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

December 3-5, 2001

Meeting 23 Highlights

Holiday Inn Riverwalk
217 N. St Mary's Street
San Antonia, Texas 78205

INTRODUCTION

George Rusch, NAC/AEGL Chair, opened the meeting with brief remarks and along with AEGL Program Director, Roger Garrett, welcomed the committee members and guests. Thanks were expressed to John Hinz and Eric Stephens, Director, Air Force Institute for Environmental Safety and Occupational Health Risk Analysis (AFIERA) for hosting the meeting and Lacey Young for providing the excellent support prior to and during the NAC/AEGL-23 meeting.

John Hinz and Lacey Young briefly described the meeting logistics and evening activities for the NAC/AEGL-23 meeting. Eric Stephens, Director of AFIERA, welcomed the NAC/AEGL Committee members and guests and presented an overview of AFIERA (Attachment 1). The AFIERA mission statement includes the following points: (1) Enhance mission effectiveness, protect health, improve readiness and reduce costs (Air Force Health Protection) and (2) Assess and manage risks (Radiological, Biological, Chemical & Operational). He briefly highlighted the ongoing research project on JP-8 Jet Fuel. The research findings from the AFIERA research team will be incorporated into the JP-8 TSD and be reviewed at the meeting.

The highlights of the NAC/AEGL-22 meeting were reviewed and briefly discussed. John Morawetz submitted a brief note on carbon tetrachloride (Attachment 2) for inclusion in the revised highlights of NAC/AEGL-22. Afterwards, a motion was made by Bob Benson and seconded by Marinelle Payton to accept the draft meeting highlights with two minor changes. The motion was passed unanimously (Appendix A). The revised highlights of NAC/AEGL-22 are attached (Appendix B).

The highlights of the NAC/AEGL-23 meeting are presented below along with the meeting agenda (Attachment 3) and the attendee list (Attachment 4). Ballots were taken during the meeting and are incorporated into the appropriate chemical specific section as Appendices.

Visit by NAS/COT/AEGL Subcommittee

Dan Krewski, Chair, and John Doull from the COT/NAS/AEGL Subcommittee attended the NAC/AEGL-23 meeting. Dan Krewski praised the productive working relationships with EPA, NAC/AEGL, and ORNL and commented that the technical quality of the TSDs is excellent in general. NAS plans to have two more volumes of AEGL documents published in 2002. Later, Dan and John made the following specific remarks associated with the AEGLs development:

(1) Scientific validity of procedures: need transparency in the area of quantitative, qualitative, and completeness of data review. How do you get to the decision? Even though you never have enough data to do a perfect job you must look at the weight of the evidence and use valid extrapolation procedures. (Can't spend 8 hours on one topic, though.)

(2) AEGL-1 Values: we really need numbers for all chemicals; otherwise the emergency planners and others in the field will use AEGL-2 values. Liked the *Odor Annoyance* paper by Doorn, Ruijen and van Harreveld because it separates odor data from pure irritation data; however, they cautioned that it "bends" the definition for AEGL-1.

(3) AEGL values may be too low. If values don't agree with or are way out of line with previously derived numbers published by NAS for similar chemicals and scenarios, the NAC/AEGL creates a big problem for the NAS. The AEGL PROCESS NEEDS CREDIBILITY. One must look at the "real world" vs worst-case. Don't be so overly conservative that no one will believe the numbers.

(4) PK/PD Modeling: Jim Bruckner (AEGL/COT Subcommittee member) wants to see pharmacokinetic/pharmacodynamic modeling used more often. These data should help in the evaluation of actual dose to the target tissue(s).

(5) Benchmark Dose (BD) Calculations: BD is replacing NOELs as the standard analysis technique. Some questions remain to be addressed - "How do you go from BD to RfD (NOEL)?" Still, the committee would like to see more of this approach.

(6) Categorical Regression Analysis: discussion at the COT/NAS/AEGL August 2001 meeting led by Judy Strickland was impressive. It's recognized that we don't always have enough data to do this, but the committee would like to see more of this approach in the future.

John Doull brought up the possibility of visiting these and other major issues at a workshop that would be sponsored by The Academy at the request of the NAC/AEGL committee. Dan Krewski added that there is much interest in the work of this committee from overseas, Canada, EU. ...etc.
He also commented on a "data-needs" section for AEGLs.

TOPICAL ITEMS FOR DISCUSSION

GUIDANCE FOR THE USE OF ODOR IN AEGL-1 DEVELOPMENT

Due to a car accident, the originally scheduled presentation by Ton van Harreveld on Monday was postponed to Tuesday. Ton van Harreveld is the Managing Director of Ordournet Company. The revised paper of "*Guidance for the Application of Odor in the Derivation of AEGL-1*" by Reind van Doorn, Marc Ruijten, and Ton van Harreveld was distributed before the meeting to the NAC/AEGL, COT/NAS/AEGL and guests so that they could participate in the discussion (Attachment 5). Ton focused his presentation on why application of odor should be considered as an AEGL-1 endpoint and how the proposed methodology fit into the AEGL Standing Operating Procedures (AEGL SOPs). A few AEGL-1 values based on the proposed methodology were presented for comparison with the current AEGL values. Reasons for development of the AEGL-1 based on odor are briefly summarized below:

Any individual can perceive unusual odor as a threat, especially in the context of chemical incidents. Awareness of exposure might cause anxiety and manifest itself by somatic symptoms of arousal, such as dyspnea, sweating and hyperventilation. Although these symptoms are normal physiologic responses to frightening occurrences, they could lead to avoidance behavior (e.g., closing windows, seeking contact with environmental agencies and/or health authorities). Therefore, health professionals would be greatly served by the availability of practically applicable information about the odor annoyance potential of compounds, as much as they need information about irritative and toxic properties of these compounds.

Notification (i.e., informing the public about properties of the unusual odor) can modulate appraisal of odor and the resulting behavior. This guidance provides criteria for the derivation
of a 'Level of Odor Annoyance' (LOA) for emergency exposure. If this LOA is lower than the concentration which causes other responses, such as irritation, it is considered the best
estimate for an AEGL-1. By default, the LOA can be obtained by multiplying the odor threshold, C_0 by 12 (LOA= 12* C_0).

MONITORING DEVICES LINKED TO AEGL VALUES

Lisa K. Stallsworth, Straughan Technical, presented the Gastec Gas Detection System (Attachment 6). The advantages of detector tubes over electronic devices are: they are always ready and easy to use; they require no power source and no calibration. The detector tubes are thin glass tubes filled with an inert support on which is impregnated a chemical. The chemical will react colorimetrically with the contaminant of interest. The length of stain of color change is proportional to the contaminant concentration.

Interchangeability refers to using a pump from one manufacturer and a tube from another manufacturer. It is prohibited or strongly discouraged by many national and international standardization organizations as pointed out by Lisa.

Gastec was the first company to attain all Safety Equipment Institute certifications (tubes and pumps and manufacturing facilities). Gastec has developed several types of tubes and accessaries for various applications.

Lisa stressed that Gastec's tubes are useful for emergency response because they are easy to use, Gastec has more tubes (over 250) and applications (over 500) which have been developed to detect all ranges for many ERPG and AEGL chemicals, and Gastec will custom design tubes for more of these chemicals if a market can be proven (chemicals must be in the gas/vapor phase; chemicals with low vapor pressures are not well detected on colorimetric tubes).

REVIEW OF PRIORITY CHEMICALS FOR AEGL VALUES

METHYL ETHYL KETONE
CAS Reg. No. 78-93-3

Chemical Manager: Mark McClanahan, CDC
Staff Scientist: Sylvia Talmage, ORNL

The chemical review was presented by Sylvia Talmage (Attachment 7). Methyl ethyl ketone (MEK) is a widely used volatile solvent with a rich data base of clinical and laboratory animal studies. Two studies with human volunteers exposed to 100, 200, or 350 ppm were evaluated for the AEGL-1; the exposure times were 5 minutes (Nelson et al. 1943) and 4 hours (Dick et al. 1992). Although a concentration of 200 ppm was judged unobjectionable in both studies, slight nose and throat irritation were noted at 100 ppm in the Nelson et al. (1943) study. Therefore, 100 ppm was selected as the threshold for sensory irritation. The safety of this value is supported by numerous clinical studies in which volunteers were routinely exposed to 200-400 ppm for up to 4 hours. Because this is a threshold value, slight irritation should not increase in intensity with time, and population response to slight irritation should not vary greatly, an intraspecies uncertainty factor of 1 was applied. Because accommodation to slight irritation occurs, the 100 ppm concentration was used across all AEGL-1 exposure durations. Furthermore, MEK is rapidly metabolized and will not accumulate in the blood or in the body which further supports using the same value for all the time intervals. A motion was made by David Belluck and seconded by Steve Barbee to adopt the 100 ppm concentration for all AEGL-1 time points. The motion passed [YES:16; No:2; Abstain:0] (Appendix C).

The AEGL-2 was based on the chronic study of Cavender et al. (1983) in which rats were exposed to 5000 ppm for 5 days/week for 90 days. No lesions were reported in this study, but the concentration is close to the threshold for neurotoxicity as evidenced by somnolence in another

repeated exposure study in which rats were exposed to 6000 ppm for several weeks (Altenkirch et al. 1978). Because this was a no-effect repeated-exposure study, no interspecies uncertainty factor was applied. Because the threshold for narcosis differs by no more than 2- to 3-fold among the general population, an intraspecies uncertainty factor of 3 was applied to protect sensitive individuals. Because the threshold for narcosis is concentration dependent, the resulting 1700 ppm concentration was applied across all AEGL-2 exposure durations. A motion was made by Bob Snyder and seconded by John Hinz to adopt the 1700 ppm concentration for all time points. The motion passed [YES:13; No:2; Abstain:3] (Appendix C)

The AEGL-3 values were based on two different studies. The 10- and 30-minute values were based on a study with mice in which a 30-minute exposure to 31,426 ppm reduced the respiratory rate by 50% but resulted in no deaths (Hansen et al. 1992). Because a 30-minute exposure of rats to 3 times this concentration (92,239 ppm) also resulted in no deaths (Klimisch 1988), the 31,426 ppm value was adjusted by an interspecies uncertainty factor of 1. Because the threshold for narcosis differs by no more than 2- to 3-fold among the general population, an intraspecies uncertainty factor of 3 was applied to protect sensitive individuals. The resulting value of 10,000 ppm was used for the 10-minute and 30-minute AEGL-3 exposure durations. The longer-term values were based on an MLE_{01} of 7500 ppm calculated by Fowles et al. (1999) from a 4-hour study with rats exposed to several concentrations for 4 hours (La Belle and Brieger 1955). In this study the 4-hour LC_{50} was 11,700 ppm and the highest concentration resulting in no deaths was 7850 ppm for 4 hours. The 7500 ppm concentration was divided by an intraspecies uncertainty factor of 3. The resulting value of 2500 ppm was used for both the 4-hour and 8-hour AEGL-3 values because MEK would reach equilibrium in the body prior to this time period. The 4-hour 2500 ppm value was time scaled to the 1 hour time using the default n value of 3 for scaling to shorter time intervals. It was moved by John Hinz and seconded by Loren Koller that we adopt AEGL-3 values for methyl ethyl ketone for 10 minutes to 8 hours of 10,000 ppm, 10,000 ppm, 4000 ppm, 2500 ppm, and 2500 ppm. In response to John Morawetz's concern that 10,000 ppm is close to the lower explosive limit of 17,000 ppm, it was stated by George Rusch, NAC/AEGL Chair, that a note to that affect will be clearly indicated in the final discussion and rationale. The motion passed [YES:15; NO: 2; Abstain:0] (Appendix C)

SUMMARY OF AEGL VALUES FOR METHYL ETHYL KETONE [ppm (mg/m^3)]

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint
AEGL–1	100 (293)	100 (293)	100 (293)	100 (293)	100 (293)	Threshold for irritation in humans
AEGL–2	1700 (4980)	1700 (4980)	1700 (4980)	1700 (4890)	1700 (4980)	Threshold for narcosis in repeated exposure study - rat
AEGL–3	10,000[a,b] (29,300)	10,000[a,b] (29,300)	4,000[c] (11,720)	2500[c] (7325)	2500[c] (7325)	[a]No deaths (30 minutes) - rats; MLE_{01} (4 hours) - mice

[a]Based on Hansen et al. (1992).

[b]This value is more than one-half of the lower explosive limit of 18,000 ppm.
[c]Based on La Belle and Brieger (1955).

JET PROPELLANT FUEL-8 (JP-8)

A series of presentations was made to inform the NAC/AEGL Committee on the status of action items from the earlier meeting when the Jet Fuel-8 TSD was first reviewed at the NAC/AEGL-13, March 1999. John Hinz made brief introductory remarks on the "Issues & Answers" to the JP-8 AEGLs development (Attachment 8). A sequence of presentations followed: (1) Epidemiology Study by Roger Gibson, (2) Health Effect Studies by Walter Kozumbo, (3) Potential Respiratory Irritation Studies by John Hinz and finally (4) TSD presentation by Sylvia Talmage.

Epidemiology Study: Lt. Col. Roger Gibson, Air Force

Lt Col. Gibson briefed the NAC/AEGL on the current status of epidemiology studies of military personnel exposed to JP-8. The investigation was undertaken in response to complaints regarding the increased irritancy of JP-8 compared to the previously used JP-4 aviation fuel (Attachment 9).

During 2000, the USAF led an investigation into the impact of acute JP-8 occupational exposure among active duty service members. The study was conducted at multiple USAF installations in the continental United States. Using an observational short-term cohort epidemiological model, biologic specimens and performance measures were collected from subjects prior to and after a four-hour work period (Attachment 9).

Results showed that JP-8 constituents were detected at significantly higher levels in the urine, breath and skin of those exposed to JP-8 compared to those unexposed. JP-8 constituents were also found at higher, but not statistically significant, levels in the blood of exposed workers. Exposed workers scored significantly more poorly on neurocognitive test batteries, had increased balance problems, and showed significantly reduced response to eye-blink conditioning (hippocampal function) testing. Exposed workers reported significantly more health symptoms and believed their work was harming their health. However, no differences were noted in health encounters (medical visits) among exposed and unexposed workers.

The results of this acute exposure study indicate workers acquire a JP-8 body burden during routine occupational operations and these exposures mildly impact neurological function. More study is needed to establish the long-term impact of exposure (Attachment 9).

Health Effect Studies: Walter Kozumbo, Air Force Research Laboratory

Walt Kozumbo described ongoing studies and results of recent studies regarding the effects of JP-8 aerosols on the lungs and immune system of the mouse (Attachment 10).
A number of effects were observed in animals inhaling JP-8 aerosol. They consisted of changes in pulmonary function and reductions in immune organ weights, in immune T

cell numbers and in immune T cell functions. The lowest concentrations of JP-8 aerosol that have produced effects in the lungs and immune systems of mice were at 50 mg/m^3 for lung edema and 100 mg/m^3 for effects on thymus immune cells. JP-8 and JP-8+100 (a newer JP-8-derived fuel) were found to be equally toxic and their effects were dose-dependent.

JP-8 applied to skin of mice was more irritating than its predecessor, JP-4 jet fuel, and induced dermal elevations in TNFalpha, IL-1 and iNOS. A topical application to mice of 50 μL per day for 5 days or of 300 μL at one time resulted in systemic T cell suppression that was preceded by elevated blood levels of interleukin-10 and prostaglandins PGE2, biologically active cellular mediators with immunosuppressive activities. In mice, the administration of antibodies against IL-10 or of a commercially available cyclooxygenase II inhibitor (Celebrex) prevented the immunosuppressive activities induced by dermal exposure to JP-8. Thus far, preliminary studies have also shown that pre-exposure to JP-8 aerosol enhances both the growth of tumor cells and the severity of influenza infectivity in mice (1, 2; unpublished data). Finally, molecular studies on cultured cells have indicated that JP-8 exposure at a 10,000-fold dilution is highly cytotoxic, with the induction of apoptotic responses in lung and immune cells and necrotic responses in epidermal cells.

Initial studies at other laboratories are expected to produce results in the near future. These studies include:

- ü Mouse lung proteomic responses above and below the JP-8 toxicity threshold
- ü Genotoxic effects on blood and bone marrow cells from dermal and aerosol exposures to JP-8
- ü Quantitative structure activity relationships (QSAR), cluster analysis and cytokine release from human keratinocytes in assessing the relative toxicity of JP-8 mixture components
- ü Mathematical modeling of JP-8 disposition in the lung
- ü Whole body toxicokinetic modeling of JP-8 mixture components

This research aims to disclose potentially toxic interactions of JP-8 with biological tissues, to understand the molecular mechanisms mediating and inhibiting these toxicities, and, ultimately, to apply novel computational and molecular approaches to the task of identifying specific components in JP-8 that are toxic. Accomplishing these objectives will enable improvement of health safety standards; development of safer fuels, of protective strategies and of rapid monitoring devices; reductions in health effects and in concomitant medical and legal costs; and, finally, enhancement of human performance during sustained military actions.

Sensory Irritation Study in Mice -- Comparative and Quantitative Characterization of JP-8's Potential for Respiratory Tract Sensory Irritation: John Hinz, AFIERA

John Hinz discussed the recently completed respiratory irritation study (Attachment 11) and distributed the ExxonMobil final report by Dr. Fred Whitman (Attachment 12). This study addressed the comparative irritancy of JP-4, JP-8 and JP-8+100 and was performed in response to the request at the NAC/AEGL meeting held in New Orleans in March, 1999. To address this request, AFIERA, in concert with Army and Navy colleagues, designed a study based on ASTM's "Standard Method E 981-84" to characterize and compare the relative potency of three jet fuels to cause respiratory tract sensory irritation.

These fuels (JP-4, JP-8 and JP-8+100) were administered for 30 minute periods by means of a head-only exposure system to groups of four male Swiss-Webster mice. Test atmospheres laden with these fuels were presented as vapor-only (JP-4) or as a vapor/aerosol mixtures (JP-8, JP-8+100). Analytical sampling data revealed differences in the distribution and relative proportions of the hydrocarbon species contained in the vapor and aerosol phases. Generally, compounds with carbon numbers in the range of C11-C12 represented the principal constituents in the aerosol phase.

Each fuel was tested over a range of air concentrations (685 - 11,430 mg/m^3 for JP-4, 681 - 3,565 mg/m^3 for JP-8, and 777 - 2,356 mg/m^3 for JP-8+100) that resulted in minimal to severe decreases in respiratory rate. All three fuels evoked breathing patterns that were characteristic of upper airway sensory irritation at all exposure levels. Within the context of this study, there was no apparent evidence of pulmonary (deep lung) irritation or narcosis at any exposure level. The concentration that reduced the respiratory rate by 50% (RD_{50}) was calculated for each fuel: JP-4 = 4842 mg/m^3; JP-8 = 2876 mg/m^3; JP-8+100 = 1629 mg/m^3. The relative irritancy of these fuels may be ranked as follows: JP-8+100 > JP-8 > JP-4. Alarie observed that 10% of the RD_{50} estimates the threshold of effect for respiratory irritation. This value for JP-8 is approximately 290 mg/m^3, a starting point for determining an AEGL-1 for this fuel. Values for AEGL-2 can be obtained from JP-8's RD_{50} in concert with other exposure data on this fuel. There was no mortality data in the available scientific literature upon which to predicate values for AEGL-3.

This study constitutes Phase I of a two-phase program to compare and characterize the potential of selected jet fuels to cause respiratory tract sensory irritation. Phase II will test the following fuels: JP-5, -7, -TS, -10, and a light marine diesel.

Chemical Manager: John Hinz, AFIERA
Staff Scientist: Sylvia Talmage, ORNL

A review of the new data on JP-8, developed since 1999, was presented by Sylvia Talmage (Attachment 13). Although JP-8 is a complex mixture of aliphatic and aromatic hydrocarbons, for the purposes of AEGL development, the vapor and vapor/aerosol of the whole fuel was treated as a single entity. Studies addressing sensory irritation,

neurotoxicity, reproductive and developmental toxicity, immunotoxicity, and carcinogenicity and using primarily rodent species were available for consideration. Exposure durations ranged from acute to chronic. The AEGL-1 was based on the sensory irritation study of Whitman (2001). In this study, the 30-minute RD_{50} of male Swiss Webster mice was 2876 mg/m^3. According to Alarie (1981), 0.1 x the mouse RD_{50} elicits "some" sensory irritation in humans but can be tolerated for hours. Therefore, the 290 mg/m^3 value was applied to all AEGL-1 exposure durations. The value is supported by the lack of adverse health effects in rodents exposed to 1000 mg/m^3 in several repeated exposure and subchronic studies (Briggs 2001, Mattie et al. 1991, Rossi et al. 2001). Adjusting the 1000 mg/m^3 value by an interspecies uncertainty factor of 1 (no species differences were noted and the exposures were repeated) and by an intraspecies uncertainty factor of 3 (no susceptible populations were identified) results in a similar value, 330 mg/m^3. The repeated nature of the support studies corroborates the use of a single value for all AEGL-1 exposure durations. A motion was made to accept the 290 mg/m^3 for all exposure durations by Bob Benson and seconded by Glen Leach. The motion passed [YES: 15; NO: 5; Abstain: 0] (Appendix D).

The AEGL-2 was based on several acute studies with rodents in which sensory irritation was evident and is supported by the repeated, no-effect exposure studies. Exposure to 3430 mg/m^3 of vapor for 4 hours (Wolfe et al. 1996), 3565 mg/m^3 vapor/aerosol for 30 minutes (Whitman et al. 2001), 4440 mg/m^3 of aerosol for 4 hours, and 5000 mg/m^3 of JP-5 aerosol for 1 hour (MacEwen and Vernot 1985) resulted in sensory irritation. The 5000 mg/m^3 concentration was the threshold for central nervous system depression in both rats and mice. The lowest concentration, 3430 mg/m^3 was adjusted by an interspecies uncertainty factor of 1 (no species differences were evident) and by an intraspecies uncertainty factor of 3 (no susceptible populations were identified and the threshold for central nervous system depression differs by no more than 2- to 3-fold in the general population. The resulting value is 1100 mg/m^3. Because no adverse health effects were identified in rodent studies with repeated exposures to 1000 mg/m^3 (6 hrs/day, 5 days/weeks, for 6 weeks), the 1100 mg/m^3 value can be used for all AEGL-2 exposure durations. Based on this discussion, a motion was introduced by Loren Koller and seconded by Ernie Falke to accept 1100 mg/m^3 as AEGL-2 for all exposure durations. The motion was approved [YES: 17; NO: 1; Abstain: 0] (Appendix D).

The above AEGL-2 studies utilized the highest JP-8 vapor/aerosol exposures that could be generated. No studies resulted in lethality. Therefore, an AEGL-3 was not determined.
A motion was made by John Morawetz and seconded by George Alexeeff not to develop AEGL-3 values due to insufficient data. The motion passed unanimously (Appendix D).

A question was raised concerning the benzene content of JP-8 and carcinogenicity. The benzene content of neat JP-8, one of the more volatile components of JP-8, is <0.005% by volume. A discussion comparing the potential exposure to benzene at the 8-hour AEGL-2 of 1100 mg/m^3 to established standards and guidelines for benzene will be incorporated into

Section 8.2 of the TSD. Also it was noted that the derived values should be applied to the vapor or vapor/aerosol of JP-8 and not to a pure aerosol.

SUMMARY OF AEGL VALUES FOR JET PROPELLANT FUEL 8 (mg/m^3)[a]						
ssification	**minute**	**-minute**	**-hour**	**-hour**	**-hour**	**Endpoint**
AEGL–1	290	290	290	290	290	rritation - mouse
AEGL–2	1100	1100	1100	1100	1100	ritation - rat and mouse
AEGL–3	etermined	letermined	letermined	letermined	letermined	

[a] The values apply to JP-8 vapor or vapor/aerosol and not to the pure aerosol; the values do not apply to JP-8+100.
[b] Lethal concentrations were not attained in the available studies.

REVIEW OF CHEMICALS WITH ISSUES FROM PREVIOUS MEETINGS

XYLENES: PBPK Modeling

The Xylene AEGL's 2 and 3 values (1,4, and 8 hours) were determined from a study that used rats exposed to 1300 ppm of mixed xylenes for 4 hours (Carpenter et al 1975). Thus, extrapolation to 10 and 30 minute values would most likely be inaccurate. Therefore, a toxicokinetic approach (PBPK model) was considered in calculating the AEGL 2 and 3 values for 10 and 30 minutes. Dr. Ursula Gundert-Remy presented 10 and 30 minute data for AEGL's 2 and 3 using the PBPK model. Several assumptions were made using this model including that data from m-xylene represents the mixture of all xylenes and the kinetics are linear in the concentration/dose range at 10 and 30 minutes. Assumptions were also made concerning the concentration, toxicological endpoint, and effects of the substance. Kinetics were based on data from human volunteers.

The data from three studies were used. The calculations were performed using the NONMEM program (Attachment 14). It was assumed that the inhalation volume and frequency were constant. Calculations were derived for the mean concentrations and at 2 and 3 standard deviations (SD) for the 10 and 30 minute values for both AEGL's 2 and 3. A motion was made by Bob Benson and seconded by Ernie Falke to accept the AEGL-2 & 3 values with 2 SD. Thus, the values proposed for AEGL-2 were: 10 minutes - 980 ppm and 30 minutes - 480 ppm. The values proposed for AEGL-3 were: 10 minutes - 2100 ppm and 30 minutes - 1000 ppm. The motion was approved for AEGL-2 values [YES:16; NO: 4; Abstain: 0] and for AEGL-3 [YES:20; NO: 0; Abstain:0] (Appendix E).

Dr. Ursula Gundert-Remy will provide justifications to be incorporated into the TSD.

NAC/AEGL RESPONSES TO *FEDERAL REGISTER* COMMENTS TO THE PROPOSED AEGL VALUES

METHANOL
CAS Reg. No. 67-56-1

Chemical Manager: Ernie Falke, U. S. EPA
Staff Scientist: Peter Griem, FoBiG

Comments from the *Federal Register Notice* (FR) of May 2, 2001, on the proposed AEGL-2 values for methanol were received and discussed. This is a continuation of the discussion of methanol's AEGL-1 values from the last meeting of NAC/AEGL-22 which was held over due to an internal EPA issue. After Roger Garrett made brief remarks on the resolution of the issue, NAC/AEGL continued the discussion on AEGL-2 levels. Bob Benson noted that all other public comments regarding methanol were addressed at the September meeting. Mark McClanahan proceeded to make a proposal to approve the AEGL values as published in the Federal Register Notice of May 2, 2001 and elevate the methanol from Proposed to Interim status. The motion was seconded by Bob Benson. The motion was approved [YES:14; NO:3; Abstain:1] (Appendix F).

PERCHLOROMETHYL MERCAPTAN
CAS Reg. No. 594-42-3

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

The status of perchloromethyl mercaptan (PCMM) was reviewed by Chemical Manager Zarena Post. She summarized that values had been voted on and accepted by the NAC/AEGL-19 in December of 2000, and the proposed AEGL values were published in the FR of May 2001. A letter of comment was received from Tomen Agro in response to the FR request for comments, and comments were discussed at the NAC/AEGL-21, June 2001 meeting. One of the comments Tomen Agro made was that data were inadequate to set AEGL values for PCMM. A letter was sent to Tomen Agro to give them the opportunity to supply any additional existing data they might have or propose to collect more. Tomen Agro replied that they had no additional data, and proposed an alternate calculation method (Attachment 15). The proposed alternate calculation was not in accordance with the

NAC/AEGL committee's SOP. After the summary was presented, a motion was made by Zarena Post and seconded by John Hinz to elevate the AEGLs of PCMM from Proposed to Interim status. The motion was approved unanimously(Appendix G).

Review of AEGL-1 Values:
ETHYLENIMINE
CAS Reg. No. 151-56-4
&
PROPYLENIMINE
CAS Reg. No. 75-55-8

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

Mark McClanahan presented the proposed AEGL-1 values for ethylenimine and propylenimine (Attachment 16 and 17). For ethylenimine the proposed derivation entailed the using a factor of 2 to divide the AEGL-2 values to obtain the AEGL-1 values. This factor was equal to the average factor for the ratio between AEGL-3 and AEGL-2 for the compound. Because the propylenimine AEGL -1 and -2 values are directly derived from those of ethylenimine, any decision made about ethylenimine directly influences these propylenimine AEGL values as well. The committee members expressed discomfort with rationale for deriving the factor and suggested looking at the factor between AEGL-2 and AEGL-1 for other similar nitrogen containing compounds. The deliberations were suspended until these data were available. With these data, deliberations resumed, the ratios ranging from 21 to 1.5 from the shortest to longest exposure times. The committee expressed no interest in deriving a factor from these data. As an alternative factor Mark suggested using 3, a value which has been used to derive AEGL-2 values from AEGL-3 values for some chemicals. Mark also presented the level of annoyance (LOA) of 8 ppm value. This value was provided by Reind van Doorn in the following material:

AIHA (1989) presents two sources that report odor thresholds for ethylenimine. Carpenter (1948) reports a threshold of 2.0 ppm. This study was rejected by AIHA because of passive exposure. Berzins (1967) reports a value of 0.68-1.9 ppm. Methodology was critiqued as insufficient. The best choice in this case would be the lowest value, because the bias introduced by older testing methodology is always towards higher odor thresholds. There is no kw determined according to VDI 3882 available. Therefore a default value of 2.33 is recommended and the LOA defaults to 12 standardized odor units. Based on this approach a LOA-derived AEGL-1 for ethylenimine would be
approximately 8 ppm (15 mg/m3). Depending on the definitive AEGL-2 and AEGL-3 values, odor may not a significant criterion for derivation of the AEGL-1 for ethylenimine.

For propyleneimine, no odor thresholds were found in Devos (1990) or in AIHA

Based on this information, Mark's recommendation to the committee was to retain the AEGL-1 values for both chemicals unchanged from those currently approved by the NAC/AEGL

Committee. The NAC/AEGL Chair, George Rusch, asked for a vote by the simple show of hands; the recommendation was unanimously supported to retain the existing designation of NR (not recommended) for AEGL-1 values for both compounds (Appendix H and I).

Review of 10-minutes AEGL Values

HYDRAZINE
CAS Reg. No. 302-01-2

Chemical Manager: Richard Thomas, ICEH
Staff Scientist: Bob Young, ORNL

George Rusch briefly presented the chemical toxicity information on hydrazine (Attachment 18). The discussion focused on the development of 10-minutes AEGL values. The AEGL-1 was based on monkeys exposed continuously by the inhalation route to 0.4 ppm (days 1-10 of 90-days exposure). They exhibited flushing of the face and eye irritation (House 1964). Because of the extremely reactive and irritative nature of hydrazine, the severity of the toxic effect depends on the chemical concentration rather than on exposure time. Therefore, the same AEGL-1 value, 0.1 ppm, was set for all time periods. The AEGL-2 was based on rats exposed for 1 hour to 750 ppm of hydrazine. The rats exhibited reversible nasal lesions following removal from exposure (Latendress et al 1995). The AEGL-2 value was extrapolated from 1 hour to the other exposure durations using n=3 and a UF of 60 (interspecies 10; intraspecies 3; and a modifying factor of 2 due to sparse data). The 10-minute AEGL-2 value is 23 ppm. The 10-minute AEGL-3 was extrapolated from a rat lethality study (HRC 1993). The lethality threshold was estimated, by a threefold reduction of the 1-hr $LC_{50,}$ as 1064 ppm; this value was adjusted by a UF of 30 (interspecies 10; and intraspecies 3) and time-scaled using n=3. The 10-minute AEGL-3 was calculated as 64 ppm. The above 10-minutes AEGL values were proposed by Mark McClanahan and seconded by John Hinz. The motion passed [YES:15; NO: 2; Abstain: 0] (Appendix J).

METHYL HYDRAZINE
CAS Reg. No. 60-34-4

Chemical Manager: Richard Thomas, ICEH
Staff Scientist: Bob Young, ORNL

George Rusch briefly introduced the chemical toxicity information for methyl hydrazine (Attachment 19). He pointed it out that no numeric AEGL-1 values were developed due to (1) the lack of adequate data, (2) an inadequate margin of safety exists between the derived AEGL-1 and AEGL-2 values because significant irritation and possible toxic effects may

occur at concentration at or below the odor threshold. The AEGL-3 was based on the 1-hour LC_{50} of 82 ppm in female squirrel monkeys; the lethality threshold was estimated as a 3-fold reduction of the LC_{50}, 27.3 ppm. A total of UF of 10 was applied (interspecies of 3 based on the fact that toxicities to the squirrel monkey, dog, rat, and mouse differed by a factor of three and interspecies of 3 due to steep dose-response curve and mechanism of toxicity). A value of n=1 was used for temporal time scaling. The lethality data for the species tested indicated a near linear relationship between concentration and time (n = 0.97 and 0.99 for monkeys and dogs, respectively). The resulting 10-minute AEGL-3 value is 16 ppm. The 10-minute AEGL-2 value was derived from a 3-fold downward adjustment of the 10-minute AEGL-3 value, 5.3 ppm. A motion was made Steve Barbee and seconded by Mark McClanahan to accept the above proposal. The motion passed [YES: 16; NO: 1; Abstain: 0] (Appendix K).

DIMETHYL HYDRAZINE
CAS Reg. No. 151-56-4

Chemical Manager: Richard Thomas, ICEH
Staff Scientist: Bob Young, ORNL

George Rusch briefly presented the chemical toxicity information on dimethyl hydrazine (DMH) (Attachment 20). George noted that no numeric AEGL-1 values were developed due to (1) the lack of adequate data, and (2) an inadequate margin of safety exists between the derived AEGL-1 and AEGL-2 values because significant irritation and possible toxic effects may occur at concentrations at or below the odor threshold, similar to monomethyl hydrazine. The AEGL-2 values were based on the exposure of dogs to 1,1-DMH at 360 ppm for 15 minutes. The dogs exhibited behavioral changes and muscle fasciculations (Weeks et al., 1963). Extrapolation was based on $C^n \times t=K$ (ten Berge, 1986), using n=1 and a total uncertainty factor of 30 (interspecies of 3 and intraspecies of 10) to obtain 18 ppm as the 10-minute value. The AEGL-3 value was derived from a 1-hour LC_{50} study in dogs (Weeks et al., 1963) by establishing a lethality threshold of 327 ppm. The 10-minute AEGL-3 was derived in the same manner (n=1, UF = 30) as the AEGL-2 to obtain 65 ppm. A motion was made by Loren Koller and seconded by John Hinz to accept the above proposal. The motion passed [YES:17; NO: 1; Abstain: 0] (Appendix L).

Literature review of Benzene and Trichloroethylene

A brief literature overview of benzene and trichloroethylene was presented by Marcel T.M. van Raaij. Basically, he described the key attributes of benzene (Attachment 21). Benzene has been used as a solvent in industry since late 1800; it is produced from coal tar and crude oil; it is a constituent of gasoline; it has vapor pressure (95 mm Hg @ 25 °C); and

inhalation is the primary route of exposure. The toxicity of benzene is well characterized by CNS depression (acute) and bone marrow toxicity (chronic). It is a human carcinogen. Marcel outlined possible endpoints for AEGL-2 development in the area of CNS effects, hematotoxicity, chromosome aberrations, and embryo/fetotoxicity. He solicited inputs from NAC/AEGL committee which endpoint should be considered the most relevant for AEGL-2 development and what would be the rationale? The presentation was supplemented by Robert Snyder, Chemical Manager and subject expert. Bob described the postulated role of benznetriol in bone marrow depression and recent human studies from China on chromosome damage with benzene exposure. The studies can be important references while we are considering the most relevant endpoints for AEGL values (Attachment 22).

The presentation, continued by Marcel, focused on trichloroethylene. Trichloroethylene is another well-documented chemical. It is a volatile liquid (69 mm Hg @ 25 °C) and inhalation is the primary route of exposure. There are several possible endpoints for considering the developments of AEGL values (Attachment 23).

Administrative Matters

The next meeting, NAC/AEGL-24, has been set for April 9-11, 2002, in Washington, D.C. More information about the lodging will be provided soon by Po-Yung Lu. The tentative NAC/AEGL-25 meeting is proposed for June 17-19, 2002 , either in Washington, D.C. or Rutgers University (hosted by Bob Snyder); and the NAC/AEGL-26 meeting is also tentatively set for September 10-12, 2002, in Washington, D.C.

The meeting highlights were prepared by Po-Yung Lu, Oak Ridge National Laboratory.

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