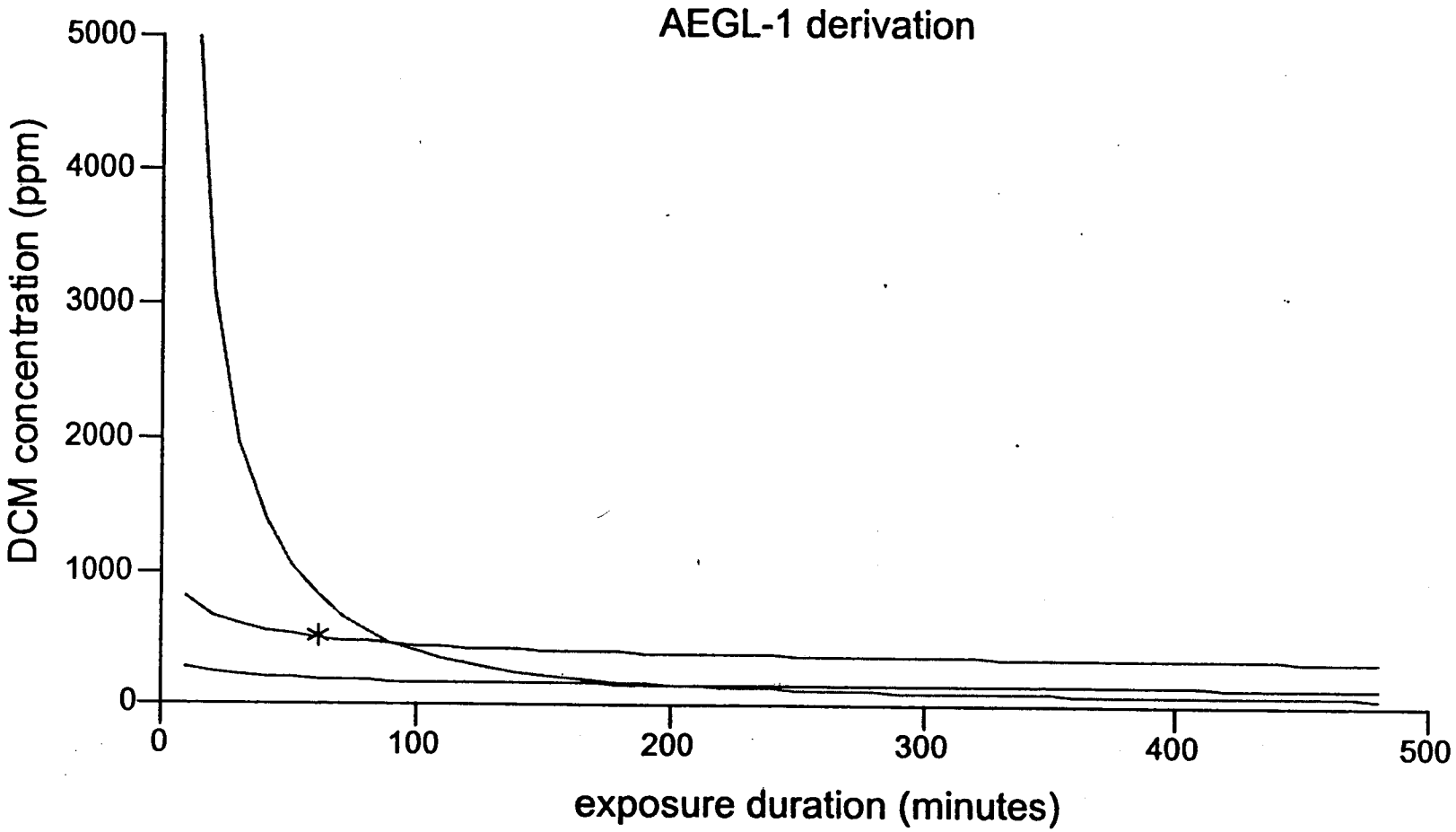
AEGL-2: human data

- Bicycle ergometer
  - 2 h to 500 ppm; up to 150 W
  - 1 h to 750 ppm; 50 W
- Occupational data (*Moynihan-Fradkin, 2001*)
  - 8-min TWA: 89-143 ppm; 41-969 ppm
  - 15-min TWA: 170-240 ppm; 140-1700 ppm
  - Effects reported: headaches (dermatitis, skin cracking), apparently no functional impairment

AEGL-1 derivation

- CNS-effects
  - NOAEL: 1-h exposure to 514 ppm *(Stewart et al. 1972)*
  - effects related to DCM in brain (5.4 µg/ml) and not CO
  - no interspecies UF
  - intraspecies UF = 3

    no great varietion between individuals


AEGL-1 derivation
DCM concentration (ppm)
5000
4000
3000
2000
1000
0
0
100
200
300
400
500
exposure duration (minutes)

AEGL-3 derivation

- CNS-related mortality
  - starting point: 4-h exposure to 11,000 ppm in rats *(Haskell Laboratory, 1982)*
  - DCM concentration in rat brain: 279 µg/ml
  - interspecies UF = 1

    susceptibility between species is small

    human PBPK-model is used
  - intraspecies UF = 3

    mechanism of action (CNS-depressing effects) will not vary greatly between individuals
- COHb level
  - 15% in compliance with AEGL-2 for carbon monoxide

Summary of AEGL values

TABLE 13. Summary of AEGL Values					
Classification	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (Nondisabling)	290 ppm	230 ppm	195 ppm	NR	NR
AEGL-2 (Disabling)	1670 ppm	1225 ppm	825 ppm	130 ppm	75 ppm
AEGL-3 (Lethal)	12,970 ppm	9210 ppm	7500 ppm	5335 ppm	4595 ppm

Appendix A

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.

Iron Pentacarbonyl
CAS Reg. No. 13463-40-6

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
Attachment 8. Public Comments on Proposed AEGL Values of Carbon Tetrachloride, Chlorine, and Chlorine Dioxide
Attachment 9. Public Comment on Proposed AEGL Values of CCl_4
Attachment 10. Response to Federal Register Comments of Carbon Tetrachloride
Attachment 11. Response to Federal Register Comments of Chlorine
Attachment 12. Response to Federal Register Comments of Chlorine Dioxide
Attachment 13. Public Comment on Proposed AEGL Values of Propylene Oxide
Attachment 14. Public Comment on Proposed AEGL Values of Propylene Oxide
Attachment 15. TSD Development Team Responses to Fed. Reg. Comments of Propylene Oxide
Attachment 16. Data Analysis of Benzene
Attachment 17. Data Analysis of Hydrogen Fluoride/ Hydrogen Chloride
Attachment 18. Abbreviated 7th COT/AEGL report
Attachment 19. Data Analysis of Tetrachloroethylene
Attachment 20. Data Analysis of Nickel Carbonyl
Attachment 21. Data Analysis of Iron Pentacarbonyl
Attachment 22. Data Analysis of Allylamine
Attachment 23. Data Analysis of Allyl Alcohol

LIST OF APPENDICES

Appendix A. Revised meeting highlights of NAC/AEGL-24
Appendix B. Ballot for Carbon Tetrachloride
Appendix C. Ballot for Chlorine
Appendix D. Ballot for Chlorine Dioxide
Appendix E. Ballot for Propylene Oxide
Appendix F. Ballot for Hydrogen Fluoride
Appendix G. Ballot for Hydrogen Chloride
Appendix H. Ballot for Tetrachloroethylene
Appendix I. Ballot for Nickel Carbonyl
Appendix J. Ballot for Iron Pentacarbonyl
Appendix K. Ballot for Allylamine
Appendix L. Ballot for Allyl Alcohol

Appendix B

NAC/AEGL Meeting 26: September 10-12, 2002

Chemical: "LOA" LEVEL OF ODOR AWARENESS (SIGNIFICANCE) **CAS Reg. No.:**

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

When we can calculate LOA 3's, we will do so & show calcn. as an appendix. No NAC/AEGL approval is needed

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:** R. Niemeier

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

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

Approved by Chair: _____ **DFO:** _____ **Date:** 9/11/02

Appendix C

NAC/AEGL Meeting 26: September 10-12, 2002

Chemical: VX **CAS Reg. No.:**

NAC Member	AEGL 1 *	AEGL 2	AEGL 3
George Alexeeff	N		
Steven Barbee	A	A	A
Lynn Beasley	A	A	A
David Belluck	A		
Robert Benson	Y		
Jonathan Borak	P	A	A
William Bress	Y		
George Cushmac	Y		
Al Dietz	A	A	A
Ernest Falke	Y		
Larry Gephart	A	A	A
John Hinz	Y		
Jim Holler	Y		
Thomas Hornshaw	P		
Doan Hansen	Y		

NAC Member	AEGL 1	AEGL 2	AEGL 3
Nancy Kim	Y		
Loren Koller	Y		
Glenn Leach	Y		
Mark McClanahan	Y		
John Morawetz	P		
Richard Niemeier	P		
Marinelle Payton	A		
Zarena Post	P		
George Rodgers	A		
George Rusch, Chair	Y		
Robert Snyder	N		
Thomas Sobotka	N		
Kenneth Still	A		
Richard Thomas	Y		
TALLY	13/16		

* RP (Relative Potency) Factor of ~~10~~ 12 for GB → VX

PPM, (mg/m³)	RP 10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	120 ,( )	,( )	,( )	,( )	,( )
AEGL 2	120 ,( )	,( )	,( )	,( )	,( )
AEGL 3	400,( )	,( )	,( )	,( )	,( )

* **AEGL 1 Motion:** Koller **Second:** John Hinz (Phylm)

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

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

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 12/10/02

Appendix D

NAC/AEGL Meeting 26: September 10-12, 2002

Chemical: Allyl amine **CAS Reg. No.:**

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

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	3.3 ,( )	3.3 ,( )	3.3 ,( )	1.8 ,( )	1.2 ,( )
AEGL 3	146 ,( )	40 ,( )	18 ,( )	5.5 ,( )	2.3 ,( )

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

AEGL 2 Motion: McClanahan **Second:** Thomas

AEGL 3 Motion: Thomas **Second:** [redacted] Hinz

Approved by Chair: _____ **DFO:** _____ **Date:** 9/11/02

Appendix E

NAC/AEGL Meeting 26: September 10-12, 2002

Chemical: METHYL MERCAPTAN **CAS Reg. No.:** CH_3SH

NAC Member	AEGL 1 *	AEGL 2 ∓	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	Y		Nancy Kim	Y	Y	
Steven Barbee	A	A	A	Loren Koller	N	P	
Lynn Beasley	A	A	A	Glenn Leach	Y	Y	
David Belluck	A	A		Mark McClanahan	N	N	
Robert Benson	Y	Y		John Morawetz	Y	Y	
Jonathan Borak	Y	Y	A	Richard Niemeier	Y	Y	
William Bress	Y	Y		Marinelle Payton	A	A	
George Cushmac	Y	Y		Zarena Post	Y	Y	
Al Dietz	A	A	A	George Rodgers	A	A	
Ernest Falke	Y	Y		George Rusch, Chair	Y	Y	
Larry Gephart	A	A	A	Robert Snyder	N	Y	
John Hinz	N	Y		Thomas Sobotka	N	N	
Jim Holler	Y	Y		Kenneth Still	A	A	
Thomas Hornshaw	Y	Y		Richard Thomas	Y	Y	
Doan Hansen	N	N		TALLY	15/21	17/20	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1 *	,( )	,( )	,( )	,( )	,( )
AEGL 2 ∓	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

* Not enough data to establish AEGL-1 ∓ SEE LOA I3 = 1.9 ppb ~~I4 = 5.0 ppb~~

AEGL 1 Motion: J. Borak **Second:** E. Falke

AEGL 2 Motion: Falke **Second:** Thomas

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

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 12/10/02

NAC/AEGL Meeting 26: September 10-12, 2002

Chemical: perchloromethyl mercaptan **CAS Reg. No.:**

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

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.015 ( )	0.015 , ( )	0.012 , ( )	0.0074, ( )	0.0049 , ( )
AEGL 2	0.044, ( )	0.044 , ( )	0.035, ( )	0.022, ( )	0.014 , ( )
AEGL 3	0.54 , ( )	0.38 , ( )	0.30 , ( )	0.075 , ( )	0.038 , ( )

AEGL 1 Motion: Snyder **Second:** Post

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

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

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 9/11/02

NAC/AEGL Meeting 26: September 10-12, 2002

Chemical: HYDROGEN SULFIDE **CAS Reg. No.:** H2S

NAC Member	AEGL 1 *	AEGL 2 †	AEGL 3 ‡		NAC Member	AEGL 1	AEGL 2 †	AEGL 3 ‡	
George Alexeeff	N	N	N	Y	Nancy Kim	P	N	Y	Y
Steven Barbee	A	A	A	A	Loren Koller	Y	Y	Y	Y
Lynn Beasley	A	A	A	A	Glenn Leach	Y	Y	Y	Y
David Belluck	A	A	A	A	Mark McClanahan	N	Y	Y	Y
Robert Benson	Y	P	Y	Y	John Morawetz	N	N	N	Y
Jonathan Borak	N	Y	A	A	Richard Niemeier	N	Y	Y	Y
William Bress	Y	N	Y	Y	Marinelle Payton	A	A	A	A
George Cushmac	Y	N	Y	Y	Zarena Post	N	N	N	Y
Al Dietz	A	A	A	A	George Rodgers	A	A	Y	Y
Ernest Falke	Y	Y	Y	Y	George Rusch, Chair	Y	Y	Y	Y
Larry Gephart	A	A	A	A	Robert Snyder	Y	N	Y	Y
John Hinz	N	Y	Y	Y	Thomas Sobotka	Y	N	A	A
Jim Holler	Y	Y	Y	Y	Kenneth Still	A	A	A	A
Thomas Hornshaw	Y	N	Y	Y	Richard Thomas	Y	N	Y	Y
Doan Hansen	P	Y	A	A	TALLY	12/19	10/20	16/19	19/19

MOTIONS DO NOT PASS

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1 *	0.75 ,( )	0.60 ,( )	0.51 ,( )	0.36 ,( )	0.33 ,( )
AEGL 2 †	2.6 ,( )	2.0 ,( )	1.7 ,( )	1.2 ,( )	1.1 ,( )
AEGL 3 ‡	0.75 ,( )	0.60 ,( )	0.51 ,( )	0.36 ,( )	0.33 ,( )

Carl

AEGL 1 Motion: R. Thomas (Hinz) * **Second:** G. Leach (Niemeier) †

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

AEGL 3 Motion: ‡ McClanahan ~~FALKE~~ ALEXEEFF **Second:** ‡ Koller RODGERS

Approved by Chair: _____ **DFO:** _____ **Date:** 12/10/02

‡ Carl
LOA I=3 0.01 ppm
Level of Odor Awareness

Appendix H

NAC/AEGL Meeting 26: September 10-12, 2002

Chemical: VINYL CHLORIDE **CAS Reg. No.:** 75-01-4

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	N	N	P (I)	Nancy Kim	N	N	Y
Steven Barbee	A	A	A	Loren Koller	A	A	A
Lynn Beasley	A	A	A	Glenn Leach	Y	Y	Y
David Belluck	A	A	A	Mark McClanahan	Y	Y	Y
Robert Benson	Y	Y	Y	John Morawetz	N	N	P
Jonathan Borak	A	A	A	Richard Niemeier	Y	Y	Y
William Bress	Y	N	Y	Marinelle Payton	A	A	A
George Cushmac	Y	Y	Y	Zarena Post	P	N	Y
Al Dietz	A	A	A	George Rodgers	A	A	A
Ernest Falke	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Larry Gephart	A	A	A	Robert Snyder	Y	Y	Y
John Hinz	P	Y	Y	Thomas Sobotka	Y	N	Y
Jim Holler	Y	Y	Y	Kenneth Still	A	A	A
Thomas Hornshaw	Y	Y	Y	Richard Thomas	N	Y	Y
Doan Hansen	Y	A	A	TALLY	13/17 (13 Y, 4 N)	12/18 (12 Y, 6 N)	16/16

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	~~310~~, (450)	310, ( )	250, ( )	140, ( )	70, ( )
AEGL 2	2800, ( )	1600, ( )	1200, ( )	820, ( )	820, ( )
AEGL 3	12,000, ( )	6800, ( )	4800, ( )	3400, ( )	3400, ( )

AEGL 1 Motion: Bob Benson **Second:** Mark McClanahan

AEGL 2 Motion: Hinz **Second:** Benson

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

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 9/11/02

OPTIONAL FORM 99 (7-90)

FAX TRANSMITTAL # of pages ▶

To Pat Jungling	From Paul Tobin
Dept./Agency ORNL	Phone # 202 564-8557
Fax # 865 241-0397	Fax # 202 564 4679

Appendix I

NAC/AEGL Meeting 26: September 10-12, 2002

Chemical: CARBON DISULFIDE **CAS Reg. No.:** 75-15-0 CS_2

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	N	Y
Steven Barbee	A	A	A
Lynn Beasley	A	A	A
David Belluck	A	A	A
Robert Benson	Y	Y	Y
Jonathan Borak	A	A	A
William Bress	Y	Y	Y
George Cushmac	Y	Y	Y
Al Dietz	A	A	A
Ernest Falke	Y	Y	Y
Larry Gephart	A	A	A
John Hinz	P	N	Y
Jim Holler	Y	Y	Y
Thomas Hornshaw	A	A	A
Doan Hansen	A	A	A

NAC Member	AEGL 1	AEGL 2	AEGL 3
Nancy Kim	Y	Y	Y
Loren Koller	A	A	A
Glenn Leach	Y	N	Y
Mark McClanahan	N	Y	N
John Morawetz	Y	N	N
Richard Niemeier	Y	A	A
Marinelle Payton	A	A	A
Zarena Post	Y	N	N
George Rodgers	Y	Y	Y
George Rusch, Chair	Y	Y	Y
Robert Snyder	P	N	Y
Thomas Sobotka	A	A	A
Kenneth Still	A	A	A
Richard Thomas	A	A	A
TALLY	13/14	9/15	13/15

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	5.0 ,( )	5.0 ,( )	4.0 ,( )	2.5 ,( )	2.0 ,( )
AEGL 2	330 ,( )	330 ,( )	260 ,( )	170 ,( )	83 ,( )
AEGL 3	600 ,( )	600 ,( )	480 ,( )	300 ,( )	150 ,( )

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

AEGL 2 Motion: Rodgers **Second:** Benson

AEGL 3 Motion: Hinz **Second:** Bress

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 9/10/02