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

December 9-11, 2002

Final Meeting-27 Highlights

Bureau of Labor Statistics, U.S. Department of Labor
Postal Square Building, G-440, Rm. 7-8
2 Massachusetts Avenue, N.E., Washington D.C. 20212

INTRODUCTION

George Rusch, NAC/AEGL Chair, opened the meeting with brief remarks including appreciation to Surender Ahir, OSHA representative, for his excellent efforts in making arrangements for the NAC/AEGL-27 meeting. He also briefly noted the absence of Roger Garrett, AEGL Program Director, due to illness.

George Rusch made remarks on the productive working history with John Henshaw, Assistant Secretary, OSHA/DOL, who is involved in the Emergency Response Planning Committee. Today, John was regrettably not able to be here and Davis Layne, Deputy Assistant Secretary, OSHA/DOL, welcomed the NAC/AEGL Committee. Davis Layne stated that OSHA mostly utilizes data from chronic studies; there are a few OSHA regulations that utilize acute toxicity data as well. For example, OSHA uses IDLH values under its confined space regulation and acute toxicity data to classify various hazardous substances under the Hazard Communication Standard. OSHA appreciates any guidance given to the workers based on scientifically sound principles.

The draft NAC/AEGL-26 meeting highlights were reviewed with one minor change to update the current affiliation of Pam Dalton. A motion was made by Mark McClanahan and seconded by George Rodgers to accept the meeting highlights as presented with the aforementioned revision. The motion passed unanimously by a voice vote. The final version of the NAC/AEGL-26 meeting highlights are attached (Appendix A) and was distributed to the NAC/AEGL by e-mail on December 26, 2002.

The highlights of the NAC/AEGL-27 meeting are summarized below along with the Meeting Agenda (Attachment 1) and the Attendee List (Attachment 2). The subject categories of the highlights do not necessarily follow the order listed in the NAC/AEGL-27 Agenda.

STATUS REPORTS

NRC/COT Publication

Ernie Falke reported that AEGL Volume 2 was published in October 2002; complementary copies were mailed to all NAC/AEGL members. Volume 3 which includes Nerve agents (GA, GB, GD, GF, and VX), Sulfur mustard, Diborane, and Methyl isocyanate is at the stage of COT external review. It is expected to be published by early spring of 2003. Upon complete analyses of the COT 8th Interim Report, we may have another publication.

Critical Health Effects Starting Points for AEGL Determination: LOAEL vs NOAEL

George Rusch solicited comments from the Committee with respect to the Summary of Category V Chemicals distributed by Po-Yung Lu prior to the meeting (Attachment 3). The NAC/AEGL accepted the Summary except George Alexeeff who had a concern on the justification of Iron pentacarbonyl. It was decided that George Rusch will look into the issue further and resolve the concern. If necessary, this chemical will be revisited at a future NAC/AEGL meeting.

TECHNICAL ISSUE DISCUSSIONS

LOA Subcommittee Report

Mark McClanahan and Marc Ruijten

The AEGL Odor Subcommittee held two conference calls prior to the December NAC/AEGL-27 meeting. The first conference call (November 7, 2002) discussed the use of the Level of Distinct Odor Awareness (LOA). The following summarizes the recommendations (Attachment 4) from the subcommittee:

> All AEGLs should be health-based. Odor, even as defined by the LOA, will not serve as a surrogate for health-based values without health-based data. The level of distinct odor awareness will not substitute for health-based values. Include the LOA in the TSD as information supplementary to health-based AEGL values. A single value of the LOA should be presented in both the executive summary and the TSD. The authors should write the **LOA as, "Level of Distinct Odor Awareness,"** and not as "Level of Significant Odor Awareness." The "Level of Distinct Odor Awareness" reported in the TSD will be based on the odor threshold (TD_{50}), where 50% of the odor panel detects the odor and 50% does not and has the odor intensity of 3 (Distinct Odor). The inclusion of the LOA within the TSD does not preclude the use of odor descriptors such as fruity, fishy, nutty, pungent, etc., where appropriate within the TSD. A population-based array of the LOA will be presented in the Appendix. When a useful relationship to Hedonic Tone becomes available this characteristic should also be incorporated in the definition of the LOA reported in the TSD. A chemical-specific development of the LOA

should be placed in a TSD Appendix. A version of "Guidance for the Application of Odor in Chemical Emergencies," should be incorporated into the SOP. At the December NAC/AEGL-27 meeting, the consensus of the members was to stop reporting odor data in Table 1. "Chemical and Physical Data" of the TSD.

The second conference call (December 4, 2002) discussed the use of LOAEL and NOAEL for definition of AEGL levels (Attachment 4).

The TSD documents should be as consistent as possible in selection of the sign or symptom chosen to define a specific AEGL level. The TSD should present a thorough justification of the sign/symptom chosen for a specific AEGL level. For AEGL-1, how do we resolve the discrepancy between the dictionary definition of the words notable and mild ? George Alexeef's recent publication reported (36 chemicals) the LOAEL-to-NOAEL ratio to be: 2 at the 50th, 5 at the 90th, and 6.3 at the 95th percentile, respectively. George Alexeef has a database listing the signs and symptoms used to define AEGL levels obtained from completed NAS/AEGL documents. George will present this listing with some analysis at a future AEGL meeting. In some places, AEGL-1 concentrations have been proposed and used as re-entry levels for releases for which evacuations or traffic stoppages have occurred. When he is able to obtain the documentation, Tom Hornshaw will report on some estimated costs incurred when expressway traffic was halted because of a chemical release.

Application of Ratios for Determination of AEGLs

Tom Hornshaw

Tom Hornshaw presented a further analysis of the ratios between the AEGL-3 to AEGL-2 and AEGL-2 to AEGL-1 values for all five time periods (originally presented in September 2002, and summarized in the Meeting 26 highlights) (Attachment 5). As a result of actions taken at the September meeting, he updated his database to add values for two new chemicals, carbon disulfide and vinyl chloride, and changed values for two original chemicals, hydrogen sulfide and perchloromethyl mercaptan. These updates resulted in minor changes in the statistics for the AEGL-3-to-AEGL-2 ratios, with the mean, median, and 95th percentiles being all marginally smaller. In contrast, the updates to the data sets for AEGL-2-to-AEGL-1 ratios resulted in major changes, since the new AEGL-1 values for hydrogen sulfide changed these ratios from being extreme to "normal" outliers and the new AEGLs for carbon disulfide introduced an additional set of outliers. The changes include: the ratio means now have a range of 8.97–10.92 instead of 12.3–25.5; the medians have a range of 3.32–4.63 instead of 3.19–4.13; and the 95th percentiles have a range of 38.6–56.2 instead of 27.1–113.6.

Tom's review of the toxicological data for the four outliers in the original analysis 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.). He suggested that this implied that for certain chemicals

there will be effects in humans that will not be predictable from the animal toxicity database. The new AEGLs for carbon disulfide shed some additional light on this suggestion. This chemical differs from the other four outliers in that both the AEGL-2 and AEGL-1 values are derived from human data, with the AEGL-2 values protecting against acute neurotoxic effects and severe irritation and the AEGL-1 values protecting against the "antabuse syndrome" caused by genetically low activity of aldehyde dehydrogenase. In this case, the Committee has specifically accommodated an endpoint in humans that is not able to be addressed by animal studies in developing the AEGL-1 values. This adds another cautionary note regarding extrapolating from a higher-level AEGL to derive a lower. Tom continues to suggest that if the Committee wishes to be protective of these types of human endpoints, a default extrapolation divisor greater than the value of 3 used in the past is indicated in most cases.

In an effort to further shed light on this issue, Tom reviewed the data for those chemicals for which the NAC/AEGL has already derived AEGL-2 values from AEGL-3 values, methyl hydrazine, methacrylonitrile, iron pentacarbonyl, dimethylformamide, and epichlorohydrin. He also reviewed three additional chemicals that provided helpful information, phosphine (which has a steep dose/response curve for lethality), and nickel carbonyl and propionitrile (which are closely related to iron pentacarbonyl and methacrylonitrile, respectively). This resulted in some further insights into the issue of when to extrapolate and how large the divisor should be. From this review, Tom found that the steepness of the dose/response curve for lethality, toxicity data for a closely related chemical (if available), and the presence or absence of irritation and/or neuropsychological effects in the human record for a chemical, are key factors to help decide whether to extrapolate from a higher-level AEGL, and what should be the appropriate divisor. He concluded his presentation with a few suggestions:

- A default divisor of 3 to derive AEGL-2 values from AEGL-3 values is only appropriate when there is a very steep dose/response curve for lethality; i.e., one in which the difference between nonlethal and 100% lethal doses is in the range of a doubling of the dose.

- Where toxicity data consistent with AEGL-2 type effects are available for a chemical closely related to a chemical for which AEGL-2 type data are poor or lacking, the data for the closely related chemical should be considered in determining the divisor for extrapolating to AEGL-2 values.

- For chemicals for which data consistent with AEGL-2 type effects are poor or lacking, that do not have very steep dose/response curves, and that do not have closely related chemicals to help in determining an appropriate divisor for extrapolating from AEGL-3 values, the choice of such a divisor should be made carefully, if at all. Factors that should be reviewed in making this choice include: the steepness of the lethality dose/response curve, with steeper curves favoring extrapolation and shallower curves suggesting extrapolation may not adequately protect against all AEGL-2 type effects; the presence, with relevant exposure information, or absence of AEGL-1 type effects in the toxicity data base, which can help guide the selection of an appropriate divisor if present and cautions against extrapolation if absent; and the presence, with or without relevant

exposure information, of effects in humans such as neuropsychological effects that are not readily predictable from animal studies, which strongly suggest that if extrapolation is desired that the divisor be relatively large and in keeping with the severity of the effects reported. If the database for a chemical lacks these factors or the factors argue caution in the choice of whether to extrapolate, then a default divisor should be at least 19.

- Since relatively large changes in the statistics for the AEGL-2-to-AEGL-1 ratios occurred when new data for hydrogen sulfide and carbon disulfide were added, it appears that the overall predictive power of this data set is not yet acceptable to determine an appropriate default divisor for extrapolating from AEGL-2 values to AEGL-1 values. There is also no basis for extrapolation from AEGL-3 values to AEGL-1 values.

- Based on reviews of the databases for iron pentacarbonyl, methacrylonitrile, and dimethylformamide, these chemicals should be reviewed by the Committee to determine if the values derived for these chemicals are still thought to be protective for all AEGL-2 type effects.

Application of AEGL Values in Emergency Responses
Bob Snyder and Brian Buckly

Bob Snyder and associates from the Environmental and Occupational Health Science Institute, Rutgers University, summarized some of the work they are doing in establishing a procedure for emergency response to the release of chemicals or biologicals in a community. The key to the project is the measurement of air levels of chemicals in various areas of the community evaluated with respect to the AEGL values for the chemical at any time. Using the ten Berge modification of Haber's rule they have plotted AEGL values as continuous lines over time and demonstrated that although the committee decides on AEGL values at 5 specific time points, an equation can be written starting with those points which defines a line made up of many points each of which defines an AEGL at that time. It can be shown that during a release concentrations of the chemical may approach and exceed the AEGL levels for that chemical suggesting a toxic response to the chemical at the location studied. Equations were derived to predict when specific AEGL values will be achieved at any location. In these studies the value of K, as in CxT=K, can be calculated and can be interpreted as a numerical expression of a response under the conditions of the experiment. These studies are still at an early stage and more detail will be presented as the data develop.

Acute Toxicity Threshold for Land Use Planning
Annick Pichard

Annick Pichard presented the overview of ACUTEX (Attachment 6). ACUTEX is a research project approved by the European Commission, started in December for a duration of three years. The objective of ACUTEX is to develop a methodology, a soft ware tool, and a Technical Guidance Document for establishing European Acute Exposure Threshold Levels (EU AETLs) for acute exposure scenarios. ACUTEX's aims toward:

1. Establishing a methodology, a software tool, and a Technical Guidance Document (TGD)
2. Developing EU AETLs for several chemicals as case studies according to the above TGD
3. Validating and improving the methodology by relevant case studies with end users and stakeholders.

EU AETLs have a great influence on the determination of the zone for land use and emergency planning. Threshold levels for acute exposures have been defined as concentrations in the air after accidental release which will cause different degrees of health impairment to human subjects exposed to the air. Air concentrations may reach to levels defined as levels, above which it is expected that the general population could experience notable discomforts which are not disabling and remain transient, to levels above which it is predicted that the general population could experience life-threatening health effects or death. The appropriate use of susceptible subpopulations such as children, elderly, and patients with defined diseases when deriving chemical-specific acute exposure levels is still a matter of controversy.

EU AETLs will speed up the harmonized implementation of the Seveso II directive on the control of major accident hazards involving dangerous substances. Nine partners belonging to research organizations and six European countries will participate in the work. Several innovative ideas, such as dose response modelling or toxicokinetics and toxicodynamics data will be used. A panel of experts from government and industry will be assembled and review the progress of the project.

REVIEW AND RESOLUTION OF COT/AEGL COMMENTS

Chloroform
CAS Reg. No. 67-66-3

Chemical Manager: Steve Barbee, Arch Chem. Inc.
Staff Scientist: Robert Young, ORNL

Prior to Federal Register submission, the proposed chloroform AEGLs were revisited. Robert Young reviewed the previously proposed values and their rationale, and identified several items in need of discussion: (1) development of 10-minute values, (2) adjustment of existing values by use of time scaling default *n* values of 1 or 3 rather than 2, and (3) justification of developmental toxicity as the critical effect for developing AEGL-2 values (Attachment 7). The chloroform AEGLs were briefly reviewed by the NRC/COT Subcommittee on AEGLs several years ago at which time concern was informally expressed regarding the use of a developmental toxicity endpoint as the critical effect for AEGL-2 development. This concern had been expressed by several NAC/AEGL members as well. Embryotoxicity as a possible critical effect resulting from acute exposure to chloroform was discussed at some length. The animal data from the key study (Schwetz et al., 1974) were discussed in detail. The endpoint was considered to be justified for AEGL-2 development due to acknowledgment of this effect in previous toxicity assessments and reviews. The recommendation that no AEGL-1 values be developed was reaffirmed. Ten-minute AEGL-2 and AEGL-3 values were derived and AEGLs for all time points were recalculated using

an *n* of 1 or 3 for time scaling to longer or shorter time periods, respectively. Additionally, the interspecies uncertainty factor of 10 previously used to develop the AEGL-3 was reduced to 3 and justified by pharmacokinetic and pharmacodynamic data indicating that rodents are more susceptible to chloroform-induced toxicity than are humans (this was the same justification for its application to AEGL-2 values as originally and currently proposed). AEGL-2 values of 120 ppm, 80 ppm, 64 ppm, 40 ppm, and 29 ppm for 10 minutes, 30 minutes, 1 hour, 4 hours, and 8 hours, respectively were accepted. Toxic effects more commonly associated with chloroform (e.g., hepatic and renal toxicity) were also taken into account in development of the AEGL-2 values. The AEGL-3 values (based on a 3-fold reduction of a 4-hr LC_{50} in rats) of 3100 ppm, 2200 ppm, 1700 ppm, 1100 ppm, and 540 ppm were also accepted. The extrapolation to 10-minutes was also justified by the fact that human experience data indicate that exposures as high as 22,500 ppm for approximately 30-120 minutes may be tolerated without fatal effects. A motion was made by Ernie Falke and seconded by Richard Niemeier to adopt the above AEGLs. The motion passed (YES:13 ; NO: 4; ABSTAIN: 1) (Appendix B). Revised TSD be circulated to NAC/AEGL.

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

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

The discussion was tabled to a later meeting because Honeywell may consider conducting a no-effect level irritation study in responding to COT/AEGL review comments.

Chlorine Trifluoride
CAS Reg. No. 7790-91-2

Chemical Manager: Bob Benson, US EPA
Staff Scientist: Sylvia Talmage, ORNL

The TSD for chlorine trifluoride, a severe respiratory irritant, was written in 1997. At that time the NAC/AEGL Committee considered time scaling the AEGL-1 values for respiratory irritants. Based on the fact that adaptation occurs to the slight irritation on which the AEGL-1 is usually based, the NAC/AEGL now uses the same value across all exposure durations. Therefore, the AEGL-1 values for chlorine trifluoride were revisited to update them before sending the TSD to the NRC/COT. The original AEGL-1 values was were based on mild sensory irritation in the dog during an exposure to 1.17 ppm for 3 hours. Mild sensory irritation was considered a NOAEL for notable discomfort which defines the AEGL-1. This value was divided by interspecies and intraspecies uncertainty factors of 3 each for a total of 10. The resulting value is 0.12 ppm (Attachment 8). Rather than time scaling this value as was done in the original TSD, it was proposed to use 0.12 ppm across all exposure durations. It was moved by George Rodgers and seconded by Richard Thomas to accept 0.12 ppm across all AEGL-1 exposure durations. The motion passed (YES: 14; NO: 0; Abstain: 0) (Appendix C).

Toluene
CAS Reg. No. 108-88-3

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

Sylvia Talmage discussed the review comments of the NRC/COT on toluene (Attachment 9). The NRC/COT basically felt that the derived interim values were inconsistent with the human data, especially those values derived for the longer-term exposures via time-scaling. They also suggested adding data that shows that many solvents, including toluene, rapidly reach equilibrium in the blood and brain, therefore, negating the need for time scaling. Furthermore, they rejected using the symptom of irritation as the basis for the AEGL-1 because many studies indicate that toluene is a pleasant-smelling, non-irritating chemical. The revised AEGL-1 was based on the preponderance of data from clinical and occupational exposures that indicate a concentration of 200 ppm would be without an effect that exceeds the definition of an AEGL-1. This value was proposed for all time periods as clinical studies indicate that this concentration of toluene rapidly reaches equilibrium in the blood and does not increase with increased exposure duration. No intraspecies uncertainty factor was applied as the value was based on several hundred individuals in clinical studies and several thousand individuals in occupational exposure studies. The motion was made by Bob Snyder and seconded by Ernie Falke to accept 200 ppm across all exposure durations. The motion passed (YES:13; NO: 2; Abstain:0) (Appendix D).
The revised interim AEGL-2 values were based on multiple studies that showed that exposure to 700 ppm for 20 minutes was a NOAEL for obvious central nervous system depression. Because equilibrium in the blood and brain may not be reached during the short exposure to this concentration, the value was time-scaled to the 10- and 30-minute exposure durations using the concentration:exposure duration relationship of $C^2 \times t = k$. The n value of 2 was based on multiple lethality studies with mice, the most sensitive species to the central nervous system effects of toluene (TSD dated NAC/Draft 5: 11/2002, Section 6.3. Derivation of AEGL-2). Based on similarity in structure and metabolism with the xylenes, the 1-hour AEGL-2 value was time scaled from the 30-minute value using a human pharmacokinetic model for xylene. Because steady state would be reached in the blood and brain within an hour, the 4- and 8-hour values were set equal to the 1-hour value (see table on page 9). It was moved by Bob Snyder and seconded by Ernie Falke to accept the proposed AEGL-2 values. The motion passed (YES: 14 ; NO: 1; Abstain: 0) (Appendix D).

The revised interim AEGL-3 values were based on the highest NOAEL in several rat and mouse studies. The NOAEL for lethality of 6250 ppm for 2 hours is supported by several other studies. Interspecies and intraspecies uncertainty factors of 1 and 3, respectively, were considered adequate as, in the first case, uptake is greater in small rodent species than in humans; and, in the second case, the minimum alveolar concentration differs by no more than 3 among the human population. Time scaling utilized $n = 2$ as above for the AEGL-2. Because the time-scaled 8-hour value of 1000 ppm was inconsistent with the human data, the 8-hour value was set equal to the 4-hour value. The motion to accept the proposed values was made by Bob Snyder and seconded by Ernie Falke. The motion passed (YES: 11; NO: 1; Abstain: 3) (Appendix D).

Summary of Interim AEGL Values for Toluene [ppm]						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL-1	200	200	200	200	200	NOAEL for definition of AEGL-1, multiple clinical studies
AEGL-2	990	570	510	510	510	NOAEL for obvious central nervous system depression in humans
AEGL-3	7200	4200	2900	1500	1500	Highest NOAEL for lethality in studies with rats and mice

REVIEW OF PRIORITY CHEMICALS FOR AEGL VALUES

1,4-Dioxane
CAS Reg. No. 123-91-1

Chemical Manager: Jim Holler, ATSDR
Staff Scientist: Peter Griem, FoBiG

The chemical review was presented by Peter Griem (Attachment 10). Dioxane is produced at about 10,000 tons per year and is mainly used as a processing solvent. The majority of the available human and animal studies have been carried out more than 60 years ago. The pharmacokinetic study of Young et al. (1977) was discussed as the key study for AEGL-1. Four healthy young men were exposed to 50 ppm for 6 hours. Eye irritation was a frequent complaint throughout exposure. Since the authors considered 50 ppm an adequate workplace standard, the irritant effect was estimated to have been weak. This conclusion is supported by older volunteer studies (Silverman et al., 1946; Wirth and Klimmer, 1936) in which exposure levels of about 300 ppm only induced slight to moderate irritation. Since for local effects to the eyes, no toxicokinetic differences exist between individuals, a reduced intraspecies uncertainty factor of 3 was applied. Because the eye irritation was not reported to have increased with time in the key study, which is also supported by a guinea pig study (Yant et al., 1930), the 17 ppm concentration was used across all AEGL-1 exposure durations. A motion was made by Bob Benson and seconded by Jim Holler to adopt the 17 ppm concentration for all AEGL-1 time points. The motion passed (YES:17; NO: 0; Abstain:1) (Appendix E).

As additional information for emergency responders, a level of distinct odor awareness was derived. On a standardized 5-step scale of odor intensity, the level of distinct odor is between the level of faint odor and the level of strong odor. Based on a reported odor detection threshold of 0.8 ppm (Hellman and Small, 1974) and the threshold of 0.3 ppm for the reference chemical n-butanol measured in the same study, a corrected odor threshold of 0.11 ppm (using the reference odor threshold of 0.04 ppm for n-butanol) was derived. By application of a default factor of 16, a level of distinct odor awareness of 1.7 ppm was calculated. At this level about 50 percent of the

population are expected to experience a distinct odor. Assuming log-normal distribution, the 10- and 90-percentile concentrations for distinct odor awareness are 0.34 ppm and 8.8 ppm, respectively. A motion was made by Nancy Kim and seconded by Dave Belluck to adopt a level of distinct odor awareness of 1.7 ppm. The motion passed (YES:18; NO: 0; Abstain:1) (Appendix E).

With regard to the AEGL-2, both effects on the central nervous system and effects on the liver were discussed. In a study by Goldberg et al. (1964), exposure of rats to 6000 ppm for 4 hours resulted in a significant decrease of a conditioned response (pole climbing in response to buzzer to avoid electrical shock), but did not affect the escape behavior (pole climbing in response to electrical shock without buzzer). This level was considered an adequate starting point because at 8300 ppm for 3.5 hours, narcosis was observed in mice (Wirth and Klimmer, 1936). A total uncertainty factor of 30 was applied. The intraspecies factor was reduced to 3 because application of the default factor would lower the AEGL-2 values to a level that was used in the pharmacokinetic study by Young et al. (1977); i.e., a level that humans are known to tolerate without adverse effect. An interspecies factor of 10 was applied. Due to the lack of chemical-specific data, time extrapolation was done using the default values for the exponent *n* (1 for longer and 3 for shorter time periods). Time extrapolation was continued to the 10-minute period because even at the considerably higher concentrations of 1600 ppm for 10 minutes (Yant et al., 1930) or 1400 ppm for 5 minutes (Wirth and Klimmer, 1936) exposed human subjects did not experience more severe effects than irritation. In the study by Drew et al. (1978) slight liver damage in rats was indicated by a two- to threefold increase in the serum levels of three liver enzyme activities following an exposure to 2000 ppm for 4 hours. The endpoint of hepatotoxicity was also considered relevant because liver necrosis occurred in cases of fatal dioxane exposure at the workplace and repeated liver cytotoxicity is the mechanism suggested as the mechanism of the carcinogenic effect of dioxane. Application of a total uncertainty factor of 10 (3 for interspecies and 3 for intraspecies uncertainty factors) based an the same reasoning as above and, additionally, on the fact that the observed effect was considered below the level that could be tolerated according to the AEGL-2 definition and application of time extrapolation as above results in exactly the same AEGL-2 values. A motion was made by Loren Koller and seconded by Mark McClanahan to adopt AEGL-2 values for 1,4-dioxane for 10 minutes to 8 hours of 580 ppm, 400 ppm, 320 ppm, 200 ppm and 100 ppm. The motion passed (YES: 18; NO: 0; Abstain: 0) (Appendix E).

The AEGL-3 values were based on a 4-hour LC_{50} of 14300 ppm in rats (Pozzani et al., 1959). Although this study did not use the most sensitive species (cats), it was used as key study because it was the only study that was adequately described in the publication. A factor of 3 was used for extrapolation to a LC_{01}. A total uncertainty factor of 10 (3 for interspecies and 3 for intraspecies uncertainty factors) was applied because a higher uncertainty factor would have resulted in AEGL-3 values of 480 ppm for 10 and 30 minutes, which contrasts with the observation that exposure of human subjects to 1600 ppm for 10 minutes (Yant et al., 1930) resulted in moderate irritation, but not in more severe effects. Due to the lack of chemical-specific data, time extrapolation was done using the default values for the exponent n (1 for longer and 3 for shorter time periods). It was moved by Steve Barbee and seconded by Mark McClanahan to adopt AEGL-3 values for 1,4-

dioxane for 10 minutes to 8 hours of 950 ppm, 950 ppm, 760 ppm, 480 ppm, and 240 ppm. The motion passed (YES:17; NO: 1; Abstain:0) (Appendix E).

SUMMARY OF AEGL VALUES FOR 1,4-DIOXANE						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL–1	17 ppm (60 mg/m³)	17 ppm (60 mg/m³)	17 ppm (60 mg/m³)	17 ppm (60 mg/m³)	17 ppm (60 mg/m³)	Slight eye irritation in humans (Young et al., 1977)
AEGL–2	580 ppm (2100 mg/m³)	400 ppm (1400 mg/m³)	320 ppm (1100 mg/m³)	200 ppm (720 mg/m³)	100 ppm (360 mg/m³)	Slight behavioral effects (Goldberg et al., 1964), slight liver cytotoxicity (Drew et al., 1978) in rats
AEGL–3	950 ppm (3400 mg/m³)	950 ppm (3400 mg/m³)	760 ppm (2700 mg/m³)	480 ppm (1700 mg/m³)	240 ppm (860 mg/m³)	No deaths in rats (4 hours) (Pozzani et al., 1959)
Level of distinct odor awareness					1.7 ppm (6.1 mg/m³)	Odor detection threshold in humans (Hellman and Small, 1977)

Sulfur Dioxide
CAS Reg. No. 7446-09-5

Chemical Manager: Loren Koller, OSU
Staff Scientist: Cheryl Bast, ORNL

The discussion on sulfur dioxide was led by Cheryl Bast (Attachment 11). An AEGL-1 of 0.25 ppm was proposed based on the weight-of-evidence from several studies with exercising asthmatics. This value was a NOAEL for bronchoconstriction in exercising asthmatics. A motion to accept the AEGL-1 was made by Loren Koller and seconded by Mark McClanahan. The motion passed (YES:16; NO: 0; Abstain:1) (Appendix F). It was noted that the Shepard et al. (1981) and Linn et al. (1987) studies should be added to the weight-of-evidence argument. It was further noted that 0.25 ppm is a NOAEL for clinical symptoms, that this lack of response occurs in cool, dry air, and that the data do not include studies out to 8 hours.

An AEGL-2 of 1.0 ppm across time was proposed based on a weight-of-evidence approach. The endpoint was an increase in airway resistance of 102%-580% in exercising asthmatics exposed to 1.0 ppm. It was moved by Ernest Falke and seconded by Loren Koller to accept this value. The motion did not pass (YES: 8; NO: 8 ; Abstain: 0) (Appendix F). Following further discussion on the short time periods of the studies and lack of exercise in one of the studies, values of 1.0, 1.0, 1.0, 0.75, and 0.75 ppm were proposed by Richard Thomas. The 0.75 ppm value was considered a NOAEL for the longer time periods. The motion was seconded by Robert Snyder. The motion passed (YES: 12; NO: 3; Abstain: 2) (Appendix F). It was suggested that data on atopic individuals be added to the justification.

The data leading to derivation of AEGL-3 values was discussed by Cheryl Bast. The discussion included the reason for time scaling, the mechanism of action of sulfur dioxide, and the *n* value of 4 derived from mouse lethality data. Jonathan Borak pointed out that the response for the AEGL-3 burns and constriction of the bronchi - would be the same for asthmatics and non-asthmatics. The benchmark dose approach was utilized (using the 5% response of the lower 95% confidence interval). The lethality data from a 4-hour study with rats was used. The total uncertainty factor was 30. It was moved by Ernest Falke and seconded by Bob Benson to accept the values. The motion passed (YES: 13; NO: 3; Abstain: 1) (Appendix F).

Summary of Proposed AEGL Values for Sulfur Dioxide [ppm]						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL-1	0.25	0.25	0.25	0.25	0.25	NOAEL for clinical symptoms in exercising asthmatics
AEGL-2	1.0	1.0	0.75	0.75	0.75	NOAEL for severe respiratory response in exercising asthmatics
AEGL-3	42	32	27	19	16	Benchmark dose approach; 4-hour study with the rat

Dimethyldichlorosilane: CAS Reg. No. 75-78-5
Methyltrichlorosilane: CAS Reg. No. 75-79-6
Trimethylchlorosilane: CAS Reg. No. 75-77-4

Chemical Manager: Ernie Falke, EPA
Staff Scientist: Cheryl Bast, ORNL

Cheryl Bast reminded the NAC/AEGL Committee that acute toxicity from dimethyldichlorosilane and methyltrichlorosilane is due to the hydrolysis product, HCl.(Attachment 12) Because the 4- and 8-hour AEGL-2 values as well as the 8-hour AEGL-3 value for HCl were modified in response to NRC/COT comments, the respective values for the two silanes needed modification. Therefore, it was proposed that for dimethyldichlorosilane the 4-hour AEGL-2 value be raised from 3.3 to 6.5 ppm, that the 8-hour AEGL-2 value be set equal to the 4-hour value, and that the 8-hour AEGL-3 value be set equal to the 4-hour AEGL-3 value of 13 ppm. It was moved by John Hinz and seconded by Nancy Kim to accept the proposed changes. The motion passed (YES:17; NO: 0; Abstain: 0) (Appendix G).

A similar change was proposed for methyltrichlorosilane. The 4- and 8-hour AEGL-2 values were raised to 3.1 and 3.1 ppm and the 8-hour AEGL-3 value was set equal to the 4-hour value of 7.0 ppm. The motion to accept these changes was made by John Hinz and seconded by George Rodgers. The motion passed (YES:16; NO: 0; Abstain:0) (Appendix H). The statement that the values are conservative will be changed to say that the previous values were inconsistent with the human data.

For trimethylchlorosilane, the proposed AEGL-1 value of 1.8 ppm was based on its breakdown to 1 mole of hydrogen chloride (Attachment 13). This 1.8 ppm concentration of hydrogen chloride was a NOAEL for pulmonary function changes in exercising asthmatics. The motion to accept 1.8 ppm across all AEGL-1 exposure durations as well as the proposed values for the AEGL-2 and AEGL-3 was made by John Hinz and seconded by Mark McClanahan. The motion passed (YES:18; NO:1; Abstain:0)(Appendix I). The proposed AEGL-2 values were based on severe eye and respiratory tract irritation in rats exposed to 3171 ppm for 1 hour. Intraspecies and intraspecies uncertainty factors of 10 and 3 were applied, and a modifying factor of 3 was applied, the latter to account for data in a single species and use of a LOAEL. The total adjustment was 100. Time scaling utilized the same value as calculated for hydrogen chloride (n = 1). Based on the extensive scrubbing of hydrogen halides by the respiratory tract, the 4- and 8-hour values were set equal as was done for hydrogen chloride. Values are listed in the table below. The motion for AEGL-2 passed (YES:19; NO:0; Abstain:l) (Appendix I). The AEGL-3 was based on a calculated LC_{01} of 3970 ppm in rats exposed to trimethylchlorosilane for 1 hour. Interspecies and intraspecies uncertainty factors of 10 and 3 were applied, and time scaling was based on n = 1. The 4- and 8-hour values were set equal as was done for hydrogen chloride. The motion for AEGL-3 was also passed (YES:19; NO: 0; Abstain: l)(Appendix I). It should be noted that the values may be conservative as the hydrolysis of trimethylchlorosilane may not be complete.

Summary of Proposed AEGL Values for Trimethylchlorosilane [ppm]						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL-1	1.8	1.8	1.8	1.8	1.8	NOAEL for clinical symptoms in exercising asthmatics (based on hydrolysis to hydrogen chloride
AEGL-2	192	64	32	16	16	Severe respiratory response in rats adjusted by modifying factor
AEGL-3	790	270	130	33	33	Calculated 1-hour LC_{01} in rats

Nitrogen Dioxide
CAS Reg. No. 10102-44-0

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

Ed Faeder, SRF Environmental, Inc., made a presentation entitled Surface Coal Mining in Wyoming – an NO_2 Exposure Issue" (Attachment 14) along with representatives Terri Lorenzon, State of Wyoming, Wendy Hutchinson, Thunder Basin Coal Wyoming Environmental Quality Council, and Blair Gardener, Jackson Kelly, PLLC.

More than one-third of all the coal mined in the United States during fiscal year 2002 was produced from surface mines in the state of Wyoming. It is mined by removing rock and other material overlying the coal seam(s), fracturing, extracting, and crushing the coal, and loading it into railcars for shipment. Much of the mining process involves the use of explosive charges to fracture the coal and overburden to facilitate coal extraction. For a variety of reasons, the explosive of choice is a mixture of ammonium nitrate and fuel oil ("ANFO"). Hundreds of millions of pounds of ANFO are used annually in the production processes. The blasting operation ideally converts ANFO into nitrogen, carbon dioxide, and water. However, under real-world conditions, combustion of ANFO is incomplete and a variety of by-products are formed including oxides of nitrogen. Nitrogen dioxide ("NO_2") can form in sufficient quantities and concentrations to be seen as a red or orangish-brown cloud, under certain conditions. By regulating the blasting processes, as mines currently do, the likelihood of high levels of NO_2 impacting a single receptor more than once *in a long time* is low. This translates to the likelihood that a given human is exposed to a *high* level of NO_2 for more than a *short* time is very *infrequent*.

The purpose for this talk was to present their opinions on the development of AEGLs to the National Advisory Committee ("Committee") , and solicit input through the development of realistic AEGL-1 and AEGL-2 10-minute values. From a public safety standpoint, the distinction between *noticeable detectability* and *notable discomfort* is quite important. If the AEGL-1 level is set at this notable discomfort threshold, it could assist Wyoming officials charged with responsibility of promoting the safety of individuals who might be exposed. It could also help the Committee understand the application of AEGL values to actual settings. To the extent that the 10-minute AEGL-1 value reflects notable physiologic changes in people or organoleptic detectability, rather than modest discomfort, that value becomes more significant for the establishment of an exposure criterion "not to be exceeded more than once in a long time" than the 10-minute AEGL-2 value.

Nitrogen Dioxide TSD Discussion:
Previous NAC/AEGL action on nitrogen dioxide was reviewed and current concerns were addressed in a presentation by Carol Forsyth (Attachment 15). On September 15, 1998, the NAC/AEGL had adopted by unanimous vote the 30-minute, 1-, 4-, and 8-hour values for all three AEGL levels. At a subsequent meeting, a concern was expressed by the committee that the basis for AEGL-2, Henschler et al., 1960, was a secondary citation. It was explained that the study was translated, details were added to the TSD, and that the development team believed this to be a well-conducted study. Another concern was for the quality of the study used as the basis for AEGL-3, Henry et al., 1969. The development team considers this to be a well-conducted study and the lead author is respected in the field of inhalation toxicology; some details have been added to the TSD. No additional concerns were raised by the NAC/AEGL following this discussion. Derivation of the 10-minute values followed the SOP, used previously accepted key studies and endpoints, are supported by human and animal data, and time-scaled for AEGL-2 and -3 because the key studies had exposure durations $\leq$2 hours. The 10-minute values for all three AEGL levels were then proposed by Bob Benson and seconded by Tom Hornshaw as 0.50, 20, 34 ppm for AEGL-1, 2, and 3, respectively. The motion was voted separately and passed with majority votes (AEGL-1: YES: 14; NO:4; Abstain:0, AEGL-2: YES: 14; NO:3; Abstain: l, and AEGL-3:

YES:17; NO: 0; Abstain: l) (Appendix J). The NAC/AEGL requested the following of the development team: (1) add back-up/supporting information for AEGL-2 and -3 as suggested by Steve Barbee; (2) include the magnitude of the decrease in arterial pO_2 measured in COPD individuals; (3) evaluate information presented at the meeting by George Alexeef; and, (4) resend the TSD to the committee after these revisions are completed.

Summary of AEGL Values (ppm [mg/m^3])					
AEGL Level	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	0.50 [0.94]	0.50 [0.94]	0.50 [0.94]	0.50 [0.94]	0.50 [0.94]
AEGL-2	20 [38]	15 [28]	12 [23]	8.2 [15]	6.7 [13]
AEGL-3	34 [64]	25 [47]	20 [38]	14 [26]	11 [21]

Nitric Oxide
CAS Reg. No. 10102-43-9

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

Carol Forsyth briefly pointed out (Attachement 15) that on September 15, 1998, the NAC/AEGL voted to adopt the nitrogen dioxide values for nitric oxide because the major effects are from nitrogen dioxide. A note will be included in the nitric oxide (NO) TSD that short-term exposures below 80 ppm NO should not constitute a health hazard. No additional discussions or comments were made by the NAC/AEGL Committee.
Carol expressed concern on the AEGLs development of Nitric acid (Attachment 15) and proposed the AEGLs as stated in the current TSD or to develop alternatives. A report summarized the study of Gray et al. (1954) by W. F. ten Berge was suggested for incorporation if it is appropriate. A revised TSD will be presented at the next meeting.

Benzene
CAS Reg. No. 71-43-2

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

Benzene was discussed for the third time (Attachment 16). The TSD of benzene was only modified at some specific points. First, this includes the addition of studies described by Von Oettingen in 1940 with various C x T combinations resulting in narcosis. These studies provide evidence for N= ±1.

It is proposed not to use these data directly but to use these data to support the concept that *n*=3 for extrapolating to shorter duration is too conservative and that *n*=2 is a good alternative. Secondly, a general paragraph on occupational exposure was prepared to be added to the TSD.
In the NAC/AEGL-26 (June 2002), John Morawetz made comments on the human studies in the TSD and urged for a rewrite. In addition, Exxon and API offered to provide additional data on human / occupational exposure (and health effects). No additional data on acute exposure data were received by the December 2002 meeting.

Because no decisions were made on the selection of endpoints that should be used for AEGL development at the June 2002 meeting, the current TSD did not reflect a total rewrite. The NAC/AEGL considered irritation and mild CNS effects endpoints for developing possible AEGL-1 values. First, a study by Sbrova 1950 (110 ppm, 2 h, no subjective symptoms) was considered as a NOAEL for irritation. That would have resulted in 37 ppm as AEGL-1 for all exposure time periods. A motion was made by Ernie Falke and seconded by George Rodgers to adapt the proposed 37 ppm for AEGL-1. The motion failed (YES:5; NO; 7; Abstain: 1) (Appendix H). Alternatively, the NAC/AEGL considered mild CNS effects for AEGL-1. The interspecies factor was 1, the intraspecies factor was 3 since CNS effects do not vary more than a factor 2-3 within the population. N-values were 2 (to shorter duration) and 1 (to longer durations). The resulting AEGL-values were:127, 73, 52, 18, and 9 for 10-min., 30-min, 1, 4, and 8 h, respectively. A motion was made by John Hinz and seconded by Mark McClanahan to accepted the proposed AEGL values. The motion for AEGL-1 passed (YES: 11; NO: 0; ABSTAIN: 1) (Appendix H)".

Toward the end of the meeting, there was not a quorum to vote for the AEGL-2 and AEGL-3 values. However, NAC/AEGL continued to discuss the choices and the approach to be taken for the AEGL-2 and AEGL-3 levels. It was concluded that for acute exposure, CNS effects are the endpoint to be used and that no values should be developed based on hematotoxicity or developmental toxicity. Similar to toluene (which has been reviewed already by the COT), the developmental effects of benzene appear to be similar to an "alcohol-like" pattern of effects on the fetus which is most likely the consequence of repeated exposure.

The committee members were supportive of the approach presented in the TSD for AEGL-2 and 3 values including the use of *n*=2 and *n*=1 (see above). (Because the default values for n are 3 and 1, the only significant change for benzene is the use of n = 2 rather than the default value of 3 when time scaling to shorter time periods.) In addition, the NAC/AEGL present had a rather uniform opinion and supported the historic value of all occupational exposure data providing a picture on benzene exposure and health effects were provided and distributed to NAC/AEGL prior to the meeting. It was acknowledged that many of the "old" studies do not fulfill current SOP criteria but that the concentrations reported in different factories and workplaces, and the number of people involved, provides insight on the order of magnitude of the exposure. Such conditions were not associated with an inability to escape. The TSD of benzene will be reviewed at a future meeting.

John Morawetz was unable to attend the NAC/AEGL-27 meeting; however, he sent his comments regarding his pre-meeting review of benzene TSD and submitted his comment (Attachment 17) and requested to be noted in the meeting highlights as the following:

"Mr. Morawetz sent comments describing a number of serious problems with the characterizations of many of the human studies described in the Benzene TSD and summarized in the Derivation Sections for AEGL-1, 2 and 3. Mr. Morawetz requested that the committee decide if any changes in the descriptions of the human studies need to be made and communicate to him that decision."

Administrative Matters

Dr. Oscar Herandez provided an update on the human subject study clearance status and distributed two handouts: *Environmental News- Agency requests National Academy of Sciences (NAS)* input on consideration of certain human toxicity studies (Attachment 18) And the scope of NAS project "Use of Third Party Toxicity Research with Human Research Participant." (Attachment 19). In addition, George Rusch asked NAC/AEGL members to comment on the Draft write up "Application of Acute Exposure Guideline Levels" (Attachment 20) and send comments to him since this is the first time the Committee got a chance to read it and the discussion was deferred to a later meeting.

The site and time of the next meeting, NAC/AEGL-28 was discussed. Pending the availability of the meeting facility at Salt Lake City, Utah and EPA off-site travel approval, the meeting will be held in conjunction with the SOT Annual Meeting. The date is set for March 7-9, 2003, at Salt Lake City, Utah. The alternate proposal was on March 25-27, 2003, in Washington, DC. The dates for NAC/AEGL-29 and 30 have been set tentatively on June 17-19, and September16-18, 2003, respectively. More information regarding the NAC/AEGL-28 will be coming from Po-Yung Lu as soon as the determination and decision is made.

All items in the agenda were discussed as thoroughly as the time permitted. 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. NAC/AEGL-27 Meeting Agenda
Attachment 2. NAC/AEGL-27 Attendee List
Attachment 3. Summary Category V chemicals: Crtical Health Effect Starting Points for AEGL Determination: LOAEL vs. NOAEL
Attachment 4. Summary Report of LOA Subcommittee
Attachment 5. Summary Report of Application of Ratios for Determination of AEGLs
Attachment 6. Acute Toxicity Threshold for Land Use Planning
Attachment 7. Data Analysis and Response to COT/AEGL Comments of Chloroform
Attachment 8. Data Analysis and Response to COT/AEGL Comments of Chlorine Trifluoride
Attachment 9. Data Analysis and Response to COT/AEGL Comments of Toluene
Attachment 10. Data Analysis of 1,4-Dioxane
Attachment 11. Data Analysis of Sulfur Dioxide
Attachment 12. Data Analysis of Dimethyldichlorosilane and Methyltrichlorosilane
Attachment 13. Data Analysis of Trimethylchlorosilane
Attachment 14. Surface Coal Mining in Wyoming - an NO_2 Exposure Issue
Attachment 15. Data Analysis of Nitrogen dioxide and Nitric acid
Attachment 16. Note on Benzene from John Morawetz
Attachment 17. Data Analysis of Benzene
Attachment 18. EPA Environmental News
Attachment 19. Scope of NAS Project Study: Use of Third Party Toxicity Research with Human Research Participant
Attachment 20. Application of Acute Exposure Guideline Levels - Draft

LIST OF APPENDICES

Appendix A. Revised meeting highlights of NAC/AEGL-26 (sent to NAC/AEGL on 12/26/2002 by E-mail).
Appendix B. Ballot for Chloroform
Appendix C. Ballot for Chlorine Trifluoride
Appendix D. Ballot for Toluene
Appendix E. Ballot for 1,4-Dioxane
Appendix F. Ballot for Sulfur Dioxide
Appendix G. Ballot for Diemthyldichlorodilsne
Appendix H. Ballot for Methyltrichlorosilane
Appendix I. Ballot for Trimethylchlorosilane
Appendix J. Ballot for Nitrogen Dioxide
Appendix K. Ballot for Benzene

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-27
December 9-11, 2002

Attachment 1

Bureau of Labor Statistics, US Department of Labor
Postal Square Building, G-440, Rm. 7,8
2 Massachusetts Avenue, N.E., Washington DC 20212

Metro Subway Union Station(Red line)

AGENDA

Monday, December 9, 2002

10:00 a.m.	Introductory remarks and approval of NAC/AEGL-26 Highlights (George Rusch, Roger Garrett, and Paul Tobin)
10:05	Welcome to OSHA (John Henshaw/Surender Ahir)
10:15	COT/AEGL January meeting and publication status report (Roger Garrett)
10:30	Review of 1,4-Dioxane (Jim Holler/Peter Griem)
12:00 noon	Lunch
1:00	Review of 1,4-Dioxane (continued)
1:30	Review of Sulfur dioxide (Loren Koller/Cheryl Bast)
3:00	Break
3:15	Review of Sulfur dioxide (continued)
3:45	LOA applications and examples: Allylamine and Perchloromethylmercaptan (Mark McClanahan)
4:45	Application of Ratios for determination of AEGLs (Tom Hornshaw)
5:15	Administrative matters
5:30	Adjourn for the day

Tuesday, December 10, 2002

8:00 a.m.	Review and resolution of COT/AEGL comments: Chloroform-10-minutes AEGLs and developmental toxicity (Steve Barbee/Robert Young)
9:00	Review of Dimethyldichlorosilane, Methyltrichlorosilane, and Trimethylchlorosilane (Ernie Falke/Cheryl Bast)
10:15	Break
10:30	Review and resolution of COT/AEGL comments: Toluene (Larry Gephart/Sylvia Talmage)
12:00 noon	Lunch
1:00	Review of Nitric oxide, Nitrogen dioxide, and Nitric acid (Loren Koller/Carol Forsyth)
3:00	Break
3:15	Presentation of the European Research Project ACUTEX (Annick Pichard)
3:45	Review of Benzene (Marcel van Raaij/Bob Snyder)
5:45	Adjourn for the day

Wednesday, December 11, 2002

8:00 a.m.	Application of AEGL values in emergency responses (Bob Snyder)
9:00	Review of Chlorine trifluoride: AEGL-1and related issues (Bob Benson/Sylvia Talmage)
9:15	Review and resolution of COT/AEGL comments: BF3(Claudia Troxel/George Rusch)
9:30	International Symposium on Counter Terrorism: Decision Making Tools for Responding to Terrorist Use of Hazardous Substances - Minimizing Health Effects on Exposed Populations (Boris Filatov)
10:00	Break
10:15	Summary of status of critical health effect starting points for AEGL determination: Chloromethyl methyl ether, *cis & trans*-Crotonaldehyde, Iron pentacarbonyl, Methyltrichlorosilane, and Dimethyldichlorosilane, and Propionitrile (George Rusch)
10:45	Review of Hydrogen bromide (Larry Gephart/Sylvia Talmage)
12:00 noon	Adjourn meeting

Attachment 2

NAC/AEGL Meeting-27

December 9-11, 2002
Washington, D.C.

Name	Affiliation	Phone No.
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NAC/AEGL:

Attachment 3

This is a status report on the discussion of the critical health effect starting points for AEGLs determination. George Alexeeff submitted a letter (February 6, 2002, distributed at the NAC/AEGL-25 meeting) with a list of 33 chemicals where he is concerned that the NAC/AEGL Committee is not consistently following the Standing Operations Procedures Manul (2001), as described on pages 36 ,40, and 42. The chemicals presented in the letter are examples of his concern that NAC/AEGL Committee did not identify the NOAEL, but rather used the LOAEL as the starting point for AEGL development, without an additional safety (UF/MF) factor correction to obtain a "NOAEL". Subsequently, the EPA AEGL Program (Roger Garrett and Letty Tahan) conducted an analysis and subdivided the 33 chemicals in question into the following five categories below for ease of discussion (also distributed at the NAC/AEGL-25 meeting). They are:

Category I:	Observed effect level is < the AEGL threshold level
Category II:	Observed effect is adjusted from a LOAEL to a NOAEL using a UF, or a MF, or an adjustment factor, e.g. $LC_{50}/3$.
Category III:	Observed effect level is adjusted from a LOAEL to a NOAEL based on circumstances surrounding the study in question, e.g., multiple exposures.
Category IV:	Revisions expected based on NRCS/COT Subcommittee review.
Category V:	Observed effect > the AEGL threshold level.

After George and Roger's presentations and discussion at NAC/AEGL-25, it was agreed only Category V chemicals need further clarification and justification. Roger asked the TSD Development Team to prepare the responses to address the concerns of Category V chemicals. They are presented in the following paragraphs for your review. If you have any comments, please send to Po-Yung by Dec. 4. I will compile your comments so we can discuss effectively during the December meeting.

1. *Cis & trans* -Crotonaldehyde:

A review of the publication (Rinehart, 1967) showed that the concentration on which the AEGL-2 was based (8000 ppm-min) caused impaired pulmonary function (reversible) and was a threshold for bronchiolar lesions in rats. The original TSD mistakenly stated that the cardiotoxicity occurred "at 8,000 ppm-min" instead of "above 8,000-ppm." The end point is based a NOAEL.

2. Chloromethyl Methyl Ether:

The AEGL-2 for chloromethyl methyl ether (CMME) was based on a 30-exposure (6 hours/day) study. One of five rats had slight bilateral lung hemorrhage immediately after the 30 exposures, and 2/13 rats allowed to live without further treatment had minimal mucosal effects (regenerative hyperplasia and/or tracheobronchial squamous metaplasia). The AEGL-2 was based on one 6-hour exposure, which was considered a NOAEL because (1) the lesions were of minimal severity and low frequency (seen in only one of the five rats sacrificed at the end of the exposures and are therefore close to a NOAEL for 30 exposures, and it is very likely that no effect would be seen from a single exposure (2) if one exposure caused slight bilateral lung hemorrhage immediately after treatment, 30 exposures would be expected to cause more severe effects, which were not seen. Therefore, it is extremely unlikely that AEGL-2 tier effects would have resulted from a single exposure, which is considered the NOAEL for AEGL-2 effects.

3. Iron Pentacarbonyl:

A 6-hr exposure of rats to 2.91 ppm (approximately 17.5 ppm·hrs) caused 10% mortality (one out of ten) (BASF, 1995). This was used as the driver for the AEGL-3 values. Biodynamics (1988), however, reported a 4-hour exposure of rats to 5.2 ppm (21 ppm·hrs) as a lethality threshold. Biodynamics (1988) also reported a 16% mortality in rats following a 4-hour exposure to 6.99 ppm (28 ppm·hrs). Both the NAC/AEGL-25 (June 2002) and the NRC/COT Subcommittee (July 2002) meetings supported the selection of the 6-hr exposure to 2.91 ppm as the driver for the AEGL-3.

That the BASF data represent a defensible lethality threshold estimate is supported by the higher lethality threshold of 21 ppm·hrs (4-hr exposure to 5.2 ppm) reported by Biodynamics (1988) and the 4-hr LC_{16} of 6.99 ppm (28 ppm·hrs). If the 2.91 ppm exposure were linearly scaled (shown to be appropriate for iron pentacarbonyl) to a 4-hour exposure, the resulting exposure concentration (4.38 ppm) is below both the 4-hour 5.2 ppm lethality estimate and the 6.99 ppm 4-hr LC_{16} reported by Biodynamics (1988).

Conversely, if the 6-hour 2.91 ppm exposure were further reduced by 3-fold to estimate a lethality threshold (2.91 ppm/3 = 0.97 ppm), the resulting estimate would not be consistent with available data. For example, linear scaling of this 6-hour lethality estimate of 0.97 ppm to a 4-hour exposure would result in a 4-hour lethality estimate of 1.5 ppm, which is inconsistent with the 4-hour value of 5.2 ppm reported by Biodynamics. However, scaling the 6-hour, 2.91 ppm exposure to 4 hours results in a value of 4.38 ppm which is quite consistent with the 5.2 ppm lethality threshold reported by Biodynamics and also compatible with the 4-hour LC_{16} of 6.99 ppm and 4-hour LC_{50} of 10 ppm reported by Biodynamics.

Overall, it does not appear that reduction of the 2.91 ppm "starting point" is justified when other data are simultaneously evaluated.

4. Dimethyldichlorosilane:

The concern of AEGL-2 selection: Corneal opacity and grey spots on the lungs of rats exposed to 1309 ppm dimethyldichlorosilane for 1 hour (Dow Corning, 1997). **The entire TSD will be reviewed in NAC/AEGL-27 meeting.**

5. Methyltrichlorosilane:

The concern of AEGL-2 selection: Ocular opacity, clear fluid around the eyes, nose, and mouth, nasal staining, and hunched posture observed in rats exposed to 622 ppm methyltrichlorosilane for 1 hour (Dow Corning, 1997). **The entire TSD will be reviewed in NAC/AEGL-27 meeting.**

6. Propionitrile:

This compound is currently under NRC/COT Subcommittee review. COT suggested to prepare a general TSD to includes several nitrile compounds. If the relative potency approaches are used, this document will be significantly revised. The current concern may be eliminated.

Attachment 4

ODOR SUBCOMMITTEE

MEMBERS

George Alexeef	Thomas Hornshaw
Cheryl Bast	Nancy Kim
David Belluck	Po-Yung Lu
Doan Hansen	Mark A McClanahan
John Hinz	George Rusch
Jim Holler	Richard Thomas

RECOMMENDATIONS

ALL AEGLS SHOULD BE HEALTH-BASED.

ODOR, EVEN AS DEFINED BY THE LOA, WILL NOT SERVE AS A SURROGATE FOR HEALTH-BASED VALUES WITHOUT HEALTH-BASED DATA.

THE LEVEL OF DISTINCT ODOR AWARENESS (LOA) WILL NOT SUBSTITUTE FOR HEALTH-BASED VALUES.

INCLUDE THE LOA IN THE TSD AS INFORMATION SUPPLEMENTARY TO HEALTH-BASED AEGL VALUES.

A SINGLE VALUE OF THE LOA SHOULD BE PRESENTED IN BOTH THE EXECUTIVE SUMMARY AND THE TSD.

THE LOA SHOULD BE WRITTEN AS "LEVEL OF DISTINCT ODOR AWARENESS."

THE TSD SHOULD NOT USE THE TERM "LEVEL OF SIGNIFICANT ODOR AWARENESS."

THE LOA WILL BE BASED ON THE ODOR THRESHOLD (TD_{50}), WHERE 50% OF THE ODOR PANEL DETECTS THE ODOR AND 50% DOES NOT. COMBINING THE TD_{50} WITH ODOR INTENSITY DATA PERMITS THE DETERMINATION OF THE LOA FOR ODOR INTENSITY 3 (DISTINCT ODOR). THE "LEVEL OF DISTINCT ODOR AWARENESS" REPORTED IN THE TSD

THE INCLUSION OF THE LOA WITHIN THE TSD DOES NOT PRECLUDE THE USE OF ODOR DESCRIPTORS SUCH AS FRUITY, FISHY, NUTTY, PUNGENT, ETC. WHERE APPROPRIATE WITHIN THE TSD

POSSIBLE DATA ARRAY FOR APPENDIX

CHEMICAL XYZ				
LEVEL OF DISTINCT ODOR AWARENESS[1]				
-2 σ	- 1 σ	OT_{50}	+ 1 σ	- 2 σ
2	18	27	36	52

1. The LOA with odor intensity 3 (distinct odor)
NOTE: The population estimates are based upon the odor panel population and not the general population, which includes, anosmic, insensitive, sensitive and hypersensitive individuals. Typical odor panels contain 6 to 10 people.

QUESTION: DOES A MEASUREMENT THAT DOES NOT REACH THE LEVEL OF A BASIS FOR AN AEGL VALUE DESERVE SUCH ELABORATION WHEN WE DO NOT DO SO WITH HEADACHE, EYE, NOSE, OR PULMONARY IRRITATION?

THE NAC/AEGL COMMITTEE SHOULD FOLLOW THE CONTINUING DEVELOPMENT OF THE ODOR METHODOLOGY. WHEN VALID TECHNIQUES BECOME AVAILABLE THE NAC/AEGL SHOULD INCORPORATE THE OTHER ATTRIBUTES (HEDONIC TONE AND ODOR QUALITY) INTO THE LOA.

ESTIMATES FOR THE "ODOR THRESHOLD" AS PUBLISHED IN THE OPEN LITERATURE WILL CONTINUE TO BE PRESENTED IN THE TSD IN "TABLE 1: CHEMICAL AND PHYSICAL DATA."

THE TSD SHOULD CONTAIN A STATEMENT DISCOURAGING THE SUBSTITUTION OF THE LOA VALUE WHEN HEALTH-BASED AEGL-1 VALUES DO NOT EXIST.

A CHEMICAL SPECIFIC DEVELOPMENT OF THE LOA SHOULD BE PLACED IN A TSD APPENDIX.

A VERSION OF "GUIDANCE FOR THE APPLICATION OF ODOR IN CHEMICAL EMERGENCIES" SHOULD BE INCORPORATED IN THE SOP.

LOAEL VS NOAEL

GEORGE ALEXEEF'S RECENT PUBLICATION REPORTED (36 CHEMICALS) THE LOAEL-TO-NOAEL RATIO TO BE:
2 FOR THE 50th PERCENTILE,
5 FOR THE 90th PERCENTILE, AND
6.3 FOR THE 95th PERCENTILE.

THE PAPER CONTAINED A TABLE LISTING MILD HISTOCHEMICAL AND PATHOLOGICAL EFFECTS AND A SECOND TABLE LISTING SIGNS AND SYMPTOMS CATEGORIZED AS MILD ADVERSE HEALTH EFFECTS.

GEORGE ALEXEEF HAS A DATA BASE LISTING THE SIGNS AND SYMPTOMS USED TO DEFINE AEGL LEVELS OBTAINED FROM COMPLETED NAS/AEGL DOCUMENTS. GEORGE WILL PRESENT THIS LISTING AT A FUTURE AEGL MEETING.

AEGL-1 CONCENTRATIONS HAVE BEEN PROPOSED AND USED AS REENTRY LEVELS FOR RELEASES FOR WHICH EVACUATIONS OR TRAFFIC STOPPAGES HAVE OCCURRED. TOM HORNSHAW WILL REPORT ON SOME COST ESTIMATES INCURRED WHEN EXPRESSWAY TRAFFIC WAS HALTED BECAUSE OF A CHEMICAL RELEASE.

THE COMMITTEE NEEDS EITHER CONSISTENCY IN, OR A SUBSTANTIAL JUSTIFICATION FOR, THE CHOSEN (SIGN/SYMPTOM) USED TO DEFINE A SPECIFIC AEGL LEVEL.

SPECIFICALLY FOR AEGL-1 HOW DO WE RESOLVE DISCREPANCY BETWEEN THE DICTIONARY DEFINITION OF THE WORDS NOTABLE AND MILD

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

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

- DELETE ALL VALUES BASED ON POTENCY RELATIVE TO ANOTHER CHEMICAL

- VALUES AVAILABLE FOR ~~59~~ *61* CHEMICALS FOR AEGL-3/2 RATIOS AND ~~19~~ *20* AEGL-2/1 RATIOS

- STATISTICAL EXAMINATION OF ALL DATA SETS

AEGL-3:AEGL-2 RATIOS

10-MINUTE RATIOS

- N = ~~32~~ *33*
- MEAN = ~~5.34 +/- 6.66~~ *5.31+/-6.55*
- MEDIAN = ~~3.05~~ *3.07*
- RANGE = 1.55 – 34.55
- 95th PERCENTILE = ~~16.58~~ *16.30*

30-MINUTE RATIOS

- N = ~~57~~ *58*
- MEAN = ~~5.13 +/- 5.34~~ *4.98+/-5.27*
- MEDIAN = ~~3.65~~ *3.55*
- RANGE = 1.46 – 36.36
- 95th PERCENTILE = ~~13.71~~ *13.70*

60-MINUTE RATIOS

- N = ~~59~~ *61*
- MEAN = ~~5.19 +/- 5.49~~ *5.10+/-5.42*
- MEDIAN = 3.67
- RANGE = 1.45 – 35.42
- 95th PERCENTILE = ~~14.14~~ *14.00*

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

4-HOUR RATIOS

- N = ~~56~~ *58*
- MEAN = ~~5.23 +/- 6.52~~ *5.15+/-6.42*
- MEDIAN = 3.17
- RANGE = 1.43 – 34.62
- 95th PERCENTILE = ~~16.91~~ *16.36*

8-HOUR RATIOS

- N = ~~52~~ *53*
- MEAN = ~~5.28 +/- 7.34~~ *5.22+/-7.29*
- MEDIAN = ~~3.16~~ *3.14*
- RANGE = 1.16 – 40.77
- 95th PERCENTILE = ~~18.69~~ *18.52*

AEGL-2:AEGL-1 RATIOS

10-MINUTE RATIOS

- N = ~~8~~ *9*
- MEAN = ~~25.51 +/- 57.72~~ *10.92+/-17.33*
- MEDIAN = ~~4.13~~ *4.56*
- RANGE = ~~1.50 — 168.0~~ *1.50-56.00*
- 95th PERCENTILE = ~~113.6~~ *38.60*

30-MINUTE RATIOS

- N = ~~19~~ *20*
- MEAN = ~~12.91 +/- 35.75~~ *10.40+/-17.21*
- MEDIAN = ~~4.00~~ *4.63*
- RANGE = ~~1.50 — 160.0~~ *1.50-66.00*
- 95th PERCENTILE = ~~27.25~~ *53.97*

60-MINUTE RATIOS

- N = ~~19~~ *20*
- MEAN = ~~13.05 +/- 36.85~~ *10.31+/-17.29*
- MEDIAN = ~~3.55~~ *4.31*
- RANGE = ~~1.50 — 164.7~~ 1.50-65.00
- 95th PERCENTILE = ~~27.72~~ *55.41*

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

4-HOUR RATIOS

- N = ~~19~~ *20*
- MEAN = ~~12.91 +/- 37.35~~ *10.31+/-17.94*
- MEDIAN = ~~3.28~~ *3.99*
- RANGE = ~~1.46 — 166.7~~ *1.46-68.00*
- 95th PERCENTILE = ~~27.54~~ *56.18*

8-HOUR RATIOS

- N = 19
- MEAN = ~~12.31 +/- 34.59~~ *8.97+/-13.70*
- MEDIAN = ~~3.19~~ *3.32*
- RANGE = ~~1.50 — 154.5~~ *1.50-51.52*
- 95th PERCENTILE = ~~27.10~~ *42.50*

HIGHLIGHTS

- **ALL DATA SETS SKEWED, NEITHER NORMAL NOR LOGNORMAL**

- **RANGE OF MEDIANS = ~~3.05—4.13~~ *3.07-4.63***

- **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*S* = H2S (ALL RATIOS ~~160+)~~*50+*) *& CS2 (RATIOS 51.5-68.0)***

- **ALL OUTLIERS *EXCEPT CS2* = ANIMAL DATA FOR HIGHER AEGL & HUMAN DATA FOR LOWER AEGL**

- ***CS2 = HUMAN DATA FOR AEGL-1 AND AEGL-2***

AEGLs ALREADY DERIVED USING RATIOS

- METHYL HYDRAZINE – AEGL-2 = AEGL-3/3 BECAUSE OF VERY STEEP D/R CURVE (10% DIFFERENCE BETWEEN 0% AND 100% LETHAL DOSES)

- METHACRYLONITRILE – AEGL-2 = AEGL-3/3 BECAUSE AEGL-2 EFFECTS (CONVULSIONS) NOT SEEN UNTIL DAY 39 OF STUDY

- IRON PENTACARBONYL – AEGL-2 = AEGL-3/3 BECAUSE OF STEEP D/R CURVE (300% DIFFERENCE BETWEEN 0% AND 50-100% LETHAL DOSES)

ALREADY DERIVED (CONTD)

- **DIMETHYLFORMAMIDE – AEGL-2 = AEGL-3/2 BECAUSE VALUES WOULD BE SIMILAR TO THOSE DERIVED USING AEGL-1 EFFECTS**

- **EPICHLOROHYDRIN – AEGL-2 = AEGL-3/3 BECAUSE ASSUMED TO BE PROTECTIVE OF AEGL-2 EFFECTS (PULMONARY EDEMA) SEEN AFTER BRIEF EXPOSURES**

DISCUSSION

PRECEDENT SET TO DIVIDE AEGL-3 WHEN D/R CURVE IS STEEP; BUT WHAT IS STEEP, WHAT IS APPROPRIATE DIVISOR?

- **GOOD PRECEDENT = METHYL HYDRAZINE - 10% DIFFERENCE BETWEEN 0% AND 100% LETHAL, 1st SYMPTOM IRRITATION, 2nd DEATH MAKES DIVISOR OF 3 PROTECTIVE**

- **POOR PRECEDENT = IRON PENTACARBONYL - 300% DIFFERENCE BETWEEN 0% AND 100% LETHAL, REPRO/TERATO EFFECTS SEEN WITH NICKEL CARBONYL (AEGL-3:AEGL-2 RATIOS 3.5-5.7) MAKE DIVISOR OF 3 QUESTIONABLE**

DISCUSSION (CONTD)

OTHER STEEP D/R CURVES

- **EPICHLOROHYDRIN: 100-120% DIFFERENCE BETWEEN 0% AND 100% LETHAL (BUT OTHER DATA SHOWS MAY BE AS HIGH AS 800%); BUT 10-MIN AEGL-2 OF 190 ppm FROM AEGL-3/3 TOO HIGH BASED ON HUMAN DATA (PULMONARY EDEMA FROM BRIEF 100 ppm EXPOSURE), FLATLINED INSTEAD; IS DIVISOR OF 3 OK?**

Not enough?

- **PHOSPHINE: MAY BE 100-200% DIFFERENCE BETWEEN 0% AND 100% LETHAL, AEGL-3:AEGL-2 RATIO FOR ALL TIMES = 1.8 SAYS DIVISOR OF 3 OK; BUT AEGL-2 BASED ON AEGL-1 EFFECT (RED MUCOID DISCHARGE), AEGL-2 EFFECTS SEEN IN HUMANS NOT READILY MODELED IN ANIMALS**

DISCUSSION (CONTD)

HELP FROM RELATED CHEMICALS

- **IRON PENTACARBONYL EXAMPLE**

- **METHACRYLONITRILE: ONLY AEGL-2 EFFECT AVAILABLE IS CONVULSIONS SEEN ON 39th DAY OF EXPOSURE, DIVISOR OF 3 THOUGHT PROTECTIVE OF AEGL-2 EFFECTS FROM SINGLE EXPOSURE; BUT AEGL-2 FOR PROPIONITRILE BASED ON NEUROPSYCHOLOGICAL EFFECTS IN HUMANS, AEGL-3:AEGL-2 RATIOS 5.27-5.45, AND MECHANISM OF TOXICITY FOR BOTH IS CONVERSION TO CYANIDE; IS DIVISOR OF 3 OK?**

not protective

INCONSISTENCIES IN AEGL-2 FOR DIMETHYLFORMAMIDE: DIVISOR OF 2 USED BECAUSE 3 WOULD BE IN SAME RANGE AS AEGL-1 EFFECTS, AND D/R CURVE SHALLOW, 1050% DIFFERENCE

SUGGESTIONS

- **DIVISOR OF 3 FOR DERIVING AEGL-2 FROM AEGL-3 ONLY OK WHEN D/R CURVE IS VERY STEEP (DIFFERENCE BETWEEN 0% AND 100% LETHAL DOSES IS NO MORE THAN 100%)**

- **DATA FROM RELATED CHEMICALS SHOULD BE USED WHEN AVAILABLE TO GUIDE SELECTION OF DIVISOR**

- **IF D/R CURVE NOT VERY STEEP AND NO RELATED CHEMICAL DATA AVAILABLE, CHOICE OF DIVISOR FOR DERIVING AEGL-2 SHOULD BE MADE CAREFULLY, IF AT ALL; CONSIDER STEEPNESS OF CURVE, AEGL-1 EFFECTS & CONCENTRATIONS REPORTED, ESPECIALLY NEUROPSYCHOLOGICAL; IF STILL NO HELP, CONSIDER DIVISOR OF 19**

SUGGESTIONS (CONTD)

- PREDICTIVE POWER OF DATABASE NOT YET ACCEPTABLE TO OFFER GUIDANCE FOR DERIVING AEGL-1 FROM AEGL-2

- NO BASIS FOR EXTRAPOLATING FROM AEGL-3 TO AEGL-1

- BASED ON REVIEWS, IRON PENTACARBONYL, DIMETHYLFORMAMIDE, AND METHACRYLONITRILE MAY NEED FURTHER DISCUSSION

Attachment 6

ACUTEX PROJECT

Methodology to develop Acute exposure Threshol levels in case of Chemical release. (transparent 1)

Dr Annick PICHARD – INERIS B.P N°2 – F 60550 Verneuil en Halatte – France

The ACUTEX project is a research project which has been approved in 2002 by the DG-RESEARCH under the 5 th Framework Research Programme of the European Commission

The Council Directive 96/82/EC (December 1996) addresses the control of major accident hazards involving dangerous substances ("SEVESO II" directive). It aims at the prevention of major accidents and the limitation of their consequences for man and the environment. Whereas the directive is intended to ensuring high levels of protection throughout the Community in line with the expectation of the public, currently different approaches are in place for land-use planning. It has been stated in the Report EUR 18695 " Guidance on land use planning as required by Council Directive 96/82/EC (Seveso II)" that it would be advantageous to consider further developments in the definition of the acute exposure thresholds used to determine the safety distances.

Besides their use in land-use planning, short-term exposure limits are essential for emergency planning and response in line with the aim to protect the public health in cases of accidental release of chemical substances.

So, the objective of ACUTEX is to develop a methodology, software tools and a Technical Guidance Document (TGD) for establishing European Acute Exposure Threshold Levels (EU AETLs) in case of accidental chemical release (transparent 2).

The methodology will be used as a supportive tool to derive European acute exposure thresholds Levels (EU AETLs) relevant to the various situations as land use planning or emergency situations.

In particular, it will speed-up the harmonised implementation of the Council Directive 96/82/EC of 9 December 1996 known as the SEVESO II Directive on the control of major-accident hazards involving dangerous substances.

Accordingly, this tool will be flexible enough to take into account the different national practices in accidental industrial risk assessment related to decision making process, so that the new methodology could become a recommended and harmonised tool used by risk experts and endorsed by the risk decision-makers in the whole European Union.

From the beginning of the project, a close co-operation with Competent Authorities of the EU Member States, responsible for the implementation of the SEVESO II Directive, and with Industry will be ensured through the constitution of a Critical Review Panel.

Ineris (France) is the co-ordonator of this project and there are 8 partners from Germany, UK, Belgium, Italy belonging to public organisms or european industry (transparent 3).

Presently, US EPA develops Acute Exposure Guidelines Levels (AEGLs) for emergency situations. However the range of the applicability of these values needs more investigations specifically in the case of landuse planning for EU. Consequently, efforts to develop acute exposure levels in Europe would be beneficial for both Europe and US by sharing data and common principles to produce acute exposure information at international level (transparent 4).

This approach supports the European Research Area concerning the improvement of the knowledge, encouragement of the Science-Industry dialogue and harmonisation in decision-making process.

In technical terms, ACUTEX aims at (transparent 5) :

1 - Establishing a methodology, the associated Technical Guidance document and a software tool

2 – Developping EU AETLs for several chemicals as cases studies according the above T.G.D

3 - Validating and improving the methodology by relevant cases studies with end-users and stakeholders

ACUTEX project is aimed too the development of innovative approaches to define a set of acute toxic levels to be used in both areas, land-use planning as described in SEVESO II directive and also in emergency planning. Indeed the thresholds have a great influence on the determination of the zones for landuse planning and emergency planning. Threshold levels for acute exposure have been defined as concentrations in the air after accidental release which will cause different degrees of health impairment to human subjects exposed to the air.

Airborne concentrations may reach levels defined as levels, above which it is expected that the general population could experience notable discomfort which are not disabling and remains transient, to levels above which it is predicted that the general population could experience life-threatening health effects or death. It is highly controversial in which way susceptible subpopulations such as children, elderly and patients with defined diseases, e.g. asthmatics have to be taken into consideration when deriving acute exposure levels.

Current methodologies in use are widely diverse resulting in figures which show up to 100 fold difference, a difference which is not defendable in front of the public. This difference is mainly due to the choice of safety factors which are used to account for uncertainty in the data. Further safety factors are used to scale up from animal to man and to take intraspecies/intrahuman variability into account. To ensure public credibility it is necessary to develop scientific methodologies by applying innovative approaches which can be accepted throughout the member States of European Union.

The state of the art and reference to the scientific literature including the methodology of the development of the AEGL programme will be done.

In the first part of this project compared to currently used methodologies, several innovative elements are introduced. :

- the priority setting procedure, which makes use of modern decision making algorithms in the choice of chemicals to be examined.
- the definition of a set of toxic levels by exploiting the full range of dose effect relationship.
- a highly innovative approach for modelling the dose effect relationship for toxic effects whereby instead of selecting only the 'key study' and discarding other information that might be relevant, all available data are used applying population approaches as a method for meta-analysis. This approach will estimate the set of doses which are connected with a defined intensity/incidence of adverse effect. The so-called threshold levels, with less uncertainty and smaller confidence intervals would allow to adopt smaller safety factors. Applying the data analysis to different species allows to estimate interspecies variation with higher precision, resulting in smaller scaling factors.
- the matrix approach which will be developed in this project makes use of kinetic and of dynamic properties of the toxic substances, thus enabling to define more exactly what degree of susceptibility is to be expected in special subpopulations as well as a better extrapolation of the time to effect relationship.

These points will be developed in 4 workpackages called (transparent 6) :

- Criteria to develop the list of priorities substances
- Thresholds and human health endpoints definitions

- Definition of subpopulation and use of specific extrapolation factors
- Dose-response modelling

The second part of the project is aimed at an iterative process of validating, implementing and improving the developed approaches by cases studies, end-users and stakeholders. Dissemination and validation is an important step to acceptance of the final Technical Guidance Document. Acceptance throughout the European Union is the first step in the way to setting world-wide accepted health standards for land-use planning and emergency planning (transparent 7).

ACUTEX started on the 1st December 2002 and the duration of the project is 3 years.

Attachment 7

CHLOROFORM AEGL REVISIT

- **AEGL-2 Development**
- **Time Scaling**

NAC/AEGL-27
December 9-11, 2002

Bureau of Labor Statistics, U.S. Department of Labor
Postal Square Building, G-440, Rm 7,8
2 Massachusetts Avenue N.E.
Washington DC

CHLOROFORM AEGL-2 ISSUES

- **Current AEGL-2 critical effect**

  - **embryo/fetotoxicity in rats; gestational exposure (100-300 ppm, days 6-15); Schwetz et al., 1974**

  - **assumed single 7-hour exposure for derivation of AEGL-2 values**

Currently Proposed AEGL-2 Values for Chloroform				
30 -min	**1 hr**	**4-hrs**	**8-hrs**	**Critical effect**
120 ppm	**88 ppm**	**44 ppm**	**31 ppm**	**Fetotoxicity in rats exposed for 7 hrs/day on gestation days 6-15 (Schwetz et al., 1974)**

Total UF = 3; $n = 2$

CHLOROFORM AEGL-2 ISSUES

- **Is the critical effect of fetotoxicity appropriate for AEGL-2 ?**

  - **NRC/COT acknowledged this effect in development of 1-hr EEL of 100 ppm (NRC, 1984); also acknowledged in Casarett & Doull's Toxicology (6^{th} ed)**

  - **Schwetz et al., (1974) specifically noted no relationship between maternal toxicity and embryo/fetal toxicity**

  - **1-hr AEGL-2 of 88 PPM consistent with 1-hr ERPG (50 ppm), and 1-hr EEL of 100 ppm**

  - **also evidence of fetal toxicity in mice (100 ppm, gestational exposure; Land et al., 1981)**

  - **10-minute to 8-hr single exposure → developmental effects ??**

CHLOROFORM AEGL-2 ISSUES

- **Alternate approaches ??**

  - **narcosis threshold; data are limited and exposure-response poorly defined**

  - **hepatotoxicity indices are of insufficient severity for AEGL-2**

10-MINUTE AEGL VALUES

- **Time scaling previously used default of $n = 2$**
  - **justified by similarity to empirically derived n of 2.5 for carbon tetrachloride**
  - **is currently accepted default of $n = 1$ or 3 more appropriate ?**
  - **revise all values using 1 and 3 defaults or remain with $n = 2$**

- **Is a 10-minute exposure to $CHCl_3$ valid relative to developmental effects ?**

PROPOSED AEGL VALUES FOR CHLOROFORM						
Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1		NR	NR	NR	NR	AEGL-1 effects unlikely in the absence of notable toxicity.
AEGL-2		120 ppm	88 ppm	44 ppm	31 ppm	Fetotoxicity in rats exposed for 7 hrs/day on gestation days 6-15 (Schwetz et al., 1974)
	80 ppm*	**80 ppm**	**64 ppm**	**40 ppm**	**29 ppm**	**n= 1 or 3**
		351ppm	*248ppm*	*124 ppm*	*88 ppm*	*narcosis threshold in humans (Lehmann and Hasegawa, 1910)*
AEGL-3		920 ppm	650 ppm	330 ppm	230 ppm	Estimated lethality threshold for rats; 3-fold reduction in 4-hr LC_{50} of 9780 ppm to 3260 ppm (Lundberg et al., 1986)
	940 ppm	**650 ppm**	**520 ppm**	**330 ppm**	**160 ppm**	**n = 1 or 3**

Original AEGLs for $CHCl_3$ were developed prior to the use of default *n* values of 1 and 3 for time scaling. **Bolded values derived using default *n* of 1 or 3.** *Italicized script represents originally proposed AEGL-2 values (06/98) based on estimated narcosis threshold in humans.*

*Time scaling not applied due to uncertainties in extrapolating to 10 minutes from a 7-hour exposure.

ACUTE EXPOSURE GUIDELINES FOR CHLOROFORM
(CAS NO. 67-66-3)

AEGL-1 VALUES			
30 minutes	1 hour	4 hours	8 hours
Not recommended	Not recommended	Not recommended	Not recommended

Reference: not applicable

Test Species/Strain/Number: not applicable

Exposure Route/Concentrations/Durations: not applicable

Toxicity Endpoint: not applicable

Time Scaling: not applicable

Concentration/Time Selection/Rationale: not applicable

Uncertainty Factors/Rationale
Total Uncertainty Factor: not applicable

Modifying Factor: not applicable

Animal-to-Human Dosimetric Adjustments: not applicable

Data Adequacy: AEGL-1 values were not recommended by the NAC/AEGL due to properties of the chemical. Based upon the available data it was not possible to identify a definitive effect consistent with the AEGL-1 definition. Exposures to concentrations approaching those inducing narcosis or hepatic and renal effects are not accompanied by overt signs or symptoms. Furthermore, the odor of chloroform is not unpleasant or irritating.

ACUTE EXPOSURE GUIDELINES FOR CHLOROFORM
(CAS NO. 67-66-3)

AEGL-2 VALUES

30 minutes	1 hour	4 hours	8 hours
120 ppm	88 ppm	44 ppm	31 ppm

Reference: Schwetz, B.A. et al., 1974.

Test Species/Strain/Number: Sprague Dawley rats; 68, 8, 22, 23, and 3 dams for the control, pair-fed control, low-, mid-, and high-dose groups, respectively

Exposure Route/Concentrations/Durations: inhalation (whole body); 0, 30, 100, or 300 ppm, 7 hrs/day on gestation days 6-15.

Toxicity Endpoint: fetotoxicity (total gross anomalies) expressed as litters affected/litters examined

Effect	Control	Pair-fed	30 ppm	100 ppm*	300 ppm
Total gross anomalies	1/68	0/8	0/22	3/23[a]	0/3
Total skeletal anomalies	46/68	3/8	20/22[a]	17/23	2/3
Total soft tissue anomalies	33/68	3/8	10/22	15/23	3/3
Reduced fetal bw(g)	5.69	5.19	5.51	5.59	3.42[a]
Fetal crown/rump length (mm)	43.5	42.1	42.5[a]	43.6	36.9[a]

[a] $p<00.05$

* Determinant for AEGL-2; although the reported effects were the result of 7-hr exposures on gestation days 6-15, for AEGL-2 it was assumed that the effects were the result of a single 7-hr exposure.

Time Scaling: $C^n \times t = k$ (ten Berge et al., 1986), where n =2. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical-specific data, an approximate midpoint value of n=2 was used for scaling across time.

Concentration/Time Selection/Rationale: a 7-hr exposure to 100 ppm was selected based upon total anomalies occurring in rat fetuses from dams exposed on gestation days 6-15. The mid dose was chosen in conjunction with the assumption of a single 7-hr exposure. The fetotoxicity endpoint is considered to represent a sensitive indicator of potential serious and irreversible effects in a susceptible population.

Uncertainty Factors/Rationale:

Total Uncertainty Factor: 3

Interspecies:	**none; available metabolism/kinetics data and PB-PK models (Corley et al., 1990) indicate that humans are less sensitive to the toxic effects of chloroform.**
Intraspecies:	**3; to account for individual variability in metabolism and disposition of chloroform and protection of individuals with altered metabolism/disposition(e.g.,users of alcohol); the fetus is considered as a sensitive population and, therefore, no additional reduction is warranted.**

Modifying Factor: none

Animal-to-Human Dosimetric Adjustments: insufficient data

Data Adequacy: Because the AEGL-2 values are based upon a sensitive endpoint using a conservative approach to select the determinant (assumption of a single 7-hr exposure), the values are considered to be protective of human health consistent with the AEGL-2 definition. AEGL-2 values based upon prevention of narcosis and hepatic or renal injury in humans would be notably higher (i.e., 351, 248, 124, and 88 ppm, respectively, for 30 minutes, 1, 4, and 8 hours). Furthermore, another study (Dilley, 1978) found that gestational exposure of rats to chloroform at concentrations as high as 2232 ppm (1 hr/day on gestation days 7-14) did not cause developmental effects.

ACUTE EXPOSURE GUIDELINES FOR CHLOROFORM
(CAS NO. 67-66-3)

AEGL-3 VALUES			
30 minutes	1 hour	4 hours	8 hours
920 ppm	650 ppm	330 ppm	230 ppm

Reference: Lundberg et al., 1986

Test Species/Strain/Number: female Sprague-Dawley rats/10 per group

Exposure Route/Concentrations/Durations: inhalation/ exposed to a geometric series of concentrations equivalent to ½, 1/4, 1/8, 1/16, or 1/32 the LC_{50} or the saturation concentrations

Toxicity Endpoint: lethality threshold estimated as 3-fold reduction of the 4-hr LC_{50} of 9780 ppm)

Time Scaling: $C^n \times t = k$, where n =2. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$ (ten Berge et al., 1986), where the exponent n ranges from 0.8 to 3.5. In the absence of chemical-specific data, an approximate midpoint value of n=2 was used for scaling across time.

Concentration/Time Selection/Rationale: estimated lethality threshold for 4-hour exposure (3-fold reduction in the 4-hr LC_{50} of 9780 ppm)

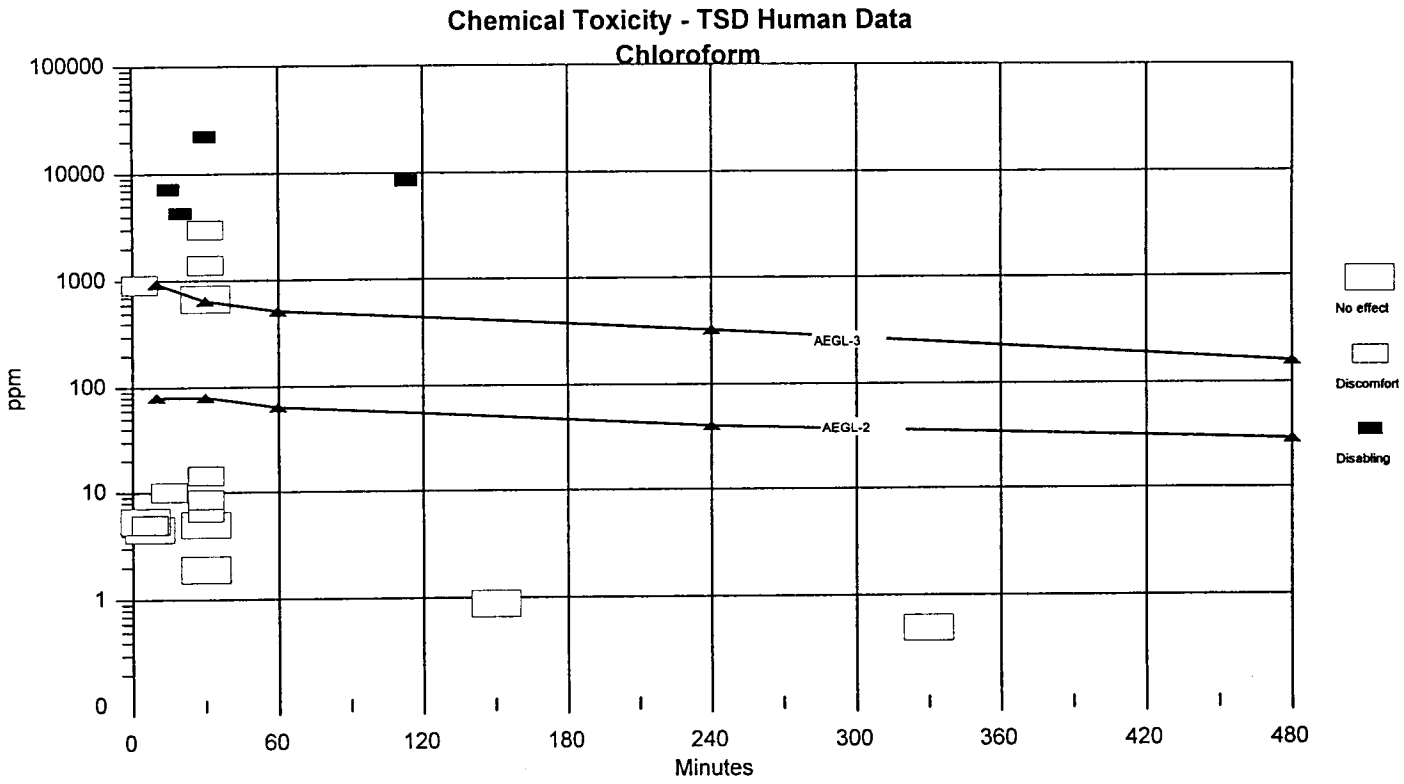
Uncertainty Factors/Rationale:
Total Uncertainty Factor: 10 (geometric mean of 10 which is 3.16, hence 3.16 x 3.16 = 10.)

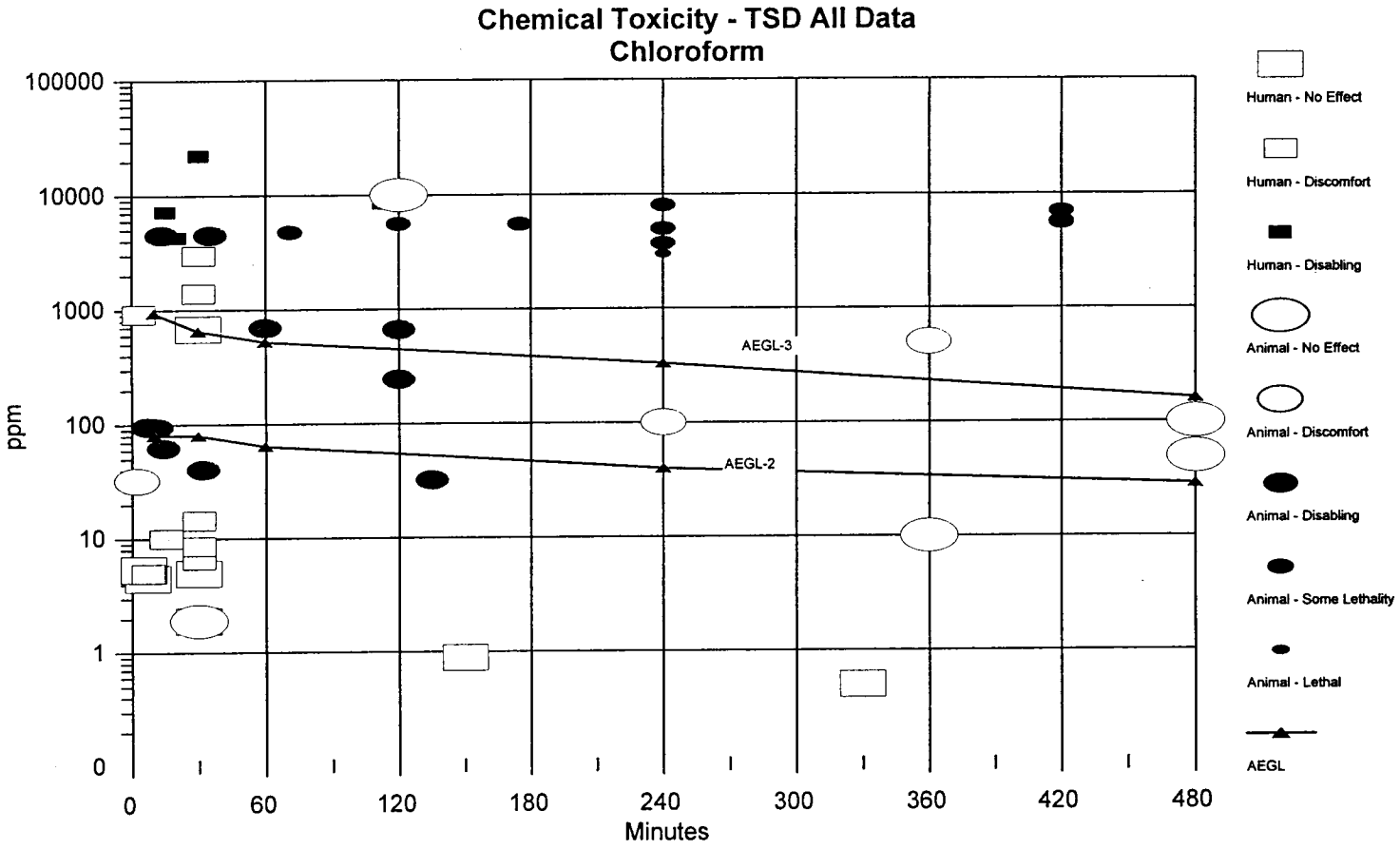
Interspecies:	3 to account for possible interspecies variability; currently available data indicate that laboratory species metabolize chloroform more rapidly than do humans and, therefore, are likely to be more susceptible to the toxic effects of the more rapidly formed toxic intermediates. PB-PK models (Corley et al., 1990) justify the adequacy of the uncertainty factor. However, due to the absence of definitive quantitative lethality data in humans, a factor of 3 has been applied to account for possible differences in the lethal response of humans relative to animals.
Intraspecies:	3 to account for individual variability in the sensitivity to chloroform-induced toxicity (e.g., alcohol-potentiated hepatotoxicity)

Modifying Factor: none applied

Animal-to-Human Dosimetric Adjustments: insufficient data

Data Adequacy: Confidence in the proposed AEGL-3 values is low due to the absence of human data and only limited data in laboratory species. AEGL-3 values derived from alternate animal lethality data (7-hr LC_{50} of 5687 ppm) were approximately 25% lower. However, when compared to human data (especially anesthesia exposures), the AEGL-3 values appear to be adequately protective of human health.


Chemical Toxicity - TSD Human Data
Chloroform
100000
10000
1000
100
10
1
0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
No effect
Discomfort
Disabling


Chemical Toxicity - TSD All Data
Chloroform
100000
10000
1000
100
10
1
0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

EXECUTIVE SUMMARY **Attachment 8**

Chlorine trifluoride is an extremely reactive and corrosive oxidizing agent used in nuclear reactor fuel processing, as a fluorinating agent, as an incendiary, igniter and propellant for rockets, and as a pyrolysis inhibitor for fluorocarbon polymers. It is unstable in air and rapidly hydrolyses to hydrogen fluoride (HF) and a number of chlorine-containing compounds including chlorine dioxide (ClO_2). The toxic effects of ClF_3 are likely due to HF and ClO_2.

Chlorine trifluoride is a mucous membrane irritant. Contact with the skin and eyes produces burns and inhalation causes pulmonary irritation and edema. Inhalation studies with the monkey, dog, rat, and mouse for several endpoints and exposure durations were located. Data on irritant effects were available for the dog and rat; data on sublethal and lethal concentrations were available for the monkey, rat, and mouse. Although human exposures have occurred, no data on exposure concentrations were located.

The AEGL-1 was based on slight irritation as evidenced by rhinorrhea (nasal discharge) observed in two of two dogs during the first 3 hours of a 6-hour exposure to an average concentration of 1.17 ppm (Horn and Weir, 1956). Nasal discharge in response to an irritant gas in the sensitive nose of dogs was considered a NOAEL for the AEGL-1. No signs were observed in 20 rats exposed to this concentration for 6 hours. Exposure of the dogs for longer than 3 hours resulted in "obvious" lacrimation. Repeated, daily exposures of rats and dogs to this concentration resulted in increasingly severe signs of irritation. The exposure duration of 3 hours was considered the appropriate endpoint for the AEGL-1. The 1.17 ppm concentration for an exposure duration of 3 hours was divided by a combined interspecies and intraspecies uncertainty factor of 10 (3 for interspecies differences [the dog was more sensitive than the rat] and 3 for intraspecies differences in sensitivity. Time-scaling was not applied to the AEGL-1 as adaptation to slight sensory irritation occurs. Therefore, the calculated value of 0.12 ppm was used for all AEGL-1 timepoints. The 0.12 ppm value is similar to the chlorine dioxide AEGL-1 of 0.15 ppm and is one-eighth of the hydrogen fluoride AEGL-1 value of 1.0 ppm. Application of an intraspecies factor of 3 is sufficient, as application of a larger factor would result in AEGL-1 values that are not consistent with those of chlorine dioxide and hydrogen fluoride, two of the major breakdown products of chlorine trifluoride.

The AEGL-2 was based on signs of irritation (salivation, lacrimation, rhinorrhea, and blinking of the eyes) in two of two dogs exposed to a concentration of 5.15 ppm for 6 hours (Horn and Weir, 1955). These effects were reversible by the end of the first exposure day (i.e. dogs "did not appear markedly affected"), and therefore, were not considered an impairment to the ability to escape. Twenty rats exposed to this concentration for 6 hours appeared unaffected. However, repeated daily exposures of rats and dogs to this concentration resulted in increasingly severe signs of irritation. The 6-hour concentration of 5.15 ppm was divided by a combined interspecies and intraspecies uncertainty factor of 10 (3 for interspecies differences as the dog was more sensitive than the rat and 3 for intraspecies differences). The resulting value of 0.52 ppm was scaled across time using $C^n \times t = k$ where $n = 1$; this concentration-exposure duration relationship was determined from several lethality studies. Because of the long exposure duration of the key study, the 10-minute AEGL-2 was set equal to the 30-minute AEGL-2. An

intraspecies uncertainty factor of 3 is sufficient as these AEGL-2 values are considerably lower than those of hydrogen fluoride (10- and 30-minute and 1-, 4-, and 8-hour values of 95, 34, 24, 12, and 12 ppm, respectively) and similar to the longer-term AEGL-2 values for chlorine dioxide. The 10- and 30-minute AEGL-2 values for chlorine trifluoride (both 6.2 ppm) are higher than those of chlorine dioxide (both 1.4 ppm) because information was available for time-scaling the chlorine trifluoride values, whereas, in the absence of time-scaling information, the conservative value of n = 1 was used for chlorine dioxide.

Lethality data (1-hour LC_{50} values) were available for the monkey, rat, and mouse. The AEGL-3 was based on the calculated 1-hour LC_{01} for the mouse, the most sensitive species based on LC_{50} values (MacEwen and Vernot, 1970). This concentration, 135 ppm, was divided by a combined interspecies and intraspecies uncertainty factor of 10 and scaled across time using the same reasons and relationships as for the AEGL-2 above. In cases where animals died, death was due to extreme irritation resulting in massive lung hemorrhaging. Data from another study in which dogs exposed to a concentration of 21 ppm for 6 hours showed extreme signs of irritation but no deaths resulted in essentially the same AEGL-3 values when adjusted by an uncertainty factor of 10 and scaled across time using n = 1.

The proposed values appear in the Table below. The original AEGL-1 values appear first, followed by the revised value in **bold**.

Summary of Proposed AEGL Values for Chlorine Trifluoride

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	0.70 ppm (2.7 mg/m^3) **0.12 ppm**	0.70 ppm (2.7 mg/m^3) **0.12 ppm**	0.35 ppm (1.3 mg/m^3) **0.12 ppm**	0.09 ppm (0.34 mg/m^3) **0.12 ppm**	0.04 ppm (0.15 mg/m^3) **0.12 ppm**	Slight irritation - dog (Horn and Weir, 1956)
AEGL-2 (Disabling)	6.2 ppm (24 mg/m^3)	6.2 ppm (24 mg/m^3)	3.1ppm (12 mg/m^3)	0.77 ppm (2.9 mg/m^3)	0.39 ppm (1.5 mg/m^3)	Threshold, impaired ability to escape - dog (Horn and Weir, 1955)
AEGL-3 (Lethal)	81 ppm (308 mg/m^3)	27 ppm (103 mg/m^3)	14 ppm (53 mg/m^3)	3.4 ppm (13 mg/m^3)	1.7 ppm (6.5 mg/m^3)	Lethality (LC_{01}) - mouse (MacEwen and Vernot, 1970)

References

Horn, H.J. and R.J. Weir. 1955. Inhalation toxicology of chlorine trifluoride. I. Acute and subacute toxicity. *A.M.A. Archives of Industrial Health* 12:515-521.

Horn, H.J. and R.J. Weir. 1956. Inhalation toxicology of chlorine trifluoride. II. Chronic toxicity. *A.M.A. Archives of Industrial Health* 13:340-345.

MacEwen, J.D. and E.H. Vernot. 1970. Toxic Hazards Research Unit Annual Technical Report: 1970. AMRL-TR-70-77, Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH; National Technical Information Service, Springfield, VA.

ACUTE EXPOSURE GUIDELINE LEVELS
FOR
TOLUENE

National Advisory Committee for AEGLs Meeting
December 9-11, 2002

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Larry Gephart

Chemical Reviewers:
David Belluck
Robert Snyder

Attachment 9

TOLUENE

Human Studies (con'd)

Numerous metabolism studies at 200 ppm:
- Equilibrium in blood in 20-30 minutes at rest
- Exercise doubles blood level

Numerous monitoring studies
- Chronic exposures at workplace guidelines of 100 and 200 ppm; up to 800ppm
- Accidental exposures to 1500 ppm

Table 2. Sensory and neurobehavioral effects of toluene in controlled human studies			
100 100 (TWA with peaks to 300)	7 hours (3 15-minute exercise periods)	sensory irritation of nose and lower airways in toluene-exposed groups; increase in dizziness and feeling of intoxication; slight decrement in one of four psychomotor performance tests; no differences in symptoms or performances between constant and varying concentrations	Baelum et al. 1990
75 150	7 hours/3 days 7 hours/3 days	mean 7% decrement in several neurobehavioral tests at 150 ppm; slight increases in headache, eye irritation, sleepiness on first day	Echeverria et al. 1989; 1991
100[a], 200[a]	30, 60 minutes	no difference in heart rate, pulmonary ventilation, oxygen consumption or blood lactate, either at rest or during a work load of 50 W	Astrand et al. 1972
100, 200	3 hours or 7 hours with 1-hour break	decrease in pulse rate at 200 ppm for 3 hours; tendency to prolonged reaction time at 200 ppm; no clear concentration-response relationship	Ogata et al. 1970
50, 100 200 300, 400, 600 800	8 hours 8 hours 8 hours 3 hours	moderate fatigue, sleepiness, mild headache fatigue toward end of exposure, occasions of weakness, confusion and paresthesias of the skin increasingly severe symptoms with increasing concentrations: incoordination, nausea, confusion, dilated pupils, and extreme fatigue; severe fatigue, nausea, confusion, incoordination, loss of self control, bone marrow suppression	von Oettingen et al. 1942
100[a] 300[a] 500[a] 700[a]	successive 20-minute exposure periods (one 5-minute break); total 85 minutes	no effect on reaction time or perceptual speed increase in simple reaction time increase in complex reaction time decrease in perceptual speed at end of exposure; no effect on heart rate during total exposure	Gamberale and Hultengren 1972
200, 400, 600, 800	7-8 hours	subjective symptoms ranged from transitory mild throat and eye irritation and slight exhilaration at 200 ppm to metallic taste, transitory headache, lassitude, inebriation, and slight nausea at 800 ppm; threshold for "steadiness" task = 800 ppm	Carpenter et al. 1944
220[b] 427[b]	15 minutes 15 minutes	6/6 subjects willing to work for 8 hours negligible sensory symptoms 3/6 subjects willing to work for 8 hours - 2 of the subjects reported slight "lightheadness" 1 reported a "stuffy, drowsy feeling"	Carpenter et al. 1976
200	6 hours	no changes in respiration; increased heart rate	Suzuki 1973
240	three 30-minute sessions	impaired vigilance in third session; decreased fatigue during second session	Horvath et al. 1981

[a] Subjects exposed via a mouthpiece.

[b] measured as toluene in "toluene concentrate."

TOLUENE

Widely used as a solvent
Primary effect: central nervous system depression

Human Studies
- 19 clinical studies
  - Concentrations of 40 to 800 ppm for up to 8 hours
  - Generally no notable effects at 100 and 200 ppm (13 studies; Table 2)
    - Some studies indicate slight eye, nose irritation (no annoyance)
    - Toluene is not a sensory irritant (mouse RD_{50} of 5300 ppm)
    - Some studies indicate subtle CNS effect in one of many tests
  - Peaks to 300 ppm with exercise (Baelum et al. 1990)
    - Similar slight effects
  - 300 ppm for 20 minutes (Gamberale and Hultengren 1972)
    - Significant difference in reaction time measured in milliseconds
  - 500, 700 ppm, each for 20 minutes (Gamberale and Hultengren 1972)
    - Subtle effects - neurobehavioral indicators
  - Exposures up to 800 ppm, 8 hours
    - (von Oettingen et al. 1942; Carpenter et al. 1944)
    - threshold for unsteadiness, gross CNS effects; poor analytical methods

PROPOSED TOLUENE AEGLs (in bold)

Classification	Exposure Duration				
	10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1 (Nondisabling)	260 ppm **200 ppm**	120 ppm **200 ppm**	82 ppm **200 ppm**	41 ppm **200 ppm**	29 ppm **200 ppm**
AEGL-2 (Disabling)	600 ppm **990 ppm**	270 ppm **570 ppm**	190 ppm **500 ppm**	94 ppm **500 ppm**	67 ppm **500 ppm**
AEGL-3 (Lethal)	1600 ppm **7200 ppm**	900 ppm **4200 ppm**	630 ppm **2900 ppm**	320 ppm **1500 ppm**	220 ppm **1000 ppm**

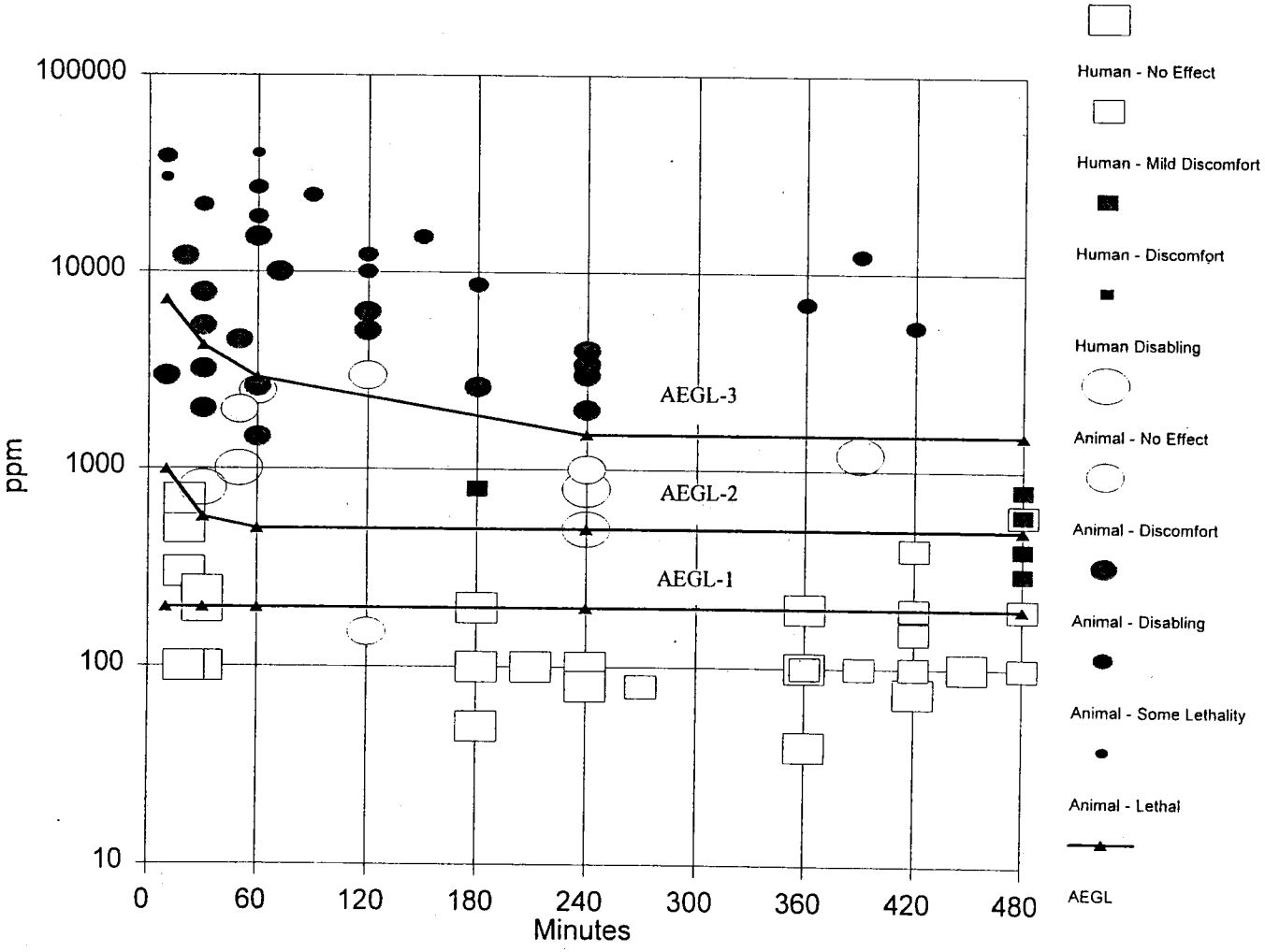
AEGL-1: Based on multiple studies of human exposures to 200 ppm for up to 8 hours and intermittently to 300 ppm with exercise. Additional exposures to 800 ppm for 3 and 8 hours with CNS effects. Routine metabolism studies at 200 ppm. Occupational (chronic) exposures at 100 and 200 ppm with range up to 800 ppm.

Not irritating; not highly objectionable. Intraspecies UF of 1(the hundreds of subjects in the clinical studies (some with exercise) and the thousands of subjects in working situations represent a broad spectrum of the population).

No time scaling (equilibrium rapidly reached in the blood).

Support: 700 ppm for 20 minutes = subtle CNS effect; UF of 3.

Table 2. Sensory and neurobehavioral effects of toluene in controlled human studies			
Concentration (ppm)	Duration	Effects	Reference
10, 40, 100	6 hours	slight irritation of eyes and nose at 100 ppm; no effect on mood, fatigue, or sleepiness; increase in occurrence of headache, dizziness, and feeling of intoxication rated slight to moderate; no effect on lung function or nasal mucous flow; no significant effect on performance of eight psychomotor tests	Andersen et al. 1983
50[a]	3 hours	no subjective symptoms	Luderer et al. 1999
80	4 hours	no impairment of neurobehavioral tasks	Cherry et al. 1983
80	4 hours	no differences in subjective symptoms between control and exposed group; no impairment in tests of simple reaction time, short-term memory, or choice reaction time; no effect on heart rate	Anshelm Olson et al. 1985
80	4.5 hours	increase in subjective symptoms (nausea, headache, irritation), but rated negligible; no impairment in tests of simple and choice reaction time, color-word vigilance, or memory; no effect on heart rate, EEG, or sleep latency	Iregren et al. 1986
100	3.5 hours	no behavioral deficits in psychomotor tests	Winneke 1982
100	4 hours	no serious impairment in series of neuro-behavioral tests (small impairment in one measure of a visual-vigilance test)	Dick et al. 1984
100	6 hours	no significant effect on lung function (subjects exercised for 30 minutes); slight effect on some multitask and neuropsychological tests (increased latency but not accuracy on neurobehavioral tasks); symptoms investigated through a double-blind questionnaire - none found	Rahill et al. 1996
100	6.5 hours	4 groups tested: 2 exposed and 2 controls: sensory irritation (no annoyance), sleepiness, decreased performance on 4/10 tests for one or both exposure groups (manual dexterity, color discrimination, visual perception); no changes in kidney function	Baelum et al. 1985; Nielson et al. 1985
100	1, 3, or 7.5 hours, several days	No decrement in psychomotor tests on first day of exposure; slight decrement in females on one of many cognitive tests at 7.5 hours, days 3 and 5; similar subjective symptoms between exposed and control groups	Stewart et al. 1975


100000
10000
1000
100
10
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Mild Discomfort
Human - Discomfort
Human Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

TOLUENE

Animal Studies

LC_{50} values:

mouse: 1-hour = 19,018 ppm (Moser and Balster 1985)
3-hour = 8600 ppm (Bruckner and Peterson 1981a)
6-hour = 6940 ppm (Bonnet et al. 1979)

rat: 1-hour = 26,700 ppm (Pryor et al. 1978)
2-2.5 hour = 12,200 (Kojima and Kobayaski 1973)

Highest non-lethal values

mouse: 12,000 ppm for 20 minutes (Bruckner and Peterson 1981a)
6100 ppm for 24 hours (Cameron et al. 1938)

rat: 15,000 ppm for 1 hour (Hinman 1987)
6250 ppm for 2 hours (Mullin and Krivanek 1982)
5000 ppm for 2 hours (Kojima and Kobayaski 1973)

Good data base

Studies on reproduction/development, repeated/chronic exposures, neurotoxicity, genotoxicity, carcinogenicity

AEGL-2: 10- and 30-minute values based on human exposure to 700 ppm for 20 minutes (NOAEL for CNS depression) and 800 ppm for 8 hours. 1-Hour value proportionally time-scaled from 30-minute value using modeling data of xylenes. Because equilibrium reached in blood by 1 hour, the 4- and 8-hour values were set equal to the 1-hour value.
UF of 1 (multiple studies).
Support: 50-minute 2000 ppm no-adverse CNS effects in monkeys; UF of 3.

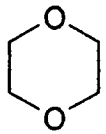
AEGL-3: Based on highest non-lethal value in rats, 6250 ppm for 2 hours. UF of 3.
Time-scaled using lethality data from mice.
Support: 1000 ppm was chronic NOAEL in rats and mice.
No deaths in human at exposure to >1842 ppm for 2.5 hours, 1500 ppm for 8 hours.

Acute Exposure Guideline Levels (AEGLs)

for

1,4-Dioxane

(CAS No. 123-91-1)



NAC/AEGL Meeting 27, 9-11 December 2002, Washington, D.C.

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Attachment 10

1,4-Dioxane

PROPERTIES

- colorless liquid
- characteristic, unpleasant odor
- high vapor pressure

PRODUCTION

- acid-catalyzed conversion of diethylene glycol
- catalyzed cyclo-dimerization of ethylene oxide
- ring closure of 2-chloro-2'-hydroxyethyl ether
- about 10,000 tons/year

USES

- mainly as a processing solvent

TOXICITY MECHANISM AND CONCERNS

- eye and respiratory tract irritation in humans and animals;
  water extraction, membrane disturbance
- acute inhalation toxicity studies in animals mostly old;
  death by narcosis after single exposure (animals), death by kidney and liver necrosis after repeated exposure (animals and humans)
- oral exposure causes tumors of liver, nasal cavity and gallbladder in animals;
  carcinogenic effects likely through repeated cytotoxicity, but some evidence for genotoxic effects at high doses

DATA RELEVANT TO AEGL-1

HUMAN

Odor detection threshold about **12 ppm** (AIHA, 1983)
Odor recognition threshold about **22 ppm** (AIHA, 1983)

- Young et al. (1977): human pharmacokinetic study, 4 healthy males

  50 ppm for 6 hours
  eye irritation was a frequent complaint throughout exposure; odor perception diminished with time

- Silverman et al. (1946): experimental study, 12 subjects

  300 ppm for 15 min
  irritation to eyes, nose and throat; odor not objectionable

  200 ppm for 15 min
  presence of absence of symptoms not described in study

- Wirth and Klimmer (1936): experimental study, 5 subjects

  0.7, 1.4, 2.8, 5.6, 8.4, 280, 1400 and 2800 ppm, unspecified period

  280 ppm slight mucous membrane irritation
  1400 ppm quite distinct irritation
  2800 ppm very strong initial irritation, slight pressure in chest, metallic bitter taste

DATA RELEVANT TO AEGL-1

HUMAN (con'd)

- Fairley et al. (1934): experimental study, 4-6 subjects

  1000 ppm for 5 min
  sickly odor, warm sensation in the throat and chest, which faded rapidly; one subject experienced constriction in the throat

  2000 ppm for 3 min
  initial strong odor, no lacrimation or cough were noted

- Yant et al. (1930): experimental study, 5 subjects

  1600 ppm for 10 min
  immediate burning of the eyes with lacrimation, slight nose and throat irritation, alcohol-like odor

  5500 ppm for 1 min
  irritation to eyes with blinking, squinting and lacrimation; burning sensation in nose and throat; slight vertigo

DATA RELEVANT TO AEGL-1

ANIMAL

- Yant (1930): inhalation exp. in guinea pigs

  1000 ppm for up to 6 hours
  no eye irritation, squinting or lacrimation

  2000 ppm for up to 6 hours
  eye irritation, squinting or lacrimation within 8 minutes

- Frantik (1994): inhalation exp. in rats and mice

  EC_{10} 1200 ppm for 4 h in rats
  EC_{10} 580 ppm for 2 h in mice
  effects on propagation and maintenance of the electrically evoked seizure discharge

- Drew (1978): inhalation exp. in rats

  1000 and 2000 ppm for 4 h
  2-3 fold increased serum activities of liver enzymes (ASP und ALA aminotransferase, ornithine carbamyl transferase)

DERIVATION OF AEGL-1

Key study: **Young et al. (1977)** exposure of humans to 50 ppm for 6 hours

pros
- irritation is relevant effect because reported in several studies
- only study with analytical measurement of exposure concentration and with adequate study discription

cons
- pharmacokinetic study, no emphasis on symptoms
  only description: "eye irritation was a frequent complaint throughout exposure"
  effect considered mild because authors considered 50 ppm adequate workplace standard

use as AEGL-1 derivation starting point because

- irritative effects of dioxane increase slowly with concentration:
  300 ppm irritation to eyes, nose and throat (Silverman et al., 1946),
  280 ppm slight mucous membrane irritation (Wirth and Klimmer, 1936)

AEGL-1

Keystudy: Young et al. (1977)

Endpoint: Eye irritation in humans at exposure to 50 ppm throughout the exposure duration of 6 h

Scaling: flat line because effect occurred throughout exposure and did not increase with exposure time

supported by irritation in guinea pigs (Yant et al., 1930): irritation at 2000 ppm starting at 8 min, but no irritation at 1000 ppm for up to 6 hours

Total uncertainty factor: 3

Intraspecies: **3**

The intraspecies uncertainty factor is used to compensate for both, toxicokinetic and toxicodynamic differences between species. For local effects on the eyes, no toxicokinetic differences exist between individuals. Therefore, a reduced uncertainty factor of 3 was applied for intraspecies variability.

AEGL-1 Values for 1,4-Dioxane				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
17 ppm (60 mg/m³)	17 ppm (60 mg/m³)	17 ppm (60 mg/m³)	17 ppm (60 mg/m³)	17 ppm (60 mg/m³)

Supporting data:
The AEGL-1 value is between the odor detection and odor recognition thresholds for dioxane of 12 and 22 ppm, respectively (AIHA, 1983) and thus is considered to have warning properties

DERIVATION OF LOA

	May (1966)	Hellman and Small (1974)
odor detection threshold for dioxane:	170 ppm	0.8 ppm
odor detection threshold for n-butanol:	11 ppm	0.3 ppm
OT_{50}: OT(dioxane) * 0.04 ppm /OT(n-butanol)	0.62 ppm	0.11 ppm
arithmetic mean:	0.37 ppm	

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I=3) is derived using the Fechner function: $I = k_w * \log (C / OT_{50}) + 0.5$. The default of $k_w = 2.33$ will be used due to the lack of chemical-specific data:

$3 = 2.33 * \log (C / 0.37) + 0.5$ $C = 4.4$ ppm

Field correction factor: adjustment for distraction (4-fold increase of odor threshold and peak exposure (3-fold reduction for concentration peaks over mean concentration): 4 / 3 = 1.33

LOA for 1,4-dioxane = 4.4 ppm * 1.33 = 5.9 ppm

DATA RELEVANT TO AEGL-2

HUMAN

- Yant et al. (1930): experimental exposure, 5 subjects

  5500 ppm for 1 min

  burning sensation in nose and throat, slight vertigo in 3/5

- Wirth and Klimmer (1936): experimental study, 5 subjects

  2800 ppm for unspecified period

  very strong initial irritation and slight pressure in the chest

  1400 ppm for unspecified period

  quite distinct irritation with stinging in the nose and dryness in the throat

- Fairley et al. (1934): experimental study, 4-6 subjects

  2000 ppm for 3 min

  strong initial odor, rapidly diminishing; no strong irritation effects, such as lacrimation or cough

DATA RELEVANT TO AEGL-2

ANIMAL

- Goldberg et al. (1964): inhalation exp. using 8 rats

  6000 ppm for 4 h/d, 5 d/w for 2 weeks

  delay of the avoidance response after 1st in 6/8 and subsequent exposures; no effects on escape response (only in 3/8 after 3rd exposure); effect was temporary and reversible

- Drew et al. (1978): inhalation exp. in rats

  1000 and 2000 ppm for 4 h

  2-3 fold increased serum activities of liver enzymes (ASP und ALA aminotransferase, ornithine carbamyl transferase)

- Fairley et al. (1934): inhalation exp. in rabbits, rats and guinea pigs

  5000 ppm for 2x1.5 h/d for up to 3 weeks

  death after several exposure days with renal tubular and liver necrosis

DERIVATION OF AEGL-2

Human exp. studies reporting moderate to strong **irritation**:

- inadequate study description, no analytical determination of exposure concentration
- therefore, not adequate as key study, but may be supportive evidence

Two endpoints in **animal experiments**

- nervous system

6000 ppm for 4 h/d (5 d/w for 2 weeks) suppressed conditioned response, but not escape response in rats (Goldberg et al., 1964); symptoms during exposure not reported

- likely prenarcotic effect on CNS at high concentrations
- cf. data on narcosis:
mice: LOEL 8300 ppm x 3.5 h, NOEL 2800 ppm x 9.6 h (Wirth and Klimmer, 1936)
guinea pigs: LOEL 30000 ppm x 1.5-2.4 h, NOEL 10000 ppm x 8 h (Yant et al., 1930)
- narcosis is beyond AEGL-2 level because animals died 1-2 days after exposure including animals that were not narcotic during exposure

- liver toxicity

1000 and 2000 ppm for 4 h caused 2-3 fold increased serum activities of liver enzymes (Drew et al., 1978)

- considered relevant because lower lethal concentrations caused death by liver and kidney necrosis and because repeated cytotoxic liver damage implicated in mechanism of carcinogenesis

- 5000 ppm for 2x1.5 h/d caused death (liver and kidney necrosis) of rats after several days (Fairley et al., 1934)

therefore, 1000 ppm for 4 h (Drew et al., 1978) as AEGL-2 derivation starting point

AEGL-2

Keystudy: Drew et al. (1978)

Endpoint: slight, and probably reversible, liver enzyme increase in serum of rats after exposure to 1000 ppm for 4 hours; considered a NOEL for serious, long-lasting liver damage

Scaling: $C^n \times t = k$, default n = 3 for shorter and n = 1 for longer periods

Time extrapolation was continued to the 10-minute period because even at considerable higher concentrations of 1600 ppm for 10 minutes (Yant et al., 1930) or 1400 ppm for 5 minutes (Wirth and Klimmer, 1936) exposed subjects did not experience more than moderate irritation.

Total uncertainty factor: 10

The total uncertainty factor was reduced because application of a factor of 30 would reduce the AEGL-2 level to an exposure concentration of 17 ppm for 8 hours and 33 ppm for 4 hours, which humans are known to tolerate without adverse effect (pharmacokinetic study exposing subjects to 50 ppm for 6 hours; Young et al., 1977). The total uncertainty factor of 10 was formally split up into an interspecies factor of 3 and an intraspecies factor of 3.

Interspecies: 3 **Intraspecies:** 3

AEGL-2 Values for 1,4-Dioxane				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
290 ppm (1000 mg/m³)	200 ppm (720 mg/m³)	160 ppm (570 mg/m³)	100 ppm (360 mg/m³)	50 ppm (180 mg/m³)

Derived values considered adequate with respect to the carcinogenicity assessment. Assuming a body weight of 70 kg, a ventilation rate of 20 m³/d, and an absorption rate of 43 % (Young et al., 1977), the AEGL-2 values correspond to total body doses between 0.85 mg/kg (10 min) and 7.4 mg/kg (8 h). This level was far below that associated with metabolic saturation or proliferative liver effects implicated in dioxane carcinogenicity.

DATA RELEVANT TO AEGL-3

HUMAN

- Barber (1934): case report on 5 workers

  death of 5 men which were repeatedly exposed to a unknown concentration of dioxane at the workplace

- Johnstone (1959): case report on 1 worker

  man became hospitalized after 6 days on work and died 6 days later; liver and kidney necrosis; estimated exposure concentration 208-650 ppm; additional dermal exposure because dioxane was used to remove glue from hands

ANIMAL

- Pozzani et al. (1959): inhalation exp. on rats
  LC_{50} for 4 hours: 14300 ppm
- Pilipyuk et al. (1977): inhalation exp. on rats
  LC_{50} for 4 hours: 12800 ppm
- BASF (1973; 1980): inhalation exp. on rats
  at saturated vapor (about 40000 ppm)
  no deaths after exp. for 1 hour
  50-100 % mortality after exp. for 3 hours

ACUTE LETHAL INHALATION DATA IN ANIMALS

Sp	Conc. (ppm)	Time	Effect	Reference
r	40000 (sat.)	7 h	death in 4/18 animals	BASF, 1980
r	40000 (sat.)	4 h; 3h	death in 6/6 animals	BASF, 1973
r	40000 (sat.)	3 h	death in 6/12 animals	BASF, 1980
r	40000 (sat.)	1 h	no deaths in 12 animals	BASF, 1980
r	40000 (sat.)	1 h	no deaths in 12 animals	BASF, 1973
r	14300	4 h	LC_{50}	Pozzani et al, 1959
r	12800	4 h	LC_{50}	Pilipyuk et al, 1977
r	10000	2 x 1.5 h /d	1/3 rats died d1, others died later	Fairley et al, 1934
r	5000	2 x 1.5 h /d	no deaths d 1, but all died later	Fairley et al, 1934
m	39000	1 h	4/4 mice died	Wirth & Klimmer 1936
m	28000	1 h	2/4 mice died	Wirth & Klimmer 1936
m	25000	1 h	4/4 mice died	Wirth & Klimmer 1936
m	18000	2 h	LC_{50}	Pilipyuk et al, 1977
m	17000	1 h	4/4 mice died	Wirth & Klimmer 1936
m	12500	1 h	4/4 mice died	Wirth & Klimmer 1936
m	10109	1 h	LC_{50}	Izmerov et al, 1982
m	10000	2 x 1.5 h /d	death of 3/3 mice on d1	Fairley et al, 1934
m	8300	1 h	2/2 mice died	Wirth & Klimmer 1936
m	5000	2 x 1.5 h/d	1/3 mice died d1, others later	Fairley et al, 1934
m	2800	1 h	no deaths in 6 mice	Wirth & Klimmer 1936
gp	30000	3 h	died (number not stated)	Yant et al, 1930
gp	10000	2 x 1.5 h /d	no deaths d1, but 6/6 died later	Fairley et al, 1934
cat	3100	3 h	4/4 animals died	Wirth & Klimmer 1936
cat	2400	4.1 h	4/4 animals died	Wirth & Klimmer 1936
cat	1800	4.3 h	4/4 animals died	Wirth & Klimmer 1936
cat	1200	7.2 h	2/4 animals died	Wirth & Klimmer 1936

DERIVATION OF AEGL-3

Old case studies from Barber (1934) and Johnstone (1959):

- deaths of humans from progressing kidney and liver necrosis after repeated (about 5-10 d) exposure to high concentrations at the workplace
- inhalation exposure can be lethal to humans

LC_{50} studies in animals

- only a few, rather old and not well described studies are available

Key study: Pozzani et al. (1959): 4-hour LC_{50} in rats: 14300 ppm

- because study details far better described than in the russian study of Pilipyuk et al. (1977) (4-hour LC_{50} in rats: 12800 ppm)

cons - study details not reported (24 chemicals and 51 mixtures investigated), no information on analytical determinations, post-exposure observation time, time of death

AEGL-3

Keystudy: Pozzani et al. (1959)

Endpoint: LC_{50} for 4 hours: 14300 ppm

LOEL-NOEL Divisor: 2

because data indicate a very steep dose-response curve for lethality after inhalation exposure: a) Pilipyuk et al. (1977): factor of 1.3 between LC_{84} and the LC_{16}; b) at 40000 ppm (BASF) no deaths after exposure for 1 hour, but 50 and 100 % mortality after 3 hours; and c) Yant (1930): death of all guinea pigs after 3 hours at 30000 ppm, but no lethality after 10000 ppm for 8 hours

Scaling: $C^n \times t = k$ with default n = 3 for shorter and n = 1 for longer exposure periods

30-min value was applied to 10 min because no data are available for short-term exposure

Total uncertainty factor: 30

Interspecies: 3

because application of the default factor of 10 would have resulted in AEGL-3 values of 80 ppm for 4 hours and 40 ppm for 8 hours which contrasts with the observervation that exposure of volunteers to 50 ppm for 6 hours resulted in eye irritation, but no more severe effects (Young et al., 1977)

Intraspecies: 10

AEGL-3 Values for 1,4-Dioxane				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
480 ppm (1700 mg/m³)	480 ppm (1700 mg/m³)	380 ppm (1400 mg/m³)	240 ppm (860 mg/m³)	120 ppm (430 mg/m³)

AEGL Values for 1,4-Dioxane					
	10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
AEGL-1	17 ppm (60 mg/m³)	17 ppm (60 mg/m³)	17 ppm (60 mg/m³)	17 ppm (60 mg/m³)	17 ppm (60 mg/m³)
AEGL-2	~~290 ppm~~ 580 (1000 mg/m³)	~~200 ppm~~ 460 (720 mg/m³)	~~160 ppm~~ 380 (570 mg/m³)	~~100 ppm~~ 200 (360 mg/m³)	~~50 ppm~~ 100 (180 mg/m³)
AEGL-3	~~480 ppm~~ 950 (1700 mg/m³)	~~480 ppm~~ 950 (1700 mg/m³)	~~380 ppm~~ 780 (1400 mg/m³)	~~240 ppm~~ 480 (860 mg/m³)	~~120 ppm~~ 240 (430 mg/m³)

Preliminary Cancer Assessment of 1,4-Dioxane (I)

no inhalation slope factor is available

EPA (1988a): oral **slope factor of $1.1x10^{-2}$ $(mg/kg/d)^{-1}$** , LMS calculation based on results of NCI (1978) on squamous cell carcinoma of the nasal turbinates in male Osborne-Mendel rats after drinking water exposure.

Hartung (1989): LMS risk estimates based on all statistically significant tumor responses: slope factors ranged from **$3.83x10^{-5}$ $(mg/kg/d)^{-1}$** for nasal carcinomas in rats in the Kociba et al. (1974) study to **$1.83x10^{-2}$ $(mg/kg/d)^{-1}$** for hepatocellular carcinomas or adenomas in female mice in the NCI (1978) study

relevance to humans of the nasal tumors in rats observed in the drinking water studies is doubtful

Therefore, the slope factor of **$1.83x10^{-2}$ $(mg/kg/d)^{-1}$** for liver tumors in mice was used

dioxane or one of its metabolites may exert **clastogenic effects** in vivo at high oral doses and in vitro at high concentrations.

However, there is strong evidence, that dioxane causes tumors via a **non-genotoxic**, cytotoxic mechanism: no increased hepatocyte proliferation at daily oral doses of 10 mg/kg/d, but at higher doses of 1000 mg/kg/d. Even at this high dose, increased proliferation was found only after 8 days of continous exposure, but not after 1-3 days exposure.

Non-linear toxicokinetics: at doses >10 mg/kg the oxidative metabolism starts getting saturated

overall, it is concluded that there is little evidence of carcinogenicity from a short-term exposure to dioxane.

Preliminary Cancer Assessment of 1,4-Dioxane (II)

Calculation:

Inhalation slope factor = 1.83×10^{-2} $(mg/kg/d)^{-1}$ x 20 m^3/d x 1/70 kg
= 5.2×10^{-3} $(mg/m^3)^{-1}$

virtually safe dose (10^{-4} risk) = risk / slope factor
= 1×10^{-4} / 5.2×10^{-3} $(mg/m^3)^{-1}$
= 1.9×10^{-2} mg/m^3

24-hour exposure concentration = 1.9×10^{-2} mg/m^3 x 25600 days
= 486 mg/m^3

adjustment factor of 6 for uncertainties in assessing potential cancer risks:
486 mg/m^3 / 6

= 81 mg/m^3

24-hour exposure = 81 mg/m^3 (23 ppm)
8-hour exposure = 243 mg/m^3 (68 ppm)
4-hour exposure = 486 mg/m^3 (135 ppm)
1-hour exposure = 1944 mg/m^3 (540 ppm)
30-minute exposure = 3888 mg/m^3 (1081 ppm)
10-minute exposure = 11664 mg/m^3 (3243 ppm)

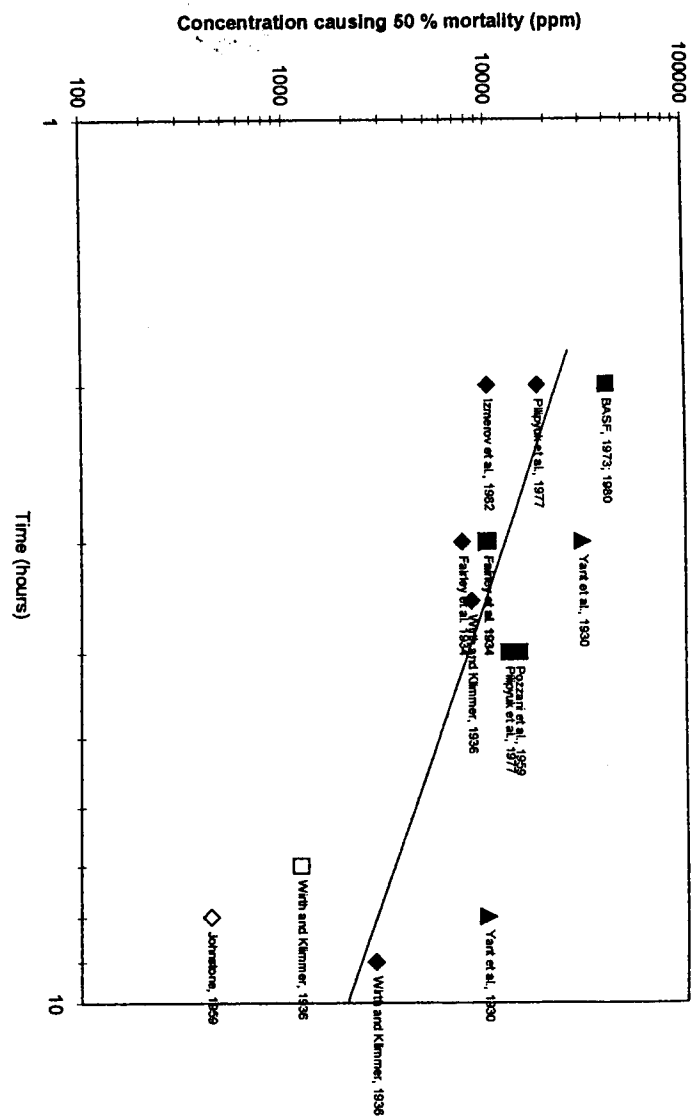
for 10^{-5} and 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold and 100-fold, respectively

Conclusion:

Values based on carcinogenicity exceed the AEGL-3 and AEGL-2 values based on non-carcinogenic effects and are, therefore, not proposed for AEGL-3 or AEGL-2. Moreover, cancer induction requires multiple exposures.

SPECIES COMPARISON OF LETHAL INHALATION EXPOSURE

Species: rat, filled square; mice, filled diamond; guinea pig, filled triangle; cat, open square, and human, open diamond. The line indicates the regression line calculated from all animal data.



Attachment 11

ACUTE EXPOSURE GUIDELINE LEVELS FOR SULFUR DIOXIDE

NATIONAL ADVISORY COMMITTEE- MEETING 27

DECEMBER 9-11, 2002

ORNL STAFF SCIENTIST: CHERYL BAST

CHEMICAL MANAGER: LOREN KOLLER

CHEMICAL REVIEWERS: STEVE BARBEE
DAVID BELLUCK

AEGL-1 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
0.25 ppm	0.25 ppm	0.25 ppm	0.25 ppm	0.25 ppm
Weight-of -evidence approach suggests 0.25 ppm is threshold for mild bronchoconstriction in exercising asthmatics				
Time Scaling: Data suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10-minutes and increases minimally or ameliorates beyond 10-minutes of exposure. Therefore, AEGL-1 values for SO_2 will be held constant across all time points.				

Concentration	Duration	Subjects	Exposure Parameters	Effect	Reference
0.2 ppm	5 min	8	23 °C, 85% RH, exercise 48 L/min	none	Linn et al., 1983b
0.25 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	none	Schacter et al., 1984
0.25 ppm	5 min	19 9	23 °C, 36% RH, exercise 60 L/min 23 °C, 36% RH, exercise 80-90 L/min	SRaw ↑134% SRaw ↑139%	Bethel et al., 1985
0.25 ppm	75 min	28	26 °C, 70% RH, exercise 42 L/min intermittent	none	Roger et al., 1985
0.4 ppm	5 min	23	23 °C, 85% RH, exercise 48 L/min	SRaw ↑69% $V_{max25-75}$ ↓10%	Linn et al., 1983b
0.5 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	none	Schacter et al., 1984

AEGL-2 VALUES				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
1.0 ppm	**1.0 ppm**	**1.0 ppm**	**1.0 ppm**	**1.0 ppm**
Weight-of -evidence approach suggests 1.0 ppm induces moderate to severe, but reversible, respiratory response in exercising asthmatics, based on the fact that asthmatics developed increased airway resistance of 102% to 580%				
Time Scaling: Data suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10-minutes and increases minimally or ameliorates beyond 10-minutes of exposure. Therefore, AEGL-2 values for SO_2 will be held constant across all time points.				

WEIGHT OF EVIDENCE FOR AEGL-2

Concentration	Duration	Subjects	Exposure Parameters	Effect	Reference
0.75 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	SRaw ↑150% FEF ↓22% FEV_1 ↓8%	Schacter et al., 1984
1.0 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	SRaw ↑470% FEF ↓27% FEV_1 ↓14%	Schacter et al., 1984
1.0 ppm	75 min	28	26 °C, 70% RH, exercise 42 L/min, intermittent	SRaw ↑300%	Roger et al., 1985
1.0 ppm	30 min	10	26 °C, 70% RH, exercise 41 L/min (3-10 min periods separated by rests of 15 min)	SRaw ↑172% SRaw ↑137% SRaw 106%	Kehrl et al., 1987
1.0 ppm	30 min	10	26 °C, 70% RH, continuous exercise 41 L/min	SRaw ↑233%	Kehrl et al., 1987
1.0 ppm	1 min 3 min 5 min	8	22 °C, 75% RH, exercise 60 L/min	SRaw ↑93% SRaw ↑395% SRaw ↑580%	Balmes et al., 1987
1.0 ppm	0.5 min 1.0 min 2.0 min 5.0 min	12	20 °C, 40% RH, exercise 40 L/min	No SRaw effect No SRaw effect SRaw ↑121% SRaw ↑307%	Horstman et al., 1988

AEGL-3 VALUES				
10 minute	30 minute	1 hour	4 hour	8 hour
20 ppm	20 ppm	20 ppm	20 ppm	20 ppm

Species: Rat
Concentration: 593 ppm
Time: 4 hours
Endpoint: Highest concentration causing no mortality
Reference: Cohen et al., 1973

Time Scaling: Data suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10-minutes and increases minimally or ~~ameliorates~~,beyond 10-minutes of exposure. Therefore, AEGL-3 values for SO_2 will be held constant across all time points.

Uncertainty Factors:

Interspecies = 10 Wide variability in response to SO_2 exposure between healthy and asthmatic humans

Intraspecies = 3 Considered sufficient because:

No deaths were reported in guinea pigs exposed to 750 ppm SO_2 for 1 hour (Amdur, 1959)

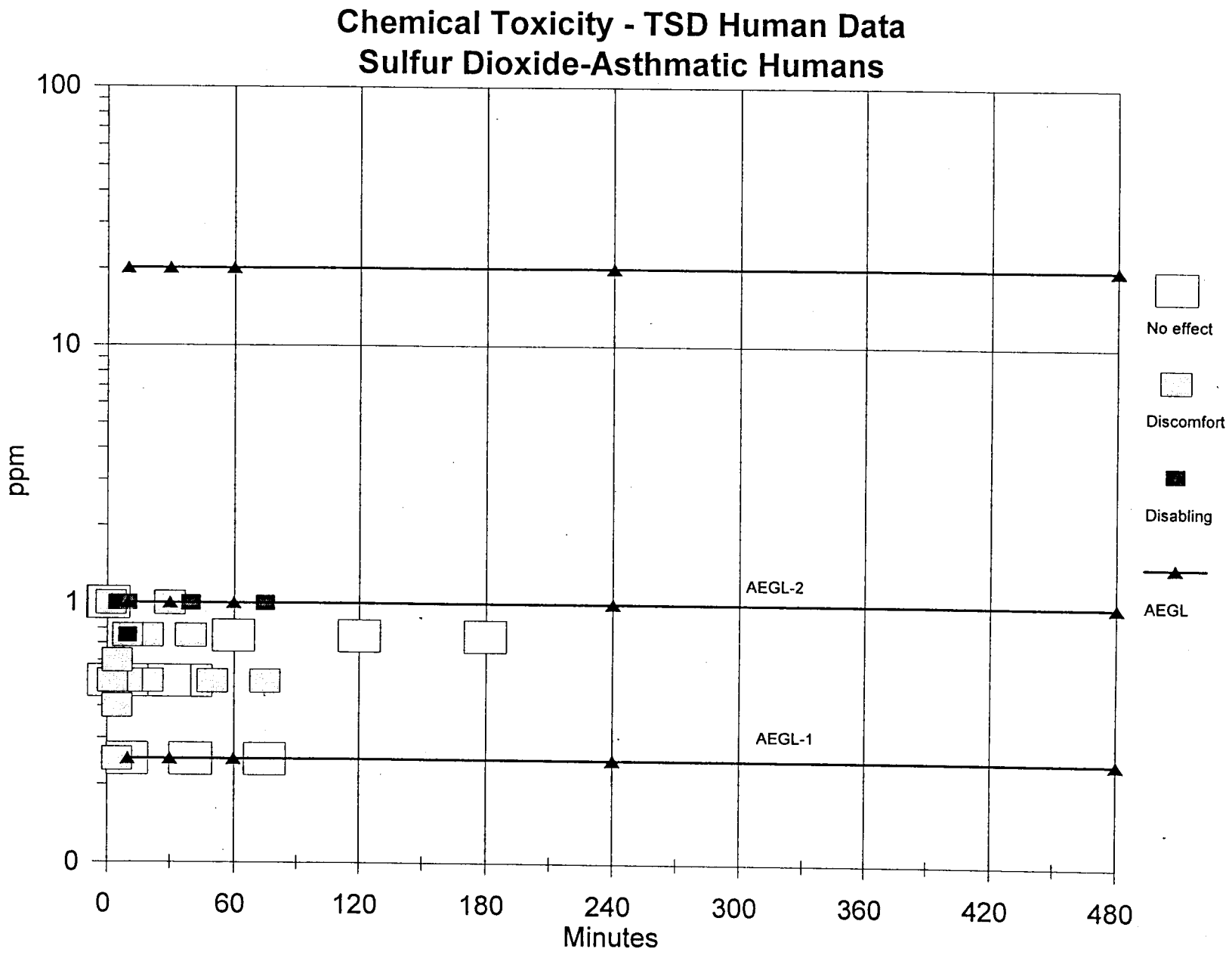
No deaths were reported dogs exposed to 400 ppm SO_2 for 2 hours (Jackson and Eady, 1988).

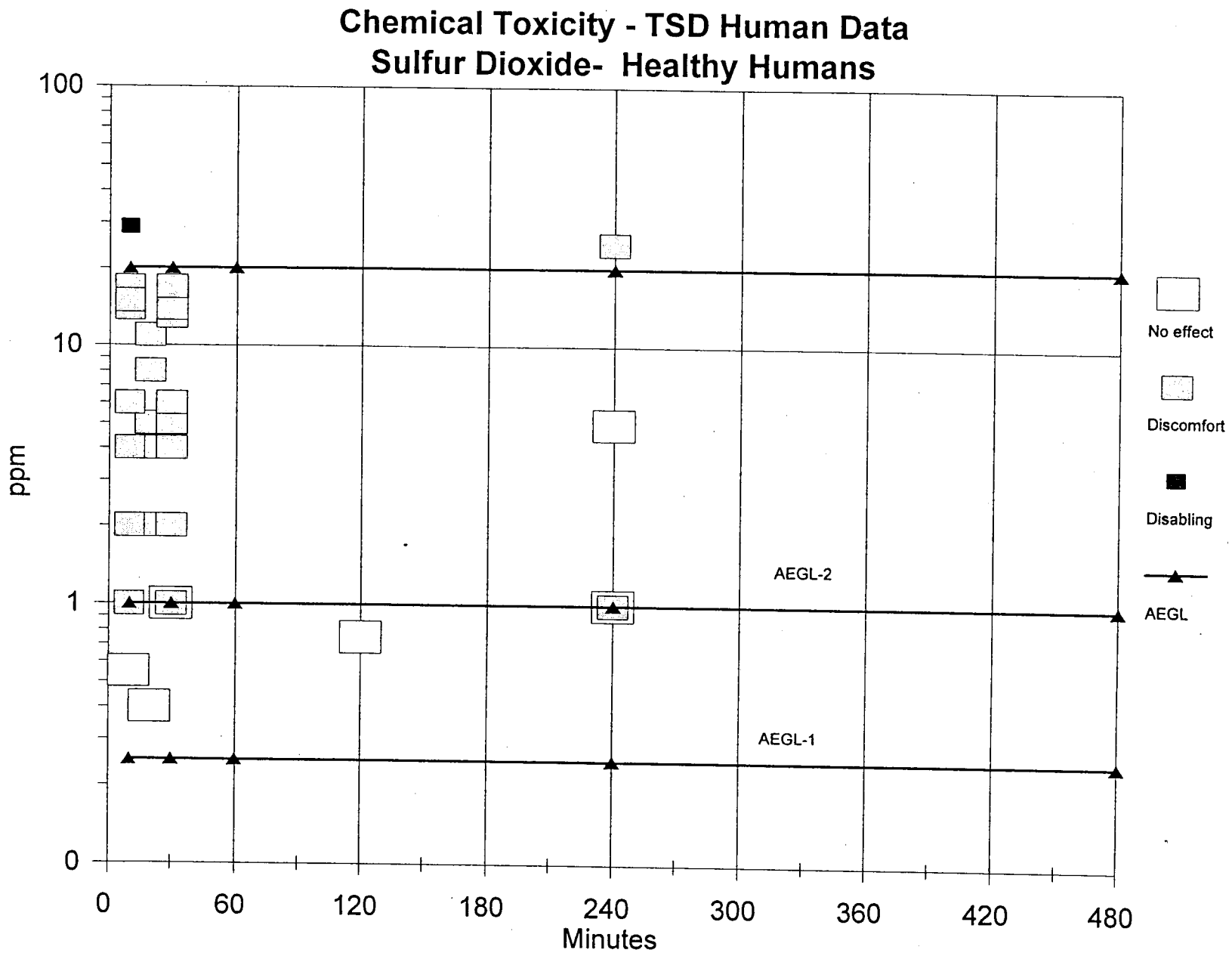
Although these exposures were of shorter duration (1 or 2 hours) compared with the key study (4 hours), the comparison is considered valid because the role of exposure duration to the magnitude of SO_2-induced effects has been shown to decrease with extended exposure, with the maximum effect occurring within 10-minutes

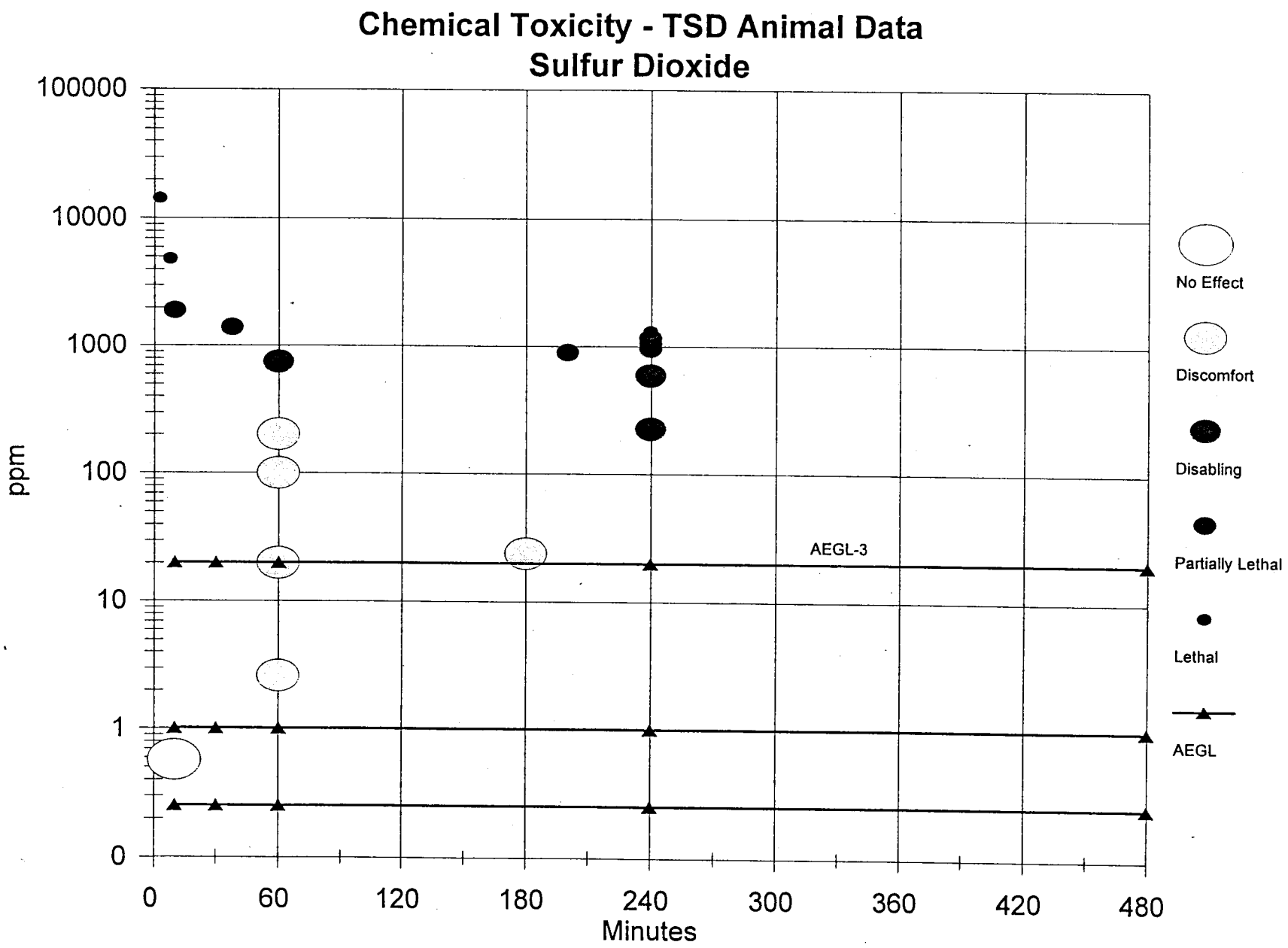
Extant Standards and Guidelines for Sulfur Dioxide					
Guideline	**Exposure Duration**				
	10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	0.25 ppm	0.25 ppm	0.25 ppm	0.25 ppm	0.25 ppm
AEGL-2	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm
AEGL-3	20 ppm	20 ppm	20 ppm	20 ppm	20 ppm
ERPG-1	0.3 ppm				
ERPG-2	3 ppm				
ERPG-3	15 ppm				
NIOSH IDLH	100 ppm				
NIOSH REL	2 ppm				
OSHA PEL-TWA					2 ppm
ACGIH TLV-TWA					2 ppm
OSHA PEL-STEL	5 ppm				
ACGIH TLV-STEL	5 ppm				
NAS EEGL[g]	30 ppm (10 min)	20 ppm (30 min)	10 ppm (60 min)		5 ppm (24 hr)
German MAK					0.5 ppm
Dutch MAC					1.9 ppm
Swedish OEL-LLV					2 ppm
Swedish OEL-CLV	5 ppm				10 ppm

National Ambient Air Quality Standard = 0.14 ppm

Significant harm level of 1.0 ppm for a 1-hour average


Chemical Toxicity - TSD Human Data
Sulfur Dioxide-Asthmatic Humans
100
10
1
0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-2
AEGL-1
No effect
Discomfort
Disabling
AEGL


Chemical Toxicity - TSD Human Data
Sulfur Dioxide- Healthy Humans
100
10
1
0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-2
AEGL-1
No effect
Discomfort
Disabling
AEGL


Chemical Toxicity - TSD Animal Data
Sulfur Dioxide
100000
10000
1000
100
10
1
0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
No Effect
Discomfort
Disabling
Partially Lethal
Lethal
AEGL

Selected Data from Exposure of Non-Asthmatic Humans to SO_2					
Concentration	**Duration**	**Subjects**	**Exposure Parameters**	**Effect**	**Reference**
1-8 ppm	10 min	14	Exposure through facemask	1-8 ppm: ↓respiratory volume ↑ respiratory rate 5 ppm: dry throat	Amdur et al., 1953
0.75 ppm	2 hours	16	21 °C, 60% RH, treadmill exercise 45 min. after entering chamber	SRaw: ↑ 2-55% (14.6% avg)	Stacy et al., 1981
0.4 ppm 2.0 ppm 4.0 ppm	20 min	8	20 °C, 50% RH, exercise 75 W, last 15 min of exposure	No effects on respiratory function parameters. Nasal irritation: 4 ppm (5/8) Throat irritation: concentration-dependent at 0.4, 2, and 4 ppm	Sandstrom et al., 1988
4.0 ppm 8.0 ppm	20 min	10 4	20 °C, 50% RH, exercise 75 W	Transient concentration-related ↑ alveolar macrophage activity	Sandstrom et al., 1989a
8.0 ppm	20 min	22	20 °C, 50% RH, exercise 75 W	Transient concentration-related ↑ alveolar macrophage activity	Sandstrom et al,1989b
4.0 ppm 5.0 ppm 8.0 ppm 11.0 ppm	20 min	22	20 °C, 50% RH, at rest	Transient ↑in alveolar macrophage activity. Concentration-related up to 8 ppm, no further increase at 1 ppm	Sandstrom et al., 1989c

1.0 ppm	4 hours	20	22.2 °C, 60% RH, exercise 100 W	No effects on lung function parameters. Upper respiratory irritation (4/20) Ocular irritation (1/20)	Kulle et al., 1984
1 ppm 5 ppm 13 ppm	10-30 min	11	resting	No effects 39%↑ pulmonary flow res. 72%↑ pulmonary flow res. Peak response 5-10 min	Frank et al., 1962
1-2 ppm 4-6 ppm 14-17 ppm	30 min	6	resting; exposures to SO_2 alone or in combination with 18 mg/m^3 NaCl	No effects ↑ pulmonary flow resistance ↑ pulmonary flow resistance	Frank et al., 1964
15 ppm 29 ppm	10 min	11	Compared nose breathing vs. mouth breathing	↑ pulmonary flow resistance 15 ppm : 3% nose; 20% mouth 29 ppm: 18% nose; 65% mouth	Frank et al., 1964
0.55 ppm	10 min	11		no nasal or eye irritation	Dautebrande and Capps, 1950
1 ppm 5 ppm 25 ppm	6 hours	15	resting	no effects irritation. ↓FEV_1, ↓nasal mucous flow irritation. ↓FEV_1, ↓nasal mucous flow	Andersen et al., 1974

ACUTE EXPOSURE GUIDELINE LEVELS for DIMETHYLDICHLOROSILANE AND METHYLTRICHLOROSILANE Modification of 4- and 8-hour AEGL-2 and AEGL-3

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

ORNL Staff Scientist:
Cheryl Bast

Chemical Manager:
Ernest Falke

Chemical Reviewer:
George Rusch

Attachment 12

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

The acute toxicity of dimethyldichlorosilane is both qualitatively and quantitatively similar to HCl.

Two moles of hydrogen chloride are released from complete hydrolysis of one mole of dimethyldichlorosilane.

1-hr rat LC_{50} for HCl =	3627 ppm (Dow Corning, 1997)
1-hr rat LC_{50} for Dimethyldichlorosilane =	2092 ppm (Dow Corning, 1999)

Data were insufficient to derive a time scaling exponent 'n' for dimethyldichlorosilane; therefore, the value of n=1, derived from HCl rat and mouse lethality data from exposure durations of ≤100 minutes was previously utilized for time scaling.

We have human HCl data that shows that the 4- and 8-hour AEGL-2 and 8-hr AEGL-3 values for dimethyldichlorosilane may be too conservative.

This conservativism may be a result of time scaling, as was the case with HCl (discussed at NAC-25 and July COT meeting).

Proposal: First, modify the AEGL-2 values by setting the 4-hour value equal to half of the 1-hour value. Then set the 8-hour AEGL-2 and -3 values equal to the respective 4-hour values.

PROPOSED DIMETHYLDICHLOROSILANE MODIFICATIONS

Classification	Exposure Duration (Values in ppm)				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	0.9	0.9	0.9	0.9	0.9
AEGL-2 (Disabling)	78	26	13	6.5 ~~3.3~~	6.5 ~~1.6~~
AEGL-3 (Lethal)	320	106	53	13	13 ~~6.6~~

AEGL-1: Based on molar adjustment of HCl AEGL-1 values that were based on no adverse effects in exercising asthmatics exposed to 1.8 ppm HCl for 45-min.

AEGL-2: Based on corneal opacity and grey spots on the lungs of rats exposed to 1309 ppm dimethyldichlorosilane for 1 hr.; UF of 30; MF of 3; n = 1.

AEGL-3: Based on 1-hour LC_{01} of 1590 ppm in rats; UF of 30; n = 1.

Rationale for Modification- Dimethyldichlorosilane:

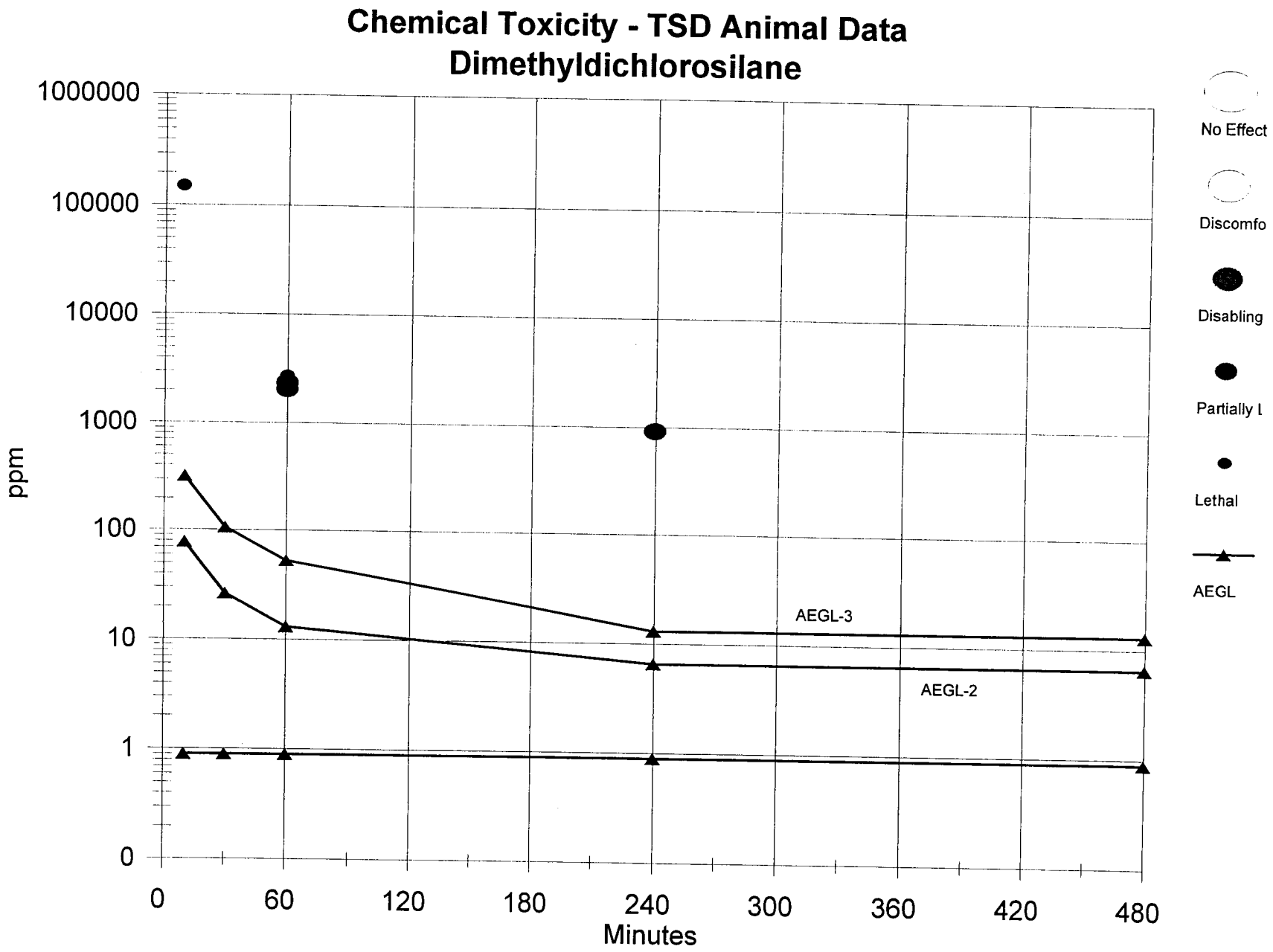
(1) The present 4- and 8-hour AEGL-2 values of 3.3 ppm and 1.6 ppm correspond to molar equivalents of 6.6 and 3.2 ppm HCl. These values are close to the 1.8 ppm HCl tolerated by exercising asthmatics without adverse health effects. It is unlikely that persons exposed to these levels would experience effects approaching those defined by AEGL-2, especially considering the steep concentration-response relationship.

The present 8-hour AEGL-3 value of 6.6 ppm corresponds to a molar equivalent of 13 ppm HCl.

(2) Repeated-exposure rat data suggest that the revised values are protective. Rats exposed to 10 ppm HCl for 6 hrs/day, 5 days/week for life exhibited only tracheal and laryngeal hyperplasia, and rats exposed to 50 ppm HCl for 6 hrs/day, 5 days/week for 90 days exhibited only mild rhinitis.

(3) The revised values are consistent with the HCl AEGL values. A much more robust database exists for HCl.

AEGL Values for Dimethyldichlorosilane (ppm) [HCL ÷ 2] HCl: dimethyldichlorosilane ratio					
Classification	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (Nondisabling)	**0.9**	**0.9**	**0.9**	**0.9**	**0.9**
AEGL-2 (Disabling)	**78 [50]** **1.3**	**26 [22]** **1.7**	**13 [11]** **1.7**	**6.5 [5.5]** **1.7**	**6.5 [5.5]** **1.7**
AEGL-3 (Lethal)	**320 [310]** **1.9**	**106 [105]** **2.0**	**53 [50]** **1.9**	**13 [13]** **2.0**	**13 [13]** **2.0**


Chemical Toxicity - TSD Animal Data
Dimethyldichlorosilane
1000000
100000
10000
1000
100
10
1
0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
No Effect
Discomfo
Disabling
Partially I
Lethal
AEGL

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

The acute toxicity of methyltrichlorosilane is both qualitatively and quantitatively similar to HCl.

Three moles of hydrogen chloride are released from complete hydrolysis of one mole of methyltrichlorosilane.

1-hr rat LC_{50} for HCl =	3627 ppm (Dow Corning, 1997)
1-hr rat LC_{50} for Methyltrichlorosilane =	1365 ppm (Dow Corning, 1999)

Data were insufficient to derive a time scaling exponent 'n' for methyltrichlorosilane; therefore, the value of n=1, derived from HCl rat and mouse lethality data from exposure durations of ≤100 minutes was previously utilized for time scaling.

We have human HCl data that shows that the 4- and 8-hour AEGL-2 and 8-hr AEGL-3 values for methyltrichlorosilane may be too conservative.

This conservativism may be a result of time scaling, as was the case with HCl (discussed at NAC-25 and July COT meeting).

Proposal: First, modify the AEGL-2 values by setting the 4-hour value equal to half of the 1-hour value. Then set the 8-hour AEGL-2 and -3 values equal to the respective 4-hour values.

PROPOSED METHYLTRICHLOROSILANE MODIFICATIONS

Classification	Exposure Duration (Values in ppm)				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	0.6	0.6	0.6	0.6	0.6
AEGL-2 (Disabling)	37	12	6.2	3.1 ~~1.6~~	3.1 ~~0.78~~
AEGL-3 (Lethal)	170	56	28	7.0	7.0 ~~3.5~~

AEGL-1: Based on molar adjustment of HCl AEGL-1 values that were based on no adverse effects in exercising asthmatics exposed to 1.8 ppm HCl for 45-min.

AEGL-2: Based on ocular opacity, clear fluid around the eyes, nose, and mouth, nasal staining, and hunched posture of rats exposed to 622 ppm methyltrichlorosilane for 1 hr.; UF of 30; MF of 3; n = 1.

AEGL-3: Based on 1-hour LC_{01} of 844 ppm in rats; UF of 30; n = 1.

Rationale for Modification- Methyltrichlorosilane:

(1) The present 4- and 8-hour AEGL-2 values of 1.6 ppm and 0.78 ppm correspond to molar equivalents of 4.8 and 2.3 ppm HCl. These values are close to the 1.8 ppm HCl tolerated by exercising asthmatics without adverse health effects. It is unlikely that persons exposed to these levels would experience effects approaching those defined by AEGL-2, especially considering the steep concentration-response relationship.

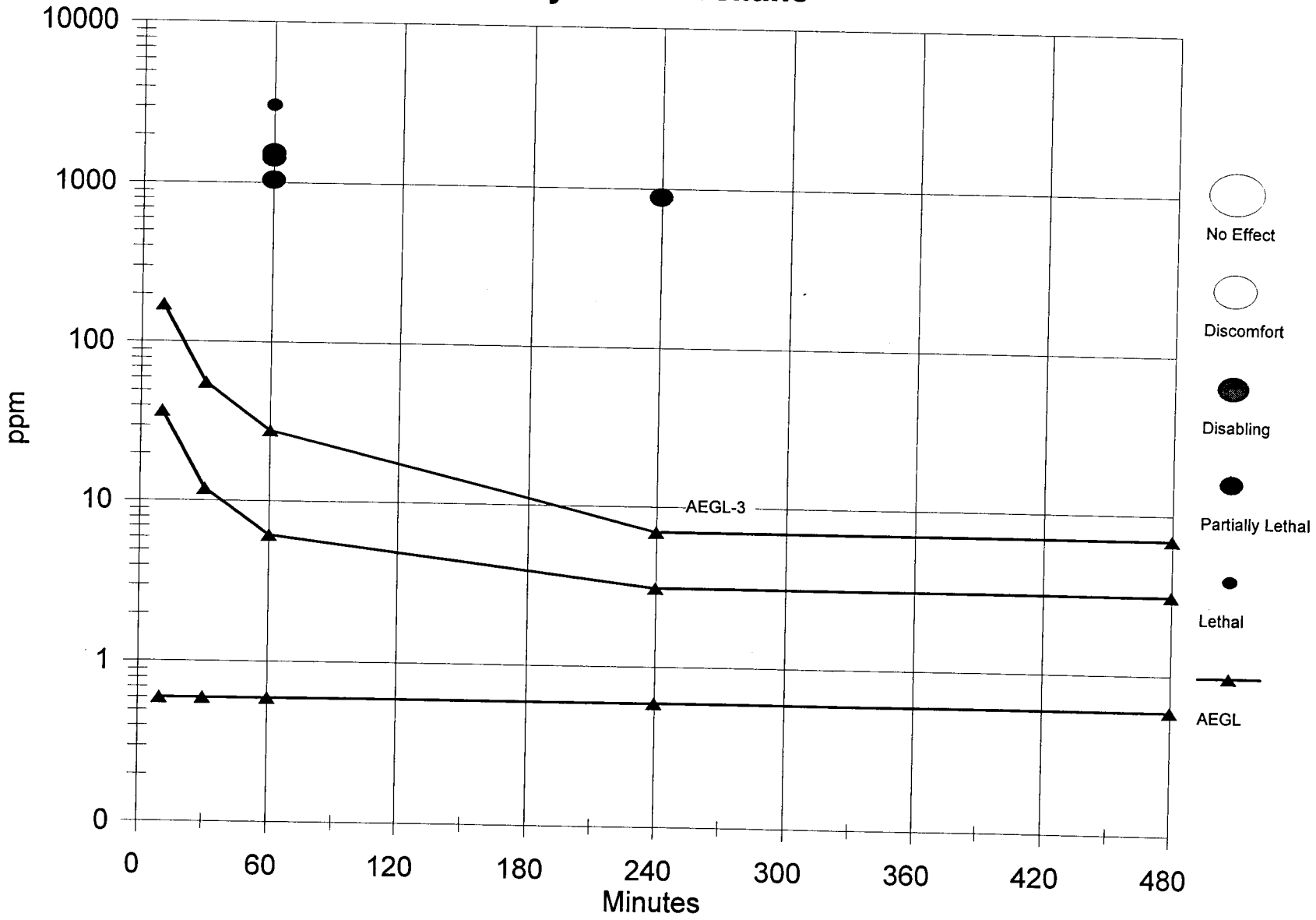
The present 8-hour AEGL-3 value of 3.6 ppm corresponds to a molar equivalent of 10.5 ppm HCl.

(2) Repeated-exposure rat data suggest that the revised values are protective. Rats exposed to 10 ppm HCl for 6 hrs/day, 5 days/week for life exhibited only tracheal and laryngeal hyperplasia, and rats exposed to 50 ppm HCl for 6 hrs/day, 5 days/week for 90 days exhibited only mild rhinitis.

(3) The revised values are consistent with the HCl AEGL values. A much more robust database exists for HCl.

AEGL Values for Methyltrichlorosilane (ppm) [HCL ÷ 3] HCl: Methyltrichlorosilane ratio					
Classification	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (Nondisabling)	**0.6**	**0.6**	**0.6**	**0.6**	**0.6**
AEGL-2 (Disabling)	**37 [33]** **2.7**	**12 [14]** **3.5**	**6.2 [7.3]** **3.5**	**3.1 [3.6]** **3.5**	**3.1 [3.6]** **3.5**
AEGL-3 (Lethal)	**170 [200]** **3.6**	**56 [70]** **3.7**	**28 [33]** **3.5**	**7.0 [8.7]** **3.7**	**7.0 [8.7]** **3.7**

Chemical Toxicity - TSD Animal Data
Methyltrichlorosilane



Attachment 13

ACUTE EXPOSURE GUIDELINE LEVELS FOR TRIMETHYLCHLOROSILANE

NAC/AEGL-26
Spetember 10-12, 2002

ORNL Staff scientist: Cheryl Bast
Chemical Manager: Ernest Flake
Chemical Reviewer: George Rusch

The acute toxicity of Trimethylchlorosilane is both qualitatively and quantitatively similar to HCl.

One mole of hydrogen chloride is released from complete hydrolysis of one mole of Trimethylchlorosilane.

1-hr rat LC_{50} for HCl = 3627 ppm (Dow Corning, 1997)

1-hr rat LC_{50} for Trimethylchlorosilane = 4257 ppm (Dow Corning, 1999)

AEGL-1 VALUES				
10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
1.8 ppm	**1.8 ppm**	**1.8 ppm**	**1.8 ppm**	**1.8 ppm**

Species: Human Adult Asthmatics
Concentration: 1.8 ppm HCl
Time: 45 minutes
Endpoint: HCl AEGL-1 values adopted as AEGL-1 values for trimethylchlorosilane AEGL-1 values
(No treatment-related effects were observed in any of the individuals tested.)
Reference: Stevens et al., 1992

Time Scaling: Values were held constant at the no-effect-level. This approach was considered valid since mild irritant effects generally do not vary greatly over time and the endpoint is inherently conservative

Uncertainty Factors:

Interspecies = 1 (test subjects were human)

Intraspecies = 1 (Test subjects were sensitive population-exercising asthmatics)

AEGL-2 VALUES				
10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
192 ppm	**64 ppm**	**32 ppm**	**16 ppm**	**16 ppm**

Species: Rat
Concentration: 3171 ppm
Time: 1 hour
Endpoint: Lacrimation, corneal opacity, rales, gasping, and nasal discharge
Reference: Dow Corning, 1999

Time Scaling: n = 1; value is for hydrogen chloride based on regression analysis of combined rat and mouse LC_{50} data (1 min. to 100 min.)

Utilized for time scaling for trimethylchlorosilane for time points up to 1 hour

AEGL-2 values for 4- and 8-hr were derived by applying a modifying factor of 2 to the 1-hr AEGL-2 value to obtain values consistent with the total data base.

Uncertainty Factors:

Interspecies = 10 (data from only one species)

Intraspecies = 3 (Utilizing a value of 10 would yield AEGL-2 values which are not supported by the total database and which would be inconsistent with the hydrogen chloride AEGL-2 values)

Modifying Factor = 3 (Sparse database for AEGL-2 effects and effects more severe than AEGL-2 definition. Considered sufficient due to steep concentration-response curve)

AEGL-3 VALUES				
10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
790 ppm	**270 ppm**	**130 ppm**	**33 ppm**	**33 ppm**

Species: Rat
Concentration: 3970 ppm
Time: 1 hour
Endpoint: Calculated 1-hr LC_{01}
Reference: Dow Corning, 1999

Time Scaling: n = 1; value is for hydrogen chloride based on regression analysis of combined rat and mouse LC_{50} data (1 min. to 100 min.)

Utilized for time scaling for trimethylchlorosilane for time points up to 4-hours

The 4-hr value was adopted as the 8-hr value to obtain values consistent with the total data base.

Uncertainty Factors:

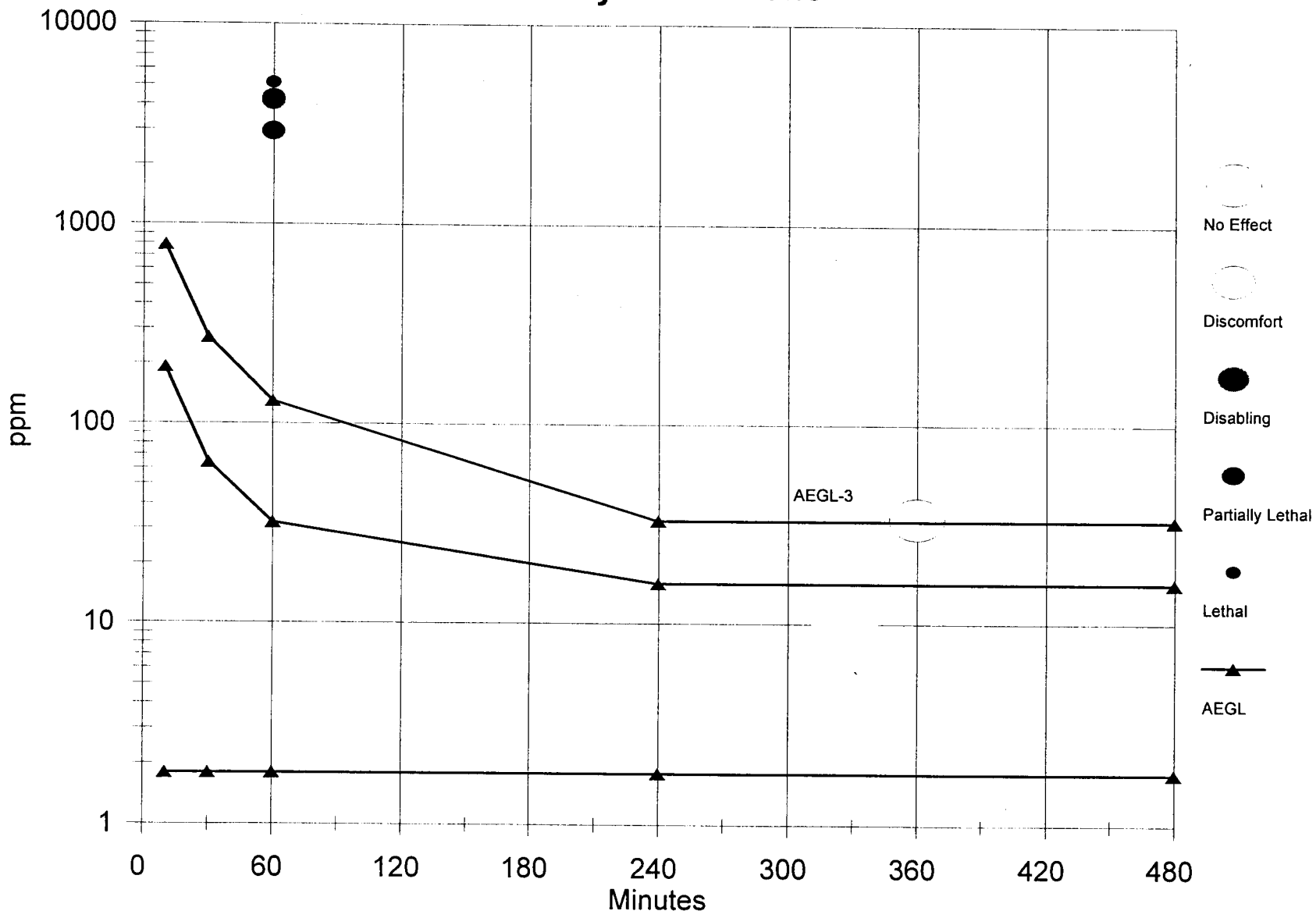
Interspecies = 10 (data from only one species)

Intraspecies = 3 (Utilizing a value of 10 would yield would yield AEGL-3 values approaching the AEGL-2 values)

Extant Standards and Guidelines for Trimethylchlorosilane					
Guideline	**Exposure Duration**				
	10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
AEGL-1	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm
AEGL-2	192 ppm	64 ppm	32 ppm	16 ppm	16 ppm
AEGL-3	790 ppm	270 ppm	130 ppm	33 ppm	33 ppm
ERPG-1	3 ppm				
ERPG-2	20 ppm				
ERPG-3	150 ppm				
WEEL	5 ppm				

AEGL Values for Trimethylchlorosilane (ppm) [HCL] HCl: Trimethylchlorosilane ratio					
Classification	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (Nondisabling)	**1.8**	**1.8**	**1.8**	**1.8**	**1.8**
AEGL-2 (Disabling)	**192 [100]** **0.5**	**64 [43]** **0.7**	**32 [22]** **0.7**	**16 [11]** **0.7**	**16 [11]** **0.7**
AEGL-3 (Lethal)	**790 [620]** **0.8**	**270 [210]** **0.8**	**130 [100]** **0.8**	**33 [26]** **0.8**	**33 [26]** **0.8**

Chemical Toxicity - TSD Animal Data
Trimethylchlorosilane



Surface Coal Mining in Wyoming

An NO_2 Exposure Issue

December 10, 2002

Edward J. Faeder, PH.D., Q.E.P.

What Am I Going to Talk About?

In 15 Minutes or Less

- Surface coal mining is a large scale industry in Wyoming
- Coal mining involves blasting, which produces NO_2
- Occasional human exposure to short duration peaks of NO_2 can occur
- The AEGL process can produce guidelines of value to public health protection
- AEGL-2s are principally of value – what do AEGL-1s tell us?

Who Am I?

- Toxicology consultant for consortium of coal companies operating in the Powder River Basin of Wyoming
- Requested to assist in portions of permit issues relating to human exposure to emissions from blasting operations

What are the Wyoming Issues?

- Concern for public health and safety
- There are no air quality standards or regulations that directly deal with NO_2 releases from blasting operations
- AEGLs come closest to exposure guidelines that can be used

Attachment 14

Acute Exposure Guideline Levels

- AEGL-1 = airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals could experience **notable** discomfort, irritation, or certain asymptomatic, nonsensory effects. Effects are not disabling and are transient and reversible upon cessation of exposure.

What Is Meant By *Notable*?

- There are very specific dictionary definitions for this word, and the very different word, noticeable:
  - **Notable** - prominent or important; conspicuous, memorable, or remarkable
  - **Noticeable** - capable of being noticed, observed, or perceived

This Distinction Important

- Where do you draw the line between detectability and discomfort
  - Irritancy and its importance at low levels
  - *Detectability* versus *adverse impacts*
    - The role of odor perception
      - ~0.12-0.42 ppm NO_2 human perception goes from slight to immediate odor recognition

The Current Draft TSD: 3: 11/2002

- AEGl-1s based upon Kerr et al (1978; 1979), 2 hr study of asthmatics
  - No PFT changes noted
  - Symptom complaints of slight burning of the eyes, slight headaches, chest tightness, labored breathing with exercise; odor recognition at this [NO_2]
  - Are these totally reversible, noticeable, clinical effects where you want to set a 10-min discriminator for AEGL-1?

Linn & Hackney, 1983, 1984

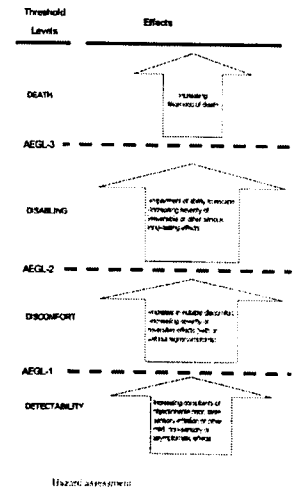
- This study was the basis for earlier NAC/AEGL draft technical support document conclusion that a 30-min AEGL-1 should be 5.2 ppm
- Human exposure studies in an open chamber
- Normal subjects (n=25)and asthmatic subjects (n=23) [volunteers], with exercise protocol
- 75 minutes of 4 ppm NO_2 exposure did not produce an effect (NOAEL)

Linn & Hackney, 1984

- An accident occurred in the chamber, with 3 asthmatic subjects
  - NO_2 monitors and backups failed
  - Subjects averaged 9-10 ppm NO_2
    - The last 15-minutes of exposure were ~ 18ppm NO_2
  - One subject doing heavy exercise experienced nausea, dizziness, headache, hypotension, but no marked respiratory symptoms
    - Symptoms alleviated within 30 minutes

Recommended Short Term Exposure in Wyoming

- Any individual should not experience this level more than once in a "long time" – e.g. several months to a year
- Realistic time frame of exposure should be ten minutes (consistent with EPA NAC/AEGLs)
- Safety factors, sensitive subpopulations, human species are all built in
- Maximum ten minute exposure ≤5 ppm
- Recommendation is consistent with human health study results and proposed emergency guidelines



National Research Council, ***Standing Operating Procedures for Developing Acute Exposure Guideline Levels***, p. 33 (2001)

Conclusion

- We would like you to consider:
  - Making a firm decision as to what the AEGL-1s mean and how they can be used by regulators
  - Adopting a realistic 10-min AEGL-1 for NO_2 at 5.2 ppm, based upon notable effects and the Linn and Hackney work

NITROGEN DIOXIDE

- Review previous action
- Discuss current concerns
- Actions needed

PREVIOUS ACTION ON NO_2

NAC/AEGL balloted on 30-minute and
1-, 4-, and 8-hour values for all three AEGL levels
on September 15, 1998.

All values passed by unanimous vote.

UPDATED TSD

- Comments from U.S. EPA OAQPS
- Information from U.S. FDA
- Comments from NAC members
- Comments from NAC members

PROPOSED AEGL-1 VALUES

AEGL-1 Values for Nitrogen Dioxide (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	(0.5)	0.5	0.5	0.5	0.5

Key study: Kerr, H.D. et al., 1978

Exposure: asthmatics; 0.5 ppm for 2 hours

Effect: slight burning of the eyes, slight headache, chest tightness or labored breathing with exercise in 7/13; no change in pulmonary function

UF: none

PROPOSED AEGL-2 VALUES

AEGL-2 Values for Nitrogen Dioxide (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	(20)	15	12	8.2	6.7

Key study: Henschler, D. et al., 1960

Exposure: normal humans; 30 ppm for 2 hours

Effect: burning sensation in nose and chest, cough, dyspnea, sputum production

UF: 3 - intraspecies

Time scaling: $C^n \times t = k$ where $n = 3.5$

Attachment 15

PROPOSED AEGL-3 VALUES

AEGL-3 Values for Nitrogen Dioxide (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	(34)	25	20	14	11

Key study: Henry, M.C. et al., 1969

Exposure: monkeys; 50 ppm for 2 hours

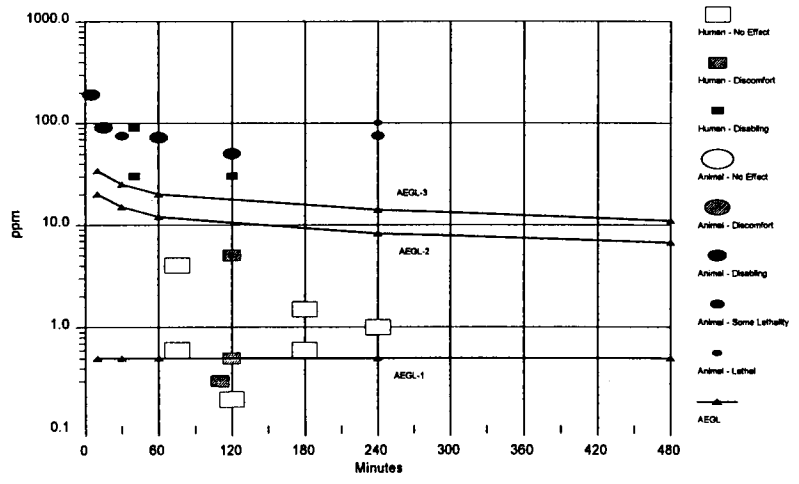
Effect: marked irritation and histopathology in lung

UF: 3 - 1: interspecies
3: intraspecies

Time scaling: $C^n \times t = k$ where n = 3.5

Summary of AEGL Values for Nitrogen Dioxide (ppm)					
Level	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	(0.5)	0.5	0.5	0.5	0.5
AEGL-2	(20)	15	12	8.2	6.7
AEGL-3	(34)	25	20	14	11

Category Plot for Nitrogen Dioxide



CURRENT CONCERNS

AEGL-2

Issue: Henschler et al. (1960) was secondary citation.

Response: -translation complete
-details added
-well-conducted study

CURRENT CONCERNS

AEGL-3

Issue: Henry et al. (1969) quality

Response: -details added
-well-conducted study
-Mary Henry respected and still working

ACTION NEEDED ON NITROGEN DIOXIDE

- Adopt 10-minute values

Derivation of 10-minute Values

- followed SOP (flatline or extrapolation)
- used previously accepted key studies and endpoints
- are supported by human and animal data
- time-scaled AEGL-2 and AEGL-3 10-minute values because key study exposure durations are ≤2 hours

AEGL Values for NITRIC OXIDE

- adopt nitrogen dioxide values (Sept. 15, 1998)
- major effects from NO_2 formation
- note that short-term exposures below 80 ppm NO should not constitute a health hazard (based on therapeutic use in human infants)

NITRIC ACID OVERVIEW

AEGL values adopted previously

Key study for AEGL-2 questioned

Key study for AEGL-3 questioned

PROPOSED AEGL-1 VALUES

AEGL-1 Values for Nitric Acid (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	0.5	0.5	0.5	0.5	0.5

Key study: Sackner and Ford, 1981

Exposure: healthy humans; 1.6 ppm for 10 minutes

Effect: NOAEL

UF: 3 - intraspecies

PROPOSED AEGL-2 VALUES

AEGL-2 Values for Nitric Acid (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	6.7	4.9	4.0	2.7	2.2

Key study: Diem, L., 1907 (cited in Henschler, D., 1991)

Exposure: one human male; 11.5-12.2 ppm for 1 hour

Effect: respiratory irritation; cough; marked secretion from nose and salivary gland; burning of eyes and facial skin; lacrimation

UF: 3 - intraspecies

Time scaling: $C^n \times t = k$ where n = 3.5

PROPOSED AEGL-3 VALUES

AEGL-3 Values for Nitric Acid (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	37	27	22	15	12

Key study: Gray, E.LeB., et al., 1954

Exposure: rats; 244 ppm for 30 minute

Effect: LC_{50}

Modifying factor: 0.33 to estimate threshold for lethality

UF: 3 - 1: interspecies
3: intraspecies

Time scaling: $C^n \times t = k$ where n = 3.5

CURRENT CONCERNS

Nitric Acid AEGL-2

Issue: -key study secondary citation

Response: -now have translation
-analytical problems
-condensation on chamber
-condensation on fur
-two humans

CURRENT CONCERNS

Nitric Acid AEGL-3

Issues: -exposure to mixture
-concentration reported as nitrogen dioxide

Response: -as stated in TSD
-alternatives ?

AEGL values for Nitric Acid

- accept as voted
- table due to lack of data
- adopt NO_2 values

Benzene - AEGL values
NAC-AEGL 27 (december 2002)

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

rivm
National Institute for Public Health and the Environment

Research for man and environment

Benzene characteristics

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

Benzene TSD development

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

Attachment 16

Human data - 1 (lethality)

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

Human data - 2

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

Acute toxicity Benzene - "Table by Gerarde"

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

Human data - 3

Occupational

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

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Human data - 4

Volunteer studies

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

Case studies

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

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Acute Lethality - animal data

Species	Exposure levels (ppm)	Exposure duration	LC50 (ppm)	Remarks	Reference
Rabbit	35000-49000 (nominal) nose only	< 71 min	Not determined	Time to death 34.2 min (22.5 - 71)	Carpenter et al., 1944
Rat	16000 (nominal)	4h	?	This exposure resulted in 3/6, 3/6 or 4/6 death in a 14d obs. period	Carpenter et al., 1949
Rat	34000 (nominal)	4h	Not determined	This exposure resulted in 66% mortality (4/6)	Smyth et al., 1962
Rat SD	-	4h	13700	Total 40 rats	Drew and Fouts 1976
Rat SD	± 7000 - 15000	4h	9536		Bonnet et al., 1982
Mouse	4620 - 13860 (no further information, likely static conditions	2h	Not determined	Loss of control at 4620 ppm, lethality at 13860 ppm	Lazarew, 1929
Mouse	± 7000 - 15000	4h	14122		Bonnet et al., 1982
Mouse Swiss	2980-14600	7h	9960	16-20 minutes per dose	Svirbely et al., 1943

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Acute lethality - animal studies

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

Possible Endpoints ☛ AEGL-2

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

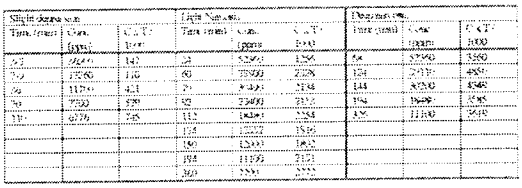
CNS effects -1

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

CNS effects -2

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

CNS effects - 3



Data Von Oettingen 1940: CNS depression in cats.

N ≈ 1

Hematotoxicity - 1

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

Hematotoxicity - 2

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

Hematotoxicity - 3

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

Chromosome aberrations (CA) -1

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

Chromosome aberrations - 2

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

Developmental toxicity - 1

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

Developmental toxicity - 2

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

AEGL -1 derivation

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

AEGL - 1 derivation

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

AEGL - 2 derivation

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

AEGL - 2 derivation

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

AEGL-2 derivation

- With regard to CNS depression benzene is about equipotent to toluene (for which much more human data are available).
- AEGL-2 levels of benzene based on CNS depression should be in the same order of magnitude than those for toluene.
- No specific N value available: Data Von Oettingen 1940 indicate that N=3 is too conservative. Use N values of n=2 and n=1.
- Interspecies factor of 3 (little species differences for CNS depression, higher factor does not comply with human experience).
- Intraspecies factor of 3: CNS depression does not vary by more than a factor 2-3 in the human population.

AEGL-2 derivation

- Use 4000 ppm for 4h as starting point (Molnar et al., 1986)
- Use N=2 and N=1
- Use total UF of 10 (3x3)

TABLE 3: AEGL-2 VALUES FOR BENZENE (ppm)

AEGL Level	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-2	1900	1100	800	400	400

AEGL-3 derivation

- No quantitative human data available for AEGL-3, only estimations. In addition, data with exposure levels without mortality are present. Use human data as supportive evidence.
- Only two adequate LC50 values in rats (4h and 6h) and two in mice (6h and 7h). Data do not allow determination of N.
- Data Von Oettingen 1940 on deep narcosis indicate N=3 is too conservative. Use N=2 and N=1 for extrapolation shorter and longer durations.
- Various studies available with exposure levels that do not show mortality in animals.

3,1 vs 2,1

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AEGL-3 derivation

Studies with single dose inhalation without any mortality

Duration	Exposure level without mortality (ppm)	Species	Ref
15 min	9302-9824	rat	Masaki et al. 1974
30 min	6700	mice	Nielsen and Alarie, 1982
2 h	10,000	rat	Furnas and Hine, 1958
2h	20,000	rabbit	Kajtsur, 1990 (abstract)
4 h	5940	rat	Molnar et al., 1986
6 h	3000	mice	Dempster et al., 1984
6 h	7500	Rabbit + cat	Esser, 1975
6 h (17 days)	2500	Rat + mice	Coate, 1983
7 h	4800	mice	Svirbely et al., 1942
8 h	3630	mice	Lloyd et al., 1977

rivm

AEGL-3 derivation

- Select animal study: quality of study, species, time frame of exposure.
- Use Molnar et al., 1986 as key study (5940 ppm for 4h, NOEL for mortality).
- Use N values of n=2 and n=1.
- Interspecies factor =1 (based on allometric arguments (see also toluene, higher factor would not comply with human experience)
- Intraspecies factor = 3 (mechanism is CNS-depression which does not vary more than a factor of 2-3 in the human population.

rivm

AEGL-3 derivation

- Use 5940 ppm for 4h as starting point (Molnar et al., 1986)
- N=2 or n=1
- Total UF is 3

AEGL-3 VALUES FOR BENZENE (ppm)

AEGL Level	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-3 (based on SMF) (ppm-h)	5940	5940	5940	1980	990

rivm

Benzene NAC AEGL 27 | MTM van Raaij

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AEGL - summary

TABLE 10: SUMMARY/RELATIONSHIP OF PROPOSED AEGL VALUES [a]

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
UFA			2		
AEGL-1 (Nondisabling)	3	3	3	3	3
AEGL-2 (Disabling)	1900	1100	800	400	200
AEGL-3 (Lethal)	9900	5900	3900	1300	990

rivm

Benzene NAC AEGL 27 | MTM van Raaij

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At the June AEGL committee meeting I raised a numbers of serious problems with the characterizations of many of the human studies described in the Benzene TSD and summarized in the Derivation Sections for AEGL-1, 2 and 3 (and reflected in the minutes). The TSD has been revised and values significantly changed but I received no contact from any member to see if any changes were needed in these studies.

These benzene studies mischaracterize a number of terms and types of samples. One way these mischaracterizations are then used is in the justification that extremely high levels of benzene (above 1,000 ppm) will not impair escape. These include:

1) Bulk samples as personal exposures
2) Samples taken in other similar workplaces
3) Samples taken at other times than human exposure
4) Samples taken from sealed containers without human exposure
5) Theoretical calculations (which, the committee has previously not used)
6) Short term direct reading samples used to characterize full shift exposures
7 Sweeping statements that summarizing studies with a 50 fold range of exposures
8) Simultaneous exposures not mentioned
9) Misattribution of symptoms to benzene rather than other substances
10) Use of a single highest 20 minute area measurement (1,800 ppm) as not impairing escape for three occupational cohorts.

Unfortunately, I have little expectation that the accurate description and use of human studies is a priority of the AEGL committee. I continue to be available to discuss these studies with any committee members but I find it difficult to justify a more detailed effort on these problems in the Benzene document unless this is mutually desired. Further, unless the membership of the AEGL committee, ORNL and other groups who draft our TSDs is more inclusive of experts in evaluating human studies, these types of problems will persist.

If Benzene is discussed at the December meeting, I am requesting that the minutes state that a statement was received from me and state:

> "Mr. Morawetz sent comments describing a number of serious problems with the characterizations of many of the human studies described in the Benzene TSD and summarized in the Derivation Sections for AEGL-1, 2 and 3. Mr. Morawetz requested that the committee decide if any changes in the descriptions of the human studies need to be made and communicate to him that decision."

United States
Environmental Protection
Agency

Communications, Education,
and Media Relations
(1703A)

Washington D.C.
20460

EPA **Environmental News**

Attachment 18

FOR RELEASE: DECEMBER 14, 2001

AGENCY REQUESTS NATIONAL ACADEMY OF SCIENCES INPUT ON CONSIDERATION OF CERTAIN HUMAN TOXICITY STUDIES; ANNOUNCES INTERIM POLICY

Contact: David Deegan, 202-564-7839

In a letter released today, the Environmental Protection Agency is requesting that the National Academy of Sciences conduct an expeditious review of the complex scientific and ethical issues posed by EPA's possible use of third-party studies which intentionally dose human subjects with toxicants to identify or quantify their effects.

EPA will ask the Academy to furnish recommendations regarding the particular factors and criteria EPA should consider to determine the potential acceptability of such third-party studies. Recently, most submissions to the Agency have concerned toxicity testing of pesticides, such as studies used to establish a No Observed Adverse Effect Level or No Observed Effect Level for systemic toxicity of pesticides. The Academy is also being asked to provide recommendations on whether internationally accepted protocols or the Protection of Human Subjects Rule ("the Common Rule," which details the protection of human subjects of EPA-conducted or supported research) could be applied to develop the scientific and ethical criteria for EPA to evaluate such studies. These third-party studies that will be the focus of the Academy review are those that have not been conducted or funded by a federal agency in compliance with EPA's Common Rule, or its equivalent.

"Our paramount concern in developing our policy on these studies must be protection of human health and adhere to the most rigorous ethical and scientific standards," said EPA Administrator Christie Whitman. "Formulating a policy that appropriately reflects our competing concerns in this matter will not be easy, and I thank the National Academy of Sciences for agreeing to assist EPA in evaluating these complex issues. The one thing that all parties agree upon is the need for EPA to formulate a formal policy on the use of human testing data, and we will do so in a transparent and responsible manner."

The Agency will ask that the Academy incorporate early in its review an open, public and participatory process through which all interested parties may raise their concerns and ideas for consideration. Following the Academy's review, EPA will engage in an open and participatory process involving federal partners, interested parties and the public during its policy development and/or rule making regarding future acceptance, consideration or regulatory reliance on such human studies.

During the Academy's consideration of the issues and until a policy is in place, the Agency will not consider or rely on any such human studies in its regulatory decision making, whether previously or newly submitted. Should EPA be legally required to consider or rely on any such human study during this interim

period, the Agency will assemble a Science Advisory Board subpanel to review and comment on scientific appropriateness and ethical acceptability of the study in question, and the Agency will provide an opportunity for public involvement. This external review would occur prior to consideration of the study and would allow the Science Advisory Board to review all available information on the study.

Notwithstanding the interim policy, existing provisions of the Federal Insecticide, Fungicide, and Rodenticide Act and the Toxic Substances Control Act, continue to require industry to report any adverse effects information from such studies. In any instance where third-party human testing data suggests a public health concern, the Agency would promptly consider that information.

Attachment

R-246

# # #

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

December 14, 2001

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Dr. Bruce Alberts
President
National Academy of Sciences
2101 Constitution Avenue, NW
Washington, D.C. 20418

Dear Dr. Alberts:

I am writing to request that the National Academy of Sciences (NAS) provide recommendations to the Agency to help address the scientific and ethical questions related to whether to accept, consider, or rely on research involving deliberate exposure of human subjects to toxicants when used to identify or quantify toxic endpoints. The Agency asks that the Academy review these issues and provide recommendations that will help EPA develop appropriate factors and criteria to apply when it makes these difficult decisions. The advice of the Academy will be weighed heavily as we develop and implement a policy to govern these decisions in future.

The Agency's particular focus of concern is on studies which, since they are not conducted or supported by a federal agency, may not be performed subject to regulations that protect human subjects, such as EPA's Protection of Human Subjects Rule ("the Common Rule"), 40 CFR 26. We are particularly concerned about 'third-party' studies submitted by regulated entities for the Agency's consideration. For these purposes, EPA is considering "third-party studies" as studies that have not been conducted or funded by a federal agency pursuant to regulations that protect human subjects. These types of studies generally come to the Agency's attention only after the research has been completed and reported. At this point it is generally too late for the Common Rule requirements to apply since these requirements cover prior review and approval of proposed research, involving fully informed, voluntary consent of the participants to protect the subjects in the research.

One particular concern of the Agency is for determining the acceptability of third-party research designed to identify or quantify toxic endpoints in human subjects, such as those done to define a No Observed Adverse Effect Level (NOAEL) or No Observed Effect Level (NOEL) for systemic toxicity in humans. Studies of this kind are submitted to the agency from time to time, and have been evaluated prior to regulatory decision in several Agency programs. In the recent past most such submissions have been of studies designed to define a NOAEL for pesticide toxicity in humans.

EPA asks the Academy to undertake a critical review of appropriate standards for the scientific and ethical assessment of research entailing deliberate dosing of human subjects with toxic agents. This review should incorporate and be informed by an early open, public, participatory process through which interested people can express their suggestions or concerns to the Academy reviewers.

The Agency subscribes fully to the principles of the Common Rule and the related rules of other federal agencies, as they protect the human subjects of research conducted or supported by the federal government. We are pleased with our record of compliance with the Common Rule in our own research, and of the favorable review by our human subjects protection program in a recent survey by the National Bioethics Advisory Commission.

The Agency will consider the Academy's advice resulting from this review as we develop a policy to guide its future decisions to accept, consider, or rely on such studies in regulatory decision making. As the Academy evaluates the scientific rationale and the ethical framework for these studies, it would be most helpful if the Academy would include in its general advice responses to the following questions:

- What factors should the Agency consider in determining whether to accept, consider, or rely on human studies performed by third parties? Are there clear boundaries between acceptable and unacceptable human research? If so, what are they? If not, what range of factors should the agency consider, and how should these factors be applied in making decisions to accept, consider, or rely on specific research?

- What range of information should the Agency consider in determining whether completed research with human subjects conducted by third parties was conducted in compliance with the appropriate ethical standards, such as the Declaration of Helsinki, which may be cited in the research report?

- Do criteria such as those in the Common Rule provide an adequate framework for assessing the scientific and ethical acceptability of such studies? Should such a standard, designed to protect human participants in research, be applied after the fact to completed research conducted by third parties to determine whether it is acceptable as the basis for regulatory action?

- Are there other standards, such as the Declaration of Helsinki or various standards of good clinical practice, relevant to assessing acceptability of research to define or quantify toxic endpoints in human research subjects? Should standards intended to govern human safety studies for diagnostic or therapeutic agents be applied to research involving deliberate exposures to environmental toxins?

I look forward to meeting with you soon to work out the details and timing of your review, and to a constructive collaboration on this project.

Sincerely,

Stephen L. Johnson
Assistant Administrator

cc: E. William Colglazier
Ann Marie Mazza

Attachment 19

Areas of Consideration
Included in the NAS Statement of Work

"The scope of information gathered by the committee and the topics on which public input shall be solicited shall include, but are not necessarily limited to:

1) Whether and if so to what extent EPA's decision to accept, consider, or rely on a third party, human toxicity study should depend on:

   a) whether the study was conducted in substantial compliance with the provisions of the Common Rule or another standard for the protection of human subjects;

   b) the type of substance tested (e.g., pharmaceutical, pesticide, environmental contaminant);

   c) whether the results of the study tend to indicate that the substance tested is more risky or less risky than is indicated by other available data;

   d) the statistical power of the study, or the ability or inability to measure the same endpoints in humans that have been observed in animal testing of the same substance, or other specific characteristics of the study design.

   e) when the study was conducted in relation to the date of any statement of policy by EPA regarding the ethical conduct of such studies;

   f) whether there are alternative methods of obtaining data of comparable scientific merit that would not involve deliberate dosing of human subjects;

   g) the nature of the test sponsor's interest in a regulatory matter that could be affected by consideration of the data;

   h) how EPA intends to use the results in its regulatory decision making (e.g., to reduce or remove the traditional tenfold interspecies uncertainty factor, or to provide an endpoint for use in calculating a reference dose for the test substance, or for some other purpose);

   i) whether the study has been submitted in response to a regulatory requirement of EPA, or whether it was conducted in conformity with an EPA Guideline;

   j) EPA's assessment of the actual or potential benefits, if any, to the individual human subjects of the research, or to society;

2) Under what circumstance(s), if any, the availability of human data should lead EPA to consider reducing or removing the customary tenfold interspecies uncertainty factor;

3) What existing standards (e.g., the Common Rule, the Declaration of Helsinki) are available for evaluating the design and the conduct of research with human subjects, and which of these standards would be most appropriate in judging whether human toxicity studies submitted to EPA in support of a regulatory decision were conducted ethically and in a way fully protective of the interests and safety of the human subjects;

4) Whether and if so how the requirements of the Common Rule should be extended to the conduct of third party research with human subjects intended for submission to EPA in support of a regulatory decision; and

5) To what extent and how the submitter of research with human subjects to EPA should be required to document or otherwise demonstrate compliance with appropriate standards for the protection of human research subjects—e.g., fully informed and fully voluntary participation, and independent oversight of research design and conduct by an Institutional Review Board."

NAS Website Address:

http://www4.nas.edu/webcr.nsf/5c50571a75df494485256a95007a091e/9303f725c15902f685256c44005d8931?OpenDocument&Highlight=0,EPA

or

go to www.nas.edu, view current projects, and select "Use of Third Party Toxicity Research with Human Research Participant."

NAS Membership
Committee on the Use of Third Party Toxicity Research with Human Research Participants

Provisional Members

CO-CHAIRS:

James F. Childress (IOM), B.A., Guilford College, B.D., Yale Divinity School, M.A and Ph.D., Yale University, is the John Allen Hollingsworth, Professor of Ethics and Professor of Medical Education at the University of Virginia, where he teaches in the Department of Religious Studies and directs the Institute for Practical Ethics. He served as Chair of the Department of Religious Studies, 1972-1975 and 1986-1994, as Principal of UVA's Monroe Hill College from 1988 to 1991, and as co-director of the Virginia Health policy Center 1991-1999. In 1990 he was named Professor of the Year in the state of Virginia by the Council for the Advancement and Support of Education. He is the author of numerous articles and several books in biomedical ethics, including Principles of Biomedical Ethics (with Tom L. Beauchamp); Priorities in Biomedical Ethics; Who Should Decide Paternalism in Health Care; and Practical Reasoning in Bioethics, along with articles and books in other areas of ethics.

Childress was vice chair of the national Task Force on Organ Transplantation, and he has also served on the Board of Directors of the United Network for Organ Sharing (UNOS), the UNOS Ethics Committee, the Recombinant DNA Advisory Committee, the Human Gene Therapy Subcommittee, the Biomedical Ethics Advisory Committee, and several Data and Safety Monitoring Boards for NIH Clinical Trials. He was a member of the presidentially-appointed National Bioethics Advisory Commission 1996-2001.

Childress is a fellow of the American Academy of Arts and Sciences and, in 1998, was elected to membership in the Institute of Medicine of the National Academy of Sciences. He is also a fellow of the Hastings Center. He has been the Joseph P. Kennedy, Sr., Professor of Christian Ethics at the Kennedy Institute of Ethics at Georgetown University (1975-1979) anda Visiting Professor at the University of Chicago Divinity School and Princeton University.

Michael R. Taylor, B.A. (Political Science), Davidson College; J.D., University of Virginia, is Senior Fellow and Director, Risk, Resource, and Environmental Management, Resources for the Future (RFF); and a member of the Board of Trustees of Resolve, Inc., a nonprofit environmental and public health mediation and dispute resolution organization. At RFF, Taylor leads a research program on the policy and institutional issued affecting the success of the global food and agricultural system in such areas as food security in developing countries, food safety as a global concern, and the natural resource and environmental sustainability of Agriculture. Publications include Redesigning Food Safety: Using Risk Analysis to Build a Better Food Safety System (2001)(co-author). Prior to coming to RFF, Taylor served in government, practiced law in Washington, and worked in private industry. He was Administrator of the USDA's Food Safety and Inspection Service; Deputy Commissioner for Policy at the Food and Drug Administration, and an FDA staff lawyer and Executive Assistant to the FDA Commissioner. He practiced food and drug

law and was a partner in the law firm of King & Spalding, and was Vice President for Public Policy at Monsanto Company. He is currently a member of The National Academies Committee on Implications of Dioxin in the Food Supply, and has served on the Subcommittee on Defining Science-Based Concerns Associated with Products of Animal Biotechnology; the Food Forum; and the Committee on Scientific and Regulatory Issues Underlying Pesticide Use Patterns and Agricultural Innovation.

MEMBERS:

James V. Bruckner, B.S. (Pharmacy), University of Texas, Austin; M.S. (Toxicology), University of Texas at Austin; Ph.D. (Toxicology), University of Michigan, Ann Arbor, is Professor of Pharmacology and Toxicology, Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy, University of Georgia. He was director of the latter university's Interdisciplinary Graduate Program in Toxicology. He was recently a member of the FIFRA Scientific Advisory Panel for Evaluation of Exposure and Hazards to Children from Contact with Chromated Copper Arsenate-Treated Wood Structures, Office of Pesticide Programs, EPA; peer reviewer of applications for Hazardous Substances Research Center Grants, National Center for Environmental Research and QualityAssurance, Office of R&D, EPA; as peer reviewer of research conducted by the experimental Toxicology Division, National Health and Environmental Effects Research Laboratory, EPA; as peer reviewer of grant applications on physiological modeling submitted to the U.S. Agency for Toxic Substances and Disease Registry; and as member of an expert panel on the pharmacokinetics of chemical mixtures, Exposure Assessment Group, Office of Health and Environmental Assessment, EPA. He has served on the editorial boards of the Journal of Toxicology and Environmental Health, Chemosphere, Toxicology, and Toxicology and Applied Pharmacology. Dr. Bruckner's research focus is on the toxicology and toxicokinetics of solvents, solvent interactions at low exposure levels, and pharmacokinetic bases for susceptibility of children to insecticides and other chemicals. The relevance of experimental designs to "real life" chemical exposures is of particular interest. He has published more than 180 journal articles, book chapters, and abstracts. He has served on National Academies Committees including (1) Board on Environmental Studies and Toxicology Subcommittee on Acute Exposure Guideline Levels, (2) Committee on Health and Safety Consequences of Child Labor, (3) Committee on Pesticides in the Diets of Infants and Children, (4) Subcommittee on Dibromochloropane, and (5) Committee on Safe Drinking Water.

Alicia Carriquiry, B.S. (Ag Engineering) Universidad del Uruguay, M.Sc. (Animal Genetics), University of Illinois, M.Sc. (Statistics), Iowa State University, Ph.D. (Statistics and Animal Science), Iowa State University, is Associate Provost and Professor of Statistics, Iowa State University. She was a Visiting Professor at the Institute for Statistics and Decision Sciences, Duke University, and at the Department of Statistics, Pontifical Catholic University of Chile. She also serves as a Consultant to Mathematica Policy Research, ABT Associates, Kemin Food Industries, and Law and Economics Consulting Group.

Dr. Carriquiry is an Elected Member of the International Statistical Institute and a Fellow of the American Statistical Association. She is Past President of the International Society for Bayesian Analysis, and serves on the Executive Committee of the Institute of Mathematical Statistics. She has

been a Trustee of the National Institute of Statistical Sciences since 1997, and currently serves in its Executive Committee. She is also a member of the Board of the Plant Sciences Institute at Iowa State University. Dr. Carriquiry is Editor of Statistical Sciences, and serves on the editorial boards of several Latin American journals of statistics and mathematics.

Dr. Carriquiry has published over 50 refereed articles and technical reports, and has co-edited four books. Her research interest is in the development of Bayesian methods, and on the application of those methods to problems in public health, human nutrition, genetics, and economics. She has also worked in the area of stochastic volatility and other non-linear models for time-dependent data. She has served on two National Academies committees: the Subcommittee on Interpretation and Uses of Dietary Reference Intakes; and the Committee on Evaluation of USDA's Methodology for Estimating Eligibility and Participation for the WIC Program. She has been a co-author on four National Academy of Sciences reports. She is a member of the Federal Steering Committee Future Directions for the CSFII/NHANES Diet/Nutrition Survey: What we Eat in America.

John Doull, B.S. (Chemistry), Montana State University; Ph.D. (Pharmacology), University of Chicago; M.D., University of Chicago; is Professor Emeritus of Pharmacology and Toxicology and Therapeutics, Department of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical Center. Prior to that he was Assistant Director of the University of Chicago Toxicity Laboratory and Associate Professor in the Department of Pharmacology at the University of Chicago. He served on the Toxicology Study Section of NIH and the Council of NIEHS. He is past president of the Society of Toxicology and the American Board of Toxicology, has chaired the Threshold Limit Value Committee of the American Conference of Governmental Industrial Hygienists, served on the Expert Panels of the International Life Sciences Institute (ILSI), FEMA, and DISCUS, and was a member of the Presidential Clean Air Commission. He has served on the scientific advisory panels of EPA, NIOSH and others and consults with many governmental, state, industrial, and private organizations. He has received numerous awards from the Society of Toxicology, Robert Wood Johnson Medical School, International Society for Regulatory Toxicology and Pharmacology, Department of the Army, University of Chicago, American Conference of Governmental Industrial Hygienists, and American College of Toxicology. Dr. Doull currently serves on The National Academies Board on Environmental Studies and Toxicology, and the Subcommittee on Acute Exposure Guidelines Levels. He has also served on the (1) Committee on Risk Assessment of Exposure to Radon in Drinking Water (Chair), (2) Committee on Interactions of Drugs, Biologics, and Chemicals in U.S. Military Forces, (3) Committee on Risk Assessment of Hazardous Air Pollutants, (4) Committee on Risk Assessment Methodology, (5) Subcommittee on Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances (Chair), (6) Committee on Toxicology (Chair), Advisory Committee on the CDC Study of the Health of Vietnam Veterans, (7)Committee on Methods for In Vivo Toxicity Testing of Complex Mixtures from the Environment (Chair), (8) Board on Toxicology and Environmental Health Hazards, (9) Committee on Identification of Toxic and Potentially Toxic Chemicals for Consideration by the National Toxicology Program, and (10) Committee on Toxicity Data Elements.

Henry T. (Hank) Greely, A.B., Stanford, J.D., Yale Law School, is the C. Wendell and Edith M. Carlsmith Professor of Law and a professor, by courtesy, of genetics at Stanford University. He chairs the steering committee of the Stanford University Center for Biomedical Ethics; co-directs

the Stanford Program in Law, Science, and Technology; and co-directs the Stanford program on Genomics, Ethics, and Society. He specializes in legal and social issues arising from advances in the biosciences and in health law and policy. He has written on issues concerning genetic testing, human cloning, the ethics of human genetics research, and policy issues in the health care financing system, among other things. He has been a member of the Stanford faculty since 1985 and is currently serving as Chair of the Stanford Faculty Senate (2002-2003). He serves on the California Advisory Committee on Human Cloning; the Scientific Advisory Committee and the Ethical Advisory Committee for theVeteran's Affairs Department?s Program on Genetic Tissue Banking in VA Clinical Research; and the North American Committee of the Human Genome Diversity Project, whose ethics subcommittee he chairs. He served as a law clerk for Judge John Minor Wisdom on the United States Court of Appeals and for Justice Potter Stewart of the United States Supreme Court.

Siobán D. Harlow, B.A., (Health Arts and Sciences), University of California, Berkeley; Ph.D., (Epidemiology), Johns Hopkins School of Hygiene and Public Health, is Associate Professor, Epidemiology, Department of Epidemiology, School of Public Health, University of Michigan and Associate Director of the International Institute, University of Michigan. She is also Director of the Advanced Studies Center, and Faculty Associate, Center for Research on Ethnicity, Culture and Health, School of Public Health, both at the University of Michigan. She was the convener of the international, interdisciplinary workshop on "Risk Assessment in the Context of Trade Disputes" and is editor of the forthcoming collection of papers to appear in Risk Assessment: An International Journal. She has served on numerous grant review panels for NIEHS, NIOSH, NICHD, and the Workplace Safety and Insurance Board of Ontario. Her research focuses on reproductive, perinatal and occupational epidemiology in developing countries. She has helped develop a generation of reproductive epidemiologists in Mexico who focus on adverse effects of environmental and occupational exposures. In collaboration with El Colegio de Sonora, she co-founded the Programa de Formación de Investigadores en Salud Reproductiva to foster the development of human resources in reproductive health research in the US-border region of Mexico with support from the Fogarty International Center. In collaboration with her Mexican colleagues, she has conducted some of the first epidemiologic studies of the health status of the maquiladora workers, evaluating the interlinkages between export-led development strategies and health. In the US she is co-principal investigator for the Michigan site of the Study of Women's Health Across the Nation, a multi-site longitudinal study of health of women as they transition through the mid-life. She has also developed new analytical approaches for the analysis of menstrual cycle data and has recently defined a lifespan approach to understanding the variability in menstrual function across the reproductive life-course including the stages of reproductive aging. Dr. Harlow's memberships include Phi Beta Kappa, Delta Omega, North American Menopause Society and the Society for Epidemiologic Research.

Lester B. Lave, (IOM), B.A. (Economics), Reed College; Ph.D. (Economics) Harvard University, is the Harry B. and James H. Higgins University Professor of Economics and Finance; Professor, Engineering and Public Policy, and The H. John Heinz III School of Public Policy and Management; Director, Green Design Initiative; and Co-Director, Carnegie Mellon University Electricity Industry Center, Carnegie Mellon University. His work has focused on environmental quality, risk perception and communication, and risk analysis and risk management: devising tools

that quantify health, safety and environmental risks and then investigating ways to manage these risks more efficiently and effectively. For example, examining the effects of air pollution on human health and devising air pollution policy that is both efficient and effective; and information content of tests for whether chemicals are toxic; value of tests in reproductive toxicology. He is the recipient of the Distinguished Achievement Award of the Society for Risk Analysis. Dr. Lave has served on committees of the American Medical Association and the AAAS, including Acting Chairman of the Assembly of Social and Behavior Sciences. He has served on many grant review panels of the NIH, NSF, and EPA. He has served on numerous Academy committees, including (1) Committee on Risk-Based Analysis for Flood Damage Reduction, (2) Committee on Industrial Competitiveness and Environmental Protection, (3) Committee on the Medical Use Program of the Nuclear Regulatory Commission, (4) Board on Natural Disasters, (5) Board on Health Promotion and Disease Prevention, (6) U.S. National Committee for the Decade for Natural Disaster Reduction, (7) Committee on Dietary Guidelines Implementation, (8) Water Science and Technology Board, (9) Committee on Dam Safety, and (10) Energy Engineering Board.

Bernard Lo (IOM), A.B. (Physics) Harvard College; M.A., (Comparative Literature), University of Sussex; A.M. (History of Science), Harvard University; M.D., (Medicine), Stanford University, is Professor of Medicine, and Director, Program in Medical Ethics, University of California, San Francisco. He directs the national coordinating office for the Initiative to Strengthen the Patient-Provider Relationship in a Changing Health Care Environment. He chairs the End of Life Committee convened by the American College of Physicians, which will develop recommendations for clinical care near the end of life. Dr. Lo was a member of the National Bioethics Advisory Commission and of the Data Safety Monitoring Board for the AIDS Clinical Trials Group at the National Institute of Allergy and Infectious Diseases. He directs the Greenwall Faculty Scholars in Bioethics Program and is a member of the Recombinant DNA Advisory Committee at NIH. He has written more than 100 articles in peer-reviewed medical journals, on such issues as decisions about life-sustaining interventions, decision-making for incompetent patients, physician-assisted suicide, ethical issues regarding HIV infection, and the doctor-patient relationship in managed care. He is the author of Resolving Ethical Dilemmas: A Guide for Clinicians, a comprehensive analysis of ethical dilemmas in adult medicine. He is also a practicing general internist who teaches clinical medicine to residents and medical studies. Dr. Lo has served on the Institute of Medicine Board on Health Sciences Policy since 1994 and has chaired since 1999. He is a former member of the Board of Directors of the American Society of Law, Medicine, and Ethics, and a Fellow of the Hastings Center. His other Academy experience includes chairing the Committee on the Role of Institutional Review Boards in Health Services Research Data Privacy Protection.

Thomas A. Louis, B.A. (honors in Mathematics), Dartmouth College, Ph.D. (Mathematical Statistics) Columbia University, is Professor, Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health. He was Assistant Professor, Department of Mathematics, Boston University (1973-1978); Associate Professor, Department of Biostatistics, Harvard School of Public Health (1978-1987); Professor, Division of Biostatistics, University of Minnesota School of Public Health (1987-2000, Division Head 1987-1999); Senior Statistical Scientist, RAND (2000-2002), and Visiting scholar, Committee on National Statistics (CNSTAT), National Academy of Sciences (1999). Dr. Louis is an elected member of the International Statistical Institute, a Fellow of the American Statistical Association and of the American Association for the Advancement of Science.

He served as President of the Eastern North American Region of the International Biometrics Society and is chair-elect of the American Statistical Association's Section on Bayesian Statistical Science. Dr. Louis is coordinating editor of The Journal of the American Statistical Association. He serves on the executive committee of the National Institute of Statistical Sciences and on the Health Review Committee of the Health Effects Institute. Dr. Louis has published more than 150 articles and books and delivered more than 250 invited presentations. His research interests include environmental, health and public policy studies and development of related statistical procedures. Methods research concentrates on Bayesian modeling including small area estimation, the analysis of observational studies and research synthesis. Current applications include assessing the health effects of airborne particulate matter, assessment of environmental justice, clinical quality improvement, cardio-pulmonary consequences of AIDS therapies, modeling pregnancy outcome history and evaluation of teacher effectiveness. Dr. Louis's Academy service includes membership on the Committee on National Statistics (CNSTAT) and on the Board of the IOM's Medical Follow-up Agency. He served on the IOM Panel to Assess the Health Consequences of Service in the Persian Gulf War, on the CNSTAT Panel on Estimates of Poverty for Small Geographic Areas and chaired the CNSTAT Panel on Formula Allocation of Federal and State Program Funds.

Gilbert S. Omenn, (IOM), B.A., Princeton University; M.D., Magna Cum Laude, Harvard Medical School; Ph.D. (Genetics), University of Washington, Seattle, is Professor of Internal Medicine, Human Genetics, and Public Health at the University of Michigan. He served as Executive Vice President for Medical Affairs and as Chief Executive Officer of the University of Michigan Health System from 1997 to 2002. He was formerly Dean of the School of Public Health, and Professor of Medicine and Environmental Health, University of Washington, Seattle. His research interests include cancer proteomics, chemoprevention of cancers, public health genetics, science-based risk analysis, and health policy. He was principal investigator of the beta-Carotene and Retinol Efficacy Trial (CARET) of preventive agents against lung cancer and heart disease; director of the Center for Health Promotion in Older Adults; and creator of a university-wide initiative on Public Health Genetics in Ethical, Legal, and Policy Context while at the University of Washington and Fred Hutchinson Cancer Research Center. He served as Associate Director, Office of Science and Technology Policy, and Associate Director, Office of Management and Budget, in the Executive Office of the President in the Carter Administration. He is a longtime director of Amgen Inc., and of Rohm & Haas Company.

Omenn is the author of 369 research papers and scientific reviews and author/editor of 17 books. He is a member of the Institute of Medicine of the National Academy of Sciences, the American Academy of Arts and Sciences, the Association of American Physicians, and the American College of Physicians. He chaired the presidential/congressional Commission on Risk Assessment and Risk Management ("Omenn Commission"), served on the National Commission on the Environment, and chaired the NAS/NRC/IOM Committee on Science, Engineering and Public Policy. He is active in cultural and educational organizations, and is a musician and tennis player.

Joseph V. Rodricks, B.S. (Chemistry), Massachusetts Institute of Technology; M.S. (Organic Chemistry), University of Maryland; Ph.D. (Biochemistry) University of Maryland; is Founding Principal, Environ International Corporation (1982). He is a Visiting Professor at The Johns Hopkins

University School of Public Health. He is an internationally recognized expert in the field of toxicology and risk analysis, and in their uses in regulation and in the evaluation of toxic tort and product liability cases. He has testified before Congress on risk assessment related to pesticides and food safety. Since 1980, he has consulted for hundreds of manufacturers, for government agencies and the World Health Organization. He currently serves on Academy committees on (1) Subcommittee on Upper Safe Reference Levels of Nutrients, (2) Committee on Gulf War and Health: Review of the Literature on Pesticides and Solvents; (3) Committee on Toxicological and Performance Aspects of Oxygenated Motor Vehicle Fuels, (4) Committee on Risk Assessment of Hazardous Air Pollutants, (5) Committee on Neurotoxicology and Models for Assessing Risk; (6) Committee on Human Health Risk Assessment of Using Antibiotics in Animal Feed, (7) Committee on Public Health Risk Assessment of Poultry Inspection, (8) Board on Toxicology and Environmental Health Hazards, (9) Subcommittee to Evaluate Effects of Short-Term Exposures to Drinking Water Contaminants (Chair), and (10) Committee on Institutional Means for Assessment of Risks to Public Health. He has more than 100 publications on toxicology and risk analysis, and has lectured nationally and internationally on these topics. Recent articles/book chapters include "Historical Perspective of Risk Assessment and Steps in the Process," "Risk Assessment and the Regulation of Pesticides," "Toxicological Risk Assessment in the Courtroom: Are Available Methodologies Suitable for Evaluating Toxic Tort and Product Liability Claims?" Dr. Rodricks was formerly Deputy Associate Commissioner, Health Affairs, and Toxicologist, U.S. Food and Drug Administration. He is a Diplomate, American Board of Toxicology. His experience includes chemical products and contaminants in foods, food ingredients, air, water, hazardous wastes, the workplace, consumer products, and medical devices and pharmaceutical products. He is the author of Calculated Risks, a nontechnical introduction to toxicology and risk analysis now in its sixth printing for which he won an award from the American Medical Writers Association.

Christopher H. Schroeder, B.A., Princeton University; M.Div., Yale University; J.D., University of California, Berkeley; is Charles S. Murphy Professor of Law and Public Policy Studies, and Director of the Program in Public Law, Duke University Law School. He has served as Acting Assistant Attorney General in the Office of Legal Counsel at the U.S. Department of Justice. He has also served as Chief Counsel to the Senate Judiciary Committee. His areas of research and scholarship include environmental and administrative law, democratic theory, legislative institutions and separation of powers. He has taught environmental law; government, business and public policy; environmental litigation; toxic substances regulation; philosophy of environmental protection. He has written on the philosophical foundations of risk regulation and liability, the regulation of toxic substances, the performance of American environmental policy, and a variety of topics in public law and theory. He co-authored a leading environmental law casebook, Environmental Regulation: Law, Science, and Public Policy. He is the editor of a forthcoming Resources for the Future book evaluating the performance of the U.S.Environmental Protection Agency. He has written extensively on environmental and administrative law, risk regulation and liability, and regulation of toxic substances.

Robert Temple, B.A., Magna Cum Laude, Harvard College; M.D., New York University School of Medicine. At NYU he was elected to Alpha Omega Alpha. He completed an internship and residency in internal medicine at the Columbia Presbyterian Medical Center in 1969. He is board-certified in internal medicine and clinical pharmacology. Dr. Temple is Director of the Office

of Medical Policy of the Food and Drug Administration's Center for Drug Evaluation and Research (CDER) and also is Acting Director of the Office of Drug Evaluation I (ODE-1). ODE-1 is responsible for the regulation of cardio-renal, oncologic and neuropharmacologic/ psychopharmacologic drug products. The Office of Medical Policy is responsible for regulation of promotion through the Division of Drug Marketing, Advertising, and Communication, for assessing quality of clinical trials, and helping to assure human subject protection through the Division of Scientific Investigations. Dr. Temple has a long-standing interest in the design and conduct of clinical trials and has written extensively on this subject, especially on choice of control group in clinical trials, evaluation of active control trials, trials to evaluate dose-response, and trials using "enrichment" designs. Dr. Temple was Clinical Associate and then Chief Clinical Associate in the Clinical Endocrinology Branch of the National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, from 1969-1972, investigating the effects of lithium on the thyroid and examining the effects of agents that disrupt microtubules on steroid secretion. He became a reviewing Medical Officer in the Division of Metabolic and Endocrine Drug Products in 1972, and moved to become Assistant to the Director of the Bureau of Drugs in 1974. In 1976, he became the Director of the Division of Cardio-Renal Drug Products, serving in that role until 1982. From 1982 to 1988 he was Acting Director and then Director of the Office of Drug Research and Review. The responsibilities of that office have been divided in various ways, most recently (since 1995) among five Offices of Drug Evaluation (ODE?s 1-5). Among other awards, he has received FDA's Award of Merit on six occasions, three Commissioner's Special Citations, the Public Health Service Superior Service award, the DHHS Distinguished Service Award, the Secretary?s Special Citation and the Drug Information Association Outstanding Service Award. He received the American Society for Clinical Pharmacology and Therapeutics Rawls-Palmer Progress in Medicine Lecture and Award in 2001. He also received the National Organization for Rare Disorders Public Health Leadership Award in 2001. In 2002, he received FDLI's Distinguished Service and Leadership Award. Dr. Temple is on the editorial board of Clinical Pharmacology and Therapeutics. He was on the Board of Directors of the Society for Clinical Trials from 1983-1987 and was President of the Society in 1987. He is an honorary Fellow of the American College of Clinical Pharmacology.

Application of Acute Exposure Guideline Levels

The Acute Exposure Level Guidelines have been developed primarily to provide guidance in situations were there can be a rare, typically accidental exposure to a particular chemical that can involve the general public. They, therefore, differ from PELs, TLV®s, WEEL®s, RELs or MAK values etc. in that they are based primarily on acute toxicology data and not subchronic or chronic data. The guidance therefore does not reflect the effects that could result from frequent exposure. Also, they are designed to protect the general population including the elderly and children, groups that are generally not considered in the development of workplace exposure levels. Users of the AEGL TSDs should first determine if there are legally enforceable standards that apply to the situation. Other organizations may also have recommended levels of exposure that more appropriately apply to the scenarios under evaluation.

It is however recognized that there may be an occasion where it may seem desirable to use these values for other exposure scenarios. In these cases, one should consult the technical support document. This document contains a comprehensive review of all identified acute toxicology data on the subject chemical and the basis for the development of the AEGL values. From this review one will have the information to determine the applicability of the AEGL to their particular situation.

Appendix A

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

Appendix B

NAC/AEGL Meeting 27: December 9-11, 2002

Chemical: CHLOROFORM **CAS Reg. No.:** 67-66-3

NAC Member	AEGL 1 *	AEGL 2 ≠	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	P	N		Nancy Kim	Y	N	
Steven Barbee	Y	P		Loren Koller	Y	Y	
Lynn Beasley	A	A		Glenn Leach	Y	Y	
David Belluck	Y	Y		Mark McClanahan	Y	Y	
Robert Benson	Y	Y		John Morawetz	A	A	A
Jonathan Borak	A	A		Richard Niemeier	Y	Y	
William Bress	A	A	A	Marinelle Payton	A	A	
George Cushmac	Y	Y		Zarena Post	A	A	A
Al Dietz	A	A		George Rodgers	Y	Y	
Ernest Falke	Y	Y		George Rusch, Chair	Y	Y	
Larry Gephart	A	A	A	Robert Snyder	P	Y	
John Hinz	Y	N		Thomas Sobotka	A	A	
Jim Holler	Y	Y		Kenneth Still	A	A	A
Thomas Hornshaw	Y	N		Richard Thomas	A	Y	
Doan Hansen	A	A		TALLY		13/~~12~~ 11	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	(NR), ( )	NR, ( )	NR, ( )	NR, ( )	NR, ( )
AEGL 2	(120), ( )	80, ( )	64, ( )	40, ( )	29, ( )
AEGL 3	(3100), ( )	(2200), ( )	(1700), ( )	(1100), ( )	(540), ( )

NR = not recommended

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

AEGL 2 Motion: ≠ Falke **Second:** Niemeier

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

Approved by Chair: [signature] **DFO:** [signature] **Date:** 12/10/02

* Move to use 100 ppm as starting point

≠ Adopt all AEGL values

Appendix C

NAC/AEGL Meeting 27: December 9-11, 2002

Chemical: CHLORINE TRIFLUORIDE **CAS Reg. No.:** 7790-91-2

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y			Nancy Kim	Y		
Steven Barbee	Y			Loren Koller	A		
Lynn Beasley	A			Glenn Leach	A		
David Belluck	Y			Mark McClanahan	Y		
Robert Benson	Y			John Morawetz	A	A	A
Jonathan Borak	A			Richard Niemeier	A		
William Bress	A	A	A	Marinelle Payton	A		
George Cushmac	A			Zarena Post	A	A	A
Al Dietz	A			George Rodgers	Y		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	A	A	A	Robert Snyder	Y		
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	A	A	A
Thomas Hornshaw	Y			Richard Thomas	Y		
Doan Hansen	A			TALLY	14/14		

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.12, ( )	0.12, ( )	0.12, ( )	0.12, ( )	0.12, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )

AEGL 1 Motion: Rodgers **Second:** Thomas

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

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

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

Appendix D

NAC/AEGL Meeting 27: December 9-11, 2002

Toluene CAS Reg. No.: 108-88-3

[redacted]	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
[redacted]Alexeeff	N	N	P	Nancy Kim	Y	Y	P
[redacted]n Barbee	Y	Y	Y	Loren Koller	A	A	A
[redacted]an Beasley	A	A	A	Glenn Leach	Y	Y	Y
David Belluck	Y	Y	Y	Mark McClanahan	Y	Y	Y
Robert Benson	N	Y	Y	John Morawetz	A	A	A
Jonathan Borak	A	A	A	Richard Niemeier	A	A	A
William Bress	A	A	A	Marinelle Payton	A	A	A
George Cushmac	A	A	A	Zarena Post	A	A	A
Al Dietz	A	A	A	George Rodgers	Y	Y	N
Ernest Falke	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Larry Gephart	A	A	A	Robert Snyder	Y	Y	Y
John Hinz	Y	Y	Y	Thomas Sobotka	A	A	A
Jim Holler	Y	Y	Y	Kenneth Still	A	A	A
Thomas Hornshaw	Y	Y	P	Richard Thomas	Y	Y	Y
Doan Hansen	A	A	A	TALLY	13/15	14/15	11/12

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	200 ,( )	200 ,( )	200 ,( )	200 ,( )	200 ,( )
AEGL 2	990 ,( )	570 ,( )	510 ,( )	510 ,( )	510 ,( )
AEGL 3	7200 ,( )	4200 ,( )	3900 ,( )	1500 ,( )	1500 ,( )

AEGL 1 Motion: Snyder **Second:** Falke

AEGL 2 Motion: ↓ **Second:** ↓

AEGL 3 Motion: ↓ **Second:** ↓

Approved by Chair: George M. Rusch **DFO:** Paul S. Tobin **Date:** 12/10/02

Appendix E

NAC/AEGL Meeting 27: December 9-11, 2002

Chemical: 1,4-DIOXANE **CAS Reg. No.:** 123-91-1

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

+ 17/17

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	17 ,( )	17 ,( )	17 ,( )	17 ,( )	17 ,( )
AEGL 2	580 ,( )	400 ,( )	320 ,( )	200 ,( )	100 ,( )
AEGL 3	950 ,( )	950 ,( )	~~760~~ ,( )	480 ,( )	240 ,( )

* LOA (KIM/BELLUCK MOTION) = 1.7 PPM

AEGL 1 Motion: Benson **Second:** Holler

AEGL 2 Motion: Koller **Second:** McClanahan

AEGL 3 Motion: Barbee **Second:** McClanahan

Approved by Chair: [signature] **DFO:** [signature] **Date:** 12/19/02

Appendix F

NAC/AEGL Meeting 27: December 9-11, 2002

Chemical: SULFUR DIOXIDE **CAS Reg. No.:** 7446-09-5

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	N Y	Y	Nancy Kim	Y	N Y	P
Steven Barbee	Y	Y Y	Y	Loren Koller	Y	Y N	Y
Lynn Beasley	A	A A	A	Glenn Leach	Y	Y A	A
David Belluck	Y	A N	Y	Mark McClanahan	Y	Y N	N
Robert Benson	Y	Y P	Y	John Morawetz	A	A A	A
Jonathan Borak	Y	A Y	Y	Richard Niemeier	Y	N Y	Y
William Bress	A	A	A	Marinelle Payton	A	A A	A
George Cushmac	A	A A	A	Zarena Post	A	A A	A
Al Dietz	A	A A	A	George Rodgers	Y	N Y	N
Ernest Falke	Y	Y Y	Y	George Rusch, Chair	Y	Y Y	Y
Larry Gephart	A	A	A	Robert Snyder	N	N Y	Y
John Hinz	P	N Y	Y	Thomas Sobotka	A	A A	A
Jim Holler	Y	N Y	Y	Kenneth Still	A	A A	A
Thomas Hornshaw	Y	Y P	N	Richard Thomas	Y	N Y	Y
Doan Hansen	A	A A	A	TALLY	16/16	8/16 12/15	13/16

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.25, ( )	0.25, ( )	0.25, ( )	0.25, ( )	0.25, ( )
AEGL 2	1.0, ( )	1.0, ( )	1.0, ( )	0.75, ( )	0.75, ( )
AEGL 3	42, ( )	32, ( )	27, ( )	19, ( )	16, ( )

AEGL 1 Motion: Koller **Second:** McClanahan

AEGL 2 Motion: Falke (Thomas) **Second:** (Snyder)

AEGL 3 Motion: Falke **Second:** Benson

Approved by Chair: [signature] **DFO:** Paul Tobin **Date:** 12/9/02

Appendix G

NAC/AEGL Meeting 27: December 9-11, 2002

Chemical: DIMETHYL DICHLOROSILANE **CAS Reg. No.:** 75-78-5

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

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	6.5 ,( )	6.5 ,( )
AEGL 3	,( )	,( )	,( )	,( )	13 ,( )

AEGL 1 Motion: Hinz (REVISE AEGL-2 + AEGL 3 AS ABOVE) **Second:** Kim

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

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

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 12/10/02

Appendix H

NAC/AEGL Meeting 27: December 9-11, 2002

75-79-6

Chemical: METHYL TRICHLOROSILANE **CAS Reg. No.:**

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

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	3.1 ,( )	3.1 ,( )
AEGL 3	,( )	,( )	,( )	,( )	7.0 ,( )

AEGL 1 Motion: J. Hinz **Second:** G. Rodgers

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

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

Approved by Chair: George M. Rusch **DFO:** Paul S. Tobin **Date:** 12/10/02

Appendix I

NAC/AEGL Meeting 27: December 9-11, 2002

Chemical: TRIMETHYLCHLOROSILANE **CAS Reg. No.:** 75-77-4

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

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	1.8 ,( )	1.8 ,( )	1.8 ,( )	1.8 ,( )	1.8 ,( )
AEGL 2	190 ,( )	64 ,( )	32 ,( )	16 ,( )	16 ,( )
AEGL 3	790 ,( )	270 ,( )	130 ,( )	33 ,( )	33 ,( )

AEGL 1 Motion: Hinz **Second:** McClanahan

AEGL 2 Motion: ↓ **Second:** ↓

AEGL 3 Motion: ↓ **Second:** ↓

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 12/20/02

Appendix J

NAC/AEGL Meeting 27: December 9-11, 2002 Vote on 10 min.

Chemical: NITROGEN DIOXIDE **CAS Reg. No.:** 10102-44-0

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	N	N	Y	Nancy Kim	N	N	Y
Steven Barbee	Y	Y	Y	Loren Koller	Y	Y	Y
Lynn Beasley	A	A	A	Glenn Leach	Y	Y	Y
David Belluck	N	Y	Y	Mark McClanahan	Y	Y	Y
Robert Benson	Y	Y	Y	John Morawetz	A	A	A
Jonathan Borak	A	A	A	Richard Niemeier	Y	Y	Y
William Bress	A	A	A	Marinelle Payton	A	A	A
George Cushmac	Y	Y	Y	Zarena Post	A	A	A
Al Dietz	A	A	A	George Rodgers	N	N	Y
Ernest Falke	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Larry Gephart	A	A	A	Robert Snyder	Y	Y	Y
John Hinz	Y	Y	Y	Thomas Sobotka	A	A	A
Jim Holler	Y	Y	Y	Kenneth Still	A	A	A
Thomas Hornshaw	Y	P	P	Richard Thomas	Y	Y	Y
Doan Hansen	A	A	A	TALLY	14/15	14/17	17/17

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.5 ,( )	0.5 ,( )	0.5 ,( )	0.5 ,( )	0.5 ,( )
AEGL 2	20 ,( )	15 ,( )	12 ,( )	8.2 ,( )	6.7 ,( )
AEGL 3	34 ,( )	25 ,( )	20 ,( )	14 ,( )	11 ,( )

AEGL 1 Motion: Benson **Second:** Hornshaw

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

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

Approved by Chair: [signature] **DFO:** Paul Tobin **Date:** 12/10/02

Appendix K

NAC/AEGL Meeting 27: December 9-11, 2002

Chemical: BENZENE **CAS Reg. No.:** 71-43-2

NAC Member	*AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A A			Nancy Kim	Y Y		
Steven Barbee	N Y			Loren Koller	A A		
Lynn Beasley	A A			Glenn Leach	A A		
David Belluck	N Y			Mark McClanahan	N Y		
Robert Benson	N Y			John Morawetz	A A	A	A
Jonathan Borak	A A			Richard Niemeier	A A		
William Eress	A A	A	A	Marinelle Payton	A A		
George Cushmac	N [ ]			Zarena Post	A A	A	A
Al Dietz	A A			George Rodgers	Y Y		
Ernest Falke	Y Y			George Rusch, Chair	P P		
Larry Gephart	A A	A	A	Robert Snyder	Y Y		
John Hinz	N Y			Thomas Sobotka	A A		
Jim Holler	Y Y			Kenneth Still	A A	A	A
Thomas Hornshaw	N Y			Richard Thomas	A A		
Doan Hansen	A A			TALLY	5/12 11/11		

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	*37 #12,?)	*37 #73,( )	*37 #52,( )	*37 #18,( )	*37 #9,( )
AEGL 2	[redacted],( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

AEGL 1 Motion: * Falke / # Hinz (PASSES) **Second:** Rodgers / McClanahan

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

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

Approved by Chair: George M Rusch **DFO:** Paul S. Tobin **Date:** 12/11/02